

**EU ACADEMY OF SCIENCES  
EUAS**

***EU ACADEMY  
2021 ANNUAL REPORT***

**The President of EUAS**

Professor E.G. Ladopoulos

**& The Board Governors of EUAS**

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# Leading Technology of the Energy World by the Theory of “Universal Mechanics” What will be Next?

by Evangelos Ladopoulos, President & CEO of EUAS

## Short Biography

*Prof. Dr. Civil Engineer, Mechanical (Aerospace) Engineer & Petroleum Engineer, D.Sc.  
Included in the list of 2000 Outstanding Scientists of 20<sup>th</sup> Century by Cambridge Bio  
Centre.*

*Included in the list of 2000 Outstanding Scientists of 21<sup>st</sup> Century by Cambridge Bio  
Centre.*

*Included in the list of 100 Top Scientists of 2007 by Cambridge Bio Centre.*

*Over 500 publications in high quality scientific journals and 5 books.*

*Project Manager for over 500 Projects in Civil Engineering, Mechanical Engineering,  
Aerospace Engineering and Petroleum Engineering.*

*Chairman and Professor by Interpaper Research Organization.*

*Visiting Professor at Universities in Europe and USA.*

*Editor-in-Chief of many SCI Engineering Journals.*

*High Index by Google Scholar.*

*President & CEO of the EU Academy of Sciences.*

*Member by several Academies in USA.*

For the design of the future spacecraft of any speed, the leading technology of “**Universal Mechanics**” is proposed and studied. The leading theory of “*Universal Mechanics*” consists of the combination of the theories of “*Relativistic Elasticity*” and “*Relativistic Thermo-Elasticity*”. Consequently, according to the above theories there is a considerable difference between the absolute stress tensor and the stress tensor of the airframe even in the range of speeds of 50,000 km/h. Besides, for bigger speeds of the absolute spacecraft, like  $c/3$ ,  $c/2$  or  $3c/4$  ( $c$ =speed of light), then the difference between the two stress tensors is very much increased. So, for the future spacecraft with very high speeds, the relative stress tensor will be therefore very much different than the absolute stress tensor. Moreover, for velocities near the speed of light, then the values of the relative stress tensor are very much bigger than the corresponding values of the absolute stress tensor. Such future spacecraft will be moving by using laser engines.

After the speed of light an energy world would appear. Is that possible ? Yes of course it is possible. Over the past many people have seen in the sky several lights in the form of spacecraft or flying saucers. So, these might be aliens much more developed than humans with their science very much developed and their spacecraft is in energy form. Thus, if the spacecraft exceeds the speed of light, then it becomes an energy spacecraft. In that case an Energy World would be possible.

Another question is what will be next ? Has the energy world to do anything with the life after death ? So, is the soul a kind of energy ? Could be the soul connected to the energy world ?

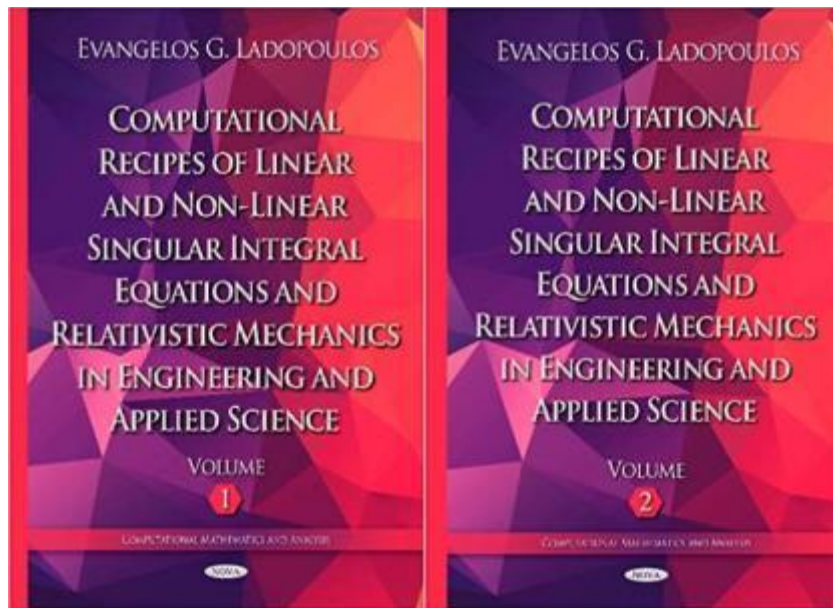
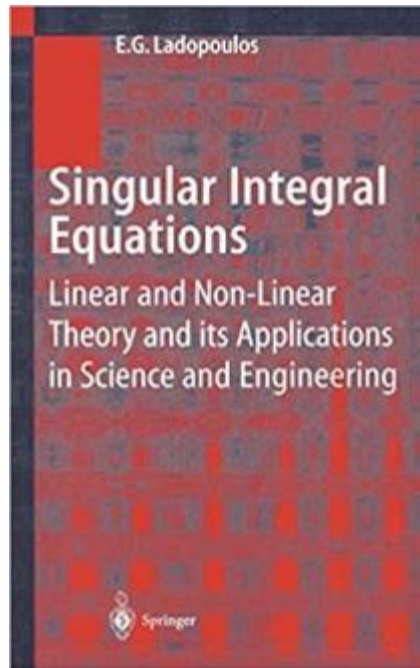
The theory of "*Relativistic Elasticity*" is a combination between the theories of "Classical Elasticity" and "Special Relativity" and results in the "***Universal Equation of Elasticity***". Beyond the above, the theory of "*Relativistic Thermo-Elasticity*" is a combination between the theories of "Classical Thermo-Elasticity" and "Special Relativity" and results in the "***Universal Equation of Thermo-Elasticity***". The "structural design" of super speed vehicles requires the consideration of mass pulsation and energy-mass interaction at high velocity space-time scale, as the relative stress intensity factors are different than the corresponding absolute stress intensity factors. Such theory results in the "***Universal Stress Intensity Factors***". Hence, the "*Universal Equation of Elasticity*", the "*Universal Equation of Thermo-Elasticity*" and the "*Universal Stress Intensity Factors*" are parts of the general theory of "*Universal Mechanics*".

The scope by the International Space Agencies is to achieve in the future, a new generation spacecraft moving with very high speeds, even approaching the speed of light. How far could be this future ? According to current author's research such future could be much closer than everybody believes. For the future spacecraft the relative stress tensor will be much different than the absolute stress tensor and so special solid should be used for the construction of the future spacecraft.

Also, in order the future spacecraft to achieve very high speed, even approaching the speed of light, then such new generation spacecraft should be moving by using laser engines. Laser is light and so their speed is the speed of light. Consequently, the use of laser engines for the future spacecraft would be the best device. Also special material should be used for the construction of such spacecraft.

One second question is the following: What happens with our theory if somebody in the very future proves that the speed of light is not the maximum speed in the whole universe, but there is another type of energy with higher speed ? The answer is that our theory of "Universal Mechanics" will valid over the centuries and the milleniums, as the spacecraft when reaching the speed of light then becomes energy and will not be mass any more. Thus, after the speed of light there is no mass available, but only energy. According to NASA the Large and Small Magellanic clouds were thought to be the closest galaxies to ours, until 1994, when the Sagittarius Dwarf Elliptical Galaxy (SagDEG) was discovered. In 2003, the Canis Major Dwarf Galaxy was discovered - this is now the closest known galaxy to ours. So, The Canis Major Dwarf Galaxy is only 25,000 light years from the Sun, and 42,000 light years from the Galactic center. It too, is well-hidden by the dust in the plane of the Milky Way - which is why it wasn't discovered until recently. To get to the closest galaxy to ours, the Canis Major Dwarf, at Voyager's speed, it would take approximately 749,000,000 years to travel the distance of 25,000 light years! If we could travel at the speed of light, it would still take 25,000 years. On the other hand, the galaxy MACS0647-JD appears very young and is only a fraction of the size of our own Milky Way. The galaxy is about 13.3 billion light-years from Earth, the farthest galaxy yet known, and formed 420 million years after the Big Bang. The universe itself is only 13.7 billion years old, so this galaxy's light has been traveling toward us for almost the whole history of space and time.

More details can be seen by the following books:

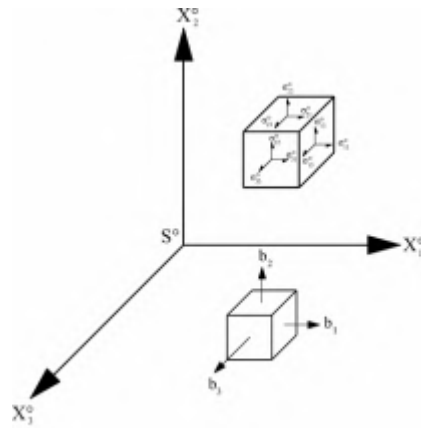


Consider the state of stress at a point in the stationary frame  $S^0$ , defined by the following symmetrical stress tensor: (Fig.1)

$$\sigma^0 = \begin{bmatrix} \sigma_{11}^0 & \sigma_{12}^0 & \sigma_{13}^0 \\ \sigma_{21}^0 & \sigma_{22}^0 & \sigma_{23}^0 \\ \sigma_{31}^0 & \sigma_{32}^0 & \sigma_{33}^0 \end{bmatrix} \quad (1)$$

where:

$$\sigma_{21}^0 = \sigma_{12}^0, \sigma_{31}^0 = \sigma_{13}^0, \sigma_{32}^0 = \sigma_{23}^0 \quad (2)$$



**Fig. 1** The state of stress  $\sigma_{ik}^0$  in the stationary system  $S^0$ .

Additionally, we consider an infinitesimal face element  $df$  with a directed normal, defined by a unit vector  $\mathbf{n}$ , at definite point  $p$  in the three-space of a Lorenz system. The matter on either side of this face element experiences a force which is proportional to  $df$ .

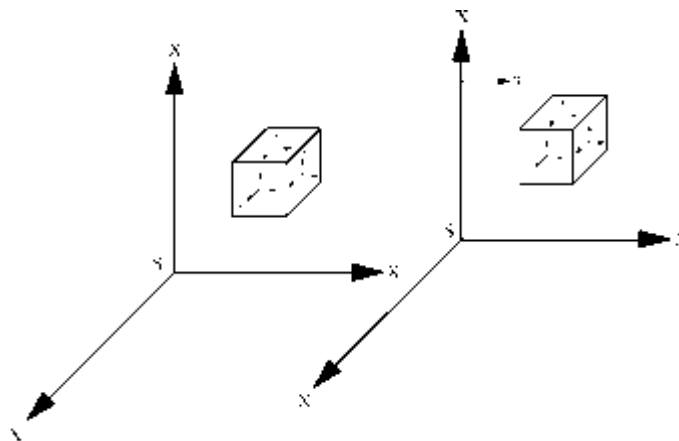
So, the force is valid as:

$$d\boldsymbol{\sigma}(\mathbf{n}) = \boldsymbol{\sigma}(\mathbf{n})df \tag{3}$$

The components  $\sigma_i(\mathbf{n})$  of  $\boldsymbol{\sigma}(\mathbf{n})$  are linear functions of the components  $n_k$  of  $\mathbf{n}$ :

$$\sigma_i(\mathbf{n}) = \sigma_{ik}n_k, \quad i, k = 1, 2, 3 \tag{4}$$

where  $\sigma_{ik}$  is the elastic stress tensor, also called as the relative stress tensor, in contrast to the space part  $\sigma_{ik}^0$  of the total energy-momentum tensor  $T_{ik}$ , referred as the absolute stress tensor (Fig. 2).



**Fig. 2** The state of stress  $\sigma_{ik}^0$  in the stationary system  $S^0$  and  $\sigma_{ik}$  in the airframe system with velocity  $u$  parallel to the  $x_1$  - axis.

Besides, the connection between the absolute and relative stress tensors is defined as:

$$\sigma_{ik}^0 = \sigma_{ik} + g_i u_k, \quad i, k = 1, 2, 3 \quad (5)$$

where  $g_i$  are the components of the momentum density  $\mathbf{g}$  and  $u_k$  the components of the velocity  $\mathbf{u}$  of the matter.

The relative stress tensor gives the *Universal Equation of Elasticity*:

$$\boldsymbol{\sigma} = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_{22} & \sigma_{23} \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix} = \begin{bmatrix} \sigma_{11}^0 & \gamma \sigma_{12}^0 & \gamma \sigma_{13}^0 \\ \frac{1}{\gamma} \sigma_{21}^0 & \sigma_{22}^0 & \sigma_{23}^0 \\ \frac{1}{\gamma} \sigma_{31}^0 & \sigma_{32}^0 & \sigma_{33}^0 \end{bmatrix} \quad (6)$$

in which  $\gamma$  is given by:

$$\gamma = 1 / (1 - u^2 / c^2)^{1/2} \quad (7)$$

with  $c$  the speed of light.

Beyond the above, consider the general system of continuously matter, inside which invisible heat conduction can take place. Then the momentum density  $\mathbf{g}$  of this system is given by the *Universal Equation of Thermo-Elasticity*:

$$\mathbf{g} = m\mathbf{u} + \frac{(\mathbf{u}, \boldsymbol{\sigma})}{c^2} + \frac{\boldsymbol{\xi}}{c^2} \quad (8)$$

where  $\mathbf{u}$  denotes the velocity of the matter at the place and time considered,  $\boldsymbol{\sigma}$  the relative stress tensor,  $m = E / c^2$  is the total mass density and  $\boldsymbol{\xi}$  is given by:

$$\boldsymbol{\xi} = \gamma [\mathbf{V} - \mathbf{u}(\mathbf{V}, \mathbf{u}) / c^2] \quad (9)$$

with  $\mathbf{V}$  the four vector.

Furthermore, “*Universal Mechanics*” gives the complete theory of mechanics for the whole universe. Then the theories of Special and General Relativity, as were proposed by Albert Einstein are completed for the whole universe by “*Universal Mechanics*”, as proposed by the current author. Hence, by the current author is completed the theory of Albert Einstein for the whole universe regarding mechanics engineering behavior.

Table 1 shows the values of  $\gamma$  of relativity theory for some arbitrary values of the velocity  $u$  of the moving aerospace structure, where  $c$  is the speed of light (300,000 km/sec):

Table 1

Velocity $u$	$\gamma = 1/\sqrt{1-u^2/c^2}$	Velocity $u$	$\gamma = 1/\sqrt{1-u^2/c^2}$
50,000 km/h	1.000000001	0.800c	1.666666667
100,000 km/h	1.000000004	0.900c	2.294157339
200,000 km/h	1.000000017	0.950c	3.202563076
500,000 km/h	1.000000107	0.990c	7.088812050
10E+06 km/h	1.000000429	0.999c	22.36627204
10E+07 km/h	1.000042870	0.9999c	70.71244596
10E+08 km/h	1.004314456	0.99999c	223.6073568
2x10E+8 km/h	1.017600788	0.999999c	707.1067812
c/3	1.060660172	0.9999999c	2236.067978
c/2	1.154700538	0.99999999c	7071.067812
2c/3	1.341640786	0.999999999c	22360.67978
3c/4	1.511857892	c	$\infty$

From Table 1 follows that for small velocities 50,000 km/h to 200,000 km/h, the absolute and the relative stress tensors are nearly the same. On the contrary, for bigger velocities like  $c/3$ ,  $c/2$  or  $3c/4$  ( $c$  = speed of light), the variable  $\gamma$  takes values more than the unit and thus, relative stress tensor is very different from the absolute one. Additionally, for values of the velocity for the moving structure near the speed of light, the variable  $\gamma$  takes bigger values, while when the velocity is equal to the speed of light, then  $\gamma$  tends to the infinity.

For the design of the future spacecraft the “*Universal Stress Intensity Factors*” are further used. Hence, as was shown by the current author, the relative first and third mode stress intensity factors are the same for both stationary and moving frames, while the relative second mode stress intensity factor is much different in the above frames. All the relative stress intensity factors (first, second and third) are important for the fracture mechanics analysis of the future spacecraft, as for their fracture mechanics analysis a combination of all the three intensity factors should be used.

The **Universal Stress Intensity Factors** are given by the formulas:

$$K_I = \lim_{x_1 \rightarrow 0} \left\{ \sqrt{2\pi x_1} \sigma_{22}^0 \right\} \tag{10}$$

$$K_{II} = \lim_{x_1 \rightarrow 0} \left\{ \sqrt{2\pi x_1} \gamma \sigma_{12}^0 \right\} \tag{11}$$

$$K_{III} = \lim_{x_1 \rightarrow 0} \left\{ \sqrt{2\pi x_1} \sigma_{23}^0 \right\} \tag{12}$$

So, from eqs (10) to (12) follows that the relative first and third mode stress intensity factors are the same for both stationary and moving frames, while the relative second mode stress intensity factor is much different in the above frames. So, because of the above difference of the stress intensity factors, follows that the fracture behavior of the future spacecraft would be much different and thus special materials should be used for their construction.

When the relative stress intensity factors are taken into consideration the whole theory is known as “*Universal Fracture Mechanics*”.

## Liquid Crystal Displays & Photonic Devices

by Vladimir Chigrinov, Member EUAS



### Short Biography

*Professor Vladimir G. Chigrinov is Professor of Hong Kong University of Science and Technology since 1999 and become Professor Emeritus since 2015. He is an Expert in Flat Panel Technology in Russia, recognized by the World Technology Evaluation Centre, 1994, and SID Fellow since 2008. He is an author of 6 books, 31 reviews and book chapters, about 318 journal papers, more than 672 Conference presentations, and 121 patents and patent applications including 36 US patents in the field of liquid crystals since 1974. He got Excellent Research Award of HKUST School of Engineering in 2012. He obtained Gold Medal and The Best Award in the Invention & Innovation Awards 2014 held at the Malaysia Technology Expo (MTE) 2014, which was hosted in Kuala Lumpur, Malaysia, on 20-22 Feb 2014. He is a Member of EU Academy of Sciences (EUAS) since July 2017. He got A Slottow Owaki Prize of SID in 2018 <http://www.ee.ust.hk/ece.php/enews/detail/660>. He is a Distinguished Fellow of IETI (International Engineering and Technology Institute). He is 2020-2024 Vice President of Institute of Data Science and Artificial Intelligence (IDSAI) and Distinguished Fellow of Institute of Data Science and Artificial Intelligence. Since 2018 until 2021 he works as Professor in the School of Physics and Optoelectronics Engineering in Foshan University, Foshan, China as Third Level Distinguished Professor, in Talents Special Zone.*

### **RESEARCH INTERESTS**

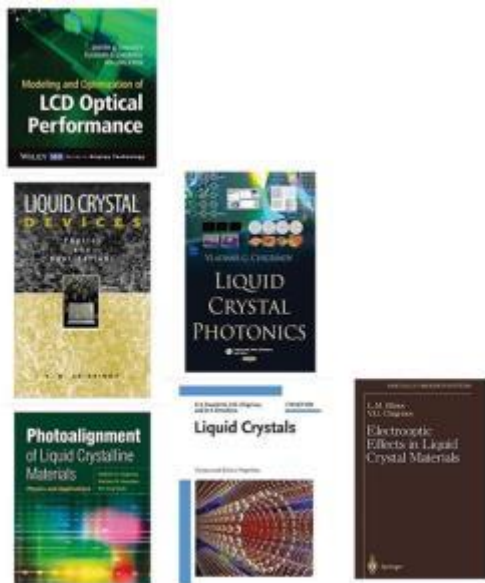
- Computer modeling of various electrooptical effects in Liquid Crystals.
- Photo-aligning technique for LCD applications .
- LC devices in fiber optics.
- Liquid Crystal Applications in Photonics
- Liquid Crystal Devices for Non-Display Applications
- Fast Ferroelectric Liquid Crystal Display for Field Sequential Applications
- New Optically Rewritable Electronic Paper Liquid Crystal Displays

**Future of Liquid Crystal devices: photoalignment, ferroelectric liquid crystals, photonics**

Liquid crystal (LC) devices for displays and photonics are dominating in the market and will be the basic technology for advanced display and electronics in the nearest 10 years.

Photoalignment materials can be effectively used in LC alignment and patterning for new generations of LC devices that provide extremely high resolution and optical quality of alignment both in glass and plastic substrates, photonics holes etc. New liquid crystal devices include ORW E-paper, field sequential color ferroelectric liquid crystal (FLC) projectors, photo-patterned quantum rods and 100% polarizers, q-plates, sensors, switchable lenses, windows with voltage controllable transparency, security films, switchable antennas.

Books



36 US Patents (US)

1	10 028 724	Photoalignment, systems and associated items
2	10 027 520	Display systems for ferroelectric liquid crystal devices
3	10 021 044	Modular data structures, liquid crystal devices
4	10 281 731	2D/3D compatible liquid crystal lens
5	9 928 433	Field sequential color ferroelectric liquid crystal device
6	9 923 020	Switchable liquid crystal channel lens
7	9 920 048	Cryostat's liquid crystal, sensitive detection and method
8	9 791 743	Material photo-alignment layer for liquid crystal
9	9 727 440	External polarization matrix polarization element
10	9 629 226	Synthesis and liquid crystal alignment layer including canal coated layer
11	9 579 046	Fast re-charge and high diffusion efficiency, matrix ferroelectric liquid crystal cell
12	9 483 083	External polarization element
13	9 366 014	Field sequential color ferroelectric liquid crystal device
14	9 341 055	Polarization converter by external polarization element
15	9 289 018	External polarization element
16	9 228 020	Transfer to glass and substrate use of film technology liquid crystal device
17	9 046 229	Thinners, liquid crystal systems
18	8 930 032	Applied liquid crystal cell with fast response and continuous operation
19	8 926 484	Photo-induced di-ferro, re-orientation and fabrication methods thereof
20	8 922 978	Photoaligned liquid crystal microstructure array and its manufacturing method
21	8 823 003	Low voltage liquid crystal lens with variable focal length
22	8 728 724	Transferable liquid crystal device
23	7 827 711	Low impedance suspension for electro-optical film, water dispersion and method for the same
24	7 753 144	Electro-optic variable transmittance array photoaligned liquid crystal
25	7 700 026	Transferable liquid crystal device
26	7 683 882	Photo induced ferro re-orientation films
27	7 629 013	Photo-induced di-ferro, re-orientation and fabrication methods thereof
28	6 623 026	Modular data structures, liquid crystal cell
29	6 619 202	Photo induced ferro re-orientation films
30	6 553 726	Method of manufacturing electro-optical element layer
31	6 528 882	Applied liquid crystal cells
32	6 324 129	Transferable device
33	6 228 100	Transferable liquid crystal cell
34	6 128 830	Transferable liquid crystal cell
35	5 285 028	Process for making electro-optical device, control modulation array, light source and receiver
36	5 227 714	Transferable ferroelectric liquid crystal device

AWARDS

Senior Member of the Society for Information Display (SID) since 10.10.04.

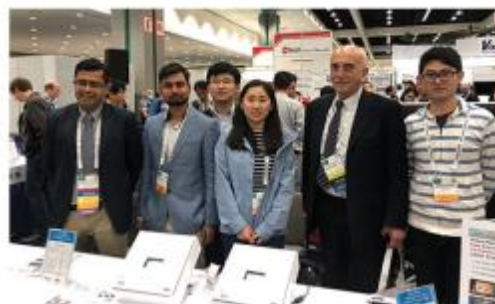
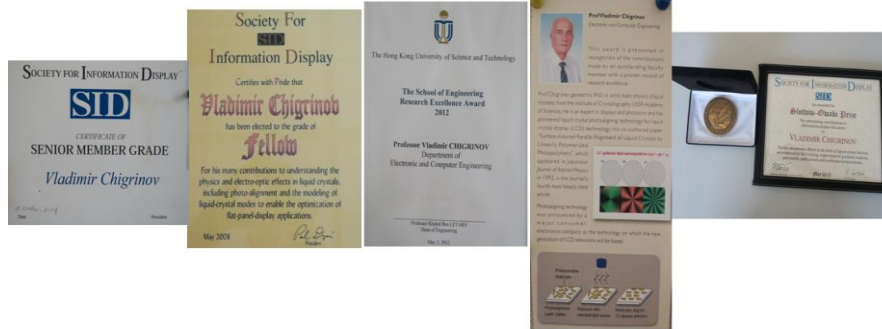
SID Fellow since 15.01.08

The Research Excellence Award of SENG, HKUST, that recognizes the efforts of an outstanding faculty member with a proven record of research excellence, May 2012.

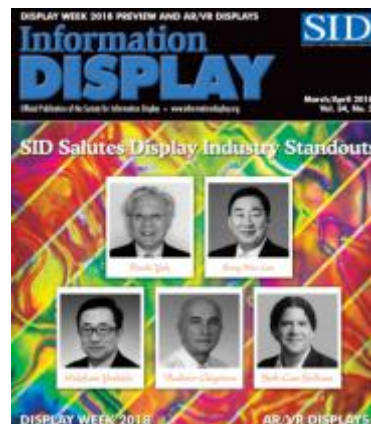
Gold Medal and The Best Award in the Invention & Innovation Awards 2014 held at the [Malaysia Technology Expo \(MTE\) 2014](#), which was hosted in Kuala Lumpur, Malaysia, on 20-22 Feb 2014.

Member of EU Academy of Sciences (EUAS) of distinguished members worldwide since July 2017.

2018 Slotow-Owaki Prize "For his educational efforts in the field of liquid-crystal devices, as evidenced by his teaching, supervision of graduate students, and prolific publications and conference presentations."



The team from Hong Kong University of Science and Technology stands in the J-Zone with its award-winning display technology. Pictured from left to right: Abhishek Kumar Srivastava, Swadesh Gupta, Alex Cheung, Liangyu Shi, Vladimir Chigrinov, and Chenxiang Zhao, all of Hong Kong University. Photo: Steve Seivast



**Recent publications ( year 2021)****Journal**

1. Vladimir Chigrinov, Aleksey Kudreyko, Tunable optical properties of ORW e-paper, *Liquid Crystals*, 48 (7) , pp.1073-1077(2021).
2. Vladimir Chigrinov, Aleksey Kudreyko, and Qi Guo, Patterned Photoalignment in Thin Films: Physics and Applications, *Crystals*, 2021, 11, 84.
3. Shi, Yue, Lai, Yingming, Li, Yong, Liu, Yan Jun, Chigrinov, Vladimir G, Kwok, Hoi-Sing, Luo, Dan, Sun, Xiao Wei, Circularly polarised lasing from all-solid organic semiconductor activated external distributed feedback based on polarisation grating, *Liquid Crystals*, Vol. 48, No. 8, pp. 1186–11193 (2021).
4. MINGKUI YIN, YUHANG SHAN, XIAOYU LIU, SHUXIA QI, VLADIMIR G. CHIGRINOV, HOI-SING KWOK, AND JIANLIN ZHAO, Ferroelectric liquid crystal Pancharatnam-Berry lens with a fast control of output light's polarization-handedness YING MA, *Optics Express*, Vol. 29, No. 17, pp. 27472-27480 (2021).

**Conference**

1. Vladimir G. Chigrinov, Photoaligned and photopatterned liquid crystals: new materials for displays and photonics, International Workshop on Advanced Display Materials, HKUST, Hong Kong, January 2021.
2. Vladimir Chigrinov, Jiatong Sun, Mikhail Kuznetsov, Victor Belyaev, Denis Chausov, Invited Talk: Liquid crystal applications in E-paper and security films: new trends, SID'21 Conference, 38.1 , San Jose, USA, May, 2021.
3. Vladimir Chigrinov, Invited Talk: New electrooptical modes in photoaligned ferroelectric liquid crystals: physics and applications, iCDT'21 ,Conference, 33.2 , Beijing, China, May-June, 2021.
4. Vladimir Chigrinov, Invited Talk:Photoaligned liquid crystals:new trends, Int. Conf. on Materials and Engineering, Seoul, June 2021, <https://www.icematerialsci.com/>.
5. Vladimir Chigrinov, Invited Talk: Electrooptical modes in Photoaligned Ferroelectric Liquid Crystals: New Trends, EU ACADEMY OF SCIENCES (EUAS) e-SYMPOSIUM, July 2021.

**Patents**

- Srivastava Abhishek Kumar, Zhang Wanlong, Chigrinov Vladimir Grigorievich, Kwok Hoi Sing, *Photoaligned quantum rod enhancement films*, US Patent, 10,948,774, March 16, 2021.

## Tumor Vaccine Development for Head and Neck Cancer

by Dong Moon Shin, Member EUAS



### Short Biography

**Dong Moon Shin, MD, FACP, FAAAS**

**Professor of Medical Oncology and Francis Kelly Blomeyer Chair in Cancer Research  
Emory University School of Medicine**

*Dr. Dong Moon Shin is currently Professor of Medical Oncology, Otolaryngology and Biomedical Engineering, and holds Frances Kelly Blomeyer Distinguished Endowed Chair in Cancer Research in the Department of Hematology and Medical Oncology at Winship Cancer Institute of Emory University. He graduated from Yonsei University College of Medicine and trained for Residency in Internal Medicine at Cook County Hospital, Chicago, IL and fellowship of Medical Oncology at the University of Texas M. D. Anderson Cancer Center, Houston, TX.*

*He has served as a faculty member in the Department of Thoracic/Head and Neck Medical Oncology at M. D. Anderson Cancer Center and University of Pittsburgh as Professor and Director of Head and Neck Cancer Program before he joined Emory University. He has been consecutively selected for last 18 years as a Best Doctor from Best Doctors in America since he was elected first in year 2003 and he has been also consecutively selected one of the Top Doctors from Castle Connolly Medical Ltd. and Atlanta Magazine for last 16 years since he was elected first in year 2005. Distinguished Leadership Award for Cancer Research from American Biographical Institute, Georgia Cancer Coalition Distinguished Scholar Award, the 2009 Yonsei University's Medicine Grand Prize Award, Honorary Professor at Central South University, China, the Frances Kelly Blomeyer Distinguished Endowed Chair in Cancer Research, and the 18th KBS Global Korean Award (in the category of Science and Technology). And he was also bestowed for Fellow of American Association of Advancement of Science (FAAAS) and many others.*

*Dr. Shin has also chaired numerous peer-review committees, including but not limited to the American Head and Neck Society, American Association of Cancer Research and the American Society of Clinical Oncology. He has also served as a member of many study sections at the National Cancer Institute, NIH and on the editorial boards (more than 15 scientific journals) including the Journal of Clinical Oncology, Clinical Cancer Research, Cancer Prevention Research, Molecular Cancer Therapeutics, International Journal of Oncology and others. He has published more than 360 articles in peer-reviewed journals (H-index of 70 and more than 27,000 citation numbers as of January 2021) in addition to more than 370 other publications including meeting abstracts, books, book chapters and monographs.*

*Dr. Shin's research has been well funded through funding from NIH/NCI (R01s, U01s, R21, etc.) and other funding agencies. Specifically he has been Principal Investigator of Emory University's Head and Neck Cancer SPORE program (Specialized Programs of Research Excellence), which was awarded to Emory in 2007 by the National Cancer Institute (NCI). Another area of his interest has been nanotechnology based anti-cancer drug delivery in*

*collaboration with several other investigators including biomedical engineers, chemists, material scientists, imaging experts and animal scientists.*

**In this annual report I would like to emphasize TMV (tumor membrane vesicle) vaccine development in collaboration with Dr. Periasamy Selvaraj, Professor of Pathology at Emory University School of Medicine.**

Recent treatment of head and neck squamous cell carcinoma (HNSCC) with immune checkpoint inhibitors (ICIs) has resulted in improved survival of patients with metastatic HNSCC; however, the majority of patients (>80%) fail this treatment regardless of tumor human papilloma virus (HPV) status or demographic factors (1,2,3,4,5,6,7). Further, the incidence of HNSCC continues to increase with more than 64,690 new cases and 13,740 deaths estimated in 2020 in the US. Based on the building on our exciting ongoing collaborations at Emory between basic and clinical oncologists and experts in cancer immunology, vaccine development, T cell biology, and cancer metabolism, we are developing a personalized vaccine immunotherapy approach in a preclinical animal models and will eventually develop clinical trials in patients with advanced SCCHN with high risk of recurrence.

Although therapeutic cancer vaccines showed promising results in animal models, they have conferred only modest anti-tumor activity in several human clinical trials for many cancers, including HNSCC [8,9,10]. Many of the previous approaches employed genetically modified allogeneic tumor cell lines or cell lines developed from patients or single tumor antigens or tumor antigen-specific peptides as vaccine sources (11). These approaches induced anti-tumor immunity in patients, but clinical benefit was not achieved because the tumors might have escaped immune attack due to their heterogeneity, since the vaccines might not have represented all the variations found in the patient's tumor. It has been shown that the HNSCC tumor from each patient is distinct in its gene mutations and target antigens (12,13,14,15,16,17,18), a major challenge in developing targeted vaccine immunotherapy approaches for these patients. To address these limitations, personalized vaccine immunotherapy approaches that include patient-specific antigens are being developed. These include the use of patient-specific neoepitope peptide vaccines (19,20,21) and whole tumor lysate pulsed dendritic cell (DC) approaches (22,23). This suggests that it is critical to use patient-specific antigens in developing efficacious therapeutic cancer vaccines. Therefore, our goal is to induce anti-tumor immunity in HNSCC patients using the patient's own tumor tissue as the multi-antigen source.

In this study, we are investigating a tumor membrane vesicle (TMV)-based vaccine immunotherapy approach for HNSCC in syngeneic mouse models. These TMVs are uniform in size (300–500 nm) and are suitable for uptake and processing by antigen presenting cells such as DCs. Tumor membrane vesicles derived from the patients' own surgically removed tumor tissues which will be modified via a protein transfer approach with glycolipid-anchored forms of immuno-stimulatory molecules (GPI-ISM), such as B7-1 and IL-12. We try to investigate immune correlates of efficacy, mechanism of action, and synergy with immune check point inhibitors of TMV vaccine in murine tumor models of SCCHN. Our preliminary data show that TMV vaccine induced the regression of SCCVII tumors in syngeneic mice, and to determine the effect of dose and dosing schedule of TMV vaccine alone and/or TMV vaccine plus immune check-point inhibitors in a mouse model (24).

A.1. TMV vaccine plus anti-PD1 mAb combination therapy inhibits MOC1 tumor growth better than monotherapy. Mice were inoculated s.c. with  $2 \times 10^6$  MOC1 tumor cells on the right flank and then starting on day 3 they were vaccinated with weekly doses of 100  $\mu$ g of TMV vaccine (4 doses) s.c. on the left flank and anti-PD1 mAb (4 doses, rat anti-mouse PD1, clone RMP1-14, BioXCell) i.p. While there are no statistically significant differences between monotherapy groups, a significant decrease in tumor size between the PBS control vs. TMV vaccine + anti-PD-1 mAb (rat anti-mouse PD1 mAb, clone RMP1-14) treatment groups suggest an additive effect of TMV vaccine and anti-PD1 mAb on controlling tumor growth ( $p < 0.05$ ). TMV vaccine + anti-PD1 antibody therapy also extended the survival of tumor-bearing mice (data not shown). Two mice completely protected in the combination group were rechallenged with MOC1 tumor cells after 100 days of primary challenge to confirm the long lasting anti-tumor immunity in vaccinated mice (data not shown).

A.2. TMV vaccine inhibits tumor growth, increases T cell infiltration and inhibits MOC2 metastasis. To test our hypothesis that TMV vaccine enhances T-cell infiltration and converts immunologically cold tumors into hot tumors, mice were challenged with MOC2 cells and vaccinated with TMV vaccine every 5 days starting 3 days after tumor challenge and euthanized 4 days after the last dose of TMV vaccine. Tumors were analyzed for immune cell infiltration by multi-color flow cytometry and lungs were assessed for metastasis. The data show that TMV vaccine significantly inhibits tumor growth, and increases CD4<sup>+</sup> and CD8<sup>+</sup> T cell infiltration, suggesting that cold tumors could become hot tumors upon TMV vaccine therapy. To determine whether TMV vaccine inhibits lung metastasis of MOC2 cells, lungs were harvested and digested with collagenase and single cell suspension was prepared in sterile conditions. Cells (lung digest) were cultured in a G418 selection medium for 3 days to kill lung fibroblasts and then in regular culture medium for 11 days. Cells were harvested and enumerated by trypan blue dye exclusion, which showed that lung metastases were significantly decreased (data not shown).

Currently we are conducting TMV vaccine and ICI combination which may inhibit MOC2 tumor growth in a synergistic way in the animal models. We hope that the combination of the TMV vaccine with anti-PD1 mAb may further enhance the anti-tumor activity compared to TMV vaccine or anti-PD-1 alone and eventually move on the clinical trials and potential benefit in HNC.

## References

1. Saba N.F., Blumenschein G., Jr., Guigay J., Licitra L., Fayette J., Harrington K.J., Kiyota N., Gillison M.L., Ferris R.L., Jayaprakash V., et al. Nivolumab versus investigator's choice in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: Efficacy and safety in CheckMate 141 by age. *Oral Oncol.* 2019;96:7–14. doi: 10.1016/j.oraloncology.2019.06.017.
2. Moskovitz J., Moy J., Ferris R.L. Immunotherapy for Head and Neck Squamous Cell Carcinoma. *Curr. Oncol. Rep.* 2018;20:22. doi: 10.1007/s11912-018-0654-5.
3. Cohen E.E.W., Soulieres D., Le Tourneau C., Dinis J., Licitra L., Ahn M.J., Soria A., Machiels J.P., Mach N., Mehra R., et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. *Lancet (London, England)* 2019;393:156–167. doi: 10.1016/S0140-6736(18)31999-8.
4. Harrington K.J., Ferris R.L., Blumenschein G., Jr., Colevas A.D., Fayette J., Licitra L., Kasper S., Even C., Vokes E.E., Worden F., et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): Health-related quality-of-life results from a randomised, phase 3 trial. *Lancet Oncol.* 2017;18:1104–1115. doi: 10.1016/S1470-2045(17)30421-7.
5. Bauml J., Seiwert T.Y., Pfister D.G., Worden F., Liu S.V., Gilbert J., Saba N.F., Weiss J., Wirth L., Sukari A., et

- al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. *J. Clin. Oncol.* 2017;35:1542–1549. doi: 10.1200/JCO.2016.70.1524.
6. Ferris R.L., Blumenschein G., Jr., Fayette J., Guigay J., Colevas A.D., Licitra L., Harrington K., Kasper S., Vokes E.E., Even C., et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N. Engl. J. Med.* 2016;375:1856–1867. doi: 10.1056/NEJMoa1602252.
7. Hanna G.J., Liu H., Jones R.E., Bacay A.F., Lizotte P.H., Ivanova E.V., Bittinger M.A., Cavanaugh M.E., Rode A.J., Schoenfeld J.D., et al. Defining an inflamed tumor immunophenotype in recurrent, metastatic squamous cell carcinoma of the head and neck. *Oral Oncol.* 2017;67:61–69. doi: 10.1016/j.oraloncology.2017.02.005.
8. Schuler P.J., Harasymczuk M., Visus C., Deleo A., Trivedi S., Lei Y., Argiris A., Gooding W., Butterfield L.H., Whiteside T.L., et al. Phase I dendritic cell p53 peptide vaccine for head and neck cancer. *Clin. Cancer. Res.* 2014;20:2433–2444. doi: 10.1158/1078-0432.CCR-13-2617.
9. Schutt C.A., Mirandola L., Figueroa J.A., Nguyen D.D., Cordero J., Bumm K., Judson B.L., Chiriva-Internati M. The cancer-testis antigen, sperm protein 17, a new biomarker and immunological target in head and neck squamous cell carcinoma. *Oncotarget.* 2017;8:100280–100287. doi: 10.18632/oncotarget.22213.
10. Zolkind P., Dunn G.P., Lin T., Griffith M., Griffith O.L., Uppaluri R. Neoantigens in immunotherapy and personalized vaccines: Implications for head and neck squamous cell carcinoma. *Oral Oncol.* 2017;71:169–176. doi: 10.1016/j.oraloncology.2016.09.010.
11. Srivatsan S., Patel J.M., Bozeman E.N., Imasuen I.E., He S., Daniels D., Selvaraj P. Allogeneic tumor cell vaccines: The promise and limitations in clinical trials. *Hum. Vaccin. Immunother.* 2014;10:52–63. doi: 10.4161/hv.26568.
12. Zhang P., Mirani N., Baisre A., Fernandes H. Molecular heterogeneity of head and neck squamous cell carcinoma defined by next-generation sequencing. *Am. J. Pathol.* 2014;184:1323–1330. doi: 10.1016/j.ajpath.2014.01.028.
13. Peysner N.D., Grandis J.R. Cancer genomics: Spot the difference. *Nature.* 2017;541:162–163. doi: 10.1038/nature21112.
14. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015;517:576–582. doi: 10.1038/nature14129.
15. Loyo M., Li R.J., Bettegowda C., Pickering C.R., Frederick M.J., Myers J.N., Agrawal N. Lessons learned from next-generation sequencing in head and neck cancer. *Head Neck.* 2013;35:454–463. doi: 10.1002/hed.23100.
16. Agrawal N., Frederick M.J., Pickering C.R., Bettegowda C., Chang K., Li R.J., Fakhry C., Xie T.X., Zhang J., Wang J., et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science.* 2011;333:1154–1157. doi: 10.1126/science.1206923.
17. Stransky N., Egloff A.M., Tward A.D., Kostic A.D., Cibulskis K., Sivachenko A., Kryukov G.V., Lawrence M.S., Sougnez C., McKenna A., et al. The mutational landscape of head and neck squamous cell carcinoma. *Science.* 2011;333:1157–1160. doi: 10.1126/science.1208130.
18. Gaykalova D.A., Mambo E., Choudhary A., Houghton J., Buddavarapu K., Sanford T., Darden W., Adai A., Hadd A., Latham G., et al. Novel insight into mutational landscape of head and neck squamous cell carcinoma. *PLoS ONE.* 2014;9:e93102. doi: 10.1371/journal.pone.0093102.
19. Hellmann M.D., Snyder A. Making It Personal: Neoantigen Vaccines in Metastatic Melanoma. *Immunity.* 2017;47:221–223. doi: 10.1016/j.immuni.2017.08.001.
20. Sahin U., Derhovanessian E., Miller M., Kloke B.P., Simon P., Lower M., Bukur V., Tadmor A.D., Luxemburger U., Schrors B., et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature.* 2017;547:222–226. doi: 10.1038/nature23003.
21. Ott P.A., Hu Z., Keskin D.B., Shukla S.A., Sun J., Bozym D.J., Zhang W., Luoma A., Giobbie-Hurder A., Peter L., et al. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature.* 2017;547:217–221. doi: 10.1038/nature22991.
22. Tanyi J.L., Bobisse S., Ophir E., Tuyraerts S., Roberti A., Genolet R., Baumgartner P., Stevenson B.J., Iseli C., Dangaj D., et al. Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. *Sci. Transl. Med.* 2018;10 doi: 10.1126/scitranslmed.aao5931.
23. Carreno B.M., Magrini V., Becker-Hapak M., Kaabinejadian S., Hundal J., Petti A.A., Ly A., Lie W.R., Hildebrand W.H., Mardis E.R., et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. *Science.* 2015;348:803–808. doi: 10.1126/science.aaa3828.
24. Bommireddy R., Munoz L.E., Kumari A., Huang L., Fan Y., Monterroza L., Pack C.D., Ramachandiran S., Shaker J.C. Reddy, Kim J., Chen Z.G., Saba N.F., Shin D.M., and Selvaraj P. Tumor Membrane Vesicle Vaccine Augments the Efficacy of Anti-PD1 Antibody in Immune Checkpoint Inhibitor-Resistant Squamous Cell Carcinoma Models of Head and Neck Cancer. *Vaccines (Basel).* 2020 Jun; 8(2):182. Published online 2020 Apr 14. doi: 10.3390/vaccines8020182

## Geochemical Processes related to the Self-cleansing Capacity of Aquatic Systems

by Peter H. Santschi, Member EUAS



### Short Biography

Dr. Peter H. Santschi is a Regents Professor of Oceanography and Marine Sciences at the Texas A&M University, Galveston, TX, USA. He received his training in Geochemistry and Oceanography during his post-graduate work at L-DEO at Columbia University, N.Y., after graduating from the University of Bern, Switzerland, with a Ph.D. in Chemistry. Dr Santschi's research interests include Marine Chemistry, Environmental Chemistry and Environmental Radiochemistry; trace element interactions with natural organic matter; Tracer applications in natural water systems using stable and radioactive isotopes. Since 2000, he is associate editor of the journal *Marine Chemistry*. He is an author of well over 300 journal articles and 45 book chapters on these subjects, which, over the years, have received more than 15,000 citations. More on his research can be found at <https://www.tamug.edu/mars/faculty-bios/PeterHSantschi.html> and <https://scholar.google.com/citations?user=ZKGyOTsAAAAJ&hl=en&oi=ao>.

His total of 400+ peer-reviewed publications, according to the ISI Web of Science (all databases as of August 3, 2020), attest to his productivity, while his citation record is a testimony of his impact. Santschi's record is thus not only of quantity alone but predominantly of quality. Metrics establishing scientific impact are difficult to come by, but if the citation count and other indexes (e.g., h-index from ISI, all databases) may serve as a measure of scientific impact, then his 400+ publications have been cited over 17,000 times, with an average citation per publication of over 42. Other indexes for his publications (ISI h-index = 71 and productivity m-index =  $h/\Delta t = 1.51$  with  $\Delta t = 47$  years since the 1st publication in 1974; g-index = 137; and Google Scholar h-index = 87 and i-10 index = 293, with well over 25,000 citations) are exceptional.

Peter H. Santschi received **numerous national and international awards**, e.g., he was elected Member of the European Union Academy of Sciences (EUAS) (2020), Geochemical Fellow of the Geochemical Society and the European Association of Geochemistry (2017); Fellow of the American Geophysical Union (2014), which are given annually to only 0.1% of the 60,000 members; received the Distinguished Achievement Awards in Graduate Student Mentoring (2013) from Texas A&M's Association of Former Students; Regents Professor of Texas A&M University (2009), and received the Association of Former Student Distinguished Achievement Award for Research from Texas A&M University (2004). These awards were not possible without many collaborative and/or supportive scientists.

**His international pre-eminence** is not only demonstrated by the prestigious awards that he received, but also by the fact that he was invited as a member of Academic Advisory or Review Panels, as well as a Visiting Professor at national and international Universities, e.g., at Lamont-Doherty Earth Observatory of Columbia University (1982-1988), University of Rhode Island, School of Oceanography (1986), Dept. of Geology and Dept. of Chemistry, University of Geneva, Geneva, Switzerland (1996), Dept. of Chemistry and Biochemistry, University of Bern, Bern, Switzerland (2002), Dept. of Chemistry, University of Geneva, Geneva, Switzerland (2003), Swiss Institute of Technology, ETH, Zurich, Switzerland (2003), National Taiwan University, Taipei, Taiwan (2003), and Hong Kong University of Science and Technology (2004), National Center for Oceanographic Research, NCOR (2008).

**Summary of Accomplishments in Environmental Science.** During his 45-plus year career in environmental science, Santschi has gained and communicated novel insights into some of the blueprints of the aquatic environment, spanning from rain water, rivers and lakes to groundwater, from surface to deep ocean. During his long research career, he, together with 40+ graduate students, post-doctoral fellows and scientists all over the world, was able to pioneer new concepts and approaches that were truly **transformational**. The unifying theme of his research has been the **study of the self-cleansing capacity of natural aquatic systems:**

in particular, the importance of natural organic matter compounds for particle, radionuclide, and trace element cycling in aquatic systems. The importance of natural organic matter was not obvious in aquatic chemistry, as for many decades, the dogma was that metal behavior is mostly controlled by inorganic ligand interactions. His research involves the main agents that can ameliorate impact (e.g., toxicity, mobility) of potential pollutants to aquatic biota, i.e., microbially produced macromolecular substances that occur in the colloidal phase. This phase is mostly composed of nano-sized exopolymeric substances, as well as terrestrially derived humic substances, both of which can, at times, greatly help to control the efficiency of the self-cleansing capacity of aquatic systems. Natural colloids in aquatic systems are thus, to a large extent, derived from biological production and degradation of natural particles. Therefore, Peter's main contributions and impacts in environmental geochemistry are on the role of macromolecular natural organic matter, trace metal, and radionuclide speciation, transport, and cycling.

Dr. Santschi's **seminal contributions** to science, more specifically to the field of environmental biogeochemistry and radiochemistry, have thus included major **transformational** breakthroughs, e.g., the Colloidal (or Brownian) Pumping Concept that led to paradigm shifts in aquatic science (see below), and sustained impact, with his most cited papers providing unifying chemical and physico-chemical concepts explain pollutant behavior in aquatic environments, including articles published from the 1980s, 1990s, and 2000s. This transformational "Colloidal or Brownian Pumping Model" was able to simulate observations of apparent particle concentration effects on both the widely observed particle-water distribution coefficients and the model kinetic constants of trace element and radionuclide uptake onto natural particles, given the observed colloidal fractions of trace metals and radionuclides. His work then stimulated many other researchers to build on these novel concepts. Over the years following this transformational work, he tackled the challenging question of macromolecular organic compounds that occur in the colloidal phase and act as carrier molecules for specific trace elements and radionuclides. Due to the numerous difficulties in finding such compounds at relevant but trace levels in the midst of thousands of other compounds, selective separation and purification chemistry had to be thoroughly tested, before state-of-the-art instrumentation can be applied.

#### RECENT REVIEWS OF ENVIRONMENTAL CHEMISTRY SUBJECT AREAS

Santschi, P.H., Chin, W.C., Quigg, A., Xu, C., Kamalanathan, M., Lin P. **2021**. Marine gel interactions with hydrophilic and hydrophobic pollutants. Gels; Special Issue on Marine Gels, Gels 2021, 7, 83. <https://doi.org/10.3390/gels7030083>

**Abstract:** *Microgels play critical roles in a variety of processes in the ocean, including element cycling, particle interactions, microbial ecology, food web dynamics, air–sea exchange, and pollutant distribution and transport. Exopolymeric substances (EPS) from various marine microbes are one of the major sources for marine microgels. Due to their amphiphilic nature, many types of pollutants, especially hydrophobic ones, have been found to preferentially associate with marine microgels. The interactions between pollutants and microgels can significantly impact the transport, sedimentation, distribution, and the ultimate fate of these pollutants in the ocean. This review on marine gels focuses on the discussion of the interactions between gel-forming EPS and pollutants, such as oil and other hydrophobic pollutants, nanoparticles, and metal ions.*

Quigg A, Santschi PH, Xu C, Ziervogel K, Kamalanathan M, Chin W-C, Burd AB, Wozniak A and Hatcher PG. **2021** Aggregation and Degradation of Dispersants and Oil by Microbial Exopolymers (ADDOMEx): Toward a Synthesis of Processes and Pathways of Marine Oil Snow Formation in Determining the Fate of Hydrocarbons. *Front. Mar. Sci.* 8:642160. doi: 10.3389/fmars.2021.642160

**Abstract:** *Marine gels (nano-, micro-, macro-) and marine snow play important roles in regulating global and basin-scale ocean biogeochemical cycling. Exopolymeric substances (EPS) including transparent exopolymer particles (TEP) that form from nano-gel*

precursors are abundant materials in the ocean, accounting for an estimated 700 Gt of carbon in seawater. This supports local microbial communities that play a critical role in the cycling of carbon and other macro- and micro-elements in the ocean. Recent studies have furthered our understanding of the formation and properties of these materials, but the relationship between the microbial polymers released into the ocean and marine snow remains unclear. Recent studies suggest developing a (relatively) simple model that is tractable and related to the available data will enable us to step forward into new research by following marine snow formation under different conditions. In this review, we synthesize the chemical and physical processes. We emphasize where these connections may lead to a predictive, mechanistic understanding of the role of gels in marine snow formation and the biogeochemical functioning of the ocean.

Quigg, A.; Santschi, P.H.; Burd, A.; Chin, W.-C.; Kamalanathan, M.; Xu, C.; Ziervogel, K. **2021** From Nano-Gels to Marine Snow: A Synthesis of Gel Formation Processes and Modeling Efforts Involved with Particle Flux in the Ocean. *Gels* **2021**, 7, 114. <https://doi.org/10.3390/gels7030114>

**Abstract:** *Microbes (bacteria, phytoplankton) in the ocean are responsible for the copious production of exopolymeric substances (EPS) that include transparent exopolymeric particles (TEP). These materials act as a matrix to form marine snow. After the Deepwater Horizon oil spill, marine oil snow (MOS) formed in massive quantities and influenced the fate and transport of oil in the ocean. The processes and pathways of MOS formation require further elucidation to be better understood, in particular we need to better understand how dispersants affect aggregation and degradation of oil. Towards that end, recent work has characterized EPS as a function of microbial community and environmental conditions. We present a conceptual model that incorporates recent findings in our understanding of the driving forces of MOS sedimentation and flocculent accumulation (MOSSFA) including factors that influence the scavenging of oil into MOS and the routes that promote decomposition of the oil post MOS formation. In particular, the model incorporates advances in our understanding of processes that control interactions between oil, dispersant, and EPS in producing either MOS that can sink or dispersed gels promoting microbial degradation of oil compounds. A critical element is the role of protein to carbohydrate ratios (P/C ratios) of EPS in the aggregation process of colloid and particle formation. The P/C ratio of EPS provides a chemical basis for the 'stickiness' factor that is used in analytical or numerical simulations of the aggregation process. This factor also provides a relative measure for the strength of attachment of EPS to particle surfaces. Results from recent laboratory experiments demonstrate (i) the rapid formation of microbial assemblages, including their EPS, on oil droplets that is enhanced in the presence of Corexit-dispersed oil, and (ii) the subsequent rapid oil oxidation and microbial degradation in water. These findings, combined with the conceptual model, further improve our understanding of the fate of the sinking MOS (e.g., subsequent sedimentation and preservation/degradation) and expand our ability to predict the behavior and transport of spilled oil in the ocean, and the potential effects of Corexit application, specifically with respect to MOS processes (i.e., formation, fate, half-lives) and MOSSFA.*

Santschi, P.H., Xu, C., Schwehr, A.K., Lin, P., Sun, L., Chin, W.-C., Kamalanathan, M., Quigg, A. **2020**. Can the protein/carbohydrate (P/C) ratio of exopolymeric substances

(EPS) be used as a proxy for its ‘stickiness’ and other biophysical properties? Perspective article in Marine Chemistry, <https://doi.org/10.1016/j.marchem.2019.103734>.

**Abstract.** *Microbially secreted exopolymeric substances (EPS), rich in polysaccharides and proteins, make up an important part of natural organic matter in the ocean, especially marine snow. While the attention in most previous oceanographic literature focused on the role of polysaccharides in EPS functions, less is known about the role of proteins, especially the protein/carbohydrate (P/C) ratio of particles and colloids (macromolecular fraction), in marine systems. EPS associated with particles forms a biofilm, whereby proteins are not only involved in cell surface attachment, but also in the stabilization of the biofilm matrix, and the development of a three-dimensional biofilm architecture. Here, we provide a perspective based on the most recent literature on EPS, marine oil spills and waste water treatment to describe the relationship between the P/C ratio of EPS and a number of biophysical properties related to biopolymer aggregation (e.g., relative hydrophobicity, surface activity and surface tension, attachment efficiency, light-induced chemical crosslinking), and the sedimentation efficiency of marine snow in marine environments.*

Santschi, P.H. **2018.** Marine colloids, agents of the self-cleansing capacity of aquatic systems: Historical perspective and new discoveries. Marine Chemistry 207, 124–135. <https://doi.org/10.1016/j.marchem.2018.11.003>

**Abstract.** *Colloids in the ocean are mainly composed of natural organic matter (NOM), with trace amounts of metals, metalloids, radionuclides, pollutants, and variable amounts of anthropogenically produced engineered nanoparticles and nanoplastics. State-of-the-art sampling and instrumental techniques were required to unravel both size spectra and chemical composition.*

*Chemical components of colloidal macromolecular organic matter (COM) include aquagenic substances (composed of microbially produced Exopolymeric Substances (EPS), gels, transparent exopolymer particles (TEP) and TEP precursors), and pedogenic substances (mostly humic and fulvic matter). COM can be bioavailable and biodegradable. EPS in aquatic systems can form flocs of Marine Snow (MS) or Marine Oil Snow (MOS). EPS is thus important in initiating and maintaining aggregation, flocculation, and sedimentation processes of particles and microorganisms that act also as sorbents of pollutants, a process that contributes in a major way to the ‘self-cleansing capacity’ of aquatic systems. COM contains a diverse array of functionalities which can make them good metal chelating agents, amphiphilic and surface active pH-sensitive and redox-active. Due to numerous electrostatic and hydrophobic interactions between different moieties and ligand groups within a macromolecule, equilibrium constants,  $K_i$ , will become distribution functions for most reactions rather than fixed constants, as is common for low molecular weight organic molecules. Colloidal pumping of trace substances bound to EPS and other reactive macromolecular NOM compounds is counteracting the prevailing pathway of degradation of the bulk macromolecular NOM. Due to strong sorption capabilities for stable and radioactive metal ions, particle- and colloid-reactive radionuclides are useful to trace particle and organic carbon fluxes in the ocean. Open research questions include the role of different mechanisms that affect size spectra and composition of EPS in response to changing conditions, the role of macromolecular organic carrier molecules of radioactive and other trace substances that are used as oceanographic tracers; the potential use of the protein/carbohydrate ratio as a predictor of colloid or particle stickiness, aggregation or emulsification processes, and the*

*importance of reactive oxygen species (ROS) mediated polymerization reactions of proteins and other molecules, which are part of EPS, for MS and MOS formation..*

Yeager, C.M., Amachi, S., Grandbois, R., Kaplan, D.I., Xu, C., Schwehr, K.A., and Santschi, P.H. **2017**. Microbial transformation of iodine: From radioisotopes to iodine deficiency. *Advances in Applied Microbiology*, 101, 83-136.  
<https://doi.org/10.1016/bs.aambs.2017.07.002>

**Abstract.** *Iodine is a biophilic element that is important for human health, both as an essential component of several thyroid hormones, and on the other hand, as a potential carcinogen in the form of radioiodine generated by anthropogenic nuclear activity. Iodine exists in multiple oxidation states (-1, 0, +1, +3, +5 and +7), primarily as molecular iodine (I<sub>2</sub>), iodide (I<sup>-</sup>), iodate (IO<sub>3</sub><sup>-</sup>) or organic iodine (org-I). The mobility of iodine in the environment is dependent upon its speciation and a series of redox, complexation, sorption, precipitation and microbial reactions. Over the last 15 years, there have been significant advances in iodine biogeochemistry, largely spurred by renewed interest in the fate of radioiodine in the environment. We review the biogeochemistry of iodine, with particular emphasis on the microbial processes responsible for volatilization, accumulation, oxidation and reduction of iodine, as well as the exciting technological potential of these fascinating microorganisms and enzymes.*

Santschi, P.H., Xu, C., Zhang, S., Schwehr, Lin, P., K.A., Yeager, C.M., and Kaplan, D.I. **2017**. Recent advances in the detection of specific natural organic compounds as carriers for radionuclides in soil and water environments, with examples of radioiodine and plutonium. *Journal of Environmental Radioactivity*, 171, 226-233.  
<http://dx.doi.org/10.1016/j.jenvrad.2017.02.023>

**Abstract:** *Among the key environmental factors influencing the fate and transport of radionuclides in the environment is natural organic matter (NOM). While this has been known for decades, there still remains great uncertainty in predicting NOM-radionuclide interactions because of lack of understanding of radionuclide interactions with the specific organic moieties within NOM. Furthermore, radionuclide- NOM studies conducted using modelled organic compounds or elevated radionuclide concentrations provide compromised information related to true environmental conditions. Thus, sensitive techniques are required not only for the detection of radionuclides, and their different species, at ambient and/or far- field concentrations, but also for potential trace organic compounds that are chemically binding these radionuclides. GC-MS and AMS techniques developed in our lab are reviewed here that aim to assess how two radionuclides, iodine and plutonium, form strong bonds with NOM by entirely different mechanisms; iodine tends to bind to aromatic functionalities, whereas plutonium binds to N-containing hydroxamate siderophores at ambient concentrations. While low-level measurements are a prerequisite for assessing iodine and plutonium migration at nuclear waste sites and as environmental tracers, it is necessary to determine their in-situ speciation, which ultimately controls their mobility and transport in natural environments. More importantly, advanced molecular-level instrumentation (e.g., nuclear magnetic resonance (NMR) and Fourier- transform ion cyclotron resonance coupled with electrospray ionization (ESI-FTICRMS) were applied to resolve either directly or indirectly the molecular environments in which the radionuclides are associated with the NOM.*

Santschi, P.H., Xu, C., Zhang, S., Schwehr, K.A., Grandbois, R., Kaplan, D., Yeager, C.

2017. Iodine and Plutonium Association with Natural Organic Matter: A Review of Recent Advances. *Applied Geochemistry*, 85, 121-127;  
<http://dx.doi.org/10.1016/j.apgeochem.2016.11.009>

**Abstract.** Radionuclides reach the environment from natural or anthropogenic sources and are equilibrating over time with different phases through sorption and precipitation reactions onto inorganic phases and macromolecular natural organic matter (NOM). Strong binding to NOM can occur by chelation of clustered binding sites (i.e., binding sites from different branches in the macromolecule) in the absence of conventional chelating sites. Despite many years of research and strong evidence of its significance, transport of many radionuclides is still modeled without taking into consideration NOM as a redox regulator and a sorbent or chelating agent. Microbially mediated chelation and incorporation reactions can control a number of radionuclides, e.g., plutonium (Pu) and iodine (I) isotopes, leading to retardation or mobilization, depending on whether the carrier compound is in solution or particle-bound. The presence of NOM in contaminated soils complicates conventional remediation techniques for I, where base has been added to either increase the cation exchange capacity of soils or to promote direct co-precipitation of the cationic radionuclide in the waste stream. Even though Pu at waste sites did not have to be remediated, base addition would likely also bring surprises. This addition may then have unexpected consequences; while promoting the immobilization of inorganic Pu, it has been shown to also remobilize inorganic-I and low-molecular weight organic compounds that are bound to I and Pu. Iodine occurs in multiple oxidation states in aquatic systems, existing not only as inorganic species (iodide ( $I^-$ ) and iodate ( $IO_3^-$ )), but also as organic species where I is covalently bound to aromatic moieties. Thus, stable iodine,  $^{127}I$ , and its long-lived isotope,  $^{129}I$ , a major by-product of nuclear fission, undergo complex biogeochemical cycling in the environment, which renders them less mobile than when assuming that all I is in the form of the highly mobile form of iodide. In the laboratory and the field, plutonium strongly associates with NOM, when present, and is strongly chelated by specific moieties such as hydroxamate siderophores and other N-containing compounds. As a consequence, its mobility is controlled by the transport behavior of the anionic organic forms rather than the much more strongly sorbing cationic form of Pu(IV). NOM, even at trace levels, can play a significant role in controlling the fate and transport of radionuclides.

# C\* Algebras: The Multiplicative Route to Infinity

by James Glimm, Member EUAS

## Short Biography

*Department of Applied Mathematics & Statistics  
SUNY at Stony Brook, Stony Brook, NY 11794-3600  
Tel: (631) 632-8355; Fax: (631) 632-8490  
Email: james.glimm@stonybrook.edu*

## **Professional Preparation**

*Columbia University, Engineering, BA, 1956  
Columbia University, Mathematics, Ph.D. 1956-1959*

## **Appointments**

*1999- Staff Member, Computational Science Center, Brookhaven National Laboratory  
1989- Distinguished Professor, SUNY at Stony Brook  
1982-89 Professor, Courant Institute, New York University  
1974-82 Professor, The Rockefeller University  
1968-74 Professor, Courant Institute, New York University  
1960-68 Professor, Associate Professor, Assistant Professor, MIT  
1959-60 Temporary Member, Institute for Advanced Study*

## **Professional Service**

*Advisory Committee of the Center for Computational Geoscience, Xi'an University, Xi'an PRC  
2007-2009 President American Mathematical Society*

## **Prizes, Awards, Fellowships**

*2002 National Medal of Science  
Member, National Academy of Sciences  
Member, American Society of Arts and Sciences  
1993 Steele Prize for a paper of fundamental importance (AMS)  
1980 Dannie Heineman Prize for Mathematical Physics (APS)  
1965-1966 Guggenheim Fellowship  
1963-1964 Guggenheim Fellowship  
1959-1960 National Science Foundation Fellowship*

## **Fields of Expertise**

*Nonlinear partial differential equations, Computational fluid dynamics, Stochastic partial differential equations, Mathematical physics, Quantum physics, Scientific computing, Quantification of uncertainty, Turbulence modeling, Computational electromagnetics, Turbulence modeling, Financial mathematics*

## **C\* Algebras: The multiplicative route to infinity**

In his Ph. D thesis [1], Glimm constructed and analyzed infinite tensor products of finite matrix algebras. This technical result became the foundation for two major theoretical developments. The additive route to infinite (of direct sums) is totally different from the multiplicative route of infinite tensor products.

*The Stone-Weierstrauss Theorem.*

The multiplicative route to infinite was basic to a noncommutative version of the Stone-Weierstrauss theorem for C\* algebras [2]. If a sub C\* algebra B of a C\* algebra A separates all the points in the closure of the pure states of A, then  $B = A$ . The basic idea is that the C\* algebras are either very nice or are very complicated and in the latter case a very large

closure for the pure state space is found.

### ***A Structure Theorem for C\* algebras***

The simple vs. complex decomposition was made explicit [3] with a structure theorem of the most general C\* algebra constructable via the additive route to infinity, and a residual part with no finite dimensional approximation within it. In the factor representation of type I, II and III of Murray and von Neuman, the simple part is type I in the sense that all of its representations are type I. Many equivalent characterizations of this decomposition were given, including an ascending chain of ideals, introduced by Kaplansky. Relating to the Stone-Weierstrauss theorem, every limit point of a pure state of a type I C\* algebra is a pure state.

### **Nonlinear Conservation Laws: *Glimm's method (the Random Choice Method, RCM)***

The equations of nonlinear physics are generally nonlinear conservation laws or their dissipative analogues, and the Navier-Stokes equations follow this rule. The conceptual framework proposed in [4] was to regard the fluctuations as fundamental while the average quantities were derived. This is the reverse of all finite difference thinking, and gives the results their unique flavor. For nonlinear conservation laws in 1 space dimension, the fluctuations are elementary waves occurring within the solution of an isolated jump discontinuity, known as a Riemann problem.

### ***Theory***

The existence theorem [4] is even today one of the most powerful tools available for the analysis of nonlinear conservation laws. The proof is for small initial conditions in one space dimension. The proof is organized in terms of nonlinear waves, representing local solution fluctuations. This theorem has been the basis for many theoretical studies, including the proof [5] of a large time asymptotic decay property for solutions with general (small) initial data.

The convergence of RCM is an extended Neumann series, which allows summation of the total of all future wave interactions. With the solution represented as piecewise constant on mesh intervals, the jump discontinuities at the space time mesh block corners are expanded into elementary waves as the solution of local Riemann (jump discontinuity) problems, e.g., shock and rarefaction waves and contact discontinuities. Elementary waves from neighboring Riemann problems will interact (sooner or later). The key technical lemma is a bound on the out going waves in terms of the in coming wave strengths for such a Riemann problem.

As a numerical method, the Random Choice Method is the preferred algorithm for a class of 1D conservation laws. It served as the motivation for the 2D and 3D method of front tracking. And more recently in the work of Gallet and Hurisse, it is directly the basis for a 2D and 3D sharp interface numerical solution algorithm which may also become the method of choice.

### **Quantum Fields**

The mathematical construction began [6] with the first mathematical renormalization of a quantum field requiring infinite renormalization, and with the small length scale cutoffs removed. The Yukawa<sub>2</sub> quantum field was constructed in a finite volume. The original (bare) Lagrangian has two infinite divergent quantities, an infinite vacuum energy and an infinite mass. The theory satisfies the Schrodinger equation.

***The Glimm Jaffe collaboration***

This initial effort continued in a collaboration with A. Jaffe over a 20 year period, producing results that established a landmark in the foundations of Glimm and Jaffe constructed quantum fields in 2 and 3 space time dimensions mathematically. Their work showed that the two cornerstone theories of 20<sup>th</sup> century physics, special relativity and quantum fields, are mathematically compatible.

Highlights of the collaboration include the constructions of the  $\lambda\phi_3^4$  quantum theory, and in joint work with T. Spencer [12-14], verification of the Wightman axioms for the  $\lambda P(\phi)_2$  quantum field,

existence of a mass gap and of a phase transition for strong coupling, building on earlier  $P(\phi)_2$  results [7,8].

This work succeeds through development of novel mathematical methods that align with the ideas of the physics they support.

Three main themes characterize this collaborative program.

1. Mathematical renormalization of quantum physics
2. Phase cell expansions
3. Reflection positivity

***Mathematical renormalization*** allows the cancellation of infinities which arise in the formulation of quantum fields. The vacuum energy, the particle masses and the interaction strength are all infinite in the first instance. These infinities are spurious and are removed by a cancellation called renormalization. The challenge is to develop a mathematical theory which allows for these cancellations to occur while providing convergent estimates for the finite remainders needed to define the quantum field in a mathematical sense. Central roles played by the phase cell expansion and reflection positivity are to mathematical control of the finite remainders after subtraction of the infinities.

***Phase cell expansions*** lie at the heart of the more advanced papers from this collaboration. These expansions combine an iterative approach to analyze the asymptotic properties of quantum fields, with localization in both position and Fourier space. Even today, the powerful results obtained cannot be derived from more generic methods.

***Reflection positivity***, simply stated, introduces a positive quadratic form which serves as the inner product for the quantum states. This idea, interposed with translations in an iterative manner, has had a deep impact both in theoretical physics and in mathematics.

**Dispersion Relations*****Flow in porous media***

Flow in porous media is important to the petroleum industry for the production of petroleum and it is important to environmentalists for the flow of pollutants in subsurface ground water.

In the latter case the flow of a passive scalar (noninteracting with the porous media) is the simplest and the flow is assumed to occur with a mean velocity and a diffusion term modeled by a diffusion coefficient. Problems with this simple theory were well known. A new theory [15], basically a modeling breakthrough, provided the needed corrections. Acceptance of this new theory occurred in three steps.

Gelhar captured the essence of the problem by plotting the experimentally diffusion constant vs. the experimental size and found a nearly perfect correlation as a straight line in log log coordinates.

The diffusion constant was a function of the experimental size and the specific function had a simple form.

The theoretical explanation of this puzzle, explained in [15] is simple to understand. The diffusion constant is a function of the heterogeneities in the flow properties of the porous media. The heterogeneities have a fractal structure as a function of length, giving rise to a power law dependence of the diffusion constant on experimental size. This power law variability was confirmed by Lake experimentally with measurements on outcrops in Texas.

The result was a revolution of the methods and ideology of porous flow models in the petroleum industry, with detailed probabilities as input from geologists, and up scaling to obtain probabilistic flow parameters at the scales of numerical grid resolution.

### **Turbulence and Mixing**

#### ***Admissibility and physical vs. nonphysical solutions.***

It is known that multiple and presumed nonphysical solutions of the Navier-Stokes equation exist. A dynamic extension of the 2<sup>nd</sup> law of thermodynamics in the form of a maximum rate of entropy production was established [16] as an admissibility condition to exclude these unwanted and spurious solutions. Contrary ideas of Prigogine and Ziegler appear to be in conflict on this point, but properly understood they are not in conflict. The difference comes down to a choice of how to model a given experiment, as an open system, with entropy escaping to the external world and Prigogine is favored, or as a closed system, with entropy production included within the experimental model, and Zeigler is favored.

#### ***Theory for turbulent mixing***

Here the Rayleigh-Taylor instability was studied. In this flow regime, two fluids of differing densities, separated by a planar interface, are accelerated in the direction opposed to the density gradient. The main phenomena is a mixing layer growing on an acceleration time scale, that is, proportional to  $t^2$ .

The coefficient of proportionality  $\alpha_b$  has been a central object of study. A theoretical model for  $\alpha_b$  [17] is based on renormalization group ideas. It agrees with the experimental values of  $\alpha_b$ , and in fact predicts three experimentally observed quantities on the basis of one adjustable parameter.

Another dimensionless coefficient  $\alpha_s$ , characterizes the growth rate of the heavy fluid side of the mixing zone. Analogous coefficients  $\theta_b$  and  $\theta_s$  characterize growth rates after an impulsive acceleration. Analysis [18] shows a functional relation among these four parameters, with any one being independently determined, after which the others are fixed. The free parameter is taken as  $\alpha_b$ , set by the bubble merger model, and then all four are determined. According to this reasoning, the steady and impulsive flows are governed by identical drag relations in a buoyancy drag model.

#### ***Numerics for turbulent mixing.***

Extensive numerical simulations by Glimm and coworkers, of which [19] is typical, show excellent agreement with experimental data. As not all simulations (of other workers) agree with experimental data, controversies are not resolved, as is discussed in [20].

### **Front Tracking**

[21] establishes a computer science framework for the study of a discretized surface (tracked front). [22] constructs an application programming interface (API), so that implementation details are hidden from the user and only a few user specific routines are needed.

## References

- [1] J. Glimm, 1960. On a certain class of operator algebras. Trans. Amer. Math. Soc. **95**, 318-340.
- [2] J. Glimm, 1960. A Stone Weierstrass theorem for  $C^*$  algebras. Ann. Math **72** 216-244.
- [3] J. Glimm, 1961. Type I  $C^*$  algebras. Ann. Math. **73** 572-612.
- [4] J. Glimm 1965 Solutions in the large for nonlinear conservation laws. Comm Pure Appl Math **18** 697-715.
- [5] J. Glimm and P. Lax 1970. Mem. Amer. Math. Soc. **101**
- [6] J. Glimm 1967. Yukawa Coupling of quantum fields in two dimensions, I, II Commun. Math. Phys. **5** and **6**. 343-386 and 61-76.
- [7] J. Glimm and A. Jaffe 1968. A  $\lambda\phi^4$  quantum field theory without cutoffs I. Phys. Rev. **176** 1945-1961.
- [8] J. Glimm and A. Jaffe 1970 the  $\lambda(\phi^4)_2$  quantum field theory without cutoffs. The field operators and the approximate vacuum. Ann. Math **91** 362-401.
- [9] J. Glimm and A. Jaffe 1970. Self adjointness of the Yukawa<sub>2</sub> Hamiltonian J Ann. Phys. **60** 321-383.
- [10] J. Glimm and A. Jaffe 1971. The Yukawa<sub>2</sub> quantum field theory without cutoffs. Functional Anal. **7** 323-401.
- [11] J. Glimm and A. Jaffe 1973. Positivity of the  $\phi_3^4$  Hamiltonian. Fort. Phys. **21** 327-376.
- [12] J. Glimm, A. Jaffe and T. Spencer 1974. The Wightman axioms and Particle Structure in the  $P(\phi)_2$  quantum field model. Ann Math. **100** 585-632.
- [13] J. Glimm, A. Jaffe and T. Spencer 1975. Phase transitions for  $\phi_2^4$  quantum fields. Commun. Math Phys. **45** 203-216.
- [14] J. Glimm, A. Jaffe and T. Spencer 1976. A convergence expansion about mean field theory. Ann. Phys. **101** 610-630 and 631-669.
- [15] J. Glimm and D. H. Sharp 1991. A random field model for anomalous diffusion in heterogeneous porous media. J. Stat. Phys. **62** 415-424.
- [16] J. Glimm, D. Lazarev and G.-Q. Chen 2020. Maximum entropy production rate as a necessary admissibility condition for the fluid Euler and Navier-Stokes equations. Springer Nature Appl Sci. **2**.
- [17] B. Cheng, J. Glimm and D. H. Sharp 2022 A 3D RNG bubble merger model for Rayleigh-Taylor mixing. Chaos **12** 267-274.
- [18] B. Cheng, J. Glimm and D. H. Sharp 2020 Density dependence for Rayleigh-Taylor and Richtmyer-Meshkov mixing fronts. Phys Lett. A. **371**.
- [19] J. Glimm, D. H. Sharp, T. Kaman and H. Lim 2013. Phyl. Trans. Royal Soc. A **371**.
- [20] J. Glimm, B. Cheng, D. H. Sharp and T. Kaman 2020 A crisis for the verification and validation of turbulence simulations. Physica D Nonlinear Phenomena. **404**.
- [21] J. Glimm and O. McBryan 1983 A computational model for interfaces. Adv. Appl Math. **6** 432-435.
- [22] D. She, R. Kaufman, H. Liu, J. Melvin, A. Hsu and J. Glimm 2016 In: Handbook of numerical methods for hyperbolic problems **17** Elsevier 383-402.

## Design for Reliability, Electronics and Energy Systems

by Way Kuo, Member EUAS

### Short Biography

*Professor Way Kuo is President of City University of Hong Kong. Before he came to Hong Kong in 2008, he served on the senior management team at the Oak Ridge National Laboratory and as the Dean of Engineering at the University of Tennessee, Knoxville.*

*Before joining CityU, Professor Kuo was Dean of Engineering at the University of Tennessee and Head of the Department of Industrial Engineering at Texas A&M University. He received his PhD in engineering in 1980 from Kansas State University, and BS in nuclear engineering in 1972 from National Tsing Hua University, Taiwan.*

*In addition to being a member of the US National Academy of Engineering, he is a foreign member of the Chinese Academy of Engineering, a foreign member of the Russian Academy of Engineering, and a member of Academia Sinica in Taiwan. He is a pioneer in designing and modelling the reliability of electronics systems at the infant stage, renowned for his work on designing reliability in electronics systems. He is the author and co-author of ten academic books and over 200 high impact papers, some of which are deemed classics in systems optimisation design and are used as the basis for establishing the reliability standards. His book, *Importance Measures in Reliability, Risk, and Optimization*, published by N.Y.: Wiley, 2012, addresses ways to design and enhance reliability of modern systems.*

*His first popular science book, *Critical Reflections on Nuclear and Renewable Energy*, has had an impact since its publication in 2013 by Commonwealth Publishing Group in Taiwan. The book has been translated into English, Japanese, French and Russian and published in Massachusetts, Tokyo, Paris, and Moscow, respectively. His new book on higher education, *The Soulware with Higher Education*, was simultaneously published in Hong Kong, Taipei and Beijing in 2016 under three different publishing houses.*

*Professor Kuo is the Chairman of the Gnedenko e-Forum based in Moscow, Russia.*

Professor Kuo specialises in design for the reliability of electronics systems and nuclear energy. So, his book *Critical Reflections on Nuclear and Renewable Energy* has been published in Taiwan, Hong Kong, Shanghai, Massachusetts, Tokyo, Paris, Seoul, and Moscow.

He was the first foreign expert to arrive following the Fukushima Nuclear Incident. He argues that a holistic view of energy development is required, one that prioritises the production and use of reliable energy sources over that of polluting and volatile ones. He maps out a policy that encourages and rewards the conservation of energy and efficiency in energy use.

A system normally consists of multiple components, which are not necessarily equally important for the performance of the system. Such a system often needs to be designed, enhanced, or maintained efficiently using limited resources. However, for highly complex systems, it may be too tedious, or not even possible, to develop a formal optimal strategy. In these situations, it is desirable to allocate resources according to how important the components are to the system and to concentrate the resources on the small subset of components that are most important to the system. Thus follows the notion of importance measures of components.

For tackling different problems, the distinct importance measures and the associated algorithms should be appropriately designed. Various importance measures have been proposed to judge the relative strength of a component in a system with respect to different criteria. As stated in Griffith and Govindarajulu (1985), no single type of importance measure is universal, since different perspectives on the same system can lead to different views about which factors make one component more important than another. A design engineer may think of a component as being more important if a given reliability improvement in it does more to improve systems reliability than the same reliability improvement in another component. In contrast, an engineer may devise a checklist of components for finding the cause of system failure based on his or her assessment of the conditional probability that a particular component has contributed to system failure. The probabilistic interpretation describing the relation of a component to the functioning or failure of the system is different in each case.

Professor Kuo is renowned for his pioneering work in design for reliability, including electronics and energy systems. He was the first invited foreign expert to conduct post-accident assessment on the Fukushima Power Plant after the 2011 earthquakes. He states that a holistic view of energy development is required, one that prioritises the production and use of reliable energy sources over that of polluting and volatile ones. He maps out a policy that encourages and rewards the conservation of energy and efficiency in energy use.

His book on higher education, *The Soulware within Higher Education*, was simultaneously published in Hong Kong, Taipei and Beijing in 2016 by three different publishing houses, which is a rare phenomenon. Its significantly modified English edition, *Soulware: The American Way in China's Higher Education*, Wiley NJ, 2019, advocates university autonomy and promotes integration of teaching and research.

# Investigations in Atmospheric Propagation & Microwave Biophysics

by André Vander Vorst, Member EUAS

## Short Biography

*André Vander Vorst was born in Brussels in 1935. At high school, he studied classical humanities, including Latin and Greek. He graduated in 1958 as an electrical and mechanical engineer at the UC Louvain (UCL), Belgium, from which he received his Doctoral degree in 1965. During his thesis he spent two times six weeks working at Philips Natuurkundig Laboratorium, Eindhoven, The Netherlands. As a research associate, he was at M.I.T 1964-1965 where he earned a M.Sc. degree in microwaves, and at Stanford University 1965-1966, both in radioastronomy. Back in Belgium in 1966, he founded the Microwave Laboratory at UCL, which he headed for 35 years. His research interests were successively loaded waveguides and cavities, atmospheric propagation up to 300 GHz, opto-microwaves, humanitarian demining, and bio-microwaves. He has been teaching in four Belgian Universities on electromagnetics, transmission lines, and microwaves. He also taught analogue and hybrid computation, antennas, and microwave satellite communications. He supervised 27 doctoral theses and about 200 engineer's theses.*

*Prof. Vander Vorst has authored and co-authored seven books, a number of book chapters, and 400 papers in peer-reviewed journals and conference proceedings. His last book, RF/Microwave Interaction with Biological Tissues, with A. Rosen and Y. Kotsuka as co-authors was published in 2006 by Wiley, U.S.A. He recently co-authored papers on various websites on the 5G and the effect of electromagnetics on viral infections. He has written chapters on bioelectromagnetics in a collective book investigating electro-hypersensitivity and papers on the same subject.*

*Through his academic career at UCL, Prof. Vander Vorst has been Head of EE Department 1970-1971, Dean of Engineering 1972-1975, Vice-President of the Academic Council 1973-1975, and President of the Open School in Economic and Social Politics 1973-1987.*

*Over the last 50 years, Prof. Vander Vorst has been actively involved in developing the international microwave community. In 1967-2001 he was chairing Student Activities Committee and Educational Activities Committee and setting up Chapter Coordination Committee in I.E.E.E. Region 8. He was a corresponding member of the Organizing Committee of the first European Microwave Conference (EuMC) in London 1969, Chair EuMC Technical Program Committee in Brussels 1973, and Chair EuMC in Liège 1984. He has been a reviewer for every EuMC since 1969. He is a founder member of the European Microwave Association (EuMA) and has been EuMA Secretary General for 18 years. In the latter function he has set up and developed EuMA Headquarters. He is now appointed Secretary Emeritus and Data Protection Officer and is still active with EuMA.*

*Prof. Vander Vorst has offered his service to the microwave community also under the umbrella of I.E.E.E. MTT Society, in which he has been active in 1985-2006. He is a Life fellow of the I.E.E.E. He obtained a number of awards including the Microwave Career Award 2004 from I.E.E.E MTT-S, the Distinguished Service Award 2016 from EuMA and the Propagation Award 2019 from the European Association for Antennas and Propagation (EurAAP).*

*He is an emeritus member of Belgian Academia of Letters and Science, a member of Academia Europaea, the Electromagnetics Academy, and the EU Academy of Sciences. He is an Honorary Member of Belgian National Committee or URSI and of a number of international committees. He has been a member of National Health Council in both Belgium and The Netherlands. He has been cited in a number of Who'sWho. He loves music and has conducted choirs for more than 40 years.*

*He has five children and twelve grandchildren, while two grand-grandchildren are expected.*

From 1960 to 1964, André Vander Vorst investigated **fast switching of magnetic cores** for his doctoral thesis. As a research associate with a post-doctoral fellowship, he spent two years in the USA: 1964-1965 at M.I.T. and 1965-1966 at Stanford University in both Laboratories of Radioastronomy. In 1966, back in Belgium he founded the Microwave Laboratory at the Université catholique de Louvain (UCL). Some typical publications are mentioned in what follows for each research topic mentioned.

He started research on propagation in lossless closed structures at X-band like loaded

waveguides and cavities. The first doctoral thesis he supervised in the Laboratory was by F. Gardiol, 1966-1969, who analytically investigated the impact of a one-dimensional inhomogeneity on waveguide propagation [1].

Simultaneously, A. Vander Vorst started developing **numerical analysis for propagation** in diverse inhomogeneously loaded microwave transmission lines by means of variational principles [2]. He produced a numerical version of the variation-iteration method presented by Morse and Feshbach, *Methods of Theoretical Physics*, Part 1 and 2, McGraw-Hill, 1953. In 1969, he obtained the first numerical solution of a second-order partial derivative eigenvalue equation, describing the propagation in a rectangular waveguide loaded by inserts.

A number of doctoral students then investigated the impact of inhomogeneity on miscellaneous propagating structures, like microstrips, fin lines, and p-i-n transmission lines, as well as opto-induced effects on transmission lines [3]-[8].

This research ended up with propagation on lossy distributed structures at frequencies up to 100 GHz. In 2002, he co-authored with a research book on variational principles and distributed circuits [9].

**Atmospheric propagation** has been a research interest of A. Vander Vorst from 1968 [10] until about 2000. In 1970, he set up two horizontal links at 11.6 and 35 GHz, respectively, operating for a five-year period [11]. This has been the subject of the first of his five consecutive COST projects on atmospheric propagation, covering both horizontal links and slant paths.

He was the Belgian participant to the Orbital Test Satellite (OTS) of the European Space Agency (ESA), 1978-1983. For this, he obtained significant funding from the Belgian State (equivalent to 5 million EUR at today's value) to obtain one transmitting-receiving fixed television station at 14 GHz (up, 2 kW) and 11 GHz (down), as well as two receiving stations at 11 GHz, one fixed and one mobile [12]-[14].

He has been, together with D. Vanhoenacker-Janvier, the Belgian participant to the ESA Olympus experiment, 1988-1993, and obtained significant funding from the Belgian State and PTT Department, respectively, to set up two receiving stations at 12.5 and 30 GHz and 12.5 and 20 GHz in both polarisations at both frequencies, respectively. Measurements made at Louvain-la-Neuve included attenuation, depolarisation and scintillation at 12.5 and 30 GHz and radiometry in two polarisations at 12 and 35 GHz [15]. Fast measurements were available, every 34 ms, especially in view of investigating the time scale of the scintillation effects.

These experimental tools stimulated original atmospheric propagation investigations in theory, experiment, and simulation as well. With the OTS stations, the Laboratory has been one of the three research centres to experimentally point out the microwave scintillation phenomena, extensively investigated by D. Vanhoenacker-Janvier in her doctoral thesis and later. Site-shielding, in particular by a knife-edge obstacle, has been investigated with measurements from 8 to 94 GHz [16]. The research then evaluated the bit-error rate prediction of atmospheric communications links [17]. It continued until the year 2000 with the evaluation of some special effects related to the structure of linearly tapered slot antennas including the Vivaldi antenna, up to some tens of GHz [18].

A. Vander Vorst conducted research on atmospheric propagation of EM waves at frequencies up to 300 GHz [19]. He has been involved in EM wave propagation since 1960, start of his doctoral thesis, until the end of his active professional career.

**Microwave biophysics** has been another subject of interest of A. Vander Vorst. The project started at the end of the 70s by designing and implementing a system for eliminating bacteria in air by microwave heating, to proceed to open air medical surgeries. This system was patented and commercialized.

**Experimental work has been going on with rabbits** from 1987 through 1994, for the doctoral thesis by J. Teng, in three experimental steps.

The first was devoted to developing a microwave acupuncture method by inserting a miniature cable into acupuncture points and exciting these by injecting microwaves in the cable, offering a

quantitative method for measuring analgesia. The purpose was to excite the nervous system in some specific points for detecting an analgesic effect. Results were positive [20].

The second consisted of the development of a method to measure the effect of analgesia in the cervical centre of pain [Fig. 1]. This showed that by doing so the composition of the cervical liquid in the pain centre was modified similarly to what is obtained when ingesting analgesic products [21].

In the third step, a method was developed for measuring in the cervical centre of pain the effect of an electric impulse applied to a rabbit's foot in both the absence and presence of analgesia produced by microwave acupuncture. Simultaneously, the deformation of the impulse was measured on the nervous system and in particular the spinal cord, by inserting a microwave micro-antenna inside of the backbone [22], looking for a non-thermal microwave effect. The result was negative [23].



Figure 1. Measuring pain threshold on a rabbit as a function of antalgic microwave acupuncture

A cooperation went on with colleagues of the UCL School of Medicine in the years 1993-1997 to evaluate the effect of magnetic induction produced by a coil to implant on a mouse for obtaining a muscular reinforcement. The result was positive [24].

Dielectric parameters and blood absorption have been measured from 2 to 110 GHz [25] and a review of microwave effects on nervous system and nervous fibre has been performed [26].

Research has then been more oriented toward biological effects and medical applications [27] and more specifically to **biological effects on living systems and especially human beings** [28]. Face heating at the occasion of a telephone conversation has been measured in direct view of a base station, on stairs and in the basement of a building, respectively, with the measurement of an increase of 0.7°C after 10 minutes in the basement [29].

Specific very low frequency magnetic field measurements have been made on spontaneous bioelectric activity of neurons [30] while dielectric absorption microwave power has been evaluated at the scale of nucleic acids [31].

**Microwave exposure of rats** has been prepared, performed and evaluated from 1998 through 2009, for the doctoral thesis of D. Adang. Rats were submitted to a microwave level corresponding to the calculation by WHO of the limit for the human being, taking into account however a factor

10 for difference of length between the human being and the rat. The exposure duration has been long: 2 hours per calendar day of 70% of the rat lifetime which was 30 months. There were four groups of 31 rats, including three groups exposed to three different microwave schemes, respectively, and one sham-exposed group, with in particular exposure to 970 MHz CW. Fifteen blood parameters were analysed 6 times on the 124 rats, yielding more than 10.000 biological data, together with behavioural effects and mortality. A combination of positive and negative results has been obtained on monocytes, behavioural effects, and mortality, respectively [32][33].

**Planar antennas** have been designed and evaluated in view of medical applications, from 2005 through 2013, being mainly the subject of the doctoral thesis of H. Halheit. This necessitated the evaluation of a radiating structure, the operating frequencies, the influence of the substrate on the resonance frequencies of the antenna and their bandpass, the power necessary for medical applications, and mutual coupling between the elements [34].

A number of presentations have been made in medical symposia [35]. At the request of Wiley, a research book was written on the subject of *RF/Microwave interaction with biological tissues* and published by Wiley U.S. in 2006, with PhD students as a prime target [36]. During the last three years, A. Vander Vorst co-authored papers on various websites on 5G and on the effect of electromagnetics on viral infections. He wrote chapters on bioelectromagnetics (em) and bioelectromagnetic interaction with the human body in a collective book investigating **electro-hypersensitivity** (EHS) [37]. He is a co-author of a review paper on the importance of molecular biomarkers and imaging in the study of EHS [38]. Over the last years, he co-authored about ten letters concerning em in hospitals on one hand [39] and on em interaction with the human body on the other [40].

### Selected Publications

- [1] Gardiol F., Vander Vorst A., "Wave propagation in rectangular waveguide loaded with an H-Plane dielectric slab", *IEEE Trans. Microwave Theory Tech.*, vol. MTT-17, January 1969, pp. 56-57
- [2] Vander Vorst A., Govaerts R., "Application of a Variation-Iteration method to inhomogeneously loaded waveguides", *IEEE Trans. Microwave Theory Tech.*, vol. 19, March 1971, pp. 322-331
- [3] Decreton M., Loute E., Vander Vorst A., Gardiol F., "Computer optimization of E-plane resonance isolators", *IEEE Trans. Microwave Theory Tech.*, vol. MTT-19, March 1971, pp. 322-331
- [4] Cermak I., Getsinger W., Leake B., Vander Vorst A., Varon D. "The status of computer-oriented microwave practices", *IEEE Trans. Microwave Theory Tech.*, vol. 22, March 1974, pp. 229-237 (*invited paper*)
- [5] Kezai T., Vander Vorst A. "Modelling resonance in waveguide-to-microstrip junctions by unilateral fin line resonators", *IEEE Trans. Microwave Theory Tech.*, vol. 42, n° 2, February 1994, pp. 223-236
- [6] Aksas R., Vander Vorst A., "Transverse conduction current and radiation pattern of an arbitrary shaped symmetrical patch antenna coupled with a director", *Microwave Optical Technology Lett.*, November 1994, vol. 7, n° 16, pp. 737-739
- [7] Zhu Z., Vander Vorst A., "Microwave propagation in p-i-n transmission lines", *Microwave and Guided Waves Letters*, MTT-IEEE, vol. 7, n° 6, June 1997, pp. 159-161
- [8] Serres M., Huynen I., Vander Vorst A., "Wideband photo-induced carriers at the end of an open-ended microstrip line", *IEEE J. Sel. Topics Quantum Electr.*, vol. 4, n° 6, November-December 1998, pp. 948-952
- [9] Vander Vorst A., Huynen I., *Variational Principles and Distributed Circuits*, Research Studies Press, Baldock, United Kingdom, 2002, 318 p.
- [10] Benoit A., Godfroid H., Mertens H., Vander Vorst A., "Study of the satellite/Earth station/domestic receiver chain in a satellite system for television distribution", *Proc. IEE*, November 1969, pp. 1797-1806
- [11] Vander Vorst A., Gaudissart E., "Effects due to precipitation on horizontal links", *Proc. Symp. AGARD*, Gausdal, September 1972, pp. 14/1-6
- [12] Vander Vorst A., "Cross-polarization on a terrestrial path", *Alta Frequenza*, English edition, vol. 48, no 4, April 1979, pp. 201-209
- [13] Vanhoenacker D., Vander Vorst A., "Experimental evidence of a correlation between scintillations and radiometry at centimeter and millimeter wavelength", *IEEE Trans. Antennas Propagation*, vol. AP-33, January 1985, pp. 40-47
- [14] Vander Vorst A., "Atmospheric and sea-surface effects from 30 to 300 GHz", *Revue HF*, vol. XIII, n° 3,

1985, pp. 67-75

- [15] Vanhoenacker D., Vasseur H., Vander Vorst A., « Limitations de la largeur de bande dues aux phénomènes atmosphériques sur des liaisons spatiales de 10 à 300 GHz », *L'Onde Electrique*, vol. 72, mai-juin 1992, n° 3, pp. 35-38
- [16] Vyncke C., Vander Vorst A., "A new approximate formula for site-shielding by a knife-edge obstacle, based on measurements from 8 to 94 GHz", *Microwave Optical Technology Lett.*, June 1995, vol. 9, n° 4, pp. 210-214
- [17] Vander Vorst A., Vasseur H., Vyncke C., Amaya-Byrne C., Vanhoenacker-Janvier D., "From electromagnetics to system performance: a new method for the error rate prediction of atmospheric communications links", *IEEE J. Selected Areas in Communications*, Vol. 15, N° 4, May 1997, pp. 656-666
- [18] Stockbroeckx B., Vander Vorst A., "Copolar and cross-polar radiation of Vivaldi antenna on dielectric substrate", *IEEE Trans. Antennas Propagation*, Vol. 48, n° 1, Jan. 2000, pp. 19-25
- [19] Vander Vorst A., Vanhoenacker D., "Propagation limitations for transionospheric systems from 10 to 300 GHz", *AGARD*, Paris, Rome, Boston, LSP-172, June 1990, pp. 3.1-19 (*invited paper*)
- [20] Teng J., Vanhoenacker D., Vander Vorst A., "Biological effects of microwaves in acupuncture", *Proc. Eur. Microwave Conf.*, London, September 1989, pp. 918-923
- [21] Teng J., Yan H., Vanhoenacker D., Vander Vorst A., "Variations of pain threshold and norepinephrine release in rabbits due to microwave stimulation", *Proc. Microwave Theory Tech. Symposium IEEE*, Boston, June 1991, pp. 801-804
- [22] Teng J., Yan H., Vanhoenacker D., Vander Vorst A., "Inhibition of the nociceptive response of the parafascicular nucleus, due to microwave irradiation on spinal cord in rabbits", *Proc. Eur. Microwave Conf.*, Stuttgart, September 1991, pp. 1438-1443
- [23] Teng J., Carton de Tournai D., Duhamel F., Vander Vorst A., "No nonthermal effect observed under microwave irradiation of spinal cord", *IEEE Trans. Microwave Theory Tech.*, Vol. 44, n° 10, October 1996, pp. 1942-1948
- [24] Isac M., Marechal G., Vander Vorst A., Veraart C., Moens P., "Transformations in mouse soleus induced by chronic stimulations", *Journal of Muscle Research and Cell Mobility*, n° 15, August 1994, pp. 177-178
- [25] Duhamel F., Huynen I., Vander Vorst A., "Measurements of complex permittivity of biological and organic liquids up to 110 GHz", *IEEE MTT-S Int. Microwave Symp.*, Denver, June 1997, Vol. I, pp. 107-110
- [26] Vander Vorst A., Duhamel F., "1990-1995 Advances in investigating the interaction of microwave fields with the nervous system", *IEEE Trans. Microwave Theory Tech.*, Vol. 44, n° 10, October 1996, pp. 1898-1909
- [27] Rosen A., Stuchly M., Vander Vorst A., "Applications of RF/Microwaves in medicine", *IEEE Trans. Microwave Theory Tech.*, 50th Anniversary Special Issue, vol. 50, no 7, Nov. 2002, pp. 963-974 (*invited paper*)
- [28] Vander Vorst A., Stuchly M., "Impact of mobilophony", *Proc. Workshop II, Eur. Microwave Conf.*, Jerusalem, September 1997, pp. 97-123
- [29] Taurisano M., Vander Vorst A., "Experimental thermographic analysis of thermal effects induced on a human head exposed to 900 MHz fields of mobile phones", *IEEE Trans. Microwave Theory Tech.*, Special Issue, vol. 48, no 11, Nov. 2000, pp. 2022-2032
- [30] Azanza M., Pérez Bruzon R., Lederer D., Calvo A., del Moral L., Vander Vorst A., "Reversibility of the effects induced on the spontaneous bioelectric activity of neurons under exposure to 8.3 and 217.0 Hz low intensity magnetic fields" *Proc. 2nd Intl. Workshop Biol. Eff. Electrom. Fields*, Rhodes, octobre 2002, pp. 651-659
- [31] Vanderstraeten J., Vander Vorst A., "Theoretical evaluation of dielectric absorption of microwave energy at the scale of nucleic acids", *Bioelectromagnetics*, 25 :380-389 (2004).
- [32] Adang D., Campo B., Vander Vorst A., "Has a 970 MHz Pulsed Exposure an Effect on the Memory Related Behaviour of Rats?", *Eur. Conference Wireless Technologies 2006*, Manchester, Sept. 2006, Session ECWT08, pp. 135-138
- [33] Adang D., Remacle C., Vander Vorst A., "Results of a Long-Term Low-Level Microwave Exposure of Rats", *IEEE Trans. Microwave Theory Tech.*, vol. 57, No. 10, Oct. 2009, pp. 2488-2497
- [34] Halheit H., Vander Vorst A., Tedjini S., Touhami R., "Flexible Dual-Frequency Applicator for Local Hyperthermia", *Int. J. of Antennas and Propagation*, vol. 2012, Article ID 389214, 7 pages, Hindawi Publishing Corporation
- [35] Vander Vorst A., "Effets des champs micro-ondes sur les organismes vivants", *Congrès Médecine environnementale*, AMSES, La Martinique, 10 novembre 2015, 47 pages (*invited paper*)
- [36] Vander Vorst A., Rosen A., Kotsuka Y., *RF/Microwave Interaction with Biological Tissues*, Wiley USA, 2006, 300 p.

- [37] Belpomme D., Cachard O., Huss J., Irigaray Ph., Lafforgue F., Ledoigt G., Le Ruz P., Vander Vorst, A. "Ce que sont en réalité les ondes électromagnétiques" with P. Leruz and "Comment les champs électromagnétiques interagissent avec notre corps" in *Le Livre Noir des Ondes*, Marco Pietteur, 2021, 416 pp., ISBN 978-2-87434-184
- [38] Belpomme D. *et al*, Vander Vorst A., "The Critical Importance of Molecular Biomarkers and Imaging in the Study of Electrohypersensitivity. A Scientific Consensus International Report" *Int. J. Mol. Sci.*, 2021, 22, 7321,
- [39] Lintermans J., Vander Vorst A., "Effets des champs électromagnétiques en milieu hospitalier", *Neutone*, Vol. 26, 2021, no.1, p. 35-39
- [40] Lintermans J., Vander Vorst A. "Vitamine E et dysfonctionnement de la barrière hémato-encéphalique chez les EHS", *LinkedInPost*, Aug. 13, 2021, *Mieux Prévenir*, Sept. 5, 2021

## New Progress on Structural Safety and Control

by Hong-Nan Li, Member EUAS



### Short Biography

*Dr. Hong-Nan Li received his bachelor's degree from Shenyang Jianzhu University in 1982, his master's degree and PhD from the China Earthquake Administration in 1987 and 1990, respectively. He had conducted his postdoctoral research at Virginia Polytechnic Institute and State University from 1992-1994. He has been a Distinguished Professor (professor of Cheung Kong Scholars Program) of School of Civil Engineering at Dalian University of Technology (DUT), China since Sept. 2001. He is the founding director of the Research Center for Structural Health Monitoring and Control at DUT.*

*He is a Fellow of American Society of Civil Engineers (ASCE). His research interests are primarily in safety and security of civil infrastructure systems, focusing on development of innovative and interdisciplinary science and technology for sensors, health monitoring, damage assessment, structural control and disaster prevention. He is the author/co-author of 8 books and more than 400 refereed journal papers including more than 300 international journals. He is also an inventor or co-inventor of 67 invention patents and 8 computer software certificates. He has delivered over 80 keynote and invited lecture at international conferences and universities in different countries.*

*He ever edited the first standard in the area of SHM in China "Design Standard for Structural Health Monitoring Systems (CECS 333: 2012)" and other 15 standards. His related achievements have been applied to more than 70 major infrastructures, such as the Zhoushan Transmission Tower (The World's the Tallest Transmission Tower), Dalian gymnasium (The World's Largest Span Suspended Dome Structure), the long span suspension dome structure NB35-2 (Ultra Large Offshore Oil Platform), Shenyang Boguan bridge (Complicated Long-Span Arch Bridge), Dalian World Trade Center. He received various prizes in recognition of his innovative achievements in research, such as played a leading role in the 2015 National Technology Invention Award, 2010 & 2007 National Science and Technology Progress Awards, and more than 10 provincial Science & Technology awards in China. He was also awarded as the "Outstanding Technical Contribution Award" by ASCE Aerospace Division (2014)*

*With a long-term commitment to serving society, He is currently the Editor-in-Chief of Structural Monitoring and Maintenance, An international Journal, Associate Editor of Journal of Aerospace Engineering-ASCE and an editorial board member of more than 30 other journals. He also has held many extensive academic and professional leadership positions related to: vice chair of the Advanced Materials and Structures committee & vice chair Dynamics and Controls Committee, American Society of Civil Engineers (ASCE); vice chair of China Panel, International Association for Structural Control and Monitoring (IASHM); council member of The International Society for Structural Health Monitoring of Intelligent Infrastructure (ISHMII), etc.*

*Dr. Li promoted the education of undergraduate students and graduate students in Civil Engineering. He has supervised more than 56 Ph.D. students and 70 Master students. Some thesis from his students were awarded for the provincial excellent theses.*

## New Progress on Research Activities

### 1. Bayesian-Copula-based risk assessment for high-rise buildings against wind excitation with uncertainties

The aleatory and epistemic uncertainties coming from various sources will have significant impacts on the accuracy of risk estimates for structures subject to external excitations. This study proposes a hybrid Bayesian-Copula-based method for assessing the wind-induced risk of high-rise buildings incorporating some uncertainties. The main novelties of this study include that: based on the recorded wind and virtual data, the Bayes theorem is used to develop the posterior probability distributions of the unknown parameters in the marginal probability distribution of wind speed and direction as well as in the demand model for fragility analysis. Secondly, in a Bayesian-based framework, the Copula technique is applied to construct the joint probability model of wind speed and direction by linking their marginal distributions. The epistemic uncertainty in the unknown model parameters is incorporated into the risk estimates by the total probability theory. In addition, the joint effects of wind attack angles and structural orientation are considered in the deformation- and comfort-based risk estimates. The application of this study indicates that the epistemic uncertainty in the unknown model parameters has obvious influences on both the deformation- and comfort-based total damage probability. Moreover, the calculated total probability is sensitive to the wind attack angles and structural orientation, which should be carefully considered in the structural performance assessment under wind excitations. This hybrid Bayesian-Copula-based method can flexibly and efficiently account for the uncertainties that are much beneficial for improving the degree of reliability to risk estimates. Major findings are summarized as follows:

(1) Compared with the accompanying paper of this study, the posterior estimates of the parameters in the von Mises distribution of wind direction vary significantly owing to their uncertainties. Conversely, the uncertainty in the unknown parameters has little impact on the probability distribution of wind speed and the demand models.

(2) The epistemic uncertainty in the unknown model parameters has obvious influences on both the deformation- and comfort-based total damage probability, comparing to the corresponding values without the corresponding uncertainties.

(3) The wind-induced risk of this exemplary building is sensitive to the wind attack angles and structural orientation. It is necessary to account for the joint effects of wind attack angles, structural orientation and the joint model of wind

speed and direction in risk assessment for high-rise buildings under wind loads.

## **2. Research on vortex-induced vibration of a tubular transmission tower and its countermeasure**

In an ultra-high voltage (UHV) transmission engineering, the transmission towers with steel tubes, named tubular towers, are widely used because of their advantages, such as significantly improving the structural strength and stability, and reducing the wind load of the tower. However, within a specific wind velocity range, the tubular members with a high slenderness ratio may cause joint fatigue failure when the vortex-induced vibration (VIV) occurs. To deeply reveal the mechanism of VIV of tubular members in the UHV transmission tower, firstly, this study has measured the acceleration and the corresponding wind velocity of a tubular member subjected to the VIV, followed by the identification of the first-order frequency. Then, a simulation framework for the tubular members subjected to the VIV is proposed. The vibration system is simplified as a mass-spring-damping system considering the nonlinear coupling effect between the tubular member and wind field. Based on the simulation framework, the lock-in region and the maximum displacement amplitudes in the cross-wind direction are calculated, and the accuracy of the simulation framework is verified compared with the on-site measured data. Meanwhile, the influence of the damping ratio on the VIV is studied. Finally, a new type of radial spoiler is proposed to suppress the VIV of tubular members. The results of 3-D numerical simulation show that the presented radial spoiler can effectively suppress the vortex generation, and there is no noticeable vibration after the on-site installation, which indicates that the proposed countermeasure can distinctly suppress the VIV of the tubular tower. The parametric analysis reveals that the distance between two adjacent spoilers has a significant impact on the control effect and should be carefully designed for each project. The conclusions drawn from the numerical simulation and on-site measurement can be summarized as follows:

(1) The occurrence of VIV of the monitored tubular member is successfully simulated, and the lock-in region are also calculated, which is in good agreement with the on-site measured data.

(2) The displacement amplitude in the cross-wind direction in the lock-in region is much larger than that in the non-lock-in region, and the maximum displacement amplitude can reach  $0.22D$ .

(3) The 3-D simulation results of the proposed radial spoiler countermeasure show that the suppression mechanism is destroying the large vortex structure into small one, thereby reducing the frequency of vortex shedding.

(4) The parametric analysis of the layout spacing  $s$  shows that the smaller the  $s$ , the smaller the frequency of vortex shedding. The real project in this paper uses  $s=1500$  mm from an economic perspective, and other projects can refer to this parameter depending on the situation.

### **3. Seismic behaviors on free-spanning submarine pipelines subjected to multi-support earthquake motions within offshore sites**

For the submarine pipelines, free spans may be formed due to the erosion, scouring or unevenness of the seafloor. Generally, the free spans of submarine pipelines are vulnerable to severe seismic excitations. Due to the shortage of offshore seismic records and inhere difficulty in the simulating artificial offshore ground motions, numerous existing works have been however performed to investigate the seismic responses of free-spanning submarine pipelines, not only using the onshore seismic records as inputs but also adopting the uniform seismic excitations. These analytical schemes may result in severe misestimates of the seismic responses since (1) the seismic motions may vary at distinct locations along the pipeline due to the spatial variation effects; and (2) the offshore and onshore seismic motions are indeed different due to the existence of seawater and subsea soils affecting the seismic P-waves propagation in the offshore sites. Using the nonlinear finite element (FE) method, in this study the seismic behaviors of a free-spanning submarine pipeline are numerically investigated under the multi-support earthquake motions within offshore sites (MEMOSs). The soil-pipe and water-pipe interactions are modeled using the nonlinear soil spring and added mass methods, respectively. The effects of spatially varying and overlying seawater are explicitly taken into account in the simulation of MEMOSs. The seismic behavior law of the free-spanning submarine pipeline under the synthesized MEMOSs is analyzed and summarized. Moreover, the impacts of the seismic excitation type, offshore seismic motion, coherence loss, local site condition and free span length on the seismic behaviors of the submarine pipeline are examined and discussed comprehensively. This research is expected to offer a meaningful reference to the seismic analysis of the free-spanning submarine pipelines. Some significant conclusions can be drawn from the numerical results:

(1) The uncertainty of the seismic motion inputs has a significant influence on the seismic behaviors and should be taken into account in seismic analysis of the

submarine pipelines.

(2) The non-uniform seismic excitations can significantly affect the seismic behaviors of free-spanning submarine pipelines. Compared to the non-uniform seismic excitations, adopting the uniform seismic excitations may underestimate the seismic responses (up to 16.92%) and overestimate the critical bearing capacity (as much as 20.89%) of the pipeline, respectively.

(3) In contrast to the offshore seismic motions, adopting the onshore seismic motions may overestimate the seismic responses (with a maximum of 9.23%) and underestimate the critical bearing capacity (up to 20.63%) of the pipeline, respectively.

(4) Both the coherence loss and local site conditions has a significant effect on the seismic behaviors of free-spanning submarine pipelines. The lower the coherence loss level and soil stiffness are, the higher the seismic responses and the lower the critical bearing capacity are.

## Soil Liquefaction - A Case Study

by Pedro Pinto, Member EUAS



### Short Biography

- *Licenciated in Civil Engineer (6 years course, 1965-1971)(with honors);*
- *Industry from 1971 to 1975;*
- *Master of Engineering 1975 – 1977 (with high honors);*
- *Specialist in Geotechnique (Ph.D Degree) 1979 - 1983 (with high honors);*
- *Director of Research (Full Professor degree) (with high honors), since 1992.*
- *Related with ISSMGE (International Society for Soil Mechanics and Geotechnical Engineering)*
- *Appointed Board member (2017-2021)*
- *Immediate Past President (2009-2013)*
- *President (2005-2009),*
- *Vice President for Europe (2001-2005),*
- *Chairman of TC4 “Earthquake Geotechnical Engineer Committee” (1994-2000).*
- *Full Professor of Geotechnical Engineering of University of Coimbra*
- *World Bank Consulting for Dams Safety (2013-2015),*
- *Invited Professor of Master Courses "Soil Mechanics" and "Engineering Geology" of New University of Lisbon (1983-1995),*
- *United Nations Consulting for Design and Instrumentation for Dams (1988-1992).*
- *Invited Guest Lecturer of University of California, USA (1992-1994).*
- *President of Portuguese Society for Geotechnique (1996- 2000).*
- *Pedro Sêco e Pinto is a Consulting Engineer and has participated in more than 450 major projects in Dams, Power plants, Bridges, Tunnels, Landslides and Quay Walls, in Portugal, Angola, Argelie, Brazil, Cabo Verde, China, Dominican Republic, Ecuador, Guine- Bissau, Guine Ecuatorial, India, Lebanon, Malawi, Morocco, Mozambique, Senegal, Syria, Tunisie, Uganda, Venezuela and Zambia, covering field and laboratory testing, dynamic analyses, earthquake engineering, numerical analyses, ground improvement, slopes, special foundations, instrumentation and safety evaluation.*
- *He has presented more than 350 State-of-the Art Lectures and Special Lectures in 80 countries of the 5 Continents.*
- *Pedro Sêco e Pinto has organized, under the umbrella of the International Society for Soil Mechanics and Geotechnical Engineering (ISSMGE), more than 50 International Seminars, since 2006, in Africa (Ghana, Mozambique, Nigeria, South Africa, Sudan), in Asia (Bangladesh, Cambodia, China, India, Indonesia, Kazakhstan, Laos, Malaysia, Myanmar, Nepal, Pakistan, South Korea, Sri Lanka, Vietnam), in Australasia (Australia and New Zealand) in Europe (Albania, Belarus, Croatia, Germany, Hungary, Lithuania, Slovenia, Ukraine), North America (Mexico), South America (Argentina, Bolivia, Dominican Republic, Haiti, Ecuador, Panama, Paraguay, Peru, Venezuela).*
- *Pedro Sêco e Pinto has received more than 50 international Awards including American Biographical Institute USA, "Special Volume for the Contributors of Earthquake Engineering, Nagadi Lecture by Indian Geotechnical Society, Széchy Lecture by Hungarian S M Society and Hungarian Academy of Sciences, Nonveiller Lecture by Croatia Geotechnical Society, Suple Lecture by Slovenia Soil Mechanics Society, Chin Lecture by Huanzhou University (China), Qian Jia Huan Lecture by Hohai University (China) and Chin Fung Kee Memorial Lecture by Institute of Engineers of Malasia, 3<sup>rd</sup> Victor de Mello Lecture by Indian Geotechnical Society and 3<sup>rd</sup> Braja Das Lecture, GeoMeast 2019, International Congress and Exhibition, Cairo, Egypt.*

- Related his role with Editorial Boards and Reviewer he acted as:
  - Associate Editor of International Journal of Earthquake Engineering (since 2017)
  - Editor in Chief of International Journal of Case Histories (2011-2017)
  - Co-Editor of Geotechnical and Geological Engineering Journal, Springer Publisher (2005-2011)
  - Member of Editorial Board of several Journals, namely: "Geotecnia", "Bulletin of Earthquake Engineering", "Acta de Geotecnia", "International Journal of Geotechnical Engineering".
  - Editor of Proceedings of 4 International Conferences.
- Pedro Sêco e Pinto is author or co-author of 500 Technical and Scientific Reports, more than 180 papers for National and International Conferences and Journals and has contributed for 10 books.

## ABSTRACT

In this paper the potentially liquefiable soils are addressed. The ground improvement technique by vibroflotation is presented. Only one case study, namely Massingir dam, is discussed. Some final considerations are presented.

*"The important thing in science is not  
so much to obtain new facts as to discover  
new ways of thinking about them".*

(Sir W. Bragg, British Scientist, 1968)

## 1. INTRODUCTION

The potentially liquefiable soils evaluation based on SPT and CPT tests is addressed. The ground improvement technique by vibroflotation treatment is presented. Due to the lack of space very important issues such as residual shear strength and induced settlements are not referred. Also, only one case study, namely Massingir dam, is addressed. Some final considerations are presented.

## 2. POTENTIALLY LIQUEFIABLE SOILS

Following 4.1.3. (2)-Part 5-EC8 "An evaluation of the liquefaction susceptibility shall be made when the foundations soils include extended layers or thick lenses of loose sand, with or without silt/clay fines, beneath the water level, and when such level is close to the ground surface".

Soil investigations should include SPT or CPT tests and grain size distribution (Idriss and Boulanger, 2008). Normalization of the overburden effects can be performed by multiplying SPT or CPT value by the factor  $(100/\sigma'_{vo})^{1/2}$  where  $\sigma'_{vo}$  (kPa) is the effective overburden pressure. This normalization factor should be taken not smaller than 0.5 and not greater than 2.

The seismic shear stress  $\tau_e$  can be estimated from the simplified expression:

$$\tau_e = 0,65 \alpha_{gr} \gamma_f S \sigma_{vo} \quad (1)$$

where  $\alpha_{gr}$  is the design ground acceleration ratio,  $\gamma_f$  is the importance factor, S is the soil parameter and  $\sigma_{vo}$  is the total overburden pressure. This expression should not be applied for depths larger than 20 m. The shear level should be multiplied by a safety factor of

[1.25].

Two categories of remedial measures against liquefaction were proposed:

(i) Solutions aiming at withstanding liquefaction - Confinement wall: stiff walls anchored in a non liquefied layer (or a bedrock) to avoid lateral spreading in case of liquefaction; Soil reinforcement - transfer of loads to a non-liquefiable layer.

(ii) Solutions to avoid liquefaction: - Soil densification: compaction grouting to minimize the liquefaction potential; - Dewatering: to lower the water table in order to minimize the risk of liquefaction; - Drainage: to facilitate the dissipation of pore pressure; - Fine grouting: to increase the soil cohesion.

The measures to prevent of occurrence of liquefaction include the improvement of soil properties or improvement of conditions for stress, deformation and pore water pressure. In practice a combination of these two methods is adopted.

### **3. VIBROFLOTATION TREATMENT**

The vibroflotation techniques for strengthening cohesionless soils by deep compaction probably have their origins on late 1930's (Moseley, 1993).

A steel rod is introduced at the desired depth and a vibrator creates vertical and horizontal vibrations that provoke the compaction of the soil while the rod is slowly withdrawn.

The range of suitable soils to be treated by vibroflotation is indicated in Fig. 1 (Glover, 1982). Particle distributions within this zone A can be densified by vibroflotation. For depths higher than 10 m some difficulties are found for soils more than 20% of gravel material.

Grain size distributions within zone B are excellent soils for densification by vibroflotation.

For soils with grain size distribution falling within zone C require some modifications of compaction procedures due to the presence of silt and excessive fines material (over 15% passing on sieve 200).

The depth of compaction and the spacing depend of the following factors: (i) maximum allowable total settlement; (ii) maximum allowable differential settlement; (iii) requested bearing capacity; (iv) final shear strength value; and (v) increased resistance to liquefaction (Sêco e Pinto, 2012).

The treatment efficiency can be evaluated by the following methods: (i) standard penetration test (SPT) by comparing the results before and after the treatment. The well known limitations of these tests raised some doubts about the results; (ii) static cone penetration (CPT); (iii) pressurometer - the deformation modules can be correlated with the compressibility of the soil; (iv) load tests are carried using in general steel plates with diameter between 300 to 600 mm. Taking into account the size of the plate and the footing the obtained results are limited; and (v) settlement - the efficiency can be assessed by controlling the levels before and after the treatment.

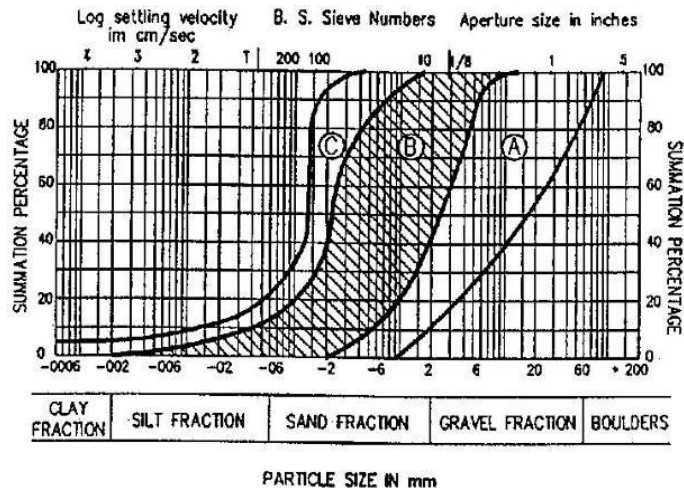


Fig. 1 Range of soils suitable for improvement by the vibroflotation process (after Glover, 1982)

#### 4. CASE STUDY OF MASSINGIR DAM

Due to the low degree of compaction of the alluvia and the seismic characteristics of the area, treatment by vibroflotation was adopted in order to avoid an eventual liquefaction of sands of a foundation alluvium of the main body of Massingir dam in Mozambique.

The total length of the earth dam is 4596 meters, comprising a main body with a maximum height of 48 meters and with a width of 12 meters at the crest (Fig. 2). This body extends on either side with embankments which have 32 meters of maximum height and a width of 9 m at the crest.

The valley is partial filled by sands of different grading, varying from fine to coarse, coarse sands prevailing, sometimes with boulders.

Bedrock formation was found at 26 m depth approximately and is formed by a hard limestone.

Average values of penetration resistance from 1 MPa to 2 MPa were obtained in the first 10 m depth; below this depth and up to bedrock formation values from 3 to 4 MPa were recorded. Such penetration resistances correspond to relative densities  $I_d$  of 0.20 and 0.35 respectively.

Due to the low compaction of alluvia existing at the main body of the dam, vibroflotation process was adopted, to improve this characteristic.

The goal was to obtain, in the first 10 meters of the alluvial bed, a relative density  $I_d \geq 0.40$  corresponding to the minimum value advised by the designers.

In order to evaluate the efficiency of the process, vibroflotation tests were conducted for influence areas equaling four, five, six and seven square meters.

Based on the obtained results influenced area of each vibroflot penetration was  $6 \text{ m}^2$  (2.63 m x 2.28 m).

Static penetration tests performed before vibroflotation, gave penetration resistance values around 2 MPa. After vibroflotation new penetration resistances were recorded, which only gave satisfactory results below 2 m depth.

Time of sinking of vibroflot, depth reached by it, and any eventual irregularity in its behavior were recorded during treatment.

On its way back up the vibroflot was stopped every 50 cm and an attempt was made to regulate pressure readings in the gauge of the vibroflot between 15 MPa to 20 MPa.

Generally time of ascension was about 50 minutes. After treatment new cone penetration

tests were performed.

Diagrams of penetration resistances given by those tests conducted before and after vibroflotation are shown in Figure 3. Breaks in penetration resistances recorded, after treatment, are due to clayey lenses, existing in alluvial layer (Sêco e Pinto, 2012).

Results expressed in terms of settlement, of treated area, gave a surface displacement around 0.6 m to 0.7 m. This fact also confirmed the efficiency of vibroflotation process adopted.

Foundation sandy material of the main body of the dam, reaching a volume of 1 million cubic meters, was treated by introducing vibroflots up to 10 m depth, after removing superficial cover of humus.

The total amount of vibrofloted points were 17635, using six cranes. Average time of each vibroflotation was one hour approximately. Due to the difficulty in defining relative densities, caused by the fluctuation of maximum and minimum density values, an attempt was made to correlate penetration resistances ( $R_p$ ) and dry densities ( $\gamma_d$ ).

Treatment by vibroflotation at depths from 2.00 m to 12.00 m, was satisfactory once values of  $R_p \geq 70$  MPa, at which no liquefaction of sands is expected, were obtained.

Superficial layer up to 2.40 m, in which vibroflotation process was not successful, was compacted with six passes of a 5 T vibratory roller, vibrating at a frequency around 1 000 to 1 200 r p m.

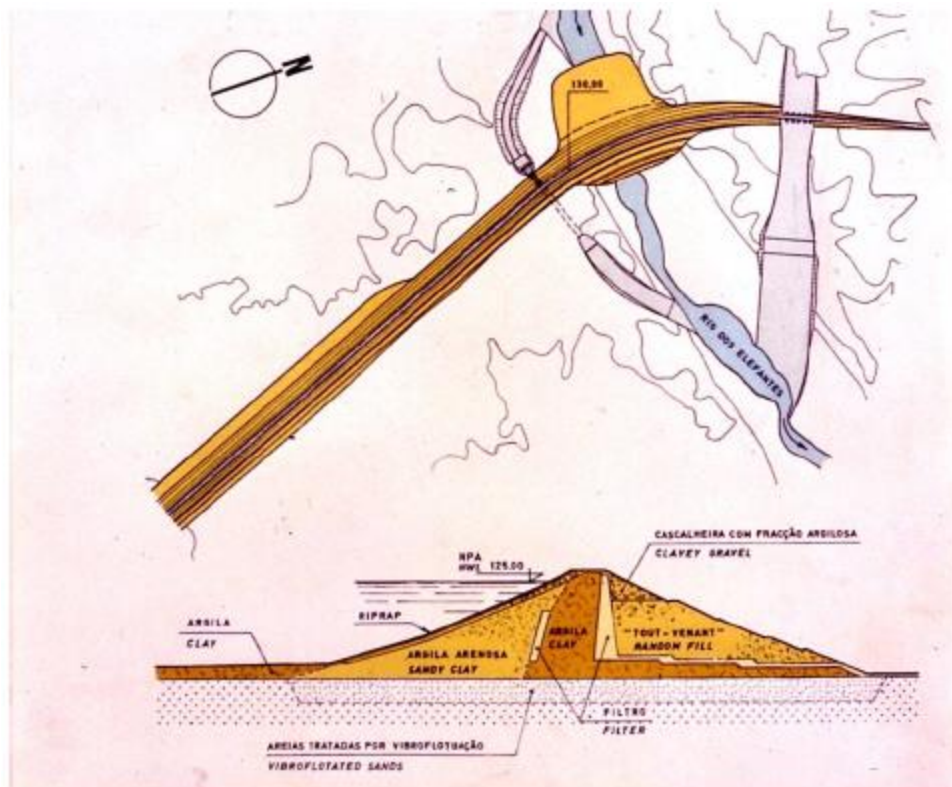


Fig. 2 Massingir dam plan and profile

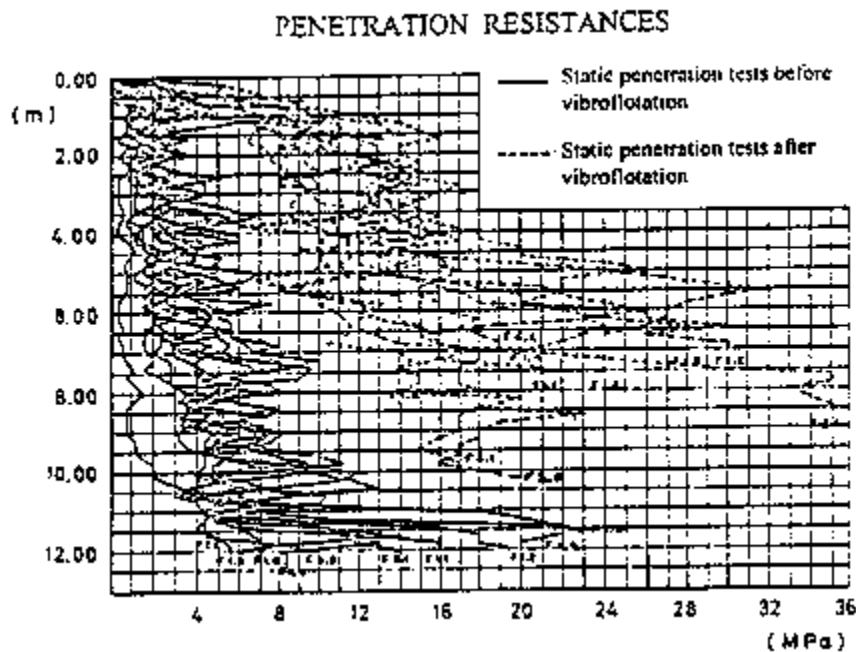


Fig. 3 Diagrams of penetration resistances

## 5. FINAL REMARKS

In spite of the impressive progress that has been made in the last years on soil liquefaction there is still space for questions that remain without a definitive answer, such as:

- i) Methodologies to assess the efficiency of vibroflotation techniques;
- ii) Liquefaction of gravel materials;
- iii) The role of fine materials.

Due to the low degree of compaction of the foundation alluvia of the main body of Massingir dam in Mozambique and the seismic characteristics of the area, treatment by vibroflotation was adopted in order to avoid an eventual liquefaction of sands, that has revealed satisfactory.

*“If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties”.*

(Francis Bacon - Advancement of Learning)

**References**

Eurocode 8 (EC1998-5) “Eurocode 8-Design of Structures to Resist to Earthquakes”. Part 5. Foundations, Retaining Walls and Geotechnical Aspects.

Glover, J. C. (1982) “Sand Compaction and Stone Columns by the Vibroflotation Process”, *Symposium on Soil and Rock Improvement Techniques Including Geotextiles, Reinforced Earth and Modern Piling Methods*, AIT, Bangkok, pp. A.7.1–A.7.18.

Idriss, I.M. and Boulanger, R.W. (2008) “Soil Liquefaction during Earthquakes”. Monograph MNO-12”, Earthquake Engineering Research Institute, Oakland, CA, 261 pp.

Mosely, M.P. (1993) “Ground Improvement”. Blackie Academic and Professional.

Seco e Pinto, P.S. (2012) “Ground Improvement and Ground Control”. Special Lecture. Wollongong International Conference.

## Further Contributions in Biorefining

by Arthur Ragauskas, Member EUAS

### Short Biography

*Arthur Ragauskas held the first Fulbright Chair in Alternative Energy and is a Fellow of American Association for the Advancement of Science, the International Academy of Wood Science and TAPPI. In 2014, he assumed a Governor's Chair for Biorefining based in University of Tennessee's Department of Chemical and Biomolecular Engineering, with a complementary appointment in the UT Institute of Agriculture's Department of Forestry, Wildlife, and Fisheries and serves in the Energy and Environmental Sciences Directorate, Biosciences Division, at ORNL. His research program is directed at understanding and exploiting innovative sustainable bioresources for the circular economy. This multifaceted program is targeted to develop new and improved applications for nature's premiere renewable biopolymers for biofuels, biopower, and bio-based materials and chemicals. His research program has been sponsored by NSF, USDA, DOE, GA Traditional Industry Program, a consortium of industry partners, and several fellowship programs which is summarized in 816 publications. His Fulbright sponsored activities at Chalmers University of Technology, Sweden were focused on the forest biorefinery and new biofuel conversion technologies for lignocellulosics. Currently, Dr. Ragauskas manages a research group of graduate students, postdoctoral research fellows, a research scientist, and visiting scientists. He is the recipient of the 2014 TAPPI Gunnar Nicholson Gold Medal Award, the 2014 ACS Affordable Green Chemistry Award, 2017 AIChE Green Processing Award, 2017 Academia Distinguished Service Award, 2019 AIChE Chase Award, and his students and postdocs have won several awards, including the ACS graduate research award, ORNL UT-Battelle Award, and the ORNL Supplementary Performance Award.*

*Ragauskas is an Associate Editor for Biofuels, Bioproducts and Biorefining, Biofuels, BioEnergy Research, Industrial Biotechnology, Taiwan Journal of Forest Service, TAPPI J., Holzforschung, Journal of Biobased Materials and Bioenergy, Journal of Petroleum Technology and Alternative Fuels, The Open Biotechnology Journal, Current Biotechnology, and J. Wood Chemistry and Technology. He is an editorial board member of Sustainability and Journal of Chemical Technology and Biotechnology. Ragauskas has served on several advisory boards and review panels including: Austrian Science Fund, European Commission Research Directorate, National Science Academy, J. Paul Getty Trust, NSF, USDA, DOE, ARAP-E, NSERC, TAPPI Research Management Committee, Netherlands Organization for Scientific Research (NWO), Swedish Foundation for Strategic Research, Swedish VINN Excellence Center, Swedish Knowledge Foundation, VTT Technical Research Centre of Finland, ERA Chemistry, Swiss National Science Foundation, Finnish Academy of Science Norway Research Council, The Technology Foundation STW, Agence Nationale de la Recherche and Singapore Agency for Science, Technology and Research. Dr. Ragauskas has been an invited visiting professor at Universidade da Beira Interior, Portugal; Chalmers University of Technology, Sweden; Royal Institute of Technology/ STFi, Stockholm, Sweden; and Southeast University, China, and South China University of Technology, China.*

### **Ragauskas Governor Chair Mission Statement**

As an academician, Ragauskas' core belief is that a professor can only be as successful as the students he educates, mentors, and graduates. As such, Ragauskas' academic mission has been, and remains, the cornerstone of his career objectives. These career objectives include:

- Develop a challenging and enriching educational and research experience that facilitates the intellectual development of the University of Tennessee, Knoxville and the University of Tennessee Institute Agriculture (UTK/UTIA) students and postdoctoral fellows and supports

the mission of the Department of Chemical and Biomolecular Engineering, and Center for Renewable Carbon.

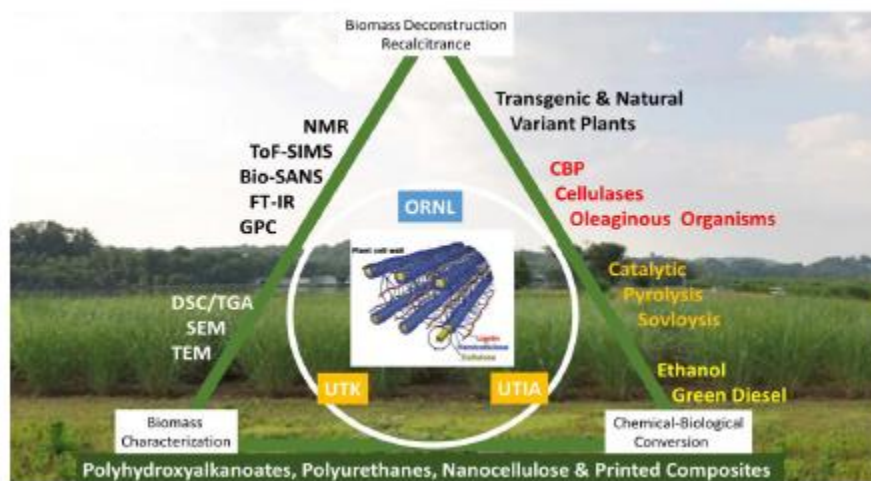
- Recruit, educate, and develop the next generation of scientists that will be nationally/internationally recognized leaders in green chemical engineering of biofuels, bio-derived materials, and chemicals.
- Develop a nationally/internationally recognized research center for sustainable green chemical engineering of biorefining, leveraging the exceptional researchers and research infrastructure located at Oak Ridge National Laboratory (ORNL), UTK, and UTIA.

### Research Accomplishments and Activities

Ragauskas assumed the ORNL-UTK-UTIA Governor's Chair in Biorefining position in June 2014. This UTK faculty position, jointly funded by UTK/UTIA and ORNL, is focused on developing a fundamental research and academic program in sustainable biomass biorefining. As summarized in Figure 1, his research program is focused on three central overlapping focus areas including:

- Fundamental lignocellulosic properties of plant cell walls and their relationship to biological biorefining of biomass to biofuels.
- Valorization of biomass components for bio-derived materials

Development of new tools and methodologies for biomass characterization



**Fig. 1.** Summary of Ragauskas' ORNL, UTK, UTIA Governor Chair Research in Biorefining.

To develop this research program, Dr. Ragauskas has developed a dynamic, internationally recognized ORNL-UTK-UTIA research team in the field of fundamental green chemical engineering of biopolymers. During this period, his research group has published over 500 manuscripts, (+800 over a life-time) of which greater than 90% were joint ORNL-UTK-UTIA publications. Ragauskas' publications are acknowledged internationally with a Google H-index of 104, i10 index of 498 and greater than 46000 citations. These overall accomplishments were noted by Publons (Clarivate Analytics), who named Ragauskas as one of the world's most highly cited researchers in his field for 2018 and 2021. The impact of these studies were recognized in a series of awards, including 2019 AIChE Chase Award, Joint Faculty Award in Science and Technology, UT-Battelle (2019), Nominated to Sigma Xi (2019), Albert Nelson Marquis Lifetime Achievement Award (2017), Green Process Engineering American Institute of Chemical Engineers Award (2017), The University of California, Bourns College of Engineering – Center for Environmental Research and Technology, Distinguished Service Award (2017), TAPPI Gunnar Nicholson Gold Medal Award (2014), ACS Award for Affordable Green Chemistry (2014), ORNL Visiting Fellow (2013), Elected American Association for the Advancement of Science Fellow (2012), Elected to Academy Board of International Academy of Wood Science (2012), and Fulbright Distinguished

Chair in Alternative Energy (2008-2009).

Six representative publications that have been published since Ragauskas assumed the Governor's Chair position include:

- Transforming biorefinery designs with "Plug-In Processes of Lignin" to enable economic waste valorization. Liu, Zhi-Hua; Hao, Naijia; Wang, Yun-Yan; Dou, Chang; Lin, Furong; Shen, Rongchun; Bura, Renata; Hodge, David B.; Dale, Bruce E.; Ragauskas, Arthur J.; Bin, Yang; Yuan, Joshua, S. *Nature Communications* (2021), 12(1), 3912.
- Elucidating the mechanisms of enhanced lignin bioconversion by an alkali sterilization strategy. Zhao, Zhi-Min; Zhang, Shuyang; Meng, Xianzhi; Pu, Yunqiao; Liu, Zhi-Hua; Ledford, William K.; Kilbey, S. Michael II; Li, Bing-Zhi; Ragauskas, Arthur J. *Green Chemistry* (2021), 23(12), 4697-4709.
- Wood-reinforced composites by stereolithography with the stress whitening behavior. Zhang, Shuyang; Bhagia, Samartha; Li, Mi; Meng, Xianzhi; Ragauskas, Arthur J. *Materials & Design* (2021), 206, 109773
- Polyurethanes Based on Unmodified and Refined Technical Lignins: Correlation between Molecular Structure and Material Properties. Wang, Yun-Yan; Scheidemantle, Brent; Wyman, Charles E.; Cai, Charles M.; Ragauskas, Arthur J. *Biomacromolecules* (2021), 22(5), 2129-2136.
- Enhancing Multifunctional Properties of Renewable Lignin Carbon Fiber via Defining Structure-Property Relationship Using Different Biomass Feedstock. Li, Qiang; Hu, Cheng; Li, Mengjie; Truong, Phuc; Li, Jinghao; Lin, Hao-Sheng; Naik, Mandar; Xiang, Sisi; Jackson, Brian; Kuo, Kuo, Winson; Wu, Wenhao; Pu, Yunqiao; Ragauskas, Arthur J.; Yuan, Joshua S. *Green Chemistry* (2021), 23(10), 3725-3739.
- Integration of renewable deep eutectic solvents with engineered biomass to achieve a closed-loop biorefinery. Kim, K.H.; Eudes, A.; Jeong, K.; Yoo, C.G.; Kim, C.S.; Ragauskas, A. *Proceedings of the National Academy of Sciences of the United States of America* (2019), 116(28), 13816-13824.

In light of the continuing controversies of LCC and methods of detecting these structures, Ragauskas was invited to submit a critical analytical review on this topic, along with research colleagues from the Royal Institute of Technology (Sweden):

- A Critical Review on the Analysis of Lignin Carbohydrate Bonds in Plants. Giummarella, N.; Pu, Y.; Ragauskas, A.; Lawoko, M. *Green Chemistry* (2019) 20, 1573 - 1595.

Working with a team of ORNL researchers, Ragauskas has examined the sugar release performance of natural *Populus* variants and correlated their biomass recalcitrance properties to the fundamental structure of cellulose, hemicellulose, and lignin, as reported in "Insights of biomass recalcitrance in *Populus trichocarpa* natural variants for biomass conversion" *Green Chemistry* (2017), 19(22), 5467-5478. Among the physicochemical properties of poplar, the lignin content, lignin molecular weight, lignin S/G ratio, and cellulose accessibility were found to strongly correlate with sugar release. The results demonstrated that the lignin content was negatively correlated with sugar release, whereas the lignin molecular weight, lignin S/G ratio, and cellulose accessibility were positively associated with poplar sugar release. These changes in biopolymer structures were then related by differential gene expression (DEG) to identify potential target gene groups that are correlated with recalcitrance factors. These results provide valuable information for future biomass studies to understand the novel genes and their regulatory mechanism in forest genetics and apply this for enhancing biomass utilization.

In all of these recalcitrance studies, lignin is a by-product that was historically viewed as either a waste product or, at best, a product for combustion. Starting with Ragauskas' publication in *Science* titled "Lignin Valorization: Improving Lignin Processing in the Biorefinery" (Ragauskas, A.J.; Beckham, G.T.; Bidy, M.J.; Chandra, R.; Chen, F.; Davis, M.F.; Davison, B.H.; Dixon, R.A.; Gilna, P.; Keller, M.; Langan, P.; Naskar, A.K.; Saddler, J.N.; Tschaplinski, T.J.; Tuskan, G.A.; Wyman, C.E. *Science*, (2014) 344(6185), 1246843-1-1246843-10) he has focused on utilizing lignin as a feedstock for novel material applications. A key focus of these studies is to demonstrate that lignin structure is a critical factor in controlling physicochemical properties. This

hypothesis was clearly illustrated in “A study of poplar organosolv lignin after melt rheology treatment as carbon fiber precursors” *Green Chemistry* (2016), 18(18), 5015-5024, whereby Ragauskas demonstrated viscosity properties of lignin at elevated temperatures could be altered by lignin’s degree of polymerization and structural features. Comparable findings have also been reported in related studies, including:

- Linking lignin source with structural and electrochemical properties of lignin-derived carbon materials. Li, W.; Zhang, Y.; Das, L.; Wang, Y.; Li, M.; Wanninayake, N.; Pu, Y.; Kim, D.Y.; Cheng, Y.T.; Ragauskas, A.J.; Shi, J., *RSC Advances* (2018) 8(68), 38721-38732.
- Understanding lignin fractionation and characterization from engineered switchgrass treated by an aqueous ionic liquid. Liu, E.; Li, M.; Das, L.; Pu, Y.; Frazier, T.; Zhao, B.; Crocker, M.; Ragauskas, A.J.; Shi, J. *ACS Sustainable Chemistry & Engineering* (2018) 6(5), 6612-6623.

In addition to genetic factors controlling the structure of lignin in bioresources, the extraction of lignin from biomass and its impact on lignin structure has been clearly defined in a series of publications. Examining the structure before and after CELF pretreatment, lignin structure was shown to exhibit a significant decrease in DP and an accompanying decrease in  $\beta$ -aryl ethers as reported in:

- Deconstruction of biomass enabled by local demixing of cosolvents at cellulose and lignin surfaces. Pingali, Sai Venkatesh; Smith, Micholas Dean; Liu, Shih-Hsien; Rawal, Takat B.; Pu, Yunqiao; Shah, Riddhi; Evans, Barbara R.; Urban, Volker S.; Davison, Brian H.; Cai, Charles M.; Ragauskas, Arthur J; O’Neill, Hugh M.; Smith, Jeremy C.; Petridis Loukas. *Proceedings of the National Academy of Sciences of the United States of America* (2020), 117(29), 16776-1678.

These findings provide a valuable tool for researchers to tune the structure of lignin for a variety of chemical, biological, and material applications. Ragauskas has highlighted these opportunities in several publications, including:

- Defining Lignin Nanoparticle Properties through Tailored Lignin Reactivity by Sequential Organosolv Fragmentation Approach (SOFA). Liu, Z.H.; Hao, N.; Shinde, S.D.; Pu, Y.; Kang, X.; Ragauskas, A.; Yuan, J.S. *Green Chemistry* (2019) 21(2), 245-260.
- High Shear Homogenization of Lignin to Nanolignin and Thermal Stability of Nanolignin-Polyvinyl Alcohol Blends. Nair, S.S.; Sharma, S.; Pu, Y.; Sun, Q.; Pan, S.; Zhu, J. Y.; Deng, Y.; Ragauskas, A.J. *ChemSusChem* (2015) 7(12), 3513-3520.
- Fast Fractionation of Technical Lignins by Organic Co-solvents. Wang, Y.Y.; Li, M.; Cai, C.; Wyman, C.; Ragauskas, A.J. *ACS Sustainable Chemistry and Engineering* (2018) 6(5), 6064-6072.

Key to Ragauskas’ research program is the development of new analytical tools to characterize the structure of biomass. This has been accomplished in several fields, including:

- Novel whole-cell NMR methodology, for example, Elucidating Structural Characteristics of Biomass using Solution-State 2D NMR with a Mixture of Deuterated Dimethylsulfoxide and Hexamethylphosphoramide. Yoo, C.G.; Pu, Y.; Li, M.; Ragauskas, A.J., *ChemSusChem* (2016) 9(10), 1090-1095.
- Phosphitylation/<sup>31</sup>P NMR to characterize lignin from biomass pretreatment, for example, Determination of Hydroxyl Groups in Biorefinery Resources via Quantitative <sup>31</sup>P Nuclear Magnetic Resonance Spectroscopy. Meng, X.; Crestini, C.; Ben, H.; Hao, N.; Pu, Y.; Ragauskas, A.J.; Argyropoulos, D.S., *Nature Protocols* (2019) 14(9), 2627-2647.
- ToF-Sims to investigate surface topochemistry of biomass and recalcitrance, for example, see: Determining the Syringyl/Guaiacyl Lignin Ratio in the Vessel and Fiber Cell Walls of Transgenic Populus Plants. Tolbert, A.K.; Ma, T.; Kalluri, U.C.; Ragauskas, A.J. *Energy & Fuels* (2016) 30(7), 5716-5720.
- SANS investigation into biomass pretreatment and recalcitrance, for example, Understanding Multiscale Structural Changes During Dilute Acid Pretreatment of Switchgrass and Poplar. Pingali, S.V.; Urban, V.S.; Heller, W.T.; McGaughey, J.; O’Neill, H.; Foston, M.B.; Li, H.;

Wyman, C. E.; Myles, D.A.; Langan, P.; Ragauskas, A.; Davison, B.; Evans, B.R., ACS Sustainable Chemistry & Engineering (2017) 5(1), 426-435.

Reflective of these accomplishments, Ragauskas was invited to provide reviews summarizing the utilization of NMR tools to characterize bio-oils generated by pyrolysis or solvolysis, as reported in:

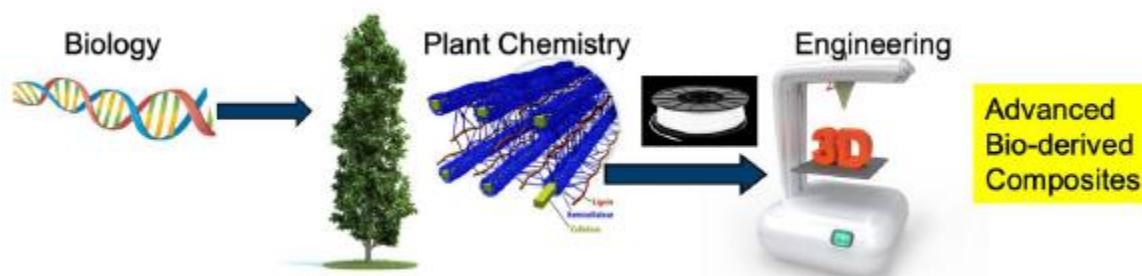
- Review of NMR Characterization of Pyrolysis Oils. Hao, N.; Ben, H.; Yoo, C. G.; Adhikari, S.; Ragauskas, A.J. Energy & Fuels (2016) 30(9), 6863-6880.
- Ethanol: A Promising Green Solvent for the Deconstruction of Lignocellulose. Tekin, K.; Hao, N.; Karagoz, S.; Ragauskas, A.J. ChemSusChem (2018) 11(20), 3559-3575.

In addition to these energy-focused studies, Ragauskas is actively involved in the utilization of bioresources for bio-derived materials with a special emphasis on the utilization of lignin and nanocellulose. His nanocellulose studies are directed at engineering the relative orientation of crystalline nanocellulose (CNC) and nanofibrillated cellulose (CNF) for advanced composites for material and human health applications. These studies employ novel methodologies including chemical crosslinking, directional freezing and layer-by-layer synthesis, as reported in:

- Chemically cross-linked cellulose nanocrystal aerogels for effective removal of cation dye. Liang, Luna; Zhang, Shuyang; Goenaga, Gabriel A.; Meng, Xianzhi; Zawodzinski, Thomas A.; Ragauskas, Arthur J. Frontiers in Chemistry (2020), 8, 570.
- Synergistic enhancement of nanocellulose foam with dual in situ mineralization and crosslinking reaction. Huang, Chen; Zhan, Yunni; Hao, Xin; Wang, Zimeng; Li, Mi; Meng, Xianzhi; Fang, Guigan; Ragauskas, Arthur J. International Journal of Biological Macromolecules (2020), 165(Part B), 3198-3205.
- Preparation and characterization of nanocellulose-polyvinyl alcohol multilayer film by layer-by-layer method. Hou, Q.; Wang, X.; Ragauskas, A.J. Cellulose (2019) 26(8), 4787-4798.
- Cross-linked poly(methyl vinyl ether-co-maleic acid)/poly(ethylene glycol)/nanocellulosics foams via directional freezing. Liang, L.; Huang, C.; Hao, N.; Ragauskas, A.J. Carbohydrate Polymers (2019) 213, 346-351.
- Porous artificial bone scaffold synthesized from a facile in situ hydroxyapatite coating and crosslinking reaction of crystalline nanocellulose. Huang, C.; Hao, N.; Bhagia, S.; Li, M.; Meng, X.; Pu, Y.; Yong, Q.; Ragauskas, A.J. Materialia 4 (2018) 237-246.

An innovative aspect of these studies is defining the fundamental molecular orientation and chemical properties of nanocellulosics to physicochemical properties. A key finding in the bone scaffold studies was that the sulfonate groups in CNC act as a binding site for hydroxyapatite.

As Ragauskas' fundamental program in bio-derived materials develops there are obvious applications in the field of advanced wound healing, organ scaffolds, active membrane separation, and advanced functional composites. A basic premise of all these investigations is that the material properties of bio-derived composites are directly related to the structure of the starting biomass polymers, and hence, these properties are controlled by plant genetics. To provide a clear foundation for the relationship between plant genetics, plant polymers, and bio-derived composites (see Figure 2) we have explored "GWAS Guided Whole Cell Printing of Bio-Derived Composites" as reported in Tensile properties of 3D-printed wood-filled PLA materials using poplar trees Applied Materials Today 21, 100832 (2020).



**Fig. 2** Genetically tailoring cell-wall polymers/structures of *Populus* to yield bio-derived 3D printed composites with enhanced physical properties, guided by Genome-Wide Association Studies.

The basic premise of this project is that researchers can genetically tailor the structural macromolecular features of biomass, specifically from *Populus*, to yield bio-derived 3D printed composites with enhanced physical properties. Hence, at the conclusion of this project, Ragauskas team related the allelic variation in *Populus* to a given structural cell wall parameter (i.e., cellulose content and/or crystallinity, lignin/hemicellulose content and/or structure) and mechanical properties of printed composites.

### Overview

In a world of continuing population growth and GDP, with limited natural resources and environmental concerns, the need for the development of sustainable energy and materials has never been as compelling. Ragauskas' research efforts are directed translational biorefining studies to address these needs in collaboration with leading researchers at ORNL, UTK, and UTIA and strategic partnerships both in this nation and internationally. His vision for the Governor's Chair position is to focus on fundamental research that allows him to establish the science underlying the goal of making Clean Energy, Chemicals and Bio-Derived Materials accessible and affordable. This vision is focused on four primary areas, 1) addressing the affordability of biofuels by increasingly focusing on biomaterials and new fuels, 2) expanding our work on identification of gene function in plants from a biofuels emphasis to a material focus that links to the biorefinery, 3) developing new biomass characterization tools, and 4) developing the 'technology space' for multifunctional bio-derived systems engineered at the nano-scale to provide unique smart physical properties.

### Future Focus

Ragauskas' envisages several strategic research thrusts for the next five years including:

- Lignin valorization studies, leveraging his competitive expertise in lignin structure along with lignin extraction, fractionation, characterization, and functionalization for bio-derived materials and fuels
- Determination of lignin genotype to material phenotype relationships for field grown transgenic switchgrass samples
- Determination of the fundamental mechanisms involved in lignin-first pretreatments of switchgrass to reduce recalcitrance
- Investigate the structure of engineered energy crops for conversion to biofuels
- Fundamentals of engineering smart nanocellulosic composites for material and health applications
- Catalytic pyrolysis and solvolysis of biomass to bio-jet, green diesel, and chemicals

In addition to these professional activities, Ragauskas has served on +60 national and international funding agencies for proposal and program evaluations and the editorial board/associated for +60 journals focused primarily on biorefining. Along with these efforts in 2018, Drs. Ragauskas and Yoo served as editors for a special issue of *Frontiers in Energy Research*, section Bioenergy and Biofuels titled "Advancements in Biomass Recalcitrance: The Use of Lignin for the Production of Fuels and Chemicals."

### Educational Mission

Dr. Ragauskas has presented a graduate 690 course in biorefining to UTK/UTIA students titled "Renewable Biopolymers." The course was directed at reviewing advanced chemical principles of biorenewable polymers including polysaccharides and lignin with a special emphasis on chemical derivatization, reactivity, and conformational analysis. Students were introduced to current concepts in conformational analysis of carbohydrates, chemical derivatization of carbohydrates and lignin, and the conversion of these biopolymers into bio-derived composites and biofuels. In

addition, Ragauskas was invited to present a short course to advanced undergraduate students and graduate students at Southeast University, Nanjing, China on biorefining of biomass to biofuels. The course examined the structure of cellulose, hemicellulose, and lignin in native bioresources, modern technologies to isolate each of these biopolymers and their conversion to biofuels utilizing either biological or thermal conversion technologies.

**Concluding Statement**

In summary, since the Governor's Chair position in the summer of 2014, Dr. Ragauskas' professional vision has been to leverage his past academic-research accomplishments in lignocellulosic chemistry to develop a nationally and internationally recognized program for fundamental sustainable green chemistry engineering of biorenewables for biofuels, bio-derived materials, and chemicals at ORNL, UTK, and UTIA.

# Data-driven Inverse Reinforcement Learning Control for Linear Multiplayer Games

by Frank Lewis, Member EUAS



## Short Biography

*Dr. Lewis was born in Würzburg, Germany, subsequently studying in Chile and Gordonstoun School in Scotland. He obtained the Bachelor's Degree in Physics/Electrical Engineering and the Master's of Electrical Engineering Degree at Rice University in 1971. He spent six years in the U.S. Navy, serving as Navigator aboard the frigate USS Trippe (FF-1075), and Executive Officer and Acting Commanding Officer aboard USS Salinan (ATF-161). In 1977 he received the Master's of Science in Aeronautical Engineering from the University of West Florida. In 1981 he obtained the Ph.D. degree at The Georgia Institute of Technology in Atlanta, where he was employed as a professor from 1981 to 1990. He is Moncrief-O'Donnell Endowed Chair Professor of Electrical Engineering at The University of Texas at Arlington.*

*Ranked at position 88 worldwide, 62 in the USA, and 3 in Texas of all scientists in Computer Science and Electronics, by Guide2Research.com/scientists. Fellow, National Academy of Inventors. Fellow of the IEEE, Fellow of IFAC, Fellow of the U.K. Institute of Measurement & Control, Member European Union Academy of Sciences, Fellow American Association for the Advancement of Sciences, Member of the New York Academy of Sciences. Registered Professional Engineer in the State of Texas and Chartered Engineer, U.K. Engineering Council. 76,800 google citations, h-index 123. Charter Member (2004) of the UTA Academy of Distinguished Scholars. UTA Academy of Distinguished Teachers 2012. IEEE Control Systems Society Distinguished Lecturer 2012-1014. Founding Member of the Board of Governors of the Mediterranean Control Association. Served as Visiting Professor at Democritus University in Greece, Hong Kong University of Science and Technology, Bristol University UK, Chinese University of Hong Kong, City University of Hong Kong, National University of Singapore, Nanyang Technological University Singapore.*

*Received IEEE Computational Intelligence Society Neural Networks Pioneer Award 2012, AIAA Intelligent Systems Award 2016, John Ragazzini Education Award 2018 from American Automatic Control Council. Received Fulbright Research Award 1988, American Society of Engineering Education F.E. Terman Award 1989, Int. Neural Network Soc. Gabor Award 2009, U.K. Inst Measurement & Control Honeywell Field Engineering Medal 2009, three Sigma Xi Research Awards, UTA Halliburton Engineering Research Award, UTA Distinguished Research Award, ARRI Patent Awards, various Best Paper Awards, IEEE Control Systems Society Best Chapter Award (as Founding Chairman of DFW Chapter), and National Sigma Xi Award for Outstanding Chapter (as President of UTA Chapter). Received Outstanding Service Award from the Dallas IEEE Section and selected as Engineer of the year by Ft. Worth IEEE Section. Listed in Ft. Worth Business Press Top 200 Leaders in Manufacturing. Appointed to NAE Committee on Space Station in 1995 and IEEE Control Systems Society Board of Governors in 1996. Received the 2010 IEEE Region 5 Outstanding Engineering Educator Award and the 2010 UTA Graduate Dean's Excellence in Doctoral Mentoring Award. Texas Regents Outstanding Teaching Award 2013.*

*Current interests include autonomous systems, unmanned aerial vehicles, distributed cooperative control on graphs, reinforcement learning, nonlinear systems, intelligent control, process control, and neurobiological systems. Author of 7 U.S. patents, 472 journal papers, 52 chapters and encyclopedia articles, 420 refereed conference papers, and 20 books including Optimal Control, Optimal Estimation, Applied Optimal Control and Estimation, Aircraft Control and Simulation, Control of Robot Manipulators, Neural Network Control, High-Level Feedback Control with Neural Networks and the IEEE reprint volume Robot Control. Editor of Taylor & Francis Book Series on Automation & Control Engineering. Served as Editor for the flagship journal Automatica. Served/serves on many Editorial Boards including International Journal of Control, Neural Computing and Applications, Optimal Control & Methods, and Int. J. Intelligent Control Systems. Recipient of NSF Research Initiation Grant and continuously funded by NSF since 1982. He has received \$12 million in funding from NSF, ARO, ONR, AFOSR and other government agencies, including significant DoD SBIR and industry funding. His SBIR program was instrumental in ARRI's receipt of the US SBA Tibbets Award in 1996.*

### **Data-driven Inverse Reinforcement Learning Control for Linear Multiplayer Games**

Bosen Lian, Wenqian Xue, Vrushabh S. Donge, Frank L. Lewis, Ali Davoudi

Automatica 8 (2021)

#### **Abstract**

This paper proposes a data-driven inverse reinforcement learning (RL) control algorithm for multiplayer games in linear continuous-time systems. The inverse RL problem in the games is solved by a learner reconstructing the unknown expert cost functions using demonstrated expert trajectories. Thus, the learner obtains the same control feedback gains and trajectories as the expert only using data along system trajectories without knowing system dynamics. We first propose a model-based inverse RL policy iteration (PI) scheme that consists of a first policy evaluation step for reconstructing cost functions, a second state-reward weight improvement step using inverse optimal control (IOC), and a third policy improvement step using optimal control. Given the model-based PI algorithm, we further develop an online data-driven off-policy inverse RL algorithm.

Both inverse RL PI and off-policy algorithms show that optimal control and IOC are solved as subproblems in inverse RL problems. Rigorous convergence and stability analysis of these algorithms are provided. Finally, simulation examples validate the effectiveness of the proposed algorithms.

### **New Solution for H1 Static OPFB Control Using Integral Reinforcement Learning**

Yusuf Kartal, Wenqian Xue, Atilla Dogan, Frank Lewis

Automatica (2021)

**Abstract**

This paper presents a new formulation for the  $H_\infty$  static output-feedback (OPFB) control problem that simultaneously guarantees stability,  $L_2$  gain boundedness, and Nash equilibrium of a Linear Time Invariant (LTI) system. The problem is treated as a zero-sum differential game by introducing a quadratic performance index. Then a novel augmented Hamiltonian functional is proposed to solve for the Nash equilibrium point consisting of minimizing extrema (input) & maximizing extrema (disturbance) for the game of this kind. Unfortunately, the standard approaches to the  $H_\infty$  control problem with static OPFB result in the sub-optimal non-Nash gain solutions for guaranteed stability. In this paper, we provide novel necessary and sufficient conditions of the optimal gain solutions that inherently stabilize the system dynamics while also guaranteeing optimal Nash equilibrium. To obtain the optimal gain solution, two off-line iterative solution algorithms are given. The first algorithm is based on Lyapunov iterations and requires an initial stabilizing gain. A second algorithm based on Riccati iterations obviates the initial stabilizing gain requirement. Then, based on the Lyapunov iterations, an off-policy Integral Reinforcement Learning (IRL) algorithm is developed to learn the optimal gain solution online without requiring any knowledge of system state, control, and disturbance matrices. Simulation results are provided to show the validity of the proposed methods.

# A Preliminary Electrochemical Study of Crosslinked Albumin and Collagen Membranes as Diffusion Barriers for Potentially Degradable Chronic Wound Biosensors

by Pankaj Vadgama, Member EUAS

## Short Biography

### **CURRENT APPOINTMENTS**

- 2000-                    *Director IRC in Biomedical Materials, Queen Mary University of London*  
 2000 -                    *Professor of Clinical Biochemistry, Queen Mary University of London*  
 2000 - 15                *Honorary consultant Chemical Pathologist Barts Health NHS Trust*  
 2003 - 15                *Head of NHS Clinical Service (Appointed NHS Consultant 1983)*  
 2015-                    *Visiting Professor Southern Medical University Guangzhou, China*  
 2017 -                    *Visiting Professor University of Grenoble Alps*

### **ACADEMIC QUALIFICATIONS**

- 1971                    *MB, BS Newcastle University*  
 1976                    *BSc Chemistry (1<sup>st</sup> Class Hon) Newcastle University*  
 1977                    *Member (later Fellow) Royal College of Pathologists*  
 1984                    *PhD Newcastle University*  
 1994                    *Fellow Royal Society of Chemistry*  
 2001                    *Fellow Institute of Materials Minerals and Mining*  
 2002                    *Fellow Institute of Physics*  
 2006                    *Fellow Royal Society of Medicine*  
 2008                    *Chartered Scientist (Institute of Materials, Minerals and Mining)*  
 2010                    *Fellow Royal Society of Biology*

### **ACADEMIC APPOINTMENTS**

- 1977-1980            *MRC Training Fellow Newcastle University*  
 1983-1988            *Director Biosensor Research Group Newcastle University*  
 1988-2000            *Professor of Clinical Biochemistry, Manchester University*  
 1998-2000            *Professor of Biomedical Materials, Manchester University*  
 1991-1997            *Head of Department of Medicine, Manchester University (Salford)*  
 1993-1996            *Postgraduate Dean, Faculty of Medicine, Manchester University*  
 1996-1998            *Research Dean, Faculty of Medicine, Manchester University*  
 1998-2000            *Head of Division of Biomedical Engineering, Manchester University*

### **Editorial Board Positions**

*Editorial Board: Physiological Measurement, Medical Engineering and Physics, Bioanalytical Reviews, Functional Biomaterials, Medical Devices and Sensors, 3D Printed Systems and Materials, Journal of Biochemistry and Molecular Biology Research, Chinese Chemical Letters. Guest Editor for Analytical and Bioanalytical Chemistry: (i) Thin film characterisation (ii) Membrane based sensors. Sub-Editor Biomaterials Series (RSC). Editor for (i) Bioelectrochemistry for the Encyclopedia of Interfacial Chemistry, Surface Science and Electrochemistry (ii) Bioinstrumentation and Bioinformatics for the Encyclopedia of Biomedical Engineering (Elsevier).*

### **National/International Committees**

*Member EPSRC (Engineering and Physical Science Research Council): Materials Strategic Advisory Team (SAT) (2004/5/7/8); Healthcare (2005). Member, Institute of Materials Minerals and Mining Smart Materials Committee, Nanotechnology Committee, Biomedical Applications Division*

and External Advisory Committee. National Measurement Systems (NMS) Grants Committees for Materials and Modelling (2002 – 15) and Innovation R&D (2012-15); NPL(National Physical Laboratory)/LGC (Laboratory of the Government Chemist) projects. Past EPSRC grants panel memberships (includes as chair of some panels) from 1986: Materials, Structural Materials, Chemistry, Multidisciplinary (Engineering), Health Care, Analytical Science, Mechanical and Medical Engineering, Follow-on Funding, DTCs (Doctoral Training Centres), Master's Training Packages, Sensors' Policy Group, SMART Technologies, Basic Sciences, Life Science Interface, Engineering Fellowships (Senior/Advanced). Nanotechnology Strategy Working Group (co-author, section on nanomedicine) (2005). ROPA (Realising our Potential) Panels EPSRC, MRC (Medical Research Council) (1995-96). MRC Joint Research Equipment Initiative Panel (JREI, 1996-7). Royal Society of Chemistry, Industrially-Sponsored Award in Electroanalytical Chemistry (1997, 2000). Member of Organisation and Delivery of Healthcare Task Force (Foresight Healthcare, 1999-2000). Member Academy of Medical Sciences/Foresight Working Group on the Detection and Identification of Infectious Disease (2004). Member Institution of Electrical Engineers Professional Group S9 (Biomedical Engineering, 1990-93). Chair (i) R&D (ii) Point of Care Testing committees, Division of Pathology Barts Health NHS Trust (2002-2011). Member BBSRC Strategic Research Studentships Panel 2004, LINK Program Medical Technologies and Molecular Sensors (1994-2001), Foresight LINK awards (2001). European Space Agency Advisory Panel on bioassay under microgravity (2000). Various EU FP IV & V Panels: Biotechnology, Biomedical and Health Research, Cell Factory, Growth, Standards, Measurements and Testing (1993-2000). Chair DTI Building up Biomaterials (BuB) Materials Healthcare Advisory Group (2001-2003). Member UK delegations (x3) to Japan (Biomaterials) and Singapore (x1) (Materials). Roadmap Champion for Diagnostics for human health, RSC (2010). Member Manchester Commonwealth Games 2002 Scientific Congress Committee.

RAE (Research Assessment Exercise, UK) Panel member Materials (2008). External Assessor Faculty of Engineering, University of Coimbra, Portugal (2013), Founder member biennial international conference series: Biomaterials Interfaces (2007-). Chair RSC Chemistry in Medicine Panel (2010). Chair, Steering Committee EPSRC IRColl Interdisciplinary Research Collaboration) in Bionanotechnology, University of Oxford (2003-5), Member 4th Generation Light Source (4GLS) Advisory Group, Daresbury. Member, international task force on environmental carcinogens (Halifax Project, 2014). Advisor, UK Biobank Project (2004). Member Special Inquiry into Regenerative Medicine Research at UCL.

RAE Advisor University of Manchester, REF Advisor University of Central Lancashire. Academic promotions advisor (Rutgers, Cranfield, Ulster, Manchester, Leeds, Flanders). Advisor, Engineering – Materials Faculty research quality, Limerick (2011). Cranfield University Senate committee panel member on Biomedicine MScs (2013). External advisor on the reorganization of the Chemistry Department, University of Surrey (2001). Scrutineer for Fellowship/Membership applications to the Institute of Materials Minerals and Mining. External assessor for staff appointments, PhD applications for Nazarbayev University (2014). Advisor to University of Ege (Turkey) on summer school biotechnology rolling Programme. International advisory member (vice-chair) of Uganda based research training foundation; advice on training needs and external funding, eg secured for geological sciences MScs. Co-Chair UK – China Biomaterials Partnership (2006-9). Global Initiative of Academic Networks (GIAN, India) lecture course at University of Tezpur (2016). Host to Commonwealth Fellows India (Tezpur, 2015; Aligarh Muslim University, 2003), PhD Fellow (Government of Pakistan, 2017). NMS research project advisor, LGC (2005-07).

Chair UK Foresight Panel on Biomaterials and member of Materials, Smart Materials panel (2004) (co-author, strategy documents). Member, DTI Innovation and Growth Team (2006), Member UK Standards Group on ISO TC 229; nanotechnology nomenclature (2006 -). Chair of ISO Working Group on Nanomedicine and member Working Group on Nanobiotechnology (2006 – 2010). Member BSI Committees on Nanotechnology, Botechnology and Cell Therapies.

Member DFG Review Panel for German Excellence Initiative: Materials 2005,2007). Member Finland Research Council panel on Bioscience and Engineering (2008). Grants reviewing national funding councils: Australia, Qatar, Hong Kong, Portugal, Austria, Netherlands, Italy, Ukraine,

*Kazakhstan, Netherlands, Romania.*

### **A preliminary Electrochemical Study of Crosslinked Albumin and Collagen Membranes as Diffusion Barriers for Potentially Degradable Chronic Wound Biosensors**

Mohammad Raja, Ilanna Campelo Lopes, Pankaj Vadgama

Electrochemical Science Advances 2021;e2100132

#### **Abstract**

The biochemical monitoring of chronic wounds may help to tailor therapy with better clinical outcomes. Wound surface sensors would be appropriate for this, but their adhesion to the wound is likely to lead to tissue damage on retrieval. Degradable sensors offer a practical solution to this, but this would necessitate external degradable diffusion control membranes. In this study, we evaluated glutaraldehyde crosslinked albumin and collagen as potentially biodegradable barrier membranes. The diffusional transport of H<sub>2</sub>O<sub>2</sub>, ascorbate, and glucose was studied electrochemically. Albumin proved more selective for H<sub>2</sub>O<sub>2</sub> against ascorbate, possibly due to its net negative charge. The thick (500–700 μm) membranes produced led to long response times (half-life [t<sub>0.5</sub>], 500–700 s) but had the advantage of stabilizing the response in unstirred solution. This was possibly because the thicker membrane on the electrode surface moved the developing diffusion layer in solution further away from the electrode surface. A dense albumin layer was produced using sebacoyl chloride as a crosslinker which was impermeable to solute and could be used in future as a degradable sensor base. Also, non-toxic poly(2,3-dihydrothieno-1,4-dioxin)-poly(styrenesulfonate) dispersed in crosslinked albumin furnished a conducting membrane able to function as a working electrode. Thus, crosslinked proteins offer scope for diverse membrane properties that might be useful for future, degradable wound monitoring sensors.

### **Monitoring of Lactate in Interstitial Fluid, Saliva and Sweat by Electrochemical Biosensor: The Uncertainties of Biological Interpretation**

Anna-Maria Spehar-Délèze, Salzitsa Anastasova, Pankaj Vadgama

Chemosensors 2021, 9, 195.

#### **Abstract**

Lactate electrochemical biosensors were fabricated using *Pediococcus* sp lactate oxidase (E.C. 1.1.3.2), an external polyurethane membrane laminate diffusion barrier and an internal ionomeric polymer barrier (sulphonated polyether ether sulphone polyether sulphone, SPEES PES). In a needle embodiment, a Pt wire working electrode was retained within stainless steel tubing serving as pseudoreference. The construct gave linearity to at least 25 mM lactate with 0.17 nA/mM lactate sensitivity. A low permeability inner membrane was also unexpectedly able to increase linearity. Responses were oxygen

dependent at  $pO_2 < 70$  mmHg, irrespective of the inclusion of an external diffusion barrier membrane. Subcutaneous tissue was monitored in Sprague Dawley rats, and saliva and sweat during exercise in human subjects. The tissue sensors registered no response to intravenous Na lactate, indicating a blood-tissue lactate barrier. Salivary lactate allowed tracking of blood lactate during exercise, but lactate levels were substantially lower than those in blood (0–3.5 mM vs. 1.6–12.1 mM), with variable degrees of lactate partitioning from blood, evident both between subjects and at different exercise time points. Sweat lactate during exercise measured up to 23 mM but showed highly inconsistent change as exercise progressed. We conclude that neither tissue interstitial fluid nor sweat are usable as surrogates for blood lactate, and that major reappraisal of lactate sensor use is indicated for any extravascular monitoring strategy for lactate.

### **Comparison of Dual Beam Dispersive and FTNIR Spectroscopy for Lactate Detection**

Nystha Baishya, Mohammad Mamouei, Karthik Budidha, Meha Qassem, Pankaj Vadgama, Panayiotis A. Kyriacou

Sensors 2021, 21, 1891.

#### **Abstract**

Near Infrared (800–2500 nm) spectroscopy has been extensively used in biomedical applications, as it offers rapid, in vivo, bed-side monitoring of important haemodynamic parameters, which is especially important in critical care settings. However, the choice of NIR spectrometer needs to be investigated for biomedical applications, as both the dual beam dispersive spectrophotometer and the FTNIR spectrometer have their own advantages and disadvantages. In this study, predictive analysis of lactate concentrations in whole blood were undertaken using multivariate techniques on spectra obtained from the two spectrometer types simultaneously and results were compared. Results showed significant improvement in predicting analyte concentration when analysis was performed on full range spectral data. This is in comparison to analysis of limited spectral regions or lactate signature peaks, which yielded poorer prediction models. Furthermore, for the same region, FTNIR showed 10% better predictive capability than the dual beam dispersive NIR spectrometer.

### **Oxidative Free Radicals and Other Species: Selective Messengers with a Reactive Capacity for Unselective Tissue Damage**

Pankaj Vadgama

Chemosensors 2021, 9, 89

#### **Abstract**

Oxygen and nitrogen free radicals (RONS) form an exceptionally reactive molecular assembly within eukaryote cells. This perspective article gives a combined overview of

different facets of research covering molecular reactivity, resultant tissue damage and final tissue outcomes as they relate to major disease. There is an emphasis on cardiovascular disease, as the damage processes are best linked to the pathology. The overriding importance of inflammation in driving damage across all tissues is highlighted. Brief coverage is also provided of measurement approaches, respectively for antioxidant status, using potentiometry, and voltammetry for selected target species. Whilst damage due to RONS is a common focus, the fundamental importance of RONS to biological signalling is also covered here as an indispensable basis for life. The article thus provides a global overview of this topic for anyone wishing to understand the current status across multiple fronts

## Recent Developments in Ion-Solid Interactions

by William J. Weber, Member EUAS



### Short Biography

**Professor, Department of Materials Science and Engineering, The University of Tennessee - Knoxville**

*Prof. William J. Weber received his PhD in Nuclear Engineering from the University of Wisconsin - Madison, USA. He joined Pacific Northwest National Laboratory (PNNL) in 1977 as a research scientist and was appointed Laboratory Fellow in 1997. During 1983, he was a visiting scientist at the Institute for Transuranium Elements in Karlsruhe, Germany. He is currently a professor in the Department of Materials Science and Engineering at the University of Tennessee and Director of the Ion Beam Materials Laboratory. From 2010 through 2020, he was the Governor's Chair Professor for Radiation Effects in Materials at the University of Tennessee, with a joint appointment at Oak Ridge National Laboratory. His research has encompassed the fundamental aspects of radiation-solid interactions, radiation effects in materials, ion beam modification and analysis of materials, and defects and defect processes in materials. Much of his current research emphasizes the coupling of electronic and atomic energy dissipation processes and their role on radiation effects, defect evolution, formation of novel nanostructures, creation of new functionalities, and the response of materials to extreme environments. He is a member of the EU Academy of Sciences (2016), Fellow of the American Ceramic Society (2000), Fellow of the American Association for the Advancement of Science (2006), Fellow of the Materials Research Society (2008), Fellow of the American Physical Society (2010) and Fellow of the Ion Beam Society of India (2016). He is the recipient of the James I. Mueller Award from the American Ceramic Society (2020); Lee Hsun Lecture Award (2015); the Outstanding Young Alumni Award (1983) and the Distinguished Alumni Award (2009) from the University of Wisconsin - Oshkosh; the PNNL Laboratory Director's Award for Individual Lifetime Achievement in Science & Technology (2009); the PNNL Laboratory Director's Award for Scientific and Engineering Excellence (1995); the PNNL Chester L. Cooper Mentor of the Year Award (2005); and the U.S. Department of Energy's Materials Science Award for Research with Significant Implication for DOE Related Technologies (1995). He has published more than 580 journal articles, 118 peer-reviewed conference papers, and 14 book chapters. Based on the Web of Science, his publications have over 23,500 citations, with an h-index of 76; based on Scopus, his publications have over 24,700 citations, with an h-index of 76; based on Google Scholar, his publications have over 31,625 citations, with an h-index of 87.*

The interaction of energetic ions with a solid is well known to result in inelastic energy loss to electrons and elastic energy loss to atomic nuclei in the solid. However, the coupled effects of these energy loss pathways and the critical role of energy dissipation processes on defect production and the evolution of defects, nanostructures and phase

transformations under far from equilibrium conditions in materials are complex and not well understood. Particularly challenging are the dynamics of energy transfer processes to electrons and the exchange of energy between electrons and the atomic nuclei via electron-phonon coupling. In general, the electrons along the ion path undergo a high degree of excitation and electron–electron scattering, and they subsequently transfer much of their energy, via electron–phonon coupling, to atoms in the same region, causing a highly-localized thermal spike. Following thermalization of the electrons and recombination of electrons and holes, a high density of localized electronic defects (trapped electrons, holes and excitons) may remain. This partitioning of energy deposition and energy dissipation on the electronic and atomic structures are important to the control of ion beam modification methods to create defects and nanoscale structures that tailor materials properties or create new functionalities, as well as the development of radiation-tolerant materials and devices. Predicting and modeling such complex processes, which are temporally and spatially coupled, are grand challenges that demand fundamental understanding of materials processes at the level of electrons and atoms over several orders of magnitude in time scale, from femtoseconds to nanoseconds.

Silicon carbide (SiC) is an important wide-band gap semiconductor for high-temperature, high-power, and high-frequency applications. Moreover, its high corrosion, oxidation and radiation resistance make it a critical material with great potential for extremely harsh radiation environments, including nuclear power, space exploration, national security and ion-beam processing of nanostructures and opto-electronic devices. The coincidence of electronic and damage energy dissipation from energetic ions to the atomic lattice can significantly affect damage production along the ion trajectory due to spatial and temporal overlap of inelastic and elastic processes. We have investigated the spatial coupling between inelastic electronic and elastic nuclear energy dissipation in single crystal 3C-SiC irradiated at 300 K with 5 MeV Si and 10 MeV Au ions, with the accumulation or irradiation damage characterized using Rutherford backscattering spectroscopy in channeling geometry. At these energies, the Si and Au ions have similar electronic energy losses and similar ion trajectories, but the elastic damage energy dissipation is a factor of 50 lower for the Si ions. While defects are created by damage energy dissipation via elastic scattering, electronic energy dissipation via electron-phonon coupling significantly decreases defect survival along the ion trajectory for Si ions. The more energetic recoil spectrum for 10 MeV Au ions leads to weaker spatial coupling of inelastic electronic and elastic damage energy dissipation processes, and damage production is only weakly affected. Consequently, resulting radiation damage at similar doses is greater for Au ions compared to the Si ions, and Au ions have a harder recoil spectrum, more comparable to neutrons.

Ion-beam-induced luminescence (i.e., ionoluminescence) experiments using high electronic excitation densities under high-energy heavy-ion beam irradiation of single crystal SrTiO<sub>3</sub> have been performed at 100 K, 170 K and 300 K. In this study, the initial ionoluminescence stage for the self-trapped exciton (STE) emission at 2.5 eV under heavy-ion irradiation is analyzed, along with its dependence on irradiation temperature and electronic excitation rate. This initial stage quickly achieves a quasi-steady state, and it then decreases as irradiated damage to the atomic structure increases. The quasi-steady luminescence exhibits a linear dependence on the excitation rate, suggesting a constant efficiency for STEs formation. An activation energy of 55 meV, essentially independent of the incident ion mass and energy of projectile-ion, is derived from the Arrhenius

dependence on irradiation temperature. This energy is in good agreement with experimental values, measured for non-radiative STE decay under pulsed laser excitation, and is consistent with density functional theory calculations for migration of self-trapped holes (STHs) described by a small-polaron adiabatic hopping model. Based on this work, an original mechanistic model is proposed that describes the non-radiative decay of STEs based on the thermally-activated migration of STHs, via a hopping mechanism, and their recombination with the STEs. Luminescence kinetics from the chromium intrinsic impurity strongly supports this model, being consistent with the annihilation of  $\text{Cr}^{3+}$  centers through recombination with migrating STHs. This work illustrates the relevance of ionoluminescence as an *in-situ*, *real-time* and highly-sensitive tool to investigate electronic and defect processes under high electronic excitation densities.

The energy dissipation and track formation in  $\text{KTaO}_3$  has been investigated using low-energy ion-induced disordering in conjunction with highly ionizing ion irradiation. Experimental characterization and molecular dynamics simulations reveal that the size of latent ion tracks increases with increasing electronic energy loss,  $S_e$ , and the level of pre-existing damage. These results further reveal that the threshold  $S_e$  value,  $S_e^{\text{th}}$ , for track formation increases with decreasing pre-damage level. The values of  $S_e^{\text{th}}$  increase from 5.02 keV/nm for a pre-existing fractional disorder of 0.53 to 10.81 keV/nm for pristine  $\text{KTaO}_3$ . Above these thresholds, amorphous latent tracks are produced due to local melting and rapid quenching. Below a disorder fraction of 0.08 and  $S_e \leq 6.68$  keV/nm, the track formation does not occur and damage accumulation is suppressed due to a competing ionization-induced damage annealing process, similar to that observed in  $\text{SrTiO}_3$ . The results indicate that, depending on  $S_e$  and the amount of pre-existing damage, highly ionizing ions can either enhance or suppress damage accumulation in  $\text{KTaO}_3$ , thus providing a pathway to tailoring defects states. Comprehending the conflicting roles of highly ionizing ions in defective  $\text{ABO}_3$  oxides is vital for understanding and predictive modeling of ion-solid interactions in complex oxides, as well as for achieving control over ion track size in the near-surface of defective  $\text{KTaO}_3$ .

The response of  $\text{LiTaO}_3$  crystals to irradiation with 3 MeV and 1.16 GeV Au ions has been investigated using single crystal X-ray diffraction and Raman scattering measurements. Symmetric X-ray diffraction measurements identified an anisotropic strain in different oriented  $\text{LiTaO}_3$  single crystals after irradiation with 3 MeV Au ions. Strain relaxation was observed in the pre-damaged  $\langle 0001 \rangle$  oriented crystal after subsequent irradiation with 1.16 GeV Au ions. In addition, the unit cell parameters decrease by 0.2% and 0.7%, respectively along the a/b and c-axis, when the crystal was irradiated with 1.16 GeV Au ions. The shrinkage of the unit cell after the irradiation with 1.16 GeV Au ions is associated with the partial loss of Li in the lattice, which was confirmed by Raman scattering measurements. This work supports the complexity of structural response of material to ionization process.

### Select Publications Related to This Research

1. W. J. Weber, H. Xue, E. Zarkadoula, and Y. Zhang, Two regimes of ionization-induced recovery in  $\text{SrTiO}_3$  under irradiation, *Scripta Materialia* **173**: 154-157 (2019).

2. W. J. Weber and Y. Zhang, Predicting Damage Production in Monoatomic and Multi-elemental Targets using Stopping and Range of Ions in Matter Code: Challenges and Recommendations, *Current Opinion in Solid State & Materials Science* **23** [4]: 100757 (2019).
3. E. Zarkadoula, Y. Zhang, and W. J. Weber, Molecular dynamics simulations of the response of pre-damaged SrTiO<sub>3</sub> and KTaO<sub>3</sub> to fast heavy ions, *AIP Advances* **10**: 015019 (2020).
4. L. Nuckols, M. L. Crespillo, C. Xu, E. Zarkadoula, Y. Zhang, and W. J. Weber, Coupled effects of electronic and nuclear energy deposition on damage accumulation in ion-irradiated SiC, *Acta Materialia* **199**: 96-106 (2020).
5. Y. Zhang and W. J. Weber, Ion irradiation and modification: The role of coupled electronic and nuclear energy dissipation and subsequent nonequilibrium processes in materials, *Applied Physics Reviews* **7**: 041307 (2020).
6. L. Nuckols, M. L. Crespillo, Y. Yang, J. Li, E. Zarkadoula, Y. Zhang, and W. J. Weber, Effects of recoil spectra and electronic energy dissipation on defect survival in 3C-SiC, *Materialia* **15**: 101023 (2021).
7. M. L. Crespillo, J. T. Graham, F. Agulló-López, Y. Zhang, and W. J. Weber, Real-Time Identification of Oxygen Vacancy Centers in LiNbO<sub>3</sub> and SrTiO<sub>3</sub> during Irradiation with High Energy Particles, *Crystals* **11**: 315 (2021).
8. M. L. Crespillo, J. T. Graham, F. Agulló-López, Y. Zhang, and W. J. Weber, Non-radiative luminescence decay with self-trapped hole migration in strontium titanate: Interplay between optical and transport properties, *Applied Materials Today* **24**: 101041 (2021).
9. F. X. Zhang, G. Velisa, H. Xue, N. Sellami, C. Trautmann, Y. Zhang, and W. J. Weber, Ion irradiation induced strain and structural changes in LiTaO<sub>3</sub> perovskite, *J. Physics: Condensed Matter* **33**: 185402 (2021).
10. G. Velisa, E. Zarkadoula, D. Iancu, M. D. Mihai, C. Grygiel, I. Monnet, B. Kombaiyah, Y. Zhang and W. J. Weber, Near-surface modification of defective KTaO<sub>3</sub> by ionizing ion irradiation, *J. Physics D: Applied Physics* **54**: 375302 (2021).

# Ball-Cactus-Like Bi Embedded in N-Riched Carbon Nanonetworks Enables the Best Potassium Storage Performance

by Qing Jiang, Member EUAS



## Short Biography

*Qing Jiang is a Professor of the School of Materials Science and Engineering, Jilin University since 1992, and the Director of the Key Laboratory of Automobile Materials, Ministry of Education, China since 2003. He received his BSc and MSc in Materials Science from Jilin University of Technology (combined into Jilin University in 2000) in 1982 and 1984, respectively, and PhD in Chemistry from University of Stuttgart, Germany in 1990.*

*Dr. Jiang was elected as a Member of the EU Academy of Sciences in 2018, and an Academician of the Asia Pacific Academy of Materials in 2015. He is a Fellow of The Institute of Physics (U.K.), and several editor board members of academic journals.*

*Dr. Jiang current research interests include synthesis of nanomaterials as well as their applications in catalysis, energy storage and conversion (fuel cell, batteries, supercapacitors and electrocatalysis), emphasizing kinetics aspects of mass transfer and chemical reaction. He has published more than 700 papers in peer-reviewed journals, including Nat. Nanotechnol., Nat. Chem., Nat. Commun., Sci. Adv., Joule, Chem, Matter, et al. His publications have been cited more than 25,000 times with H-index = 83 (Web of Science).*

In 2021, he authored and coauthored 46 papers and several with abstracts among them are listed below:

- 1. R. C. Cui, H. Y. Zhou, J. C. Li, C. C. Yang\*, Q. Jiang\*, Ball-Cactus-Like Bi Embedded in N-Riched Carbon Nanonetworks Enables the Best Potassium Storage Performance, Adv. Funct. Mater. 2021, 31, 2103067.**

## **Abstract**

The potassium-ion battery (PIB) has emerged as a promising alternative to lithium-ion battery. The major challenges confronted by PIB anodes lie in sluggish kinetics and poor cycling stability owing to the inherent large  $K^+$  size. Here, a hybrid of ball-cactus-like Bi

nanospheres embedded in 3D N-riched carbon nanonetworks (Bi NSs/NCNs) is designed and synthesized by electrospinning. As an anode, Bi NSs/NCNs exhibits an unprecedented rate ( $489.3 \text{ mAh g}^{-1}$  at  $50 \text{ A g}^{-1}$ ) and long-cycling performance ( $457.8 \text{ mAh g}^{-1}$  at  $10 \text{ A g}^{-1}$  after 2000 cycles), outperforming all reported PIB anode materials. Such outstanding performance mainly originates from the stable solid-electrolyte interface formed in the glyme-based electrolyte and the unique interconnected porous nanostructure, both of which contribute to fast kinetics and high pseudocapacitive contributions upon cycling.

**2. B. Li, X. Liu, W. Gao\*, Q. Jiang\*, An effective scheme to determine surface energy and its relation with adsorption energy, *Acta Mater.* 2021, 212, 116895.**

#### **Abstract**

Surface energy is fundamental in controlling surface properties and surface-driven processes like heterogeneous catalysis, as adsorption energy is. It is thus essential to establish an effective scheme to determine surface energy and its relation with adsorption energy. Herein, we propose a model to quantify the effects of materials' intrinsic characteristics on the material-dependent property and anisotropy of surface energy, based on the period number and group number of bulk atoms, and the valence-electron number, electronegativity and coordination of surface atoms. Our scheme holds for elemental crystals in both solid and liquid phases, body-centered-tetragonal intermetallics, fluorite-structure intermetallics, face-centered-cubic intermetallics, Mg-based single-atom alloys, III-V semiconductors, transition metal carbides, and transition metal nitrides, which further identifies a quantitative relation between surface energy and adsorption energy and rationalizes the material-dependent error of first-principle methods in calculating the two quantities. This model is predictive with easily accessible parameters and thus allows the rapid screening of materials for targeted properties.

**3. S. F. Zai, X. Y. Gao, C. C. Yang\*, Q. Jiang\*, Ce-Modified Ni(OH)<sub>2</sub> Nanoflowers Supported on NiSe<sub>2</sub> Octahedra Nanoparticles as High-Efficient Oxygen Evolution Electrocatalyst, *Adv. Energy Mater.* 2021, 11, 2101266.**

**Abstract**

Exploring and developing high-efficiency electrocatalysts towards oxygen evolution reaction (OER) is desirable yet challenging for cost-effective transformation of renewable electricity into fuels and chemicals. Herein, a self-supported electrode of nanoflower-like Ce-modified Ni(OH)<sub>2</sub> grown on high-conductivity NiSe<sub>2</sub> octahedra nanoparticles is designed and fabricated for the first time. By virtue of i) the high conductivity of the NiSe<sub>2</sub> support for favorable electron transfer; ii) the open porous structure from the nanoflower-like Ce-modified Ni(OH)<sub>2</sub> for beneficial mass transport; iii) Ce doping for efficiently optimizing the energetics for OER intermediates based on density functional theory simulations; and iv) Ce(OH)<sub>3</sub> embedding for efficacious oxygen ion exchange and electronic transmission, the electrode exhibits remarkable OER activities with a very low overpotential of 158 mV at 10 mA cm<sup>-2</sup> and Tafel slope of 27 mV dec<sup>-1</sup>, which outperform almost all OER electrocatalysts.

**4. H. Shi, T. Y. Dai, W. B. Wan, Z. Wen, X. Y. Lang\*, Q. Jiang\*, Mo-/Co-N-C Hybrid Nanosheets Oriented on Hierarchical Nanoporous Cu as Versatile Electrocatalysts for Efficient Water Splitting, Adv. Funct. Mater. 2021, 31, 2102285.**

**Abstract**

Designing robust and cost-effective electrocatalysts based on Earth-abundant elements is crucial for large-scale hydrogen production through electrochemical water splitting. Here, nitrogen-doped carbon engrafted Mo<sub>2</sub>N/CoN hybrid nanosheets that are seamlessly oriented on hierarchical nanoporous Cu scaffold (Mo-/Co-N-C/Cu), as highly efficient electrocatalysts for alkaline hydrogen evolution reaction are reported. The constituent heterostructured Mo<sub>2</sub>N/CoN nanosheets work as bifunctional electroactive sites for both water dissociation and adsorption/desorption of hydrogen intermediates while the nitrogen-doped carbon bridges electron transfers between electroactive sites and interconnective Cu current collectors by making use of Mo-/Co-N-C bonds and intimate C/Cu contacts at interfaces. As a consequence of unique architecture having electroactive sites to be sufficiently accessible, self-supported nanoporous Mo-/Co-N-C/Cu hybrid electrodes exhibit outstanding electrocatalysis in 1 M KOH, with a negligible onset overpotential and a low Tafel slope of 47 mV dec<sup>-1</sup>. They only take overpotential of as low as 230 mV to

reach current density of  $1000 \text{ mA cm}^{-2}$ . When coupled with their electro-oxidized derivatives that mediate efficiently the oxygen evolution reaction, the alkaline water electrolyzer can achieve  $\approx 100 \text{ mA cm}^{-2}$  at 1.622 V in 1 M KOH electrolyte,  $\approx 0.343 \text{ V}$  lower than the device constructed with commercially available Pt/C and Ir/C nanocatalysts immobilized on nanoporous Cu electrodes.

**5. Y. X. Duan, Y. T. Zhou, D. X. Liu, Z. Wen, J. M. Yan\*, Q. Jiang, Boosting Production of HCOOH from CO<sub>2</sub> Electroreduction via Bi/CeO<sub>x</sub>, Angew. Chem. Int. Ed. 2021, 60, 8798-8802**

#### **Abstract**

Formic acid (HCOOH) is one of the most promising chemical fuels that can be produced through CO<sub>2</sub> electroreduction. However, most of the catalysts for CO<sub>2</sub> electroreduction to HCOOH in aqueous solution often suffer from low current density and limited production rate. Herein, we provide a bismuth/cerium oxide (Bi/CeO<sub>x</sub>) catalyst, which exhibits not only high current density ( $149 \text{ mA cm}^{-2}$ ), but also unprecedented production rate ( $2600 \mu\text{mol h}^{-1} \text{ cm}^{-2}$ ) with high Faradaic efficiency (FE, 92 %) for HCOOH generation in aqueous media. Furthermore, Bi/CeO<sub>x</sub> also shows favorable stability over 34h. We hope this work could offer an attractive and promising strategy to develop efficient catalysts for CO<sub>2</sub> electroreduction with superior activity and desirable stability.

# Hydrogen Embrittlement as a Threat to Safety of High-Pressure Hydrogen Gas Pipelines – A Thermodynamic Insight

by Y. Frank Cheng, Member of EUAS



## Short Biography

*Professor and Canada Research Chair in Pipeline Engineering, University of Calgary  
An internationally recognized researcher in Oil/Gas Pipeline Corrosion and Integrity  
Ph.D. in Materials Engineering at the University of Alberta in Canada*

### **I. Education**

*1996-2000, Ph.D. in Materials Engineering, University of Alberta, Canada  
1990-1993, M.Sc. in Corrosion, Institute of Metal Research, Chinese Academy of Sciences, China  
1986-1990, B.Sc. in Corrosion, Hunan University, China*

### **II. Professional experiences**

*2012-present, Professor, Canada Research Chair, University of Calgary, Canada  
2009-2012, Associate Professor, Canada Research Chair, University of Calgary, Canada  
2005-2009, Assistant Professor, Canada Research Chair, University of Calgary, Canada  
2002-2005, Research Scientist, Centre for Nuclear Energy Research, University of New Brunswick, Fredericton, Canada  
2000-2002, Industrial Research Fellow, NOVA Research and Technology Center, Calgary, Canada*

### **III. Awards**

*2021 Fellow, Institute of Materials, Minerals and Mining (IOM3), U.K.  
2021 Fellow, Institute of Corrosion (ICorr), U.K.  
2021 Medal, International Association of Advanced Materials (IAAM)  
2021 Fellow, Chinese Society for Corrosion Protection (CSCP)  
2021 Technical Achievement Award, NACE International, U.S.  
2020 Engineering Research Achievement Award (Individual), University of Calgary  
2020 Best Research Award, International Research Awards on New Science Inventions  
2019 Distinguished Materials Scientist Award, Canadian Metallurgy and Materials Society  
2019 Engineering Research Achievement Award (Team), University of Calgary  
2018 Elected Member, European Union Academy of Sciences (EUAS)  
2018 Engineering Research Achievement Award (Team), University of Calgary  
2018 Engineering Teaching Achievement Award, University of Calgary  
2017 Metal Chemistry Award, Canadian Metallurgy and Materials Society  
2017 Engineering Teaching Achievement Award, University of Calgary  
2016 Fellow, NACE International, U.S.  
2015 Shi Chang-Xu Award, Chinese Society for Corrosion Protection  
2015 Engineering Research Achievement Award (Individual), University of Calgary  
2014 H.H. Uhlig Award, NACE International, U.S.*

2010 Engineering Students' Society Teaching Excellence Award, University of Calgary

2010 Canada Research Chair in Pipeline Engineering (renewal)

2009 Engineering Research Excellence Award, University of Calgary

2005 Canada Research Chair in Pipeline Engineering

**IV. Publications** (By Dec. 2021, the total citations of the publications have exceeded 12,200, with a H-index of 69)

**Books:**

1. Y. Frank Cheng, Luyao Xu, *Defect Assessment for Integrity Management of Pipelines*, Wiley, Hoboken, NJ, U.S., 2022 (to be published).
2. Y. Frank Cheng, *AC Corrosion of Pipelines*, AMPP, Houston, TX, U.S., 2021.
3. Y. Frank Cheng, Richard Norsworthy, *Pipeline Coatings*, NACE, Houston, TX, U.S., 2017.
4. Y. Frank Cheng, *Stress Corrosion Cracking of Pipelines*, Wiley, Hoboken, NJ, U.S., 2013.

**Book chapters:**

1. Frank Cheng, *Pipelines for hydrogen transmission: An outlook of technology innovation for improved integrity and safety*, in: *Oil and Gas Pipelines: Integrity and Safety Handbook*, Winston Revie, Editor, Wiley, Hoboken, NJ, 2022 (ongoing).
2. Frank Cheng, *Application of micro-electrochemical techniques in corrosion research*, in: *Green Corrosion Chemistry and Engineering*, S.K. Sharma, Editor, Wiley-VCH Publisher, Germany, 2011, p. 71-96.
3. Frank Cheng, *Erosion accelerated corrosion in flow system – Behavior of aluminum alloys in the automotive cooling system*, in: *Tribocorrosion of Passive Metals and Alloys*, D. Landolt and S. Mischler, Editors, Woodhead Publishing Ltd., Cambridge, 2011, p. 475-497.
4. Frank Cheng, *Internal corrosion of pipelines in oil/gas production*, in: *Advances in Chemistry Research, Volume 6*, J.C. Taylor, Editor, ISBN 978-1-61728-982-8, Nova Science Publishers, Inc., New York, 2010.
5. Frank Cheng, *Pipeline engineering*, in: *Pipeline Engineering*, Frank Cheng, Editor, in: *Encyclopedia of Life Support System (EOLSS)*, Developed under the Auspices of the UNESCO, EOLSS Publishers, Oxford, UK, 2010.

**Journal papers:**

There are 255 papers published in peer-reviewed journals. They are not listed due to page limit.

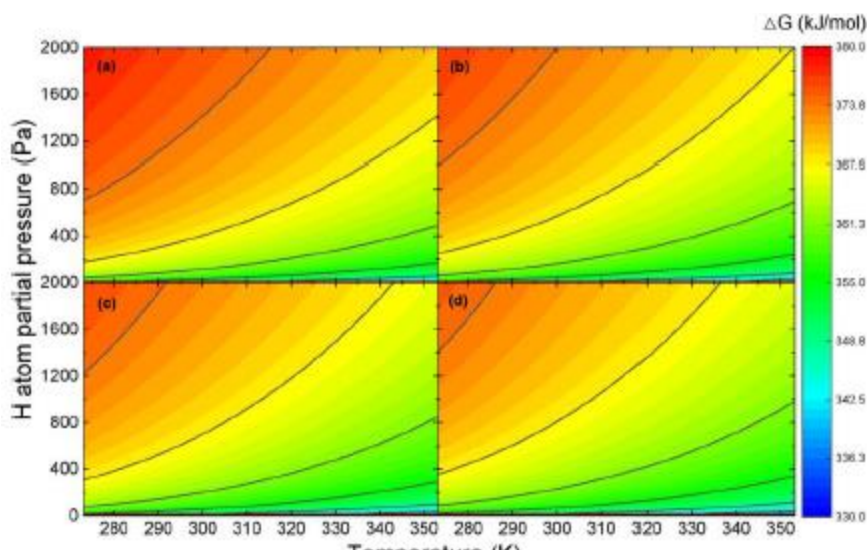
The impact of global warming and climate change is becoming alarmingly apparent. Development of new energy technology at full scale is critical to achieving the 2050 net-zero target. A recent survey shows that, with the lack of a wide range of infrastructure to keep the new energy economy on a rapid-development trajectory, existing pipeline networks provide a promising alternative for effective and economic transmission of new energies (fuels) such as hydrogen [1]. It is thus accepted that re-purposing existing natural gas pipelines will be key to developing a large-scale hydrogen economy [2,3].

Safety is paramount for hydrogen transmission by pipelines. Particularly, hydrogen embrittlement (HE) occurring on pipelines has been a major concern. Different from research work extensively conducted in aqueous environments where the so-called "cathodic" hydrogen was the investigation target, the environment potentially causing HE of hydrogen pipelines is high-pressure hydrogen gas. The hydrogen atom generation occurs at a mechanism different from the "cathodic" hydrogen.

For hydrogen pipelines, the environment where pipe steels are exposed is high-pressure hydrogen gas. The critical conditions that the HE can occur include that the gaseous hydrogen (H<sub>2</sub>) must dissociate into atomic hydrogen (H), and the atomic hydrogen then potentially enters the steels. There are two mechanisms for generation of H atoms on steel surface in hydrogen pipelines. The first is the so-called dissociative adsorption, which occurs when H<sub>2</sub> molecules approach the steel surface and dissociate into two H atoms, which become adsorbed. Another potential source for H generation and adsorption on pipe steels is spontaneous dissociation of H<sub>2</sub> molecules in the gas fluid in hydrogen pipelines. A

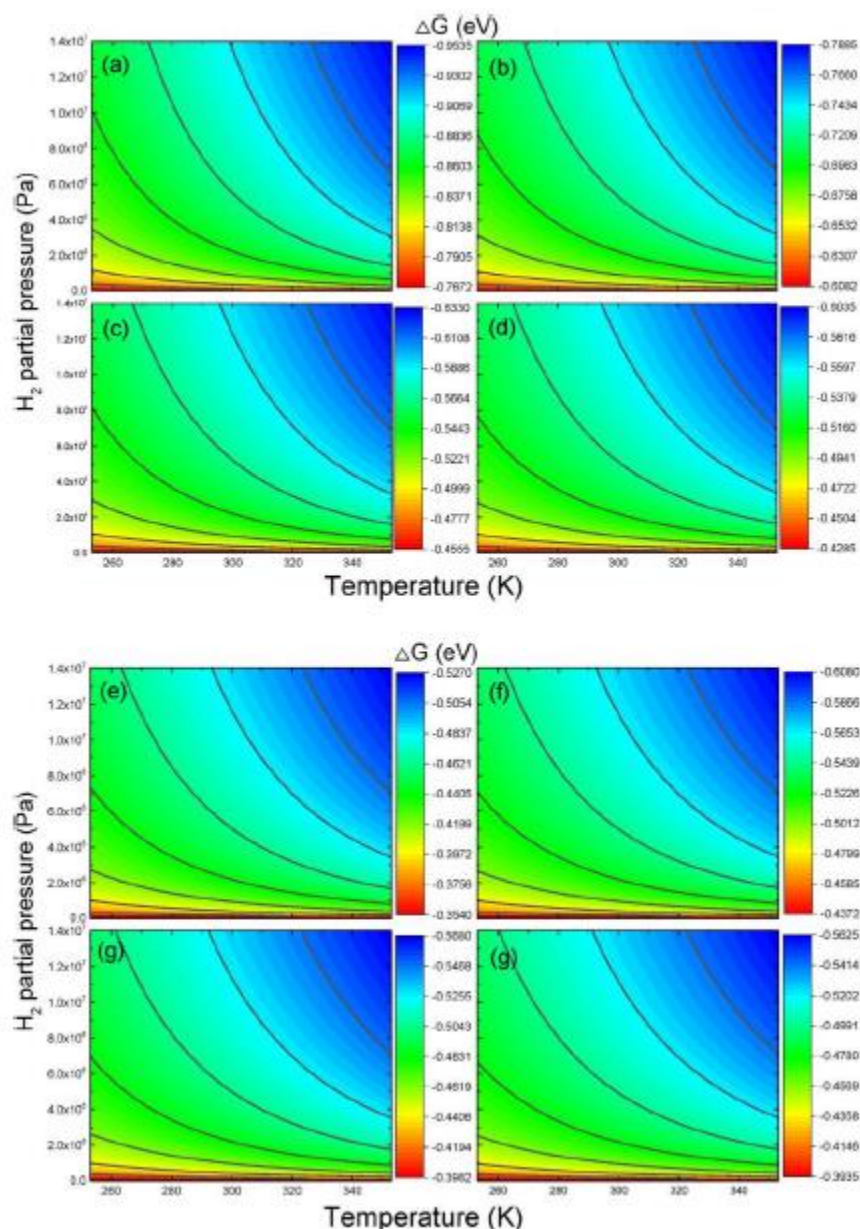
theoretical analysis is required to examine the thermodynamic possibility of the H atom generation under pipelining conditions [4].

Theoretical calculations based on Gibbs free energy changes of the H generation reactions were conducted under various conditions that are relevant to hydrogen pipeline operating conditions. **Figure 1** shows the changes of Gibbs free energy of spontaneous dissociation of hydrogen gas with various partial pressures as a function of temperature, where the y-axis is partial pressure of products, i.e., H atoms in gas phase, corresponding to the amount of generated H. It is seen that the Gibbs free energy for H atom generation by spontaneous dissociation decreases with elevated temperature and increased hydrogen gas partial pressure. It is expected that the spontaneous dissociation of hydrogen gas to generate H atoms tends to occur under high hydrogen partial pressures and temperatures. However, at all hydrogen gas partial pressures and temperatures under investigation, which are typically of pipeline operation conditions, the changes of Gibbs free energy are positive, indicating that spontaneous dissociation of hydrogen gas molecules to generate H atoms is thermodynamically impossible under the pipelining conditions.



**Figure 1.** Changes of Gibbs free energy of spontaneous dissociation of hydrogen gas with various partial pressures as a function of temperature (a) 3 MPa, (b) 6 MPa, (c) 9 MPa, (d) 12 MPa.

The change of Gibbs free energy of dissociative adsorption at 2-fold (2F) site on Fe (100) crystalline plane under various H atom coverages with motional corrections is shown in **Figure 2**. It is seen that the Gibbs free energy changes at all H coverages are negative, indicating that the dissociative adsorption is thermodynamically feasible. The change of Gibbs free energy become more negative with increased hydrogen gas partial pressure and temperature, showing the favorable conditions for dissociative adsorption. When the H coverage is below 1.00 ML, the change in Gibbs free energy is more negative as the coverage increases. However, when the coverage exceeds 1.00 ML, the free energy would not be affected significantly. Thus, the influence of H atom coverage on dissociative adsorption occurs at low coverages only, i.e., 0.25 - 1.00 ML.



**Figure 2.** Change of Gibbs free energy of dissociative adsorption at 2F site on Fe (100) under varied H atom coverages (ML) (a) 0.25, (b) 0.50, (c) 0.75, (d) 1.00, (e) 1.25, (f) 1.50, (g) 1.75, (h) 2.00.

### References

1. DNV, *Rising to the Challenge of a Hydrogen Economy* - The outlook for emerging hydrogen value chains, from production to consumption, Report, Norway, 2021.
2. Alberta Ministry of Energy, *Alberta Hydrogen Roadmap*, Edmonton, Canada, 2021.
3. M.W. Melaina, O. Antonia, M. Penev, *Blending Hydrogen into Natural Gas Pipeline Networks: A Review of Key Issues*, National Renewable Energy Laboratory (NREL), Golden, CO, US, 2013.
4. Yinghao Sun, Y. Frank Cheng, Thermodynamics of spontaneous dissociation and dissociative adsorption of hydrogen molecules and hydrogen atom adsorption and absorption on steel under pipelining conditions, *International Journal of Hydrogen Energy*, 46 (2021) 34469-34486.

# Recent Aspects of Energy Storage through Innovative Synthesis and Processing of Nanomaterials

by Leon L. Shaw, Member EUAS

## Short Biography

### Current Positions

- *Rowe Family Endowed Chair Professor in Sustainable Energy, Department of Mechanical, Materials & Aerospace Engineering, Illinois Institute of Technology (IIT), Chicago, Illinois, USA*
- *Professor of Materials Science and Engineering, Department of Mechanical, Materials & Aerospace Engineering, Illinois Institute of Technology (IIT), Chicago, Illinois, USA*
- *Director of the Thermal Processing Technology Center, Illinois Institute of Technology (IIT), Chicago, Illinois, USA*

### Education

- Ph. D. Materials Science and Engineering, University of Florida, Gainesville, Florida, USA, 1992*  
*Minor Mechanics and Engineering Science, Univers. of Florida, Gainesville, Florida, USA, 1992*  
*M. S. Materials Science and Engineering, University of Florida, USA, 1992*  
*M. Eng. Mechanical Engineering, Fuzhou University, Fuzhou, Fujian, China, 1987*  
*B. S. Materials Engineering, Fuzhou University, Fuzhou, Fujian, China, 1980*

### Professional Activities

*Member Editorial Board for "Scientific Reports"*

*Member Editorial Board for "Batteries"*

*Member Editorial Board for "Journal of Sol-Gel Science and Technology"*

*Member International Advisory Committee of THERMEC' 2011, 2013, 2016, and 2018*

*Member ASM International*

*Member TMS*

*Member American Ceramic Society*

*Member Electrochemical Society*

*Guest Editor Metallurgical and Materials Transactions (1998), Materials Science and Engineering (1998,2001, 2007), Journal of Materials Engineering and Performance (2005), Journal of Materials Science (2011)*

### Awards and Honors

- 2021 *Keynote Presentation on "Improving Battery Performance via Mechanical Activation Enhanced Synthesis" at the 7<sup>th</sup> World Congress on New Technologies (NewTech'21)*
- 2020 *Fellow, International Association of Advanced Materials (IAAM)*
- 2020 *"Illinois Researchers to Know in 2020", Illinois Science & Technology Coalition (ISTC)*
- 2020 *"Excellence in Research Award for 2020", Department of Mechanical, Materials and Aerospace Engineering, Illinois Institute of Technology, Chicago, Illinois*
- 2019 *Member, EU Academy of Sciences (EUAS)*
- 2019 *Keynote Presentation on "Coating as a Potent Method to Enhance the Specific Capacity, Charge Rate and Cycle Life of Cathodes for Next-Generation Li-ion Batteries" at the 2<sup>nd</sup> International Conference on Materials Science and Materials Chemistry, London, United Kingdom*
- 2018 *Energy Award, International Association of Advanced Materials (IAAM)*
- 2018 *Energy Award Lecture on "Hierarchical Design and Synthesis of Si Anodes for Next-Generation Li-ion Batteries" in Plenary Session at European Advanced Materials Congress (EAMC 2018), Stockholm, Sweden*
- 2018 *Rave Award, Illinois Institute of Technology for outstanding student employment service*
- 2018 *First Place in the poster competition at the 2018 Joint Advanced Photon Source/Center for Nanoscale Materials (APS/CNM) Users Meeting, Argonne National Laboratory, USA*
- 2016 *Keynote Presentation on "Hierarchical Design and Synthesis of Nanomaterials to Enable High Capacity Rechargeable Battery Electrodes," at THERMEC'2016, Graz, Austria*
- 2015 *Key Scientific Article contributing to the Excellence in Energy Research, Renewable Energy Global Innovations*

- 2014 Keynote Presentation on “High Voltage, High Capacity, Ambient Temperature Sodium-Based Flow Batteries” at Cleantech 2014, Washington DC, USA
- 2013 Keynote Presentation on “Energy Storage Enabled by Nanomaterials and Advanced Processing” at ISPlasma 2013, Nagoya, Japan
- 2011 NSF Highlights: “Next Generation Bone Implants: More Like the Real Thing”
- 2011 Outstanding Poster Award, MS&T’ 2011, Columbus, OH, USA
- 2010 The John & Virginia Towers Distinguished Lecture, Michigan Technological University
- 2006 Member, Connecticut Academy of Science and Engineering (CASE), Connecticut, USA
- 2006 “Highly Commended Paper for Excellence 2006”, Emerald Group Publishing Limited
- 2006 Outstanding Faculty Member Award, the Materials Science and Engineering Program, University of Connecticut, Connecticut
- 2005 Fellow, World Academy of Materials and Manufacturing Engineering (AMME), Poland
- 2004 Fellow, ASM International
- 2003 Best Poster Award, the Solid Freeform Fabrication Annual Meeting, Austin, TX
- 2001 Outstanding Department Member Award, Department of Metallurgy and Materials Engineering, University of Connecticut, Connecticut
- 2000 Outstanding Junior Faculty Award, School of Engineering, University of Connecticut, Connecticut
- 1999 Outstanding Department Member Award, Department of Metallurgy and Materials Engineering, University of Connecticut, Connecticut
- 1999 Honorary Advisory Professorship, Harbin Institute of Technology, Harbin, China
- 1999 Honorary Guest Professorship, Fuzhou University, Fuzhou, China
- 1995 Olin Junior Faculty Development Award, Olin Corporation, Connecticut
- 1992 First Place of the ASM International Graduate Student Paper Contest, ASM International
- 1990 Lifetime Member of Alpha Sigma Mu (International Metallurgical Honorary Society)

#### **Publications, Patents and Presentations**

- Over 300 publications (including 3 edited books, 12 book chapters, 210+ archival refereed journal articles, 4 editorial materials, and 77 conference proceedings)
- > 11,700 non-self citations with a h-index of 56 and an i10-index of 189 (Google Scholar)
- 3 US patents granted and 4 US patents pending
- 290+ presentations including more than 100 invited talks, keynote presentations and plenary lectures at various national and international conferences as well as a wide range of universities in and outside the United States.

In the last 10 years, Leon Shaw’s research fields and scientific interests were in the areas of nanomaterials synthesis, processing and microstructure control for energy storage, particularly in hydrogen storage materials, Li-ion batteries, Na-ion batteries, and redox flow batteries. Below are the abstracts of several selected journal articles published in 2021 and 2020.

**1. “Silicon Micro-Reactor as a Fast Charge, Long Cycle Life Anode with High Initial Coulombic Efficiency Synthesized via a Scalable Method” by Q. He, M. Ashuri, Y. Liu, B. Liu, and L. Shaw, ACS Appl. Energy Mater., 4 [5] 4744 – 4757 (2021).**

#### **Abstract**

Applications of silicon as a high-performance anode material has been impeded by its low intrinsic conductivity and huge volume expansion (> 300%) during lithiation. To address these problems, nano-Si particles along with conductive coatings and engineered voids are often employed, but this results in high cost anodes. Here, we report a scalable synthesis method that can realize high specific capacity (~800 mAh g<sup>-1</sup>), ultrafast charge/discharge (at 8 A g<sup>-1</sup> Si) and high initial Coulombic efficiency (~90%) with long cycle life (1000 cycles) at the same time. To achieve 1000 cycle stability, micron-sized Si particles are

subjected to high-energy ball milling to create nanostructured Si building blocks with nano-channel shaped voids encapsulated inside a nitrogen (N)-doped carbon shell (termed as Si micro-reactor). The nano-channel voids inside a Si micro-reactor not only offer the space to accommodate the volume expansion of Si, but also provide fast pathways for Li ion diffusion into the center of the nanostructured Si core and thus ultrafast charge/discharge capability. The porous N-doped carbon shell helps to improve the conductivity while allowing fast Li ion transport and confining the volume expansion within the Si micro-reactor. Submicron-sized Si micro-reactors with limited specific surface area ( $35 \text{ m}^2 \text{ g}^{-1}$ ) afford sufficient electrode/electrolyte interfacial area for fast lithiation/delithiation, leading to the specific capacity ranging from  $\sim 800$  to  $420 \text{ mAh g}^{-1}$  under ultrafast charging conditions ( $8 \text{ A g}^{-1}$ ), but not too much interfacial area for surface side reactions and thus high initial coulombic efficiency ( $\sim 90\%$ ). Since Si micro-reactors with superior electrochemical properties are synthesized via an industrially scalable and eco-friendly method, they have the potential for practical applications in the future.

2. “Thermodynamics and Kinetics Tuning of  $\text{LiBH}_4$  for Hydrogen Storage” by Z. Ding, W. Yang, K. Huo, and L. Shaw, *Progress in Chemistry*, 33 [9] 1586 – 1597 (2021).

#### **Abstract**

To meet the challenge of energy shortage and climate change, it is required to build the new renewable energy based structure and gradually abandon the conventional fossil fuel based energy structure. Hydrogen energy has attracted more and more attention, due to its high energy density, large calorific value, abundant resource and zero pollution.  $\text{LiBH}_4$ , which has been acknowledged as one of the most promising hydrogen storage alternatives for onboard energy carrier applications, is still not qualified for the industrialization, though it has been studied for years. Herein, a state-of-the-art review on the modification of stable thermodynamics and sluggish kinetics of hydrogen storage in  $\text{LiBH}_4$ , aiming to providing reference and solutions for its promotion and application. Multiple main-stream techniques along with their latest efforts have been discussed, including mechanical milling activation, nanoscaffold confinement, catalyst modification, ions substitution, reactant destabilization, and a novel process termed as high-energy ball milling with in-situ aerosol spraying (BMAS). Remarkable, BMAS is the technology of proven ability to overcome the kinetic barriers for thermodynamically favorable systems like  $\text{LiBH}_4 + \text{MgH}_2$  mixture and provide thermodynamic driving force to enhance hydrogen release at a lower temperature.

3. “Enhancing the Electrochemical Performance of  $\text{NaCrO}_2$  through Structural Defect Control” by M. Luo, A. L. Ortiz, and L. Shaw, *ACS Appl. Energy Mater.*, 3 [7] 7216-7227 (2020).

#### **Abstract**

This study clarifies, for the first time, that misplacement of  $\text{Cr}^{3+}$  ions at the  $\text{Na}^+$  site plays a more important role in dictating the specific capacity and capacity retention over cycles of  $\text{O3-NaCrO}_2$  cathodes than the  $\text{Na-O}$  bond length and the  $\text{NaO}_2$  interlayer spacing do. It is shown that  $\text{O3-NaCrO}_2$  crystals with lower degree of misplacement of  $\text{Cr}^{3+}$  ions at Na sites

and longer Na-O bond length have higher specific capacity, better capacity retention, and smaller cell impedance. Furthermore, O3-NaCrO<sub>2</sub> crystals with high degree of cation mixing at the Na plane exhibit the formation of some monoclinic O'3-NaCrO<sub>2</sub> crystals over 300 charge/discharge cycles between NaCrO<sub>2</sub> and Na<sub>0.5</sub>CrO<sub>2</sub> formulas, whereas the rhombohedral structure of O3-NaCrO<sub>2</sub> crystals with low degree of cation mixing at the Na plane is fully reversible. The effects of structural defects discovered in this study are interpreted based on the interference of Cr ions in Na transport on the Na plane and gradual migration of Cr ions to the Na plane during cycles. The insights established in this study will provide guidance in rational design and synthesis of NaCrO<sub>2</sub> cathode materials with high specific capacity and long-term cycle stability in the future.

4. “Improving Cycle Stability of Si Anode through Partially Carbonized Polydopamine Coating” by M. Ashuri, Q. He, and L. Shaw, *Journal of Electroanalytical Chemistry*, 876, 114738 (2020).

#### **Abstract**

In this study, we report the first investigation of the effectiveness of the partially converted carbon coating from polydopamine (PODA) to improve the cycle stability of Si anode for Li-ion batteries. It is hypothesized that by converting PODA to a partial carbonization condition, the resulting coating could have a higher electrical conductivity than PODA without carbonization, and at the same time may still contain some organic bonds and thus mechanical flexibility to accommodate the volume expansion of Si during lithiation. The results show that such a partial carbonization state can be obtained by carbonization of PODA at 400 °C. Furthermore, the partially converted carbon coating can offer sufficient electrical conductivity for lithiation and delithiation of Si anode while drastically reducing the charge transfer resistance for the redox reactions. In addition, the partially-converted-carbon coated hollow Si nanospheres exhibit excellent cycle stability when the volume expansion of Si anode is not very large (~88%) even though this volume expansion is significantly larger than the engineered void space (47% of the Si volume) available inside the partially-converted-carbon coated hollow Si nanospheres, unambiguously confirming the good tolerance of the partially converted carbon coating in withstanding some tensile strain without fracture. This study offers a new direction for systematic studies in the future as a means to provide a coating on Si material with sufficient electrical conductivity along with capability to withstand some tensile strain during the volume expansion of Si, thereby improving the cycle stability of Si anodes.

# Nanocellulose: A Novel Rheology Modifier for Emerging Applications

by Qinglin Wu, Member EUAS



## Short Biography

### A. EDUCATION

- 1993 *Ph.D. in Wood Science & Engineering, Oregon State Univ, Corvallis, Oregon.*  
 1989 *Master Eng. Sci. in Mechanical Engineering, University of Tasmania, Australia.*  
 1983 *BS in Agricultural Engineering, Henan Agricultural University, PR China*

### B. HONORS

- 2019 *Endowed Gordon D Cain Chair Professor, LSU College of Agriculture*  
 2009 *LSU AgCenter Rogers Research Excellence Award*  
 2008 *LSU Chapter Sigma Delta Gamma Honor Society Research Award*  
 2008 *Elected to be an International Academy of Wood Science (IAWS) Fellow*  
 2007 *Awarded JSPS Fellow, Shizuoka University, Shizuoka, Japan*  
 2005 *Forest Products Society Markwardt Wood Engineering Award, Madison, WI*  
 2004 *Endowed Professorship - Roy O Martin Sr. Professor, LSU AgCenter*  
 1993 *Wood Award, Forest Products Society Madison, WI*

### C. POSITIONS HELD

- 7/2009-present *Adjunct Professor, LSU Chemistry*  
 7/2004-present *Professor, Renewable Natural Resources, LSU AgCenter*  
 7/2000-6/2004 *Associate Professor, Renewable Natural Resources, LSU AgCenter*  
 1/1996-6/2000 *Assistant Professor, Renewable Natural Resources, LSU AgCenter*  
 7/1994-12/1995 *Research Associate, Forestry, Michigan State Univ, East Lansing, MI*  
 7/1993-6/1994 *Research Associate, Forest Products, Oregon State Univ, Corvallis, OR*  
 8/1989-6/1993 *Research Assistant, Forest Products, Oregon State Univ, Corvallis, OR*  
 1987-7/1989 *Research Assistant, Mechanical Engineering, Univ of Tasmania, Australia*

### D. SYNERGISTIC ACTIVITIES

- Fellow, EU Academy of Science, International Academy of Wood Science (IAWS)*
- Served as Panel Member for NSF SBIR, NSF SIM, USDA 1890 teaching/extension/capacity building; USDA HSI; Chinese NSF, USDA SBIR, and CSREES NRI; and as proposal reviewer for USDA NRI/SBIR/NIFA, Canadian NSRP, Swiss NSF, Chinese NSF*
- Served as proposal reviewer for NSF, USDA NRI/SBIR/NIFA, Canadian NSRP, Swiss NSF, Chinese NSF, Israel NSF, Czech NSF*
- Member of ISO, FPS, SWST, ACS, AWPA, and IRG;*
- Editorial Boards: Cellulose and Wood/Fiber Science; Editor for International Journal of Polymer Science, and reviewer for 20 journals including Science, Advanced Material, Biomacromolecules, Macromolecules, NanoScale, ACS AMI, Cellulose, ACS SCE*

Nanotechnology as the next industrial revolution is changing the world in fundamental ways every day. It not only has a far-reaching influence on almost every industry, e.g., chemistry, construction, electronics, military, aerospace and automobile; but also greatly impacts all aspects of our daily lives, e.g., food safety, health care, and environment. Nanotechnology deals with manufacturing and application of matters that are in at least one dimension size ranging from approximately 1 to 100 nm. When the matter is sized at nanoscale, it often exhibits unexpected thermal, optical, barrier, electronic, and mechanical performance due to the extremely high surface area to volume ratio. Therefore, there is an explosion of interest in the discovery and synthesis of novel nanomaterials for widespread applications from both academic researchers and industrial engineers. During the past several decades, hundreds of novel nanomaterials with zero-dimension (e.g., fullerenes, quantum dots), one-dimension (e.g., metal nanowires, carbon/halloysite nanotubes), two-dimension (e.g., graphene/montmorillonite nanosheets), and three-dimension (e.g., diamond, graphite, carbon black and silica nanoparticles) have been incidentally discovered and deliberately manufactured. More recent efforts have been devoted to synthesis of nanomaterials with precisely controlled compositions, surface chemistry, dimensions and architectures through etching, self-assembling and templating approaches. Despite the significant merits of nanotechnology, their hazard potentials and risks are still uncertain. Therefore, to minimize environmental health and safety concerns, the development of nanotechnology in a sustainable, environmentally-friendly manner is highly desired.

One of the most promising strategies for the sustainable nanotechnology development is the extraction and utilization of nanomaterials from green, cheap, abundant, renewable and biodegradable natural resources. One such attractive natural resource is cellulose, the most abundant biopolymer on earth, which is widely present in various forms of renewable biomass, such as trees, plants, tunicates and bacteria. Cellulose is being produced day-by-day from macroscopic trees to microscopic bacteria with a global annual production rate of approximately  $1.5 \times 10^{12}$  tons. Since ancient times, cellulose has been used for making paper, cloth, ropes and thread. However, the high crystalline structure of cellulose strongly limits its wide application, and therefore numerous cellulose derivatives (e.g., methyl cellulose, ethyl cellulose, carboxymethyl cellulose, and hydroxyethyl cellulose) have been synthesized through different chemical modification approaches. Those cellulose derivatives find major use in cosmetics, personal cares, pharmaceuticals, foods, packaging, and oil & gas industries.

Structurally, cellulose is a linear, high molecular weight polysaccharide containing thousands of glucose units linked by 1-4 glycosidic bonds. Owing to the presence of a large number of hydroxyl groups on the surface, those linear chains of glucose units link together through van der Waals forces and intermolecular hydrogen bonding to form elementary fibrils, which are further packed into larger aggregates known as microfibrils. Cellulose fibrils consist of disordered (amorphous) regions and highly ordered (crystalline) regions. In the crystalline regions, cellulose chains are closely packed together by a strong and highly intricate intra- and intermolecular hydrogen bonding, whereas the amorphous domains are randomly distributed along the microfibrils. Therefore, the amorphous regions are more vulnerable to both physical disintegration and chemical attack in comparison with crystalline regions, producing nanofibrillar domains broadly referred to as nanocellulose.

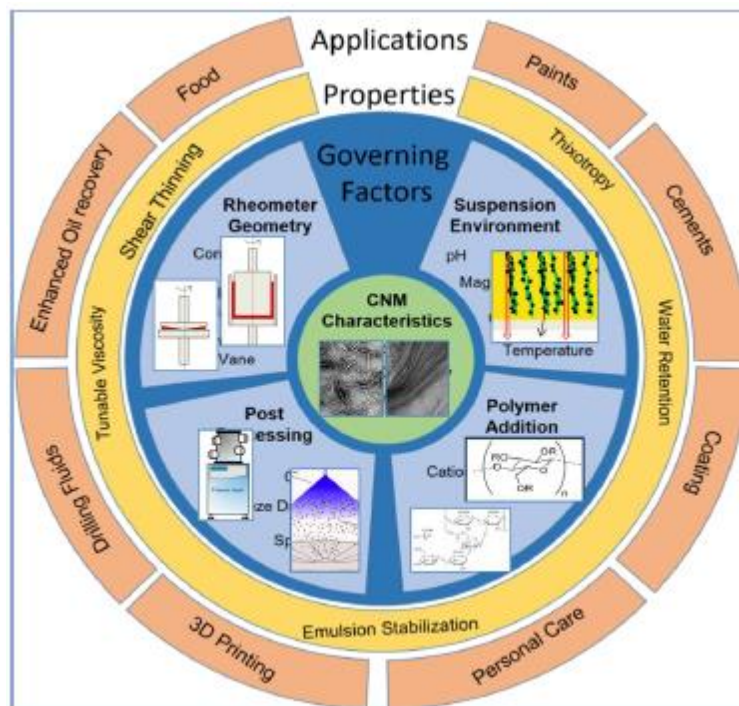
The history of nanocellulose can date back to 1920, when Staudinger determined the crystalline structure of cellulose. However, it took over twenty years to isolate those crystalline domains since their discovery. In 1947, Nickerson and Habrle firstly extracted crystallites from cellulosic fiber with a mixture of hydrochloric and sulfuric acids at

boiling temperature. The length of crystallites depends on the origin of cellulosic fiber, e.g., 280 glucose units for cotton and 110 glucose units for rayon. In 1949, Ranby reported the isolation of cellulose micelles from wood or cotton cellulose fibers using sulfuric acid. He further described the successful isolation of cellulose micelles from some other cellulosic sources, e.g., bacterial and animal (tunicin) latter in 1952. In contrast to chemical attack, the production of nanocellulose through mechanical disintegration was realized much later. In 1983, Turbak et al. and Herrick et al. reported the preparation of microfibrillated cellulose using high-pressure homogenization. The obtained microfibrillated cellulose exhibit a web of interconnected fibrils and microfibrils with diameters ranging from 10 to 100 nm, and form a stable gel above a concentration of 2%. The first report on the combined use of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO)-mediated oxidation and mechanical treatment to produce tiny cellulose nanofibers was published in 2007 by Isogai et al. The TEMPO-oxidized cellulose nanofibers are highly individualized with width of only 3-4 nm. In the past ten years, a variety of strategies have been reported to produce nanocellulose from different cellulosic sources. Depending on the strategies applied, the produced nanocellulose exhibiting distinctive dimensions and morphology are generally classified into three families: (1) short rod-shaped cellulose nanocrystals (CNCs), also associated with cellulose nanowhiskers (CNWs) or nanocrystalline cellulose (NCC); (2) long fiber-shaped cellulose nanofibers (CNFs), also known as cellulose nanofibrils (CNFs), nanofibrillated cellulose (NFC), or microfibrillated cellulose (MFC), and (3) bacterial cellulose (BC). Following the nanocellulose terminology defined in a proposed new standard by Technical Association of the Pulp and Paper Industry – TAPPI, in this review we terminated the short rod-shaped and long fiber-shaped nanocellulose only as CNCs and CNFs, respectively.

Nanocellulose researches, primarily including extraction, characterization, modification, and application, are currently receiving enormous attention from the research community, governmental agencies and industries due to their sustainability and some appealing features. Understanding the processing-structure-property relationships is critical for designing and production of nanocellulose for emerging applications. The methodologies and cellulosic sources used for nanocellulose production as well as properties of nanocellulose have been well documented in several review articles. The morphology and characteristics of nanocellulose, e.g., crystallinity, elastic modulus, thermal stability, colloidal behavior, liquid crystallinity, self-assembling, optical and barrier properties are greatly dependent on the origin of cellulose and production method. Nanocellulose possesses an abundance of hydroxyl groups, providing a facile platform for modification and functionalization through various chemical/physical strategies, which have been also reviewed in several articles. Those techniques not only offer solutions to many challenges of nanocellulose facing practical applications, but also enable fabrication of nanocellulose-based products with highly added value. During the past decade, owing to their appealing characteristics and facile modification/functionalization, nanocellulose have been explored for potential applications as functional fillers, templates or building blocks in a large variety of emerging areas, reflected in recently published review articles on polymer composites, hydrogels and aerogels, water treatment, food science, catalysis, liquid crystal template, biomedical engineering, electronics, and energy devices (Figure - Right).

In the past few years, the rheology aspect of nanocellulose has attracted significant interest. There have been several books and review articles depicting the rheological behaviors of nanocellulose suspension. A recent review [Li MC, Q Wu, R J Moon, MA. Hubbe, and MJ. Bortner. 2021. *Rheological Aspects of Cellulose Nanomaterials:*

**Governing Factors and Emerging Applications. Advanced Materials. DOI: 10.1002/adma.202006052.]** comprehensively discussed the rheological behaviors of nanocellulose suspension (including CNC, CNF and BC) in the absence/presence of different components, and further provide a critical overview of the recent progress on applications of nanocellulose as rheology modifier in a variety of emerging areas, including hydrogels, electrospinning fiber, 3D printing, food science, drilling and fracturing fluid, cementing, coatings, paints and adhesives, with particular emphasis on interfacial interaction between nanocellulose and other components.



Nanocellulose, primarily including CNFs and CNCs are emerging as versatile rheological modifiers in a wide range of industrial sectors. Their widely tailored rheological properties, high viscosity at rest, profound shear-thinning behavior, good thixotropic property, outstanding water retention capacity, and superior ability to stabilize emulsions are of critical importance for the rheological modification. The abundance, renewability, biocompatibility and biodegradability further promote their use as sustainable alternatives to replace the synthetic rheological modifiers, in order to respond to the UN's sustainable development goals. Although remarkable developments were achieved using nanocellulose as rheological modifiers, there are still several critical issues which limit their practical application and commercialization, as below:

1. The current methods used for the production of nanocellulose, including mechanical disintegration, enzymatic hydrolysis and chemical hydrolysis, are not cost-effective, energy-efficient, and entirely eco-friendly. The high cost of nanocellulose is becoming the major impediment to their commercialization. The long-term risk of nanocellulose to human and ecosystem still remains unknown.
2. Depending on the cellulosic origins and preparation methods, a wide range of nanocellulose with distinctive dimension and surface chemistry can be produced. This will yield different flow behaviors, leading to unpredictable rheological

modification capacity. Additionally, the diversity in size, shape, surface chemistry and other unknown ingredients can cause unknown influence on cells and other living organisms.

3. The rheological properties of nanocellulose, especially CNCs are highly dependent on exterior conditions, e.g., ionic strength, pH, and temperature. The strong temperature and salt sensitivity are the major bottlenecks for practical use of nanocellulose in oil well applications.
4. Nanocellulose self-assemble into film during drying and exhibit poor re-dispersibility. The rheological properties of nanocellulose were significantly impaired after drying and re-dispersion. Therefore, in order to obtain the superior rheological properties of nanocellulose, their gel state must be maintained. This will cause a surge in the cost of storage and transportation.

As a consequence, we strongly recommend the following:

1. A thorough characterization of nanocellulose should be performed prior to application. Very recent, a foundation in the chemical, morphological, and property characterization guidelines and protocols for nanocellulose was well outlined. Following those measurement protocols, it allows us to compare the dimension and characteristics of different types of nanocellulose more accurately as well as to select proper nanocellulose for targeted applications.
2. It is recommended to use the industrially-manufactured nanocellulose for laboratory research. Nowadays, as the rapid growth of nanocellulose commercialization, different industrially produced nanocellulose are available worldwide. Nanocellulose are manufactured on a large scale in pilot plant, ensuring the uniformity in the size and surface chemistry of nanocellulose. The pilot plant for nanocellulose production is energy-efficient and expecting to continuously reduce the cost of nanocellulose as technology advances.
3. The combined use of nanocellulose and other water-soluble polymers is suggested. On one hand, the coating a layer of water-soluble polymers on the surface of nanocellulose can prevent the self-assembly of nanocellulose to form compact films during drying, leading to good re-dispersability of nanocellulose. This enables them to be dried for storage and transportation. On the other hand, the presence of water-soluble polymers can impart additional functionalities to the system.
4. The long-term safety and regulatory issues should be paid more intension in the future. The *in vivo* biocompatibility and biodegradation should be tested appropriately for biomedical and food applications; and standard assessment protocols are needed. Their potential risk to oil wells and formation should be long-term monitored.

Overall, the potential of nanocellulose as rheological modifiers has not been completely explored yet, and there are still huge opportunities in this area. We anticipate future research on rheological modification using nanocellulose in a broader range of industrial sectors.

# New Improvements in Synthetic Organic and Medicinal Chemistry

by James Cook, Member EUAS

## Short Biography

*Dr. Cook graduated with a PHD in chemistry from the University of Michigan. He has been a leader in the search for safer drugs to treat patients afflicted with different CNS disorders for over thirty years, including anxiety disorders, neuropathic pain, resistant forms of epilepsy, schizophrenia, Tourette's syndrome, migraine headaches, depression as well as others. He has published 500 papers in synthetic organic chemistry and neuroscience. One of his compounds was licensed to Bristol Myers Squibb for anxiety disorders (in humans, Phase I) which led to the development of a back up, KRM-II-81, which is very active in models for treatment of pain, is anxiolytic and is a terrific anticonvulsant. He has patented and licensed this compound to RespireRx for epilepsy, as well as neuropathic pain. He has filed over 70 patents.*

*He cofounded with Marquette University, Promentis Pharmaceutical Company, which currently has a compound in Phase II for anxiety and obsessive compulsive disorders. He also developed a lead compound for asthma, which Dr. Arnold took, improved upon and formed the basis of the MIDD formed start up company, Pantherics. Very recently he cofounded a company with Dr. Soma Sengupta and Dr. Daniel Krummel from the University of Cincinnati, called Amlal Pharmaceuticals. His group's compounds are active against Group III cancers, including pediatric brain tumors and melanomas. He is currently working on a license with Alpha Cog with Dr. Etienne Sibilli at CAMH for a compound active against depression that is also precognitive. It is the precognitive and antianxiety effect that makes this compound so novel and we expect it will be active against the negative symptoms and cognitive deficits of schizophrenia. This antidepressant, procognitive agent, GL-II-73, is being targeted toward the treatment of depression, schizophrenia, and Alzheimer's Disease.*

*In our research group we have been interested in replacing Valium, Xanax, and other sedating, addictive benzodiazepine tranquilizers with ones with no side effects. We have developed potential drugs with an imidazodiazepine structure, which is called a "privileged structure". It is a hybrid of two compounds that have been in humans for over 45 years, with a minor structural change, that inhibits activity at alpha 1 receptors in the brain that cause sedation, ataxia, amnesia, addiction and dependence like Valium. Our lead compound KRM-II-81 has proven very effective in 5 animal models of resistance/refractory epilepsy, which should work in children and adults when other drugs do not, or other drugs do, but put you to sleep, or the patient develops tolerance. Secondly, the antinociceptive activity of this compound has been carried out in 7 different models and it was more active against pain than the known gabapentin or tramadol (Lilly). We believe the data indicates it should be active against diabetic neuropathy, back pain, fibromyalgia, complex regional pain syndrome, neuropathic pain and cancer pain. In a recent pain model it showed no signs of tolerance (like morphine does), nor dependence, nor was it sedating or ataxic in rhesus monkeys.*

## **Personal Statement**

I have directed a university research laboratory for >30 years focused on synthetic organic and medicinal chemistry with a particular interest in compounds that modulate CNS neurotransmission. Research under my direction has resulted in over 520 peer reviewed publications, many of which deal with fundamental and

applied studies on gamma amino butyric acid ion type A (GABA<sub>A</sub>) channels that comprise the major inhibitory neurotransmitter system in the central nervous system. Alterations of GABA<sub>A</sub> function are known to occur in many neurological and psychiatric disorders including neuropathic pain, anxiety, panic disorder, epilepsy, hypersensitive behavior, phobias, schizophrenia, alcoholism, Angleman's syndrome, and Rlett's syndrome, as well as effects that lead to or complicate drug abuse. A currently funded project is to uncover the neurochemical mechanisms underlying these disorders through the design, synthesis, and analysis of novel GABAergic ligands. An example of our progress is the discovery of a series of non-sedating  $\alpha 2/\alpha 3$  GABAA agonists that are active against neuropathic pain, as well as anxiety disorders and convulsions. These agents do not induce tolerance and are comprised of a non-toxic privileged scaffold (imidazodiazepine). Our patent, PCT published 9/29/2016 WO2016/ 154031A1 forms the backbone of the new startup (EndeavorRx Therapeutics) company targeting treatment of epilepsy and pain. Our alcoholism studies are directed at the ability of selected benzodiazepine receptor subtype selective agonists to blunt the discriminative stimulus effects of alcohol, reduce alcohol self-administration and attenuate priming-induced reinstatement of alcohol seeking at doses that do not produce a generalized disruption of behavior or debilitating side effects. For schizophrenia we are developing chiral  $\alpha 5$  and  $\alpha 2/\alpha 3/\alpha 5$  GABAergic ligands. Ligands related to our previously characterized compound SH-053-2'F-R-CH<sub>3</sub> have been shown to be active in the MAM model of schizophrenia. We currently have developed  $\alpha 3$  subtype selective Bz/GABA(A) receptor ligands and are synthesizing them on large scale for animal studies as well as developing more  $\alpha 3$  subtype selective ligands. (Namjoshi, et al. *BMC*, 2014). We have been investigating the synthesis of agents active against parasites and microbes for several years, including active against TB, MRSA infections and anthrax (Kabir, Cook et al, *BMC*,2010) as well as antimalarial, (alkaloids) and antischistosomal agents. Ongoing research in all of these areas includes the synthesis of hundreds of new compounds based on structure-activity-relationship analysis and functional evaluation. The strength of our research is the integration of synthetic organic chemistry with a network of leading experts in neuro-behavioral animal models for each of our disease areas of interest. This systems approach provides an unmatched team for the study of GABA<sub>A</sub> neurobiology and lead development for future therapeutics. I have considerable expertise designing drug functionality (blood brain barrier transport, bioconversion, metabolism, solubility, formulation) to avoid off-target effects. We have filed over 80 patents, many of which have been issued.

### Contributions to Science

1. My early publications outlined the development of rigid ligands that bound tightly (5nM) to the benzodiazepine allosteric site of the Bz/GABA(A) receptor. Because these were rigid ligands, this permitted the generation of the best pharmacophore model of the Bz /GABA(A)  $\alpha 1-6$ ,  $\beta 3\gamma 2$  receptor reported to date. It was used by Neurogen, Merck and J&J to develop pharmacophore models, the latter

of which were later published as their own models that were nearly identical to ours. This work led to an understanding of the difference in the 6 major subtypes, which resulted in the development of XHe-II-053, a nonsedating anxiolytic devoid of side effects. This was patented and licensed to BMS and made it through Phase I clinical trials. It was metabolized to rapidly to generate enough efficacy to go into Phase II trials, but it had no toxicity (BMS, unpublished results). This then led to an  $\alpha 2/\alpha 3$  subtype selective ligand (KRM-II-81), which is a nonsedating anticonvulsant and anxiolytic, which was licensed. Quite recently, this agent has been shown to be active against neuropathic and inflammatory pain. It acts via GABA  $\alpha 2/\alpha 3$ R in the spinal cord and does not develop tolerance. At present, bioisosteres, which have been shown to have a longer duration of action as anxiolytics, demonstrated great PK values and have no sedative activity, are being studied by big pharma under a CDA. Aim—clinical candidates for anxiety disorders, epilepsy and neuropathic pain (Cook et al. PCT WO2016/154031A1(9/29/16)). We have licensed KRM-II-81 and related patents to RespireRx who spun off EndeavorRx.

a. Clayton, T.; Poe, M.; Rallapalli, S.; Biawat, P.; Savic, M.; Rowlett, J. Gallows, G., Emala, C.; Kaczorowski, C.; Stafford, D.; Arnold, L.; Cook, J.M.; A Review of the Updated Pharmacophore for the Alpha 5 GABA(A) Benzodiazepine Receptor Model, *International Journal of Medicinal Chemistry*, vol. 2015, Article ID 430248, 54 pages, 2015. doi:10.1155/2015/430248). PMID: PMC4657098.

b. Lewter, L.; Fisher, J.; Siemian, J.; Methuku, K.; Poe, M.; Cook, J.M.; Li, Jun-Xu, Antinociceptive Effects of a Novel  $\alpha 2/\alpha 3$  Subtype Selective GABA(A) Receptor Positive Allosteric Modulator, *ACS Chem Neurosci*, DOI: 10.1021/acshchemneur.6b00447 (2017).

c. Witkin, J.M.; Golani, L.; Cerne, R.; Cook, J.; Jin, X.; et. al., The Positive Allosteric Modulator of  $\alpha 2/\alpha 3$  Containing GABA(A) Receptors, KRM-II-81 is Active in Pharmaco-Resistant Models of Epilepsy and Reduces hyperexcitability After Traumatic Brain Injury. *J. Pharm. Exp. Ther.* (2019), doi:10.1124/jpet.119.260968.

d. Biggerstaff, A.; Kivell, B.; Smith, J.; Mian, M.; Golani, L.; Rashid, F.; Sharmin, D.; Knutson, D. E.; Cerne, R.; Cook, J. M.; Witkin, J. M. The  $\alpha 2,3$ -Selective Potentiators of GABA(A) Receptors, KRM-II-81 and MP-III-80, Produce Anxiolytic Effects and Block Chemo Therapy – Induced Hyperalgesia in Mice without Tolerance Development. *Pharm.Biochem.Behav.* 196, 172996, 2020, doi:org/10.1016/j.pbb.2020.172996.

2. Based on our  $\alpha 5$  pharmacophore Bz/GABA(A) receptor model, we have designed  $\alpha 5\beta 3\gamma 2$  receptor agonists that are active in models of schizophrenia (SH-053-2'F-RCH<sub>3</sub>) and MDD (mood disorders). Moreover, we showed early in 2014 that if you treat rats with a known antipsychotic for 6 months and then with SH-053-2'F-RCH<sub>3</sub>, the ligand has no effect. This clearly shows that patients that have been treated for long periods of time with antipsychotics; their brains are rewired. This explains the failure in phase III of Lilly's drug for schizophrenia. This has also prompted a study into the cysteine/cystine antiporter in regard to glutamate. The studies of ligands in this project led us to cofound with Dr. David Baker, Promentus Pharmaceutical Co.,

a startup directed toward agents to treat schizophrenia and drug abuse, resulting in 12 patents that have been filed and many issued. Recently Promentus received 26 million in series C. financing to file an IND and go into Phase II.

a. Gill, K.; Lodge, D.; Cook, J.; Ava, S.; Grace, A., A novel  $\alpha 5$  GABA(A)R-positive allosteric modulator reverses hyperactivation of the dopamine system in the MAM model of schizophrenia, *Neuropsychopharmacology*, **36** 1903-1911 (2011). PMID: PMC3154109.

b. Gill, K.; Cook, J.; Poe, M.; Grace, A.; Prior antipsychotic drug treatment prevents response to novel antipsychotic agents in MAM model of schizophrenia, *Schizophrenia Bulletin* **40** 341-350 (2014). PMID: PMC3932102.

c. Cook, J.; Baker, D.; Johnson II, E.M.; Yin, W.; Verma, R., US Application No 14/148959, CIP Application Pub No. US01554410A1, June 5,2014. Notice of Allowance, 2014, 13/465383.

d. Botta, P.; Demmou, L.; Xu, C.; Lu, T.; Poe, M.M.; Xu, L.; Cook, J.M.; Rudolph, u.; Sah, P.; Luth, A.; Regulating anxiety with extra-synaptic inhibition, *Nature Neuroscience*, **18**, 1493-1499 (2015). PMID: PMC4607767.

**3.** Based on the pharmacophore models of the  $\alpha 4$  and  $\alpha 5$  subtypes, we developed  $\alpha 4$  subtype-selective ligands that are effective in relaxing bronchial smooth muscle and epithelial cells in the lung as a safer alternative to treat asthma. This is in collaboration with Charles Emala, George Gallos, and with colleagues at Columbia University, Stafford and Arnold at UWM. The  $\alpha 4$  ligands do not have activity at  $\alpha 1$ ,  $\alpha 2$   $\alpha 3$  and  $\alpha 5$  subtypes, consequently, there is no fear of CNS activity; these are benzodiazepine-insensitive (site) ligands. The  $\alpha 5$  ligands are also active against asthma models and will hydrolyze in the lung or blood (aerosol) after use and be excreted as the acid or glucuronide; will not go through the BBB.

a. Stafford, D., Cook, J., Emala, C., Gallos, G., Stephen, M., Arnold, A., Jahan,R., Novel GABA Agonists and Methods of Using to Control Airway Hyperresponsiveness and Inflammation in Asthma. Patent Pub. Nos. **US2013/060859**, **WO2014/047413**, published March 27, 2014.

b. Gallos, G; Yocum, G.; Siviski, M.; Yim, P.; Wen Fu, X.; Poe, M.; Cook, J.; Harrison, N; Perez-Zoghbi, J.; Emala, Sr., C., C., Selective targeting of the  $\alpha 5$  subunit of GABA(A) receptors relaxes airway smooth muscle and inhibits cellular calcium handling, *Am. J. Physiol. Lung. Cell Mol. Physiol.* Doi: 10.1152/ajplung.00107.2014 (2015). PMID: PMC4421780.

c. Yocum, G.; Li, G.; Rashid, R.; Stafford, D.; Arnold, A.; Cook, J.; Emala, C.W. et.al. A Novel GABA(A) Receptor Ligand MIDD0301 with Limited Blood-Brain Barrier Penetration Relaxes Airway Smooth Muscle *Ex Vivo* and *In Vivo*, *Am. J. Physiol Lung Cell Mol. Physiol.* doi.org/10/1152/ajplung.00356.2018, Nov.29, 2018.

d. Zahn, N.; Huber, A.; Mikulsky, B.; Stepanski, M.; Li, G.; Cook, J. M.; Stafford, D.; Steeber, D.; Arnold, A. MIDD0301- A First In-Class Anti-inflammatory Asthma Drug Targets GABA(A) Receptors Without Causing Systemic Immune Suppression. *Basic Clin. Pharmacol. Toxicology.* doi:10.1111/bcpt.13206, Jan, 2019.

4. We developed the first subtype selective ligand for  $\alpha 6\beta 3\gamma 2$  Bz/GABA(A) receptors reported to date. It has no efficacy at benzodiazepine-sensitive subtypes in rodents. Savic, Cook et al., showed it was devoid of sedation, ataxia and amnesia for it has zero affinity at the  $\alpha 1$  subtypes. Chou, Poe, Cook, et al., have shown it antagonized PCP induced effects on prepulse inhibition (unpublished). There are several  $\alpha 6$  subtype ligands that exert even better selectivity. These are being investigated (since  $\alpha 6$  subtypes are found exclusively in the cerebral granular layer and olfactory bulb) for treatment of migraine, Tourette syndrome, myofascial spasms, OCD and other tic related diseases.

a. Varagic, Z.; Ramerstorfer, J.; Huang, S.; Rallapilli, S.; Sarto-Jackson, I.; Cook, J.; Sicghert, W.; Ernst, M., Subtype selectivity of  $\alpha$  and  $\gamma$  site ligands of GABA(A) receptors: Identification of the first highly selective positive modulator at  $\alpha 6\beta 2/3\gamma 2$  receptors. *Br. J. Pharmacol.*, **169**,384-399 (2013); PCT Patent Pub No WO2016/19696/A1(12/8/16).

5. The clinical need for novel bronchodilators for the treatment of bronchoconstrictive diseases remains a major medical issue in asthma and COPD, as well as during some surgeries. Using our  $\alpha 5\beta 3\gamma 2$  Bz/GABA(A) subtype selective PAM (SH-053-2<sup>1</sup>F-RCH<sub>3</sub>), we showed that targeting of  $\alpha 5$  GABA(A) alpha subunits in airway smooth muscle was characteristic of electrophysiological changes indicative of GABA(A) receptor activation that can activate  $\beta$ -agonist mediated relaxation. 2) That GABA(A)  $\alpha 5$  receptor activation can directly and spontaneously relax precontracted airway smooth muscle, and that 3) a component of the mechanism involves an attenuation of  $Ca^{2+}$  handling as reductions in both  $Ca^{2+}$  entry (SOCE) in human airway smooth muscle cells, as well as calcium oscillations in ASM within peripheral lung slices. Selective targeting of the  $\alpha 5$  Bz/GABA(A) subunits in lung tissue on ASM represents a new method to treat asthma, etc.

Alleviation of Multiple Asthmatic Pathologic Features with Orally Available and Subtype Selective GABAA Receptor Modulators”, Forkuo, G.S.; Nieman, A.N.; Yuan, N.; Kodali, R.; Yu, O.B.; Zahn, N.M.; Jahan, R.; Li, G.; Stephen, M.R.; Guthrie, M.L.; Poe, M.M.; Hartzler, B.; Harris, T.W.; Yocum, G.T.; Emala, C.; Steeber, D.; Stafford, D.C.; Cook, J.M.; Arnold, L.A., *Molecular Pharmaceutics*, (2017), DOI: 10.1021/acs.molpharmaceut.7b00183. PMID: PMC5497587.

The development of MIDD0301 led to the startup company Pantherics.

## **A New Molecular Subset of Prostate Cancer 3-Fold More Common Among African- American (AA) Men than European-American Men**

**by William Nelson, Member EUAS**



### Short Biography

*Dr. Nelson is the Marion I. Knott Professor of Oncology and Director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. After completing undergraduate studies in Chemistry at Yale University, and earning doctoral degrees in Pharmacology and in Medicine at the Johns Hopkins University School of Medicine, he pursued Internship and Residency training in Internal Medicine and a Fellowship in Medical Oncology at the Johns Hopkins Hospital. Subsequently, he joined the Hopkins faculty and rose through the ranks to Professor of Oncology, Medicine, Pharmacology, Pathology, Radiation Oncology, Urology, and Environmental Health Sciences.*

*Dr. Nelson's research has focused on cancer epigenetics and on prostate cancer development. He has now authored some 320 articles and book chapters, attracting >38,000 citations with an h-index of 102. He also has secured 11 issued patents from the US Patent and Trade Office, and has conducted some 88 podcast interviews. He currently serves on the Board and as Scientific Director of the V Foundation, as a Scientific Co-Chair for Stand Up 2 Cancer, as Chair of the Board for Break Through Cancer, and on the Scientific Advisory Board for the Prostate Cancer Foundation. He is also the Executive Editor of Cancer Today, a Senior Editor of Cancer Research, and on the Editorial Board of the Journal of Clinical Investigation.*

### **A New Molecular Subset of Prostate Cancer 3-Fold More Common Among African-American (AA) Men than European-American Men**

African-American (AA) men are more likely to develop prostate cancer than European-American (EA) men, and more likely to suffer with poor outcomes if diagnosed with the disease<sup>1</sup>. The reasons for the disparity are multifaceted, including both inequities in access to high-quality prostate cancer screening,

detection, diagnosis, and treatment, and differences in disease pathogenesis and malignant progression. There are no consensus molecular mechanisms for the biological differences. For most men from all race/ethnic groups, the hallmark early molecular events in the pathogenesis of prostate cancer include relentless *MYC* activation, epigenetic silencing of *GSTP1* transcription accompanied by loss of  $\pi$ -class glutathione S-transferase (*GSTP1*) expression, and chromosomal translocations leading to fusions of androgen-regulated genes, like *TMPRSS2*, to ETS family transcription factor genes, like *ERG1*<sup>2</sup>. High-level *MYC* expression drives the metabolic activation of prostate carcinoma cells, stimulates ribosomal biogenesis and nucleolar enlargement, promotes mitochondrial biogenesis, and drives cell proliferation<sup>3</sup>. Loss of *GSTP1* expression by the cancer cells leads to enhanced tolerance of reactive oxygen species and increased vulnerability to electrophilic carcinogens<sup>4,5</sup>. *TMPRSS2-ERG1* fusions undermine the differentiated state of the prostate cancer cells, allowing androgen receptor (AR) signaling to push prostate cell proliferation and survival without triggering terminal differentiation<sup>6</sup>.

When compared to prostate cancers from EA men, prostate cancers from AA men contain fewer *TMPRSS2-ERG1* fusions (29.3% vs. 39.6%), fewer *PTEN* deletions (11.5% vs. 30.2%), and more *SPOP* mutations (20.3% vs. 10.0%)<sup>7</sup>; new data to suggest that epigenetic silencing of *GSTP1* is also less common in prostate cancer from AA men<sup>8</sup>. In a preliminary study of 5,715 tissue cores from 1,674 men with prostate cancer, including 337 AA men- the largest cohort thus far studied, we have identified a new and distinct disease subset, featuring high *MYC* levels and high *GSTP1* levels. This prostate cancer subset is substantially over-represented among prostate cancers from AA men (9.5% of prostate cancers from African-Americans versus from 3.2% from Caucasians;  $p < 0.001$ ). Though the natural history of *MYC*+/*GSTP1*+ prostate cancers has yet not been fully explored, preliminary findings hint that at least 26% of such cases in radical prostatectomy specimens exhibit histopathologic findings of Grade groups 4 and 5 associated with disease recurrence and aggressiveness (Gleason pattern scores 8-10)<sup>8</sup>. *GSTP1* expression has been associated with estrogen receptor-negative (ER-negative) breast cancer progression, including in 'triple-negative' breast cancers over-represented among young African-American women<sup>9,10</sup>. The impact of *MYC*+/*GSTP1*+ versus *MYC*+/*GSTP1*- phenotypes on lethal prostate cancer progression has not been determined.

Could a 3-fold increase in *GSTP1*+ prostate cancers among AA men versus EA men account any of the 1.8-fold increase in lifetime prostate cancer mortality (or 2.3-fold risk in age-adjusted mortality) seen for AA men<sup>11</sup>? Clearly, inequities in access to high-quality healthcare contribute significantly to the prostate cancer mortality differences, but differences in disease biology likely play a role as well. Models built with data from the National Health Interview Survey and from the Surveillance, Epidemiology, and End Results (SEER) program suggest that AA men are 1.28-1.56-fold more likely than EA men to harbor cancers in their prostates by age 85 years<sup>12</sup>. AA men are also 1.44-1.75-fold more likely to suffer with metastatic prostate cancer progression if diagnosed with the disease<sup>12</sup>. In another recent study using SEER program data, for 62,735 AA men with prostate cancer

who had a median follow-up of more than 65 months, the 12-year prostate cancer mortality rate was only 5.5%<sup>13</sup>. With such low death rates, estimates of median survival differences between AA men and EA men in studied in therapeutic clinical trials predictably show minimal differences. Certainly, from the available population-scale data thus far reported, the notion that a specific MYC+GSTP1+ disease subset, present in as many as 10% of AA men with prostate cancer and 3-fold more common in AA men than in EA men, could drive relevant biological differences in age-adjusted mortality between AA men and EA men is a valid hypothesis.

GSTP1 functions as a homodimer to catalyze reactions between reactive oxygen species, anti-cancer drugs, or carcinogens, and glutathione, sometimes ‘detoxifying’ and at other times ‘toxifying’ the substrates<sup>14</sup>. The enzyme effects on anti-cancer drugs could influence prostate cancer outcomes. To threaten life, metastatic prostate cancer typically progresses to castration-resistance despite androgen deprivation. The taxanes docetaxel and cabazitaxel comprise the most common cytotoxic drugs used to treat castration-resistant prostate cancer<sup>15-17</sup>. Taxanes are also increasingly used along with androgen deprivation as first-line treatment for metastatic disease<sup>18</sup>. For breast cancer, the presence or absence of GSTP1 expression predicts response to cytotoxic chemotherapy, particularly to the taxanes docetaxel and paclitaxel<sup>19-22</sup>. Forced expression of the enzyme in GSTP1-negative breast cancer cells confers docetaxel resistance<sup>19</sup>. In addition, an MCF-7 clone selected for taxane-resistance exhibited activation GSTP1 expression<sup>23</sup>. The general sensitivity of prostate cancer cells to taxane drugs may reflect disruption of cytoskeleton dynamics in interphase, interfering with AR shuttling into the cell nucleus, as well as in mitosis<sup>24,25</sup>. The response of MYC+/GSTP1+ versus MYC+/GSTP1- prostate cancer cells to docetaxel or cabazitaxel needs to be assessed.

A MYC+GSTP1+ prostate cancer subset 3-fold more common among AA men EA men could account for the 2.3-fold differences in age-adjusted mortality between AA men and EA men, and provide a mechanistic basis for poor response to taxane chemotherapy.

## References

1. Smith ZL, Eggener SE & Murphy AB. African-American prostate cancer disparities. *Current Urol Rep* **18**: 81 (2017).
2. Nelson WG *et al.* Prostate cancer. In *Abeloff's Clinical Oncology*, 6<sup>th</sup> Edition, Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, and Tepper JE (Eds.), Churchill Livingstone, Elsevier Inc., Philadelphia, PA (2018).
3. Koh CM *et al.* MYC and prostate cancer. *Genes Cancer* **1**, 617-28 (2010)
4. Nelson CP *et al.* Protection against 2-hydroxyamino-1-methyl-6-phenylimidazo [4,5- $\beta$ ]pyridine (N-OH-PhIP) cytotoxicity and DNA adduct formation in human prostate by glutathione S-transferase P1. *Cancer Res* **61**, 103-9 (2001).
5. Mian OY *et al.* GSTP1 loss results in accumulation of oxidative DNA base damage and promotes prostate cancer cell survival following exposure to protracted oxidative stress. *Prostate* **76**, 199-206 (2016).
6. Jindan Y *et al.* An integrated network of androgen receptor, polycomb, and TMRPEE2-ERG gene fusions in prostate cancer progression. *Cancer Cell* **17**, 443-54 (2010).

7. Yian J *et al.* Transcriptomic landscape between prostate cancer patients of predominantly African or European genetic ancestry. *PLoS Genet* **16**, e1008641 (2020).
8. Vidal I *et al.* GSTP1 positive prostatic adenocarcinomas are more common in black than white men in the United States. *PLoS One* **16**, e0241934 (2021).
9. Moscow JA *et al.* Isolation of the human anionic glutathione S-transferase cDNA and the relation of its gene expression to estrogen-receptor content in primary breast cancer. *Proc Natl Acad Sci USA* **85**, 6518-22 (1988).
10. Louie SM *et al.* GSTP1 is a driver of triple-negative breast cancer cell metabolism and pathogenicity *Cell Chem Biol* **23**, 567-78 (2016).
11. DeSantis CE *et al.* Cancer statistics for African Americans, 2019. *CA J Cancer Clin* **69**, 211-33 (2019).
12. Tsodikov A *et al.* Is prostate cancer different in black men? Answers from 3 natural history models. *Cancer* **123**, 2312-9 (2017).
13. Mahal BA *et al.* Prostate cancer-specific mortality across Gleason scores in black vs nonblack men. *JAMA* **320**, 2479-81 (2018).
14. Townsend DM, Tew KD The role of glutathione S-transferases in anti-cancer drug resistance. *Oncogene* **22**, 7369-75 (2003).
15. Tannock IF *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* **351**, 1502-12 (2004).
16. de Bono JS *et al.* Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* **376**, 1147-54 (2010).
17. Petrylak DP *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* **351**, 1513-20 (2004).
18. Vale CL *et al.* What is the optimal systemic treatment of men with metastatic, hormone-naïve prostate cancer? A STOPCAP systematic review and network meta-analysis. *Ann Oncol* **29**, 1249-57 (2018).
19. Iwao-Koizumi K *et al.* Prediction of docetaxel response in human breast cancer by gene expression profiling. *J Clin Oncol* **23**, 422-431 (2005).
20. Arai T *et al.* Association of GSTP1 expression with resistance to docetaxel and paclitaxel in human breast cancers. *Eur J Surg Oncol* **34**, 734-8 (2008).
21. Miyake T *et al.* GSTP1 expression predicts poor pathological complete response to neoadjuvant chemotherapy in ER-negative breast cancer. *Cancer Sci* **103**, 913-20 (2012).
22. Eralp Y *et al.* Predictive role of midtreatment changes in survivin, GSTP1, and topoisomerase 2alpha expressions for pathologic complete response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. *Am J Clin Oncol* **36**, 215-23 (2013).
23. Iseri OD, Kars MD, Gunduz U. Two different docetaxel resistant MCF-7 sublines exhibited different gene expression pattern. *Mol Biol Rep* **39**, 3505-16 (2012).
24. Darshan MS *et al.* Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. *Cancer Res* **71**, 6019-29 (2011).
25. Platz EA *et al.* A novel two-stage, transdisciplinary study identifies digoxin as a possible drug for prostate cancer treatment. *Cancer Discov* **1**, 68-77 (2011).

# Adrenal Masses: Evaluation with fast Gradient-echo MR Imaging & Gd-DTPA-Enhanced Dynamic Studies

by **Gabriel P. Krestin, Member EUAS**



## Short Biography

*Gabriel P. Krestin is full professor of Radiology and Chairman of the Department of Radiology & Nuclear Medicine at Erasmus MC, University Medical Center Rotterdam, the Netherlands.*

*Dr. Krestin was born in Romania and emigrated to Germany in 1974. He graduated from the Faculty of Medicine at the University of Cologne in Germany in 1981 and completed a residency in radiology at the same institution in 1988. He completed his PhD thesis (Habilitation) in 1989. Dr. Krestin moved to the Department of Radiology at the University Hospital in Zürich, Switzerland in 1990 where he became associate professor of radiology and head of the clinical radiology service in 1993. Between 1995 and May 1997 he was the acting chair of the same department before he moved into his present position in the Netherlands. Between 1998 and 2010 he was a permanent Visiting Professor at Stanford University Medical School. Between 2012 and 2021 Dr. Krestin was the Chair of the Division Diagnostics & Advise at Erasmus MC and member of the Managing Board of the medical staff. From 2017-2018 he was also the interim chair of the hospital pharmacy department.*

*Dr. Krestin is a member of numerous national and international societies. He is the Past President of ESMRMB and of AURE, Past President of ESR, Past President of IS3R, and served on the editorial and advisory boards of numerous international journals. He was the Couch-Kerley Traveling Professor to the Royal College of Radiologists in the UK in 2003, he received the Albers Schönberg Medal of DRG, the Schinz Medal of the Swiss Society of Medical Radiology and the Gold Medals of the European Society of Radiology and of the Asian-Oceanian Society of Radiology, was the recipient of the International Prize for Arts and Culture "Sebetia-ter" of the President of the Italian Republic, and was awarded the honorary membership of the Hungarian, Italian, Belgian, Spanish, Swiss, French, Colombian, Romanian, Serbian, North-American (RSNA) Israeli and Chinese Societies of Radiology as well as the Honorary Membership of ESMRMB and of the SAR. Dr. Krestin is a honorary fellow of the American College of Radiology and of the Royal College of Radiologists in the UK. In October 2017 he was elected to the National Academy of Science, Engineering and Medicine (US).*

*He is author of over 400 original articles, of over 70 book chapters, and editor of 7 books some of which have been translated in several languages. His main areas of research are: imaging of abdominal organs and cardio-vascular diseases, molecular imaging and population imaging. His research was supported by numerous grants from European and national research organizations, charities and industry.*

*Dr. Krestin has extensive experience in leadership, management and strategic planning. He was founder of MIR (Management in Radiology) and of EIBIR (the European Institute of Biomedical Imaging Research) and is presently its Scientific Director. He was a strategic advisor to GE Healthcare Europe and member of numerous scientific advisory boards to companies and academic organizations among which the Scientific Board of the Ludwig Maximilian University in Munich, the Board of Governors and Academic Committee of the Technion Institute in Israel, and the Wallenberg Foundation in Sweden. Dr. Krestin was a member of the Scientific Panel for Health, the highest advisory committee to the EC during Horizon2020. He is presently member of the supervisory board of Quantib B.V., senior strategic advisor to Bracco S.p.A. and senior medical advisor to the MTD Group.*

**Krestin GP, Steinbrich W, Friedmann G** Adrenal masses: evaluation with fast gradient-echo MR imaging and Gd-DTPA-enhanced dynamic studies. **Radiology**1989;171:675-680

#### **Abstract**

Fast gradient-echo magnetic resonance (MR) imaging of 38 adrenal masses with proved diagnosis was performed during suspended respiration with various repetition times (TRs), echo times (TEs), and flip angles. Dynamic perfusion studies after gadolinium diethylenetriamine-pentaacetic acid (DTPA) administration were performed by repeated imaging at short time intervals. With more T2 weighting (TR = 60 msec, TE = 30 msec, and flip angle = 15 degrees), malignant tumors and pheochromocytomas had a significantly higher relative signal intensity than adenomas; overlap of signal intensity led to equivocal findings in nine cases. After administration of Gd-DTPA, adenomas showed only mild enhancement and quick washout; malignant tumors and pheochromocytomas showed strong enhancement and slower washout. Five of the nine cases that were equivocal in precontrast images could thus be correctly classified. In addition to this improved classification of adrenal masses, fast, dynamic contrast material-enhanced MR imaging resulted in a reduction in total examination time.

**Yi-Xiang J Wang, Shahid M Hussain, Gabriel P Krestin.**

Superparamagnetic iron oxide contrast agents  
**European Radiology** 2001;11:2319–2331

#### **Abstract.**

Superparamagnetic iron oxide MR imaging contrast agents have been the subjects of extensive research over the past decade. The iron oxide particle size of these contrast agents varies widely, and influences their physicochemical and pharmacokinetic properties, and thus clinical application. Superparamagnetic agents enhance both T1 and T2/T2\* relaxation. In most situations it is their significant capacity to reduce the T2/T2\* relaxation time to be utilized. The T1 relaxivity can be improved (and the T2/T2\* effect can be reduced) using small particles and T1-weighted imaging sequences. Large iron oxide particles are used for bowel contrast [AMI-121 (i.e. Lumirem and Gastromark) and OMP (i.e. Abdoscan), mean diameter no less than 300 nm] and liver/spleen imaging [AMI-25 (i.e. Endorem and Feridex IV, diameter 80–150 nm); SHU 555A (i.e. Resovist, mean diameter 60 nm)]. Smaller iron oxide particles are selected for lymph node imaging [AMI-227 (i.e. Sinerem and Combidex, diameter 20–40 nm)], bone marrow imaging (AMI-227), perfusion imaging [NC100150 (i.e. Clariscan, mean diameter 20 nm)] and MR angiography (NC100150). Even smaller monocrystalline iron oxide nanoparticles are under research for receptor-directed MR imaging and magnetically labeled cell probe MR imaging. Iron oxide particles for bowel contrast are coated with insoluble material, and all iron oxide particles for intravenous injection are biodegradable. Superparamagnetic agents open up an important field for research in MR imaging.

**Shahid M. Hussain, Pieter E. Zondervan, Jan N. M. IJzermans, Solko W. Schalm, Rob A. de Man, Gabriel P. Krestin.** Benign versus Malignant

Hepatic Nodules: MR Imaging Findings with Pathologic Correlation  
**RadioGraphics 2002; 22:1023–1039**

**Abstract**

According to the currently used nomenclature, there are only two types of hepatocellular nodular lesions: regenerative lesions and dysplastic or neoplastic lesions. Regenerative nodules include monoacinar regenerative nodules, multiacinar regenerative nodules, cirrhotic nodules, segmental or lobar hyperplasia, and focal nodular hyperplasia. Dysplastic or neoplastic nodules include hepatocellular adenoma, dysplastic foci, dysplastic nodules, and hepatocellular carcinoma (HCC). Many of these types of hepatic nodules play a role in the de novo and stepwise carcinogenesis of HCC, which comprises the following steps: regenerative nodule, low-grade dysplastic nodule, high-grade dysplastic nodule, small HCC, and large HCC. State-of-the-art magnetic resonance (MR) imaging facilitates detection and characterization in most cases of hepatic nodules. State-of-the-art MR imaging includes single-shot fast spin-echo imaging, in-phase and opposed-phase T1-weighted gradient-echo imaging, T2-weighted fast spin-echo imaging with fat saturation, and two-dimensional or three-dimensional dynamic multiphase contrast material-enhanced imaging.

**Filippo Cademartiri, Koen Nieman, Aad van der Lugt, Rolf H. Raaijmakers, Nico Mollet, Peter M. T. Pattynama, Pim J. de Feyter, Gabriel P. Krestin.** Intravenous Contrast Material Administration at 16–Detector Row Helical CT Coronary Angiography: Test Bolus versus Bolus-tracking Technique.  
**Radiology 2004;233:817-823.**

**Abstract**

**PURPOSE:** To compare test bolus and bolus-tracking techniques for intravenous contrast material administration at 16–detector row computed tomographic (CT) coronary angiography.

**MATERIALS AND METHODS:** This study had institutional review board approval, and patients gave informed consent. Thirty-eight patients (mean age, 60 years; three women) were randomized into two groups according to bolus timing technique: group 1 (20-mL test bolus with 100-mL main bolus) and group 2 (bolus tracking with 100-mL main bolus). All patients underwent electrocardiography-gated 16–detector row CT coronary angiography with 12 detectors (collimation, 0.75 mm; rotation time, 420 msec). In group 1, test bolus peak attenuation was used as a delay, while in group 2, a +100-HU threshold in ascending aorta triggered angiographic acquisition, with an additional 4-second delay for patient instruction. Attenuation was measured in the longitudinal direction throughout the examination in three main vessels: ascending aorta (region of interest [ROI] 1), descending aorta (ROI 2), and main pulmonary artery (ROI 3). Mean attenuation and slope of bolus geometry curve were calculated in each patient and ROI. Attenuation at origin of coronary arteries was measured. Student *t* test was used to compare results.

**RESULTS:** Mean scan delay was 6 seconds longer in group 2 ( $P < .05$ ). Average attenuation values were 306.6 HU  $\pm$  44.0 (standard deviation) and 328.2 HU  $\pm$  58.6 ( $P > .05$ ) in ROI 1, 291.6 HU  $\pm$  45.1 and 326.4 HU  $\pm$  62.6 ( $P > .05$ ) in ROI 2, and 354.7 HU  $\pm$

78.0 and 305.3 HU  $\pm$  71.4 ( $P < .05$ ) in ROI 3 for groups 1 and 2, respectively. Average slope values were 5.8 and  $-0.8$  ( $P < .05$ ) in ROI 1, 7.7 and 0.7 ( $P < .05$ ) in ROI 2, and  $-1.0$  and  $-13.3$  ( $P < .05$ ) in ROI 3 for groups 1 and 2, respectively. Average attenuation values in left main, left anterior descending, and left circumflex arteries were higher in group 2 ( $P < .05$ ); there were no differences ( $P > .05$ ) between groups in right coronary artery.

**CONCLUSION:** Bolus-tracking yields more homogeneous enhancement than does the test bolus technique.

**Alexia Rossi , Daphne Merkus, Ernst Klotz, Nico Mollet, Pim J. de Feyter, Gabriel P. Krestin.** Stress Myocardial Perfusion: Imaging with Multidetector CT  
**Radiology 2014;270:25-46**

### **Abstract**

Computed tomographic (CT) coronary angiography is a well-established, noninvasive imaging modality for detection of coronary stenosis, but it has limited accuracy in demonstrating whether a coronary stenosis is hemodynamically significant. An additional functional test is often required because both anatomic and functional information is needed for guiding patient care. Recent developments in CT technology allow CT evaluation of myocardial perfusion during vasodilator stress, thereby providing information about myocardial ischemia. Investigators in several single-center studies have established the feasibility of performing stress myocardial perfusion CT imaging in small groups of patients and have shown that stress myocardial perfusion CT in combination with CT coronary angiography improved the diagnostic accuracy in comparison with CT coronary angiography alone. However, CT perfusion acquisition protocols must be optimized in terms of acquisition and reconstruction parameters, contrast material protocol injections, and radiation dose. Further research is needed to establish the clinical usefulness of this novel technique. The purpose of this review is to (a) provide an overview of the physiology of coronary circulation and myocardial perfusion; (b) describe the technical prerequisites, challenges, and mathematic modeling related to CT perfusion imaging; (c) note recent advances in CT scanners and CT perfusion protocols; and (d) discuss the interpretation of CT perfusion images. Finally, a review and summary of the current literature are provided, and future directions for research are discussed.

# Artificial Intelligence to Improve Understanding of Collective Aspects which Result in Failure

by Edward A. McBean, Member EUAS



## Short Biography

Edward A. McBean, Ph.D., P.Eng., P.E., FCAE, D.WRE, F.EIC, F.CSCE, F.IAH, F.AGGS

### Education

- Ph.D. Massachusetts Institute of Technology (1973) - Magna Cum Laude  
 C.E. Massachusetts Institute of Technology (1972) (Civil Engineer's Degree, equiv. to Professional Doctorate)  
 S. M. Massachusetts Institute of Technology (1970)  
 B.A.Sc. University of British Columbia (1968)

### Employment

#### University of Guelph

- Professor of Water Resources, School of Engineering, 2003-present
- Canada Research Chair of Water Supply Security (Tier 1), 2003 to 2017
- University of Guelph Research Leadership Chair Professor, Water Security 2017-present
- Executive Director, Centre for Canada Water Technology Exchange 2015-2020
- Co-Director of Sino-Canada Joint R&D Centre on Water and the Environment
- Affiliated Member, One Health Institute, University of Guelph, 2020 -present
- Affiliated Member, CARE-AI Institute (Centre for Advancing Responsible and Ethical-AI, University of Guelph, 2019-present)
- Asst. Dean External Partnerships, College of Physical and Engineering Science, 2010 to 2016
- Asst. Dean Research (Acting), College of Physical and Engineering Science, 2010 to 2012, & 2015
- Conestoga-Rovers & Associates
  - Vice-President, 1999 - 2003
  - Associate, 1995-1999
- CRA Engineering Inc., President, 1996 - 2003
- University of Waterloo, Department of Civil Engineering
  - Professor, Department of Civil Engineering, 1981 - 1991, 1992 - 1995
  - Acting Director, Institute for Risk Research, 1993
  - Associate Professor, Department of Civil Engineering, July 1977 - 1981
  - Assistant Professor, Department of Civil Engineering and School of Urban and Regional Planning, July 1974 - July 1977
- University of California at Davis
  - Professor of Water Resources, Land, Air and Water Resources, 1991 - 1992
- Cornell University
  - Water Resources and Marine Sciences Centre, Research Associate, 1973 - 1974
- Meta Systems, Inc., Cambridge, Massachusetts, Project Engineer, 1972 - 1974
- Acres Consulting Services, Niagara Falls, Canada, Engineer, 1970 - 1971
- Massachusetts Institute of Technology, Department of Civil Engineering
  - Research Assistant, 1968 - 1970 and 1971 - 1972
  - Graduate Assistant, 1972 - 1972
  - Visiting Engineer, 1973 - 1974

### Awards

Fellow, Canadian Academy of Engineering (recognizing as Academician in Canada)

D.WRE. – Diplomat, Water Resources Engineering, an award from American Academy of Water Resources Engineering and American Society of Civil Engineers (recognized as Academician in US)

Recipient, American Academy of Water Resources Engineering and American Society of Civil Engineers, "AAWRE 2021 Outstanding Research & Innovation Award", for outstanding research and education that impacts water security.

University of Guelph Research Leadership Chair Professor, Water Supply Security – 2017-present (one of seven so-designated at University of Guelph)

Recipient, Excellence in Innovation Civil Engineering Award, from Canadian Society for Civil Engineering for: Design and

*Performance of a Novel Low-Tech Water Filter System for 2021.*  
 Recipient, Gold Medal from the Institution of Engineers (India), The Nawab Zain Yar Jung Bahadur Memorial Gold Medal for 1986-87  
 Recipient, Camille A. Dagenais Award for outstanding contributions to the development and practice of hydrotechnical engineering in Canada. An award from the Canadian Society of Civil Engineers, 2009  
 Recipient, Research and Development Medal, Professional Engineers of Ontario and Ontario Society of Professional Engineers, 2009  
 Canada Research Chair, Tier 1, Water Security, 2003-2017  
 Fellow, Canadian Society of Civil Engineers  
 Fellow, Engineering Institute of Canada  
 Fellow, India Association of Hydrologists  
 Fellow, Association of Global Groundwater Scientists  
 Recipient of K. Y. Lo Award from the Engineering Institute of Canada, significant contributions at the international level and demonstrating to the world, Canadian expertise in water security, 2015  
 Recipient of the Julian C. Smith Award by the Engineering Institute of Canada, for achievement in the development of Canada. 2018.  
 Recipient, Faculty of Applied Science, Dean's Medal of Distinction, University of British Columbia, 2016  
 Recipient of 'The 2016 Engineering Excellence Lifetime Achievement Award', Faculty of Applied Science, University of British Columbia  
 Recipient of 'Ton Duc Thang University Prize, Lifetime Achievement Award', Ho Chi Minh City, Viet Nam, 2017  
 Web of Science h-index 73  
 Recipient, Award for 'One Water Approach' for Integrated Risk Management, from the Credit Valley Conservation Authority, Ontario, Canada. 2016  
 Recipient, 2021 College of Engineering and Physical Sciences Undergraduate Supervision Award, 2021  
 Recipient, Best Paper Award, "Chlorinated Ethene Plume Migration in Groundwater at Free-Phase Petroleum Sites", Keynote presentation at ModelCare -7th International Conference on Calibration and Reliability in Groundwater Modeling, Wuhan, China, September 20-23, 2009.  
 Erskine Fellow, University of Canterbury, New Zealand, 2001  
 Recipient, Japanese Promotion of Sciences Fellowship, 1987  
 Outstanding reviewer award from the Canadian Journal of Civil Engineering, 2015  
 Water's Next Award 2016, Finalist for Academia/NGO Award  
 Water's Next Award 2021, for Water Canada's national award program, Finalist for Canadian leader in the People Category  
 Recipient, Waste Management and Research Editor's Choice Award for paper entitled "A Novel Risk Assessment Method for Landfill Slope Failure: Case Study Application for Bhalswa Dumpsite, India", March 2017

Dr. Edward McBean's research over the last four decades has focused on issues of water security and attributes which may result in vulnerability/failure potential. In this area of water research his focus involves use of the principles of risk assessment and risk management and statistical analyses, to investigate the science and engineering aspects to protect humans and the environment, because 'water is without borders'. Outlined below are a number of examples of areas of his water research, all of which involve issues of water security issues.

(i) **Use of Artificial Intelligence to Improve Understanding of Collective Aspects which Result in Failure** – Research into models to characterize failure potential using Artificial Intelligence has been ongoing for several decades. In some situations, AI models have been used to evaluate breakage probability of municipal water distribution pipes. The investments involved in protection of the integrity of water distribution pipes is massive but attempts to rely upon simply age as timing for replacement of the pipes is a poor characterization. Instead, using about 20 dimensions (e.g. age of pipe, pipe type, pipe wall thickness, nearby traffic inducing vibrations, water pressure, variations in water pressure, etc.) his models have been able to greatly improve pipe methodologies to protect the integrity of water distribution performance. For example, for the city of Toronto with 55,000 pipes, it is clear the investment in protecting the integrity of water distribution pipes is enormous. AI modeling involves developing the AI model on a portion (e.g. 70%) of the data of historical pipe performance and then checking the validity of the breakage results on the remaining data. This approach has been instrumental in improving the predictions of actual pipe failure and hence, guiding replacement timing of the pipes and asset management. As well, recent innovations such as improved survival analysis in the AI modeling have been recently introduced wherein, like life insurance models which allow one to incorporate the types of issues such as remaining life for model development, have opened up entirely novel aspects of pipe break modeling.

Building on these same principles, AI modeling has been utilized to look at failure potential (in this case, causes of Boil Water Advisories (BWAs) for a water supply system) has been able to provide excellent insight into the potential for BWA prediction and ability to understand performance measures that need to be corrected, to avoid BWAs from occurring. This research has been helpful in guiding investments on how Canada's government should allocate their funding, while providing safe and secure water to the indigenous peoples in remote locations around the country.

Another dimension of AI modeling is now being used by Dr. McBean to assist in planning hospital admittance associated with COVID-19. More specifically, we are now able to accurately predict (about 95% accuracy) whether a person who tests positive for the COVID virus will ultimately be required to be admitted to a hospital and ultimately, the likelihood of a fatality. These AI models are developed using individual histories of persons (e.g. have they diabetes, how old are they, dementia, as well as such features as 'when they were tested' because the medical profession has learned a great deal about how to treat COVID-19 patients, etc. A total of about forty co-morbidity variables is improving the predictability of outcomes which has potential to improve hospitalization planning.

(ii) **Development of vulnerability models for small water systems** – This research has been particularly focused for characterizing the vulnerability of remote/isolated and small indigenous water systems. Using data mining procedures, Dr. McBean has looked at historical failures to identify the implications of features such as operator training, instrumentation design, if they are related to failure of 'safe' water to be provided to the indigenous community. Ed developed vulnerability models for small water systems in First Nations communities, identifying the importance of different attributes (using innovative data mining procedures) contributing to failure, prioritizing investments in funding to improve safe water delivery, where the results are now being utilized by INAC in delivery decisions for budget allocations for improved water security for small, remote facilities.

(iii) **Expanded research platform on wastewater epidemiology** – Dr. McBean was responsible for conceiving and implementing, a \$5million wastewater testing platform at Guelph adjacent to the City of Guelph wastewater treatment plant. This facility is providing unique opportunities to improve wastewater epidemiology by allowing testing of wastewater. For example, this facility is being used to undertake fundamental research on wastewater epidemiology for purposes of COVID-19 increases/decreases in cities by allowing focused monitoring of the degree of change in COVID-19 virus in the wastewater (as excreted in the feces of the contributing population). This facility is also allowing technology innovators to test, at pilot-scale, the utility of innovative ways to turn wastewater into a resource, not a waste, as water will become one of the most critical dimensions of the next century.

(iv) **Issues of Natural Sources of Arsenic Removal for Remote Villages** – Particularly in countries such as Bangladesh, natural sources of arsenic are causing what many have called the largest poisoning of human health in the world. Over millenia, arsenic was scoured from the Himalayan mountains and deposited in the delta at the end of the Ganges, the delta being what is now Bangladesh. These natural deposits, particularly when impacted by irrigation and fertilizers has re-mobilized the arsenic resulting in exposure in the villagers to excessive levels of arsenic both via their drinking water and their foodstuffs which are irrigated with the arsenic-contaminated water. The approximately 80,000 villages in Bangladesh primarily rely on direct ingestion and/or Arsenic-Iron Removal Plants (AIRP) for their water supplies but shortcomings of the AIRPs and failure to remove and/or limit the arsenic from the ecosystem has caused enormous impacts to arsenic as a carcinogen for the villagers. Dr. McBean's research has

identified options such as removing shortcomings of the AIRPs and the potential to use in-situ aeration to change the valence state of the arsenic, the results of which have been able to remove much of the residual arsenic in the drinking water of the villagers, making the water safer for human consumption.

(v) **Development of Analytical Models to Characterize Movement of Water at the Base of Solid Waste Landfills** - Maintaining effective water balance in landfills is key to protecting against slope failure of landfills and minimizing contaminated leachate which may drain through the base of the landfill and contaminate groundwater. Migrating leachate beyond (leakage) the refuse may result in degradation of the ambient groundwater which also serves as water supply for nearby wells. Hence, ensuring that the water balance is correctly maintained is 'key' to maintaining the correctional functioning of landfills.

Dr. McBean was instrumental in assessing an array of water balance issues in landfills, and developing in-depth characterization of landfill gas generation rates, and water balance, and how to ensure the science and engineering of solid waste landfills were understood. As one example of Dr. McBean's contribution was his development of the first (in 1982) analytical mathematical model dealing with sloped bottom liners in landfills, providing a methodology of enabling efficient calculations of water movement, and resulting in greatly improved protection of groundwater beneath landfills.

Dr. McBean successfully demonstrated at field-scale, the potential to accelerate the biodegradation of municipal solid wastes, improving capture of greenhouse gases (most notably, methane, a greenhouse gas that is more than 25 times as impactful as carbon dioxide) from refuse, while the integrity of the landfill gas collection system was new. These insights now allow more effective capture to facilitate the recovery of methane gas as an energy source which is being used to generate electricity and heat nearby greenhouses, as examples. A particularly important feature of these same activities was the realization that the contaminating lifespan of solid wastes is accelerated which translates into decreasing the potential of landfilled refuse contaminating the ambient environment. Dr. McBean successfully demonstrated use of biogases from municipal wastes, allowing its use both to disinfect medical wastes in developing countries, and its use to light a soccer field to allow evening use by residents near to the landfill. These were the first demonstrations of beneficial use of landfill gas in South America.

As part of his contribution, Dr. McBean was involved for 25 years in the offering of short-courses at the University of Wisconsin Professional Development courses in 108 offerings of his science and engineering knowledge.

(vi) **The Science and Engineering of Monitoring Water Quality** – Dr. McBean's knowledge of the science and engineering of fate and transport of water quality, and including groundwater quality parameters has identified ways to allow less intrusive sampling to provide characterization of the impacts to groundwater quality in response to spills and natural hazard sources. These have included procedures which have resulted in changes to the US Federal Register on use of statistical analyses and is the basis for considerable savings in remediating contaminated groundwater.

In this same context, Dr. McBean developed an innovative hierarchical methodology to characterize fate mechanisms for emerging contaminants based on fundamental principles to assess the fate and transport of emerging contaminants in the environment. This strategy relies upon fundamental principles where Dr. McBean developed an innovative hierarchical methodology to characterize fate mechanisms for emerging contaminants, using aspects such as adsorption coefficients, octanol water partitioning coefficient, solubility, hydrolysis, etc., a methodology now utilized by Environment Canada for their Chemical Management Plan Strategy.

**Summary**

A summary of Dr. McBean's contributions to water security and risk assessment issues is perhaps best defined as that Dr. McBean has an extensive understanding of how 'theory translates to influence practice'. Dr. McBean has developed ground-breaking, novel insights and procedures for water security and risk characterization. These innovative ideas have widely influenced legislation, provided the basis for important negotiation strategies for decision-making at governmental levels, developed novel insights for improved water security risk methodologies, and provided critical insights into causes and mitigation opportunities, to improve water security.

In the last 100 years, there has been a doubling of the length of the human lifespan but also, while population on earth has doubled in the last 100 years, the use of water has tripled. There is no opportunity to replicate this performance again, but 'water is life'. Without water, we are nothing and water bears silent witness to all things which precede a specific use, and hence, water security and vulnerability to failure is always present. Water is without borders.

Dr. McBean has written 3 books, edited 17 books and published more than 420 papers in refereed journals.

## New Trends in Energy Sustainability

by Marc A. Rosen, Member EUAS

### Short Biography

#### **Education**

- *Ph.D., 1987, Univ. of Toronto, Dept. of Mechanical Engineering*
- *M.A.Sc., 1983, Univ. of Toronto, Dept. of Mechanical Engineering*
- *B.A.Sc., 1981, Univ. of Toronto, Div. of Engineering Science, Nuclear and Thermal Power Generation Option*

#### **Recent Professional Experience**

- *Professor, Faculty of Engineering and Applied Science, Univ. of Ontario Institute of Technology, Oshawa, Ontario, 2002-pres.*
- *Dean (founding), Faculty of Engineering and Applied Science, Univ. of Ontario Institute of Technology, Oshawa, Ontario, 2002-08.*
- *Chair, Dept. of Mechanical Engineering, Ryerson Polytechnic Univ., Toronto, 1994-99.*
- *Director, School of Aerospace Engineering, Dept. of Mechanical Engineering, Ryerson Polytechnic Univ., Toronto, 1992-94.*

#### **Other Significant Professional Positions**

- *Editor, Energy Conversion and Management, 2013-pres.*
- *Editor-in-Chief, Int. Journal of Energy and Environmental Engineering, 2012-21.*
- *Editor-in-Chief, Sustainability, 2009-pres.*
- *Editor-in-Chief, Biofuels, 2014-pres.*
- *President, Engineering Institute of Canada, 2008-10.*
- *Director, Durham Strategic Energy Alliance, 2005-07.*
- *President, Canadian Society for Mechanical Engineering, 2002-04.*

#### **Honours and Awards**

- *John B. Stirling Medal, Engineering Institute of Canada*
- *Educational Award of Honour, Minerva Canada*
- *President's Award, Canadian Society for Mechanical Engineering*
- *Engineering Alumni Hall of Distinction, University of Toronto*
- *Andrew H. Wilson History Award, Canadian Society for Mechanical Engineering*
- *C.N. Downing Award, Canadian Society for Mechanical Engineering*
- *Julian C. Smith Medal, Engineering Institute of Canada*
- *Robert W. Angus Medal, Canadian Society for Mechanical Engineering*
- *Fellow, American Society of Mechanical Engineers*
- *Fellow, Engineering Institute of Canada,*
- *Fellow, International Energy Foundation*
- *Fellow, Canadian Society for Mechanical Engineering*
- *Fellow, Canadian Society for Senior Engineers*

#### **Principal Areas of Interest**

- *Thermodynamics: Second-Law Analysis. Theoretical development; use in simulation codes; application to improve efficiency and performance of engineering systems.*
- *Energy Sustainability and Energy Systems Analysis. Analysis, design, modelling, simulation and optimization; environmental assessment; energy-environment ties.*
- *Energy Technologies. District energy, thermal energy storage, solar energy, hydrogen energy, nuclear energy, electricity generation and cogeneration, chillers, synthetic fuels production, integrated energy systems.*
- *Heat Transfer. Modelling, simulation and analysis computationally and analytically.*

## Achievements Related to Energy Sustainability

Dr. Marc A. Rosen has over his entire career been active in the area of energy, including efficiency, environmental impact and sustainability. He also has taken on key leadership roles for institutions in transformation throughout his career. Many of these achievements have directly and indirectly supported energy sustainability, its applications, and developments of related journals and engineering societies.

As Founding Editor-in-Chief of the journal *Sustainability*, published by MDPI, Dr. Rosen led the journal's development and growth from its launch in 2009 to the point where it now is a leading venue for the publication of research and application articles related to sustainability and sustainable development. This journal has proven transformative in helping advance the field of sustainability while having a global extent and impact. Dr. Rosen also has been heavily involved in the lead conference sponsored by that journal, the World Sustainability Forum. He was the general chair of the first four World Sustainability Forums, and has been heavily involved in subsequent Forums, often delivering keynote presentations.

As Founding Dean of Engineering and Applied Science at Ontario Tech University (University of Ontario Institute of Technology), Dr. Rosen launched a new engineering school, premised on innovative approaches to teaching and learning and on market-oriented research. He also helped build Ontario's first new university in 40 years, one with engineering and technology as its primary area and with energy as one key research and educational focus, and sustainable energy as a theme in much of that activity. There is a strong focus on energy and energy sustainability in many graduate and undergraduate programs that Dr. Rosen helped create. In response to the need for better business and management skills in engineering, Dr. Rosen launched for each engineering program an innovative Engineering and Management version.

Dr. Rosen was instrumental in attaining for his university an institution-defining \$100 million Automotive Centre of Excellence, in collaboration with industry. The Automotive Centre of Excellence supports the development and testing of future vehicles, including sustainable vehicles (e.g., vehicles that operate on alternative fuels like hydrogen, and electric vehicles).

Prior to joining Ontario Tech University, Dr. Rosen was a professor in the Department of Mechanical, Aerospace and Industrial Engineering at Ryerson University. During his tenure there, Dr. Rosen served as department Chair, and Director of the School of Aerospace Engineering. He played a key role in launching graduate programs, expanding research, obtaining accreditation for engineering programs. Dr. Rosen also was a lead developer and player in the university's multidisciplinary program in Environmental Science and Management and he led the creation of thermofluids and energy options within Mechanical Engineering at the undergraduate and graduate levels, and helped ensure sustainability concepts and applications pervade throughout, via such avenues as advanced training in renewable energy sources.

Lately, his teaching of sustainability, and indeed much of his research and other activity, has incorporated and been guided by the new United Nations Sustainable Development Goals.

With over 70 research grants, Dr. Rosen is an active industry collaborator, with much of his research adopted by industry. His innovations have led to increased sustainability and efficiency in energy technologies, improved alternative technologies (like solar, hydrogen and storage technologies), and reduced environmental impact. He was a key player in two projects (valued at over \$10 million) to produce hydrogen from nuclear

energy and other renewable thermal forms of energy. He was co-Principal Investigator of the second of these. He also was a theme leader in a \$12 million project on net-zero energy buildings, which advanced the development of buildings that use, on average, zero energy over the year. His noteworthy accomplishments include advancing energy systems to make them more sustainable and less environmentally damaging through research, and collaborating with industry to facilitate the adoption of those innovations.

Some notable examples of Dr. Rosen's research and its impact follow. His research has led to sustainable energy systems, buildings and communities [1-3], and to improvements in the sustainability of transportation technologies of various kinds, especially automobiles, trains and aircraft [4]. Some of his research has led to improvements in the sustainability of manufacturing, production and economic systems. [5-6]. Dr. Rosen's research has also focused on the large scale, including an assessment of the sustainability national energy systems like Canada's [7].

Dr. Rosen has published over 700 journal articles in leading journals, many addressing sustainability, and authored or co-authored over 110 book chapters and 21 books, many directly linked to sustainability [8-12]. These books include the ground-breaking work by Dr. Rosen on the linkages between the thermodynamic quantity "exergy" and sustainability, extending beyond thermodynamics to environment, ecology and economics, challenging convention and leading to new understandings of sustainability. His books on thermal energy storage, exergy, exergy and the environment, and exergy and economics are considered by many to be seminal. In addition, Dr. Rosen has authored or co-authored many books that deal indirectly with sustainability [13-17]. Dr. Rosen has also published extensively on engineering ethics and safety.

As a Director of Oshawa Power for over a decade, a local electrical distribution company that serves a city of about 160,000 people, Dr. Rosen helped that utility's expansion into sustainable energy forms and technologies like solar photovoltaics, wind, and biomass and cogeneration.

During his tenure as President of the Engineering Institute of Canada (EIC), Dr. Rosen assisted in affirming its leadership role and helped in developing a vision statement for EIC that had sustainability at its core, being phrased "Engineering for a prosperous, safe and sustainable Canada." The Engineering Institute of Canada was founded in 1887 and is a federation of leading Canadian engineering societies. Dr. Rosen also helped revitalize the Canadian Society for Mechanical Engineering during his term as President. He chaired that society's Technical Division on Thermofluids Engineering for two decades, focusing on advancements in renewable energy technology and sustainable energy.

Dr. Rosen has been extensively involved in international activities, including the development of a joint distance education course in Pollution Prevention in Brazil, with the support of the Canadian International Development Agency. This project led to a book. He was also his Department's lead contact for five years in the North American Design Institute (NADI), facilitating exchanges between Mexico, the U.S. and Canada. In addition, Dr. Rosen served on several industrial and academic advisory committees, including Canadian Representative on the International Energy Agency Experts Group on Cogeneration/District Cooling.

## **Impact and Significance on Energy Sustainability**

Much of Dr. Rosen's research has been adopted by industry, and helped to improve energy use, mitigate environmental impact, and increase efficiency. He has written over 50

technical reports that attest to this. One project identified efficiency improvements in power plants at Ontario Power Generation. Another project provided compelling evidence of the benefits of cogeneration, convincing large electrical power utilities to implement cogeneration. A third project aims to have Canada's nuclear reactors produce hydrogen for transportation, industry and supporting the oil sands development. Industry benefits resulted from his service as the Canadian Representative on the International Energy Agency Experts Group on Cogeneration/District Cooling. Finally, another aims at reducing the energy use for Canada's building stock, presently responsible for a third of the nation's energy use, to zero. The economic value of the projects he has been involved with directly as a principal or co-investigator exceeds \$30 million.

Dr. Rosen has also carried out work directly on or related to sustainability for a range of national and international companies, such as Imperial Oil Ltd., General Electric, Bell Canada, Apotex Inc., FuelMaker Corporation, and Inst. for Hydrogen Systems. As well, he has carried out projects for various government agencies at the international, national and provincial levels, including International Energy Agency, Natural Resources Canada, Environment Canada, Ontario Ministry of the Environment, and Ontario Ministry of Community and Social Services.

Dr. Rosen has advanced thermodynamic methods, cogeneration, district energy, thermal storage, renewable energy, and environmental stewardship. A significant achievement of Dr. Rosen has been his work to advance the methodology and framework for holistic assessments of sustainability [18-20]. Applications are numerous and include an assessment of the contributions to regional sustainability of the Dead Sea-Red Sea project involving Israel, Jordan and the Palestinian Authority [21]. His work has also led to advanced optimization methods [22].

Dr. Rosen has advanced engineering education, through his many roles in universities. In particular, he helped create a new research intensive university focused on technology. In leading the launch of the Faculty of Engineering and Applied Science at Ontario Tech University, Dr. Rosen created the vision of a new engineering school premised on the use of innovative educational methods and technologies, and value-added research. On the teaching front, Dr. Rosen has been innovative, creating several new courses at the graduate and undergraduate levels. Two examples are graduate courses on Energy and the Environment and Pollution Prevention. In addition, Dr. Rosen helped develop a Faculty-wide course on law, ethics and professionalism for engineers, and has developed innovative options and streams in programs.

Dr. Rosen has also been involved in the American Society of Heating, Refrigerating and Air-Conditioning Engineers, by serving as corresponding member for a technical group on exergy analysis for sustainable buildings. As a member of the Advisory Committee for Sustainable Energy Solutions for the Ontario Centres of Excellence, Dr. Rosen helped advance the sustainability of various earth and environmental technologies. As a director of the Durham Strategic Energy Alliance, Dr. Rosen helped lead development of a regional energy focus. Finally, as a review committee member on the International Thermonuclear Experimental Reactor, Dr. Rosen advised the Canadian and Ontario governments on fusion energy.

Dr. Rosen has been extensively recognized for his achievements in engineering, education and research, and distinguished service to learned societies. He has received best paper awards (e.g., "Energy and Exergy Analyses of Power Generation via an Integrated Biomass Post-Firing Combined-Cycle" at an IEEE International Conference on Smart Energy Grid Engineering). Dr. Rosen is a fellow of the Canadian Society for Senior Engineers, the Canadian Academy of Engineering, the American Society of Mechanical

Engineers, the Engineering Institute of Canada, the International Energy Foundation and the Canadian Society for Mechanical Engineering. He was elected to University of Toronto's Engineering Alumni Hall of Distinction.

## References

1. Rad, F.M., Fung, A.S., Rosen, M.A. 2017. An Integrated Model for Designing a Solar Community Heating System with Borehole Thermal Storage. *Energy for Sust. Dev.* 36C:6-15.
2. Sliwa, T., Jarosz, K., Rosen, M.A., Sojczyńska, A., Sapinska-Sliwa, A., Gonet, A., Fafera, K., Kowalski, T., Ciepielowska, M. 2020. Influence of Rotation Speed and Air Pressure on the Down The Hole Drilling Velocity for Borehole Heat Exchanger Installation. *Energies* 13:2716.
3. Bingham, R., Agelin-Chaab, M., Rosen, M.A. 2019. Whole Building Optimization of a Residential Home with PV and Battery Storage in The Bahamas. *Renewable Energy* 132:1088-1103.
4. Bulucea, C.A., Nicola, D.A., Rosen, M.A., Mastorakis, N.E., Bulucea, C.A. 2016. Analysis of Torque Capability and Limits of Operation of AC Traction Motors on Sustainable High-Speed Electric Trains. *WSEAS Transactions on Power Systems* 11:156-170.
5. Jawad, H., Jaber, M.Y., Bonney, M., Rosen, M.A. 2016. Deriving an Exergetic Economic Production Quantity Model for Better Sustainability. *App. Math. Modelling* 40:6026-6039.
6. Nazzal, Y., Abuamarah, B.A., Kishawy, H.A., Rosen, M.A. 2013. Considering Environmental Sustainability as a Tool for Manufacturing Decision Making and Future Development. *Research J. Environmental and Earth Sciences* 5(4):193-200.
7. Gnanapragasam, N.V., Reddy, B.V., Rosen, M.A. 2011. Sustainability of an Energy Conversion System in Canada Involving Large-Scale Integrated Hydrogen Production Using Solid Fuels. *International Journal of Energy and Environment* 2(1):1-38.
8. Rosen, M.A., Koochi-Fayegh, S. 2017. *Geothermal Energy*. Wiley, London.
9. Rosen, M.A. (Ed.). 2015. *Renewable Energy*, Routledge/Taylor and Francis.
10. Dincer, I., Rosen, M.A. 2021. *Exergy*, 3rd ed., Elsevier, Oxford, UK.
11. Rosen, M.A. 2012. *Environment, Ecology and Exergy*. Nova Science Pub., Hauppauge, NY.
12. Rosen, M.A. 2011. *Economics and Exergy*. Nova Science Publishers, Hauppauge, NY.
13. Rosen, M.A. (Ed.). 2015. *Energy Storage*, Routledge/Taylor and Francis.
14. Dincer, I., Rosen, M.A. 2015. *Exergy Analysis of Heating, Refrigerating and Air Conditioning: Methods and Applications*, Elsevier, Oxford, UK.
15. Rosen, M.A., Koochi-Fayegh, S. 2016. *Cogeneration and District Energy Systems: Modelling, Analysis and Optimization*. Institution of Engineering and Technology, London.
16. Rosen, M.A., Ed., 2012. *Energy Storage*, Nova Science Publishers, Hauppauge, NY.
17. Dincer, I., Rosen, M.A. 2021. *Thermal Energy Storage*, 3rd ed., Wiley, London.
18. Rosen, M.A. 2012. Engineering Sustainability: A Technical Approach to Sustainability. *Sustainability* 4(9):2270-2292.
19. Rosen, M.A. 2013. Engineering and Sustainability: Attitudes and Actions. *Sustainability* 5(1):372-386.
20. Rosen, M.A. 2009. Energy Sustainability: A Pragmatic Approach and Illustrations. *Sustainability* 1(1):55-80.
21. Rosen, M.A., Abu Rukah, Y. 2011. A Pragmatic Approach for Sustainable Development of the Red-Mediterranean-Dead Seas Canal Project: A Case Study. *Int. J. Ecology & Development* 19(S11):63-75.
22. Dincer, I., Rosen, M.A., Ahmadi, P. 2017. *Optimization of Energy Systems*, Wiley, London.

# Validation of Unit 1 of the Fukushima Daiichi Nuclear Power Plant During its Accident

by Shigenao Maruyama, Member EUAS



## Short Biography

*Present Affiliation: President, National Institute of Technology, Hachinohe College, Hachinohe 039-1192, Japan*

### **Academic Qualifications**

*B.Eng. 1977, Department of Mechanical Engineering II, Tohoku University, Japan*

*M.Sc. 1979, Department of Aeronautics, Imperial College, London University, UK*

*M.Eng. 1980, Department of Mechanical Engineering, Tohoku University, Japan*

*PhD 1983, Department of Mechanical Engineering, Tohoku University, Japan*

### **Professional Carriers**

*1983 Assistant Professor, Institute of High Speed Mechanics, Tohoku University*

*1988 Visiting Scholar, School of Mechanical Engineering, Purdue University, USA*

*1989 Associate Professor, Institute of Fluid Science, Tohoku University*

*1997 Professor, Institute of Fluid Science, Tohoku University.*

*2005-2006 Specially Appointed Assistant to the President, Tohoku University*

*2006-2009 Councilor, Tohoku University*

*2006-2008 Special Advisor to President, Tohoku University*

*2006-2013 Special Advisor for Centenary Events and Alumni, Tohoku University*

*2008-2011, 2015-2017 Distinguished Professor of Tohoku University*

*2016 Visiting Professor, INSA de Lyon*

*2017- President, National Institute of Technology, Hachinohe College*

### **Awards**

*Japan Society of Mechanical Engineers (JSME), Award for Young Engineers, 1989*

*Fluid Science Foundation, Award for Fluid Science, 1995*

*Heat Transfer Society of Japan (HTSJ), Award for Scientific Contribution, 1998, 2016*

*JSME Medal for Outstanding Paper, 1999, 2013*

*HTSJ, Award for Scientific Measurement, 1999*

*JSME Tohoku Division, Award for Technical Contribution, 2001*

*Japan Society of Applied Electromagnetic and Mechanics, Best Technical Contribution Award, 2001*

*JSME Thermal Engineering Division, Award for Academic Achievements, 2001*

*HTSJ, Award for Technical Contribution, 2002*

*Societe Francaise de Themique, 2002 International SFT Award, 2002*

*JSME Thermal Engineering Division, Award for Contribution, 2003*

*JSME Fellow, 2004*

*Government of Japan, Japanese Medal of Honor (Medal with Purple Ribbon), 2012*

*JSME Thermal Engineering Division, Award for Achievements (Research), 2012*

### **Research Activities**

*Professor Shigenao Maruyama specializes in thermal engineering. He has published more than 10 books and 200 academic research papers, and has acquired 50 patents. He investigated various aspects of fluid flow and energy exchange. Based on the principle that conventional heat transfer and thermal control focuses on the enhancement of heat transfer and temperature control of equipment, he has proposed a novel concept of*

heat-transfer control, in which the heat transfer is actively enhanced or reduced. The proposed active thermal insulation system and a heat-transfer control device utilizes Peltier effects. His work is interdisciplinary utilizing knowledge from various academic disciplines. He has co-authored and edited *Thermodynamics (JSME Text series)* [1], one of the bestselling books on thermodynamics for mechanical engineering students in Japan. He has also published a book to educate the public thermal science [2], and a novel describing accidents in Fukushima Daiichi nuclear plants [3].

Some aspects of his research activities are as follows:

**Radiative heat transfer:** Detailed studies on radiative heat transfer, which is energy transfer by infrared or electromagnetic waves, has been carried out. A generalized analysis method to calculate radiative heat transfer was proposed [4], and this method was applied to analyze heat transfer in semi-conductor processes [5] and industrial furnaces. This method was also applied to large-scale environmental energy transfer processes, such as heat transfer in fogs and clouds [6]. Thermal emission from nano-scale structures was also investigated [7]. These results were published in a monograph [8] which is the first textbook on radiative heat transfer in Japan.

**Natural convection:** Natural convection induced by temperature differences in fluid and the gravitational force was studied, and a generalized description was presented [9]. These results were applied to the cooling fins of electronic devices [10]. This research has been extended to understanding large-scale natural convection in oceanography. The up-welling velocity of deep seawater in the ocean which was proposed by Stommel to be a perpetual salt fountain, was successfully measured for the first time in the world [11].

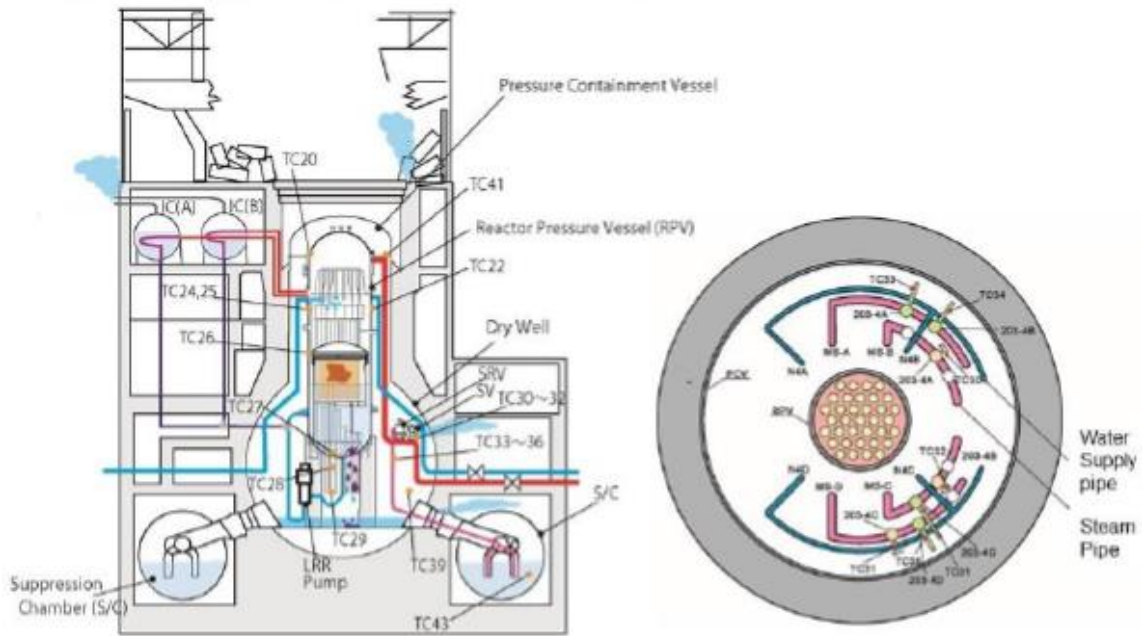
**Active heat-transfer control by Peltier elements:** Peltier elements, used as cooling equipment, have been applied to a heat-transfer control device. This device has been utilized to the heat-transfer control of equipment in a microgravity environment [12], in an active catheter, and in artificial heart muscles [13]. Furthermore, this heat-transfer control has been applied to the fields of oriental medicine and cryosurgery [14]. The concept of heat-transfer control has been expanded to fusion of thermal engineering and medical engineering [15].

## Validation of Unit 1 of the Fukushima Daiichi Nuclear Power Plant During its Accident [22]

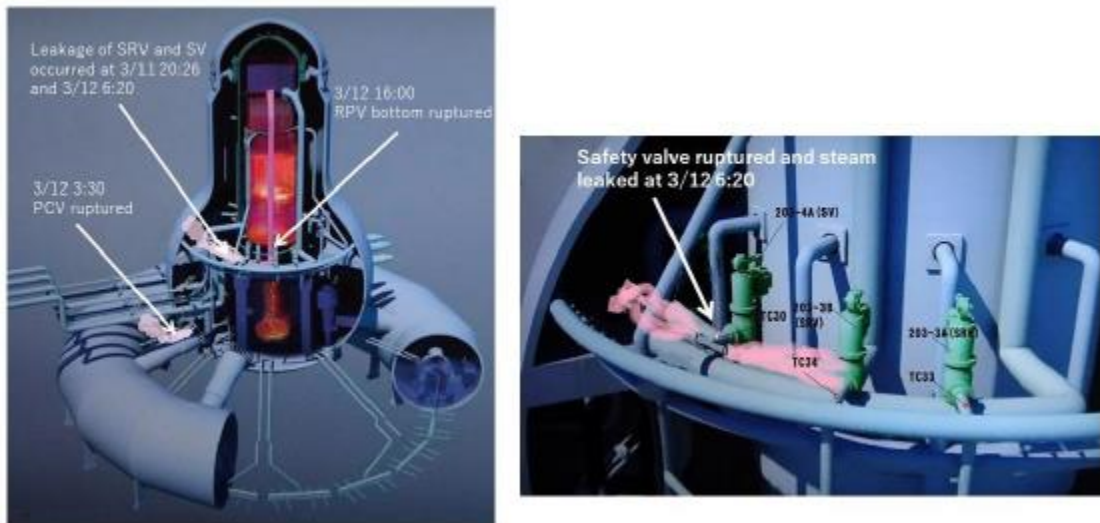
Ten years have passed since the Great East Japan Earthquake and the subsequent accident at the Fukushima Daiichi nuclear power plant (NPP) that occurred on March 11, 2011. The earthquake and tsunami caused significant loss of lives and widespread disaster in Japan.

Several reports have been published on the nuclear accident; however, the original data released at the beginning of the accident were written in Japanese, and some of these documents are no longer accessible. Some of the scenarios pertaining to the accident have become standardized theories, and these scenarios may be passed down to future generations with different descriptions, which may not fully describe the actual occurrences. To prevent future nuclear accidents, the accident at Fukushima Daiichi must be properly understood and analyzed.

Our research group had been analyzing the accident since immediately after its occurrence [2]. To investigate the process of the NPP accidents, Unit 1 of the Fukushima Daiichi NPP was analyzed using data available to the public. A phase-equilibrium thermodynamic model was used in the analysis. We proposed an accident scenario in which the isolation condenser (IC) of Unit 1 may have been working to a certain extent. Moreover, the behavior of the reactor water level meter at the time of the accident was analyzed, and we attempted to reproduce the measurement data of the reactor water level meter and the pressure data measured during the accident. Furthermore, based on the temperature data of various measuring points and the estimated accident scenario of Unit 1, we also presented a bold estimation of the locations and times of damages in the reactor pressure vessel (RPV) and primary containment vessel (PCV).



**Fig. 1** Reactor cross section and estimated temperature measurement points around SV and SRV.



**Fig. 2** Bold prediction of the positions and times of vessel ruptures according to the present accident scenario.

In the present study, the original data reported in the first stage of the accident are examined to clarify the behavior of the ICs, which are generally believed to have been nonfunctional after the tsunami and station blackout. The original data and observation reports verified that the so called “fail-safe” system to close the valves in the ICs did not work properly owing to the shutdown of AC power.

This report assumes that the leakage of the RPV occurred at 20:26 on March 11, 2011 owing to overheat of the nuclear fuel clusters. It is estimated that the leakage of the PCV occurred at 03:30 on March 12. A large break in the RPV occurred at 06:20 and again at 16:00. It is estimated that a large portion of the fuel remains in the RPV; however, the

Tokyo Electric Power Company (TEPCO) estimated that most of the fuel had melted out through the RPV. The present analysis model and accident scenario explain the data measured at the accident and several evidence and witness reports that were collected at the early stage of the accident.

The author attempted to boldly predict the positions and times of vessel ruptures according to the present accident scenario. By examining the temperature data of each part of the reactor obtained after March 23, it is presumed that leakages from the RPV or a main steam safety relief valve (SRV) at 10:26, on March 11. And the rupture of safety valves (SVs) occurred at 6:20, on March 12. The significantly high temperature of the steam that discharged through the valves had destroyed the valve seats.

## References

- [1] S. Maruyama et al.: *JSME Text series "Thermodynamics"*, Ed. S. Maruyama, JSME, (2002).
- [2] S. Maruyama: *Thermal Science for Everyone*, Tohoku University Press, (2016).
- [3] S. Maruyama: *FUKUSHIMA*, Yokendo Press, (2012).
- [4] S. Maruyama and T. Aihara: Radiation Heat Transfer of Arbitrary Three-Dimensional Absorbing, Emitting and Scattering Media and Specular and Diffuse Surfaces, *Journal of Heat Transfer*, Vol. 119, (1997), pp. 129-136.
- [5] Z. Guo, S. Maruyama and S. Togawa: Combined Heat Transfer in Floating Zone Growth of Large Silicon Crystals with Radiation on Diffuse and Specular Surfaces, *Journal of Crystal Growth*, Vol. 194, (1998), pp. 321-330.
- [6] T. Nishikawa, S. Maruyama and S. Sakai: Radiative Heat Transfer Analysis within Three-Dimensional Clouds Subjected to Solar and Sky Irradiation, *Journal of the Atmospheric Science, American Meteorological Society*, Vol. 61, (2004), pp. 3125-3133.
- [7] S. Maruyama, T. Kashiwa, H. Yugami and M. Esashi: Thermal Radiation from Two-dimensionally Confined Modes in Microcavities, *Applied Physics Letters*, Vol. 79, No. 9, (2001), pp. 1393-1395.
- [8] S. Maruyama: *Light Energy Engineering*, Yokendo Press, (2004).
- [9] T. Aihara, S. Maruyama, and J. S. Choi: Laminar Free Convection with Variable Fluid Properties in Vertical Ducts of Different Cross-Sectional Shapes, *Proceedings of The 8th International Heat Transfer Conference*, San Francisco, Vol. 4, (1986), pp. 1581-1586.
- [10] T. Aihara and S. Maruyama: Optimum Design of Natural Cooling Heat Sinks with Vertical Rectangular Fin Arrays, *Cooling Technology for Electronic Equipment*, Hemisphere, (1988), pp. 35-54.
- [11] S. Maruyama, K. Tubaki, K. Taira and S. Sakai: Artificial Upwelling of Deep Seawater Using the Perpetual Salt Fountain for Cultivation of Ocean Desert, *Journal of Oceanography*, Vol. 60, (2004), pp. 563-568.
- [12] S. Maruyama, K. Ohno, A. Komiya and S. Sakai: Description of the Adhesive Crystal Growth under Normal and Micro-Gravity Conditions Employing Experimental and Numerical Approaches, *Journal of Crystal Growth*, Vol. 245, (2002), pp. 278-288.
- [13] R. Ibuki, S. Maruyama, A. Komiya and T. Yambe: Design of Plate-type Actuator Using SMA Wire for Assistant Artificial Heart Muscle, *Journal of Intelligent Material Systems and Structures*, Vol. 19, (2008), pp. 359-365.
- [14] H. Takeda, S. Maruyama, J. Okajima, S. Aiba and A. Komiya: Development and Estimation of a Novel Cryoprobe Utilizing the Peltier Effect for Precise and Safe Cryosurgery: *Cryobiology*, Vol. 59, No. 3, (2009), pp. 275-284.
- [15] T. Okabe, J. Okajima, A. Komiya and S. Maruyama: Development of a Guard-Heated Thermistor Probe for the Measurement of Surface Temperature, *International Journal of Heat and Mass Transfer*, Vol. 108, (2017), pp. 2283-2292.
- [16] S. Maruyama, K. Deguchi, M. Chisaki, J. Okajima, A. Komiya, and R. Shirakashi: Proposal for a Low CO<sub>2</sub> Emission Power Generation System Utilizing Oceanic Methane Hydrate", *Energy*, Vol. 47, (2012), No. 1, pp. 340-347, 2012.
- [17] L. Chen, H. Sasaki, T. Watanabe, J. Okajima, A. Komiya and S. Maruyama, Production Strategy for Oceanic Methane Hydrate Extraction and Power Generation with Carbon Capture and Storage (CCS), *Energy*, Vol. 126, (2017), pp. 256-272.

- [18] L. Chen, Y. Feng, T. Kogawa, J. Okajima, A. Komiya, and S. Maruyama: Construction and Simulation of Reservoir Scale Layered Model for Production and Utilization of Methane Hydrate: The case of Nankai Trough Japan", *Energy*, Vol. 143, (2018), pp. 128-140.
- [19] S. Maruyama, T. Nagayama, G. Gonome, and J. Okajima: Possibility for Controlling Global Warming by Launching Nanoparticles into the Stratosphere, *Journal of Thermal Science and Technology*, Vol.10, No. 2, (2015), p. JTST002.
- [20] S. Maruyama: Concept design of linear-motor-accelerated projectile for nanoparticle dispersion in stratosphere, *Thermal Science and Technology*, Vol. 15, (2019), No. 1, p. 100437
- [21] S. Maruyama and S. Moriya, Newton's Law of Cooling: Follow up and exploration, *International Journal of Heat and Mass Transfer*, Vol. 164, (2020), No. 120544, pp.1-13.
- [22] S. Maruyama: Validation of unit 1 of the Fukushima Daiichi nuclear power plant during its accident, *Global Journal of Researches in Engineering: F*, Vol. 21, (2021), pp. 1-38.

# Ultrasonic Sensor Development for the Semi-Solid Metal Working Process

by Bernhard R. Tittmann, Member EUAS



## Short Biography

*Schell Professor of Engineering, Emeritus  
Director of Engineering Nanostructure Characterization Center  
The Pennsylvania State University*

### **Academic Training**

*B.S. (Physics and Mathematics), George Washington University, Washington, DC, 1957  
Ph.D. (Solid State Physics), University of California at Los Angeles, CA, 1965*

### **Teaching Experience:**

*Professor, The Pennsylvania State University, University Park, PA 16802, 1989-present;  
Visiting Professor, Fall 2017, University of California, Santa Barbara, CA  
Visiting Professor, Spring 1995-1997. Johannes Kepler University, Linz, Austria.  
Visiting Professor, University of Paris III, Physics Department, 1977, 1979, 1982.  
Assistant Professor (in residence), 1965-1966. Physics Department, University of California at Los Angeles, CA.*

### **Industrial Experience**

*Manager, Materials Characterization. Science Center, Rockwell Intern., 1979 - 1989.  
Member Staff, Materials Mechanics Group. Science Center, Rockwell, 1966-1977.  
Howard Hughes Fellow – Microwave Antenna Dept.; Hughes Research Lab., Culver City, CA, 1957-1962.*

### **Professional Societies and Activities**

*American Ceramic Society (ACS), Member 1995 – present  
American Society for Metals (ASM) International, Member 1993, Fellow 2006 – present  
American Society of Nondestructive Testing (ASNT), Member 1980 – present  
Materials Research Society (MRS), Member, 1995 – present  
American Society of Mechanical Engineers (ASME), Member, 2001 – present  
Acoustical Society of America (ASA), Fellow, 2001 – present  
Technical Program Committee - Standing Member, 1999 to present  
Institute of Electrical and Electronics Engineering (IEEE), Fellow, 1990 – present  
Distinguished IEEE – UFFC Lecturer, June 1998 – December 1999  
Vice-Chair of Awards Committee, IEEE – UFFC, 2003-present  
International Society for Optical Engineering (SPIE), Senior Member*

### **Awards/Honors**

*Penn State Acoustics and Vibration Group award, 2017  
2021 NDT Lester/Mehl Honorary Lecture Award  
Penn State Certificate of Recognition, 2014  
2019 NDT Award for Sustained Excellence in Research.  
Albert Nelson Marquis Lifetime Achievement Award 2018  
Google Scholar  
Top 100 Registry Professors of the Year, 2018  
EU Academy of Sciences, January 2018  
Schell Professor, Emeritus July 2017.  
Endowed Chair at Penn State College of Engineering Schell Professor of Engineering 1989 (renewed 5 times) to June, 2017.  
IEEE-UFFC Distinguished Service Award 2017  
IEEE-UFFC Invited Speaker at 2017 Int. Ultrasonics Symposium, Washington, D.C.  
Named Consulting Editor of Archives of Acoustics, Polish Academy of Sciences, Warsaw, 2003*

*Penn State Engineering Society Outstanding Research Award, 1998*  
*Senior Fulbright Fellowship, Spring and Summer 1999*  
*Rockwell Award for Highest IR&D Score Rockwell Science Center (1988)*  
*NASA Principal Investigator Award for "Elastic and Anelastic Properties of Lunar Rock (1979)."*  
*Howard Hughes Fellow (1957-1962).*  
*Phi Beta Kappa (1957).*  
*Graduation Cum Laude (1957).*  
*G. Washington Tuition Scholarship (1953-1957).*  
**Accomplishment**  
*Graduated 11 PhD students and 25 MS students.*  
*Citations 4949; h-index 36; i10 index 122*  
*Over 600 publications including refereed Journal publications and refereed Proceedings.*  
*8 Patents*

## **Ultrasonic Sensor Development for the Semi-Solid Metal Working Process**

### **Abstract**

Semisolid Metalworking (SSM) is a hybrid manufacturing process that incorporates the advantages of both casting and forging. However, high volume commercial production has suffered from inadequacies in process monitoring and control. A key process parameter is the SSM solid-liquid fraction, which is a sensitive indicator of the deformation and flow behavior of the material during forming. Unfortunately, no sensor currently exists to provide an in-situ measurement of this important parameter. Here we present preliminary results for an advanced ultrasonic sensor to measure solid fraction. With the aid of metal alloy phase diagrams, the binary alloy Sn-Bi was chosen to simulate behavior of Al/Si (e.g., 300 series) alloys. The phase diagram was used to provide the value of solid fraction at any given temperature. Measurements with longitudinal ultrasonic waves at 1 MHz in the selected alloy heated to different solid fractions were performed with a combination of commercial transducers and quartz buffers penetrating into a temperature-controlled furnace. Five compositions were used ranging from 83% to 100% -Bi in the binary Sn-Bi alloy. Presented are measurements of longitudinal wave velocity as a function of temperature across the entire range from totally solid to semi-solid to liquid states in both heating and cooling runs. The curves show the characteristic phase transitions. A quasi-static viscoelastic model based on Atkinson, Kytömaa and Berryman was prepared and modified for the SSM application. The comparison of the model calculations with the experimental results were in reasonable agreement. With the recent development of high temperature ultrasonics our results provide a potential solution to the development of an ultrasonic sensor for SSM.

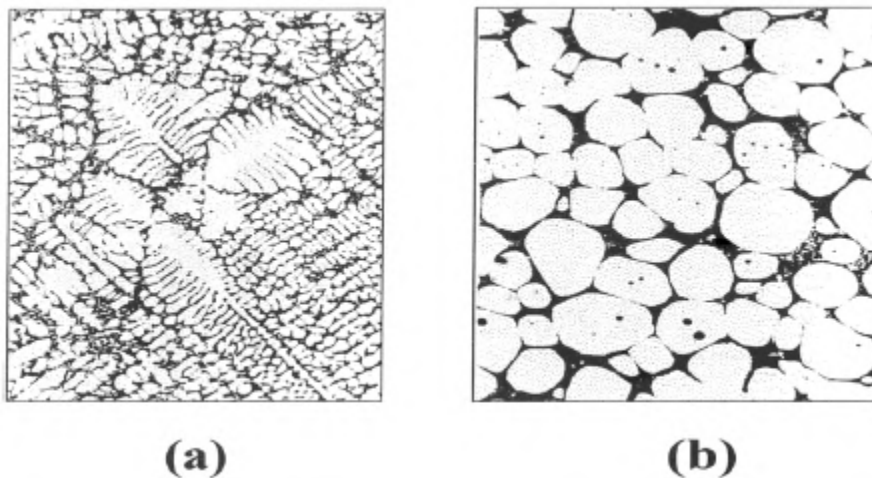
### **1. Introduction**

Semisolid Metalworking (SSM) is a hybrid manufacturing process that incorporates the advantages of both casting and forging. The superior microstructure is evident in Fig. 1. However, high volume commercial production has suffered from inadequacies in process monitoring and control. A key process parameter is the SSM solid-liquid fraction, which is a sensitive indicator of the deformation and flow behavior of the material during forming. Unfortunately, no sensor currently exists to provide an in-situ measurement of this important parameter. Here we present preliminary results for an advanced ultrasonic sensor to measure solid fraction.

## 2. Model and Algorithm Development

The work began with the realization that the wave propagation in SSM materials should be studied on the basis of the two main contributing phenomena, which are viscous losses in the melt and multiple scattering from the secondary phase. The goal of this study is to fuse various formulae into a single model in order to simulate the response of the ultrasonic sensor and provide values for the solid fraction of SSM material from the wave propagation parameters obtained for a given temperature. The model was to be as generic as possible so that it included a wide variety of rheocast materials including steel. An algorithm or method of solving the formulae comprising the model is being developed.

A self-consistent quasi-static viscoelastic model (Model I) based on Atkinson and Kytomaa [1] and Berryman [2, 3] was prepared and modified for the SSM application. The forward solution was carried out and, with the solid volume fraction as input parameter, the ultrasonic velocity was calculated. The comparison with the experimental results on Sn-98%Bi gave agreement of  $\pm 1\%$ . The frequency dependence for the ultrasonic velocity and attenuation was predicted to be weak. The model is summarized below.



**Figure 1.** Comparison of cast (a) and semisolid formed (b) microstructures

Equations 1.a-f are used to combine all of the constituents of each phase together to reduce the problem to a binary system of the two phases. The rules for combining the constituents of each phase are those as derived by Berryman [2, 3]. Each of the constituent properties is a function of temperature as is the volume fraction. In each of these equations the resulting phase effective value is function of temperature. In the forward model (a-priori knowledge of the volume fraction of solid), the equation for the volume fraction of solid must be known. The phase diagram is one source of this information as it was for the tin-bismuth alloy used in the experiments for testing this model. With the tin-bismuth alloy, the liquidus had a very good linear approximation.

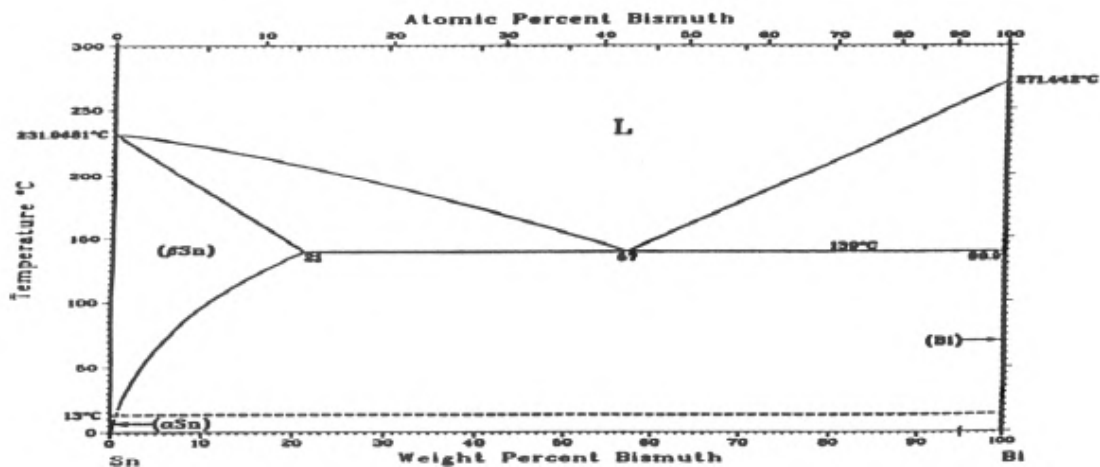
Thus the lever rule was easy to apply in a computer simulation. This proved advantageous because the density of the liquid phase is also very dependent on the phase response of the alloy with temperature. The lever rule was also applied here to compute the amount of each of the alloy's constituents that are in the liquid phase. For this to be applied, the assumption that the percent weight of the material is equal to the percent volume is used. This assumption requires that the density and volume change in such a way that the same weight of material uses the same volume of space at all temperatures in a fixed phase.

Equations 1.a-f are used to define the materials' effective properties. Up to some solid fraction amount, the solid phase of the alloy makes a path for the propagation of the acoustic wave. To account for the shear modulus effect on the wave propagation through an elastic medium, the unit step function is used to limit the shear modulus affects to the volume fractions where enough connectivity exists in the solid matrix to support shear waves (1.0 to  $v^*$ ).

### 3. Verification Experiments

The work began with a literature survey into previous experimental and modeling results for wave propagation in dense mixtures and suspensions. With the aid of metal alloy phase diagrams, the binary alloy Sn-Bi was chosen to simulate the behavior of Al/Si (e.g., 300 series) alloys. Care was taken to select an alloy with a reasonably broad range of temperatures over which the semi-solid state exists. The phase diagram, shown in Fig. 2 was used to provide the value of solid fraction at any given temperature. The solid fraction as a function of temperature for different percentages of Bi content is shown in Fig. 3.

A high temperature furnace was designed and built out of Aluminum and is shown in Fig 4.



- (a) Effective shear modulus of semi-solid metal
- (b) Effective density of semi-solid metal
- (c) Equation for algebraic convenience
- (d) Effective bulk modulus of semi-solid metal

(a) 
$$G = G\mu[v - v^*]$$

(b) 
$$\rho = v\rho_s + (1-v)\rho_L$$

(c) 
$$\rho^* = (1-v)\rho_s + v\rho_L$$

(d) 
$$\frac{1}{\bar{K}} = \frac{v}{K_s + \frac{4G}{3}} + \frac{1-v}{-K}$$

The expressions for the wave velocity and attenuation are:

- (e) Wave velocity through semi-solid metal

(e) 
$$V = \sqrt{\frac{\bar{K}}{\bar{\rho}}}$$

(f) 
$$\alpha = \left| \frac{[a\omega]^2}{[3\mu]} (1-v) \frac{\rho_s \rho - \rho\rho^*}{\sqrt{K\rho}} \right|$$

# Mesenchymal Stromal Cells for Transplant Tolerance

by Giuseppe Remuzzi, Member EUAS

## Short Biography

*Giuseppe Remuzzi completed his medical training at the University of Pavia in 1974 and then received specialty training in Haematology and Nephrology at the University of Milan in 1977 and 1980, respectively. From 1996 until 2013 he was Director of the public-private Department of Immunology and Transplant Medicine (a collaboration between the Ospedali Riuniti of Bergamo and the Mario Negri Institute) and from 1999 until 2018 he has also been Head of the Division of Nephrology and Dialysis. From 2011 until 2015 he was Director of the Department of Medicine of the Azienda Ospedaliera Papa Giovanni XXIII (formerly the Ospedali Riuniti) of Bergamo. In June 2015 he was nominated Chiara Fama Professor of Nephrology at the University of Milan. Alongside his clinical work in hospital, Prof. Remuzzi has dedicated himself to intense didactic and research activities. Since the Mario Negri Institute for Pharmacological Research opened its branch in Bergamo, Prof. Remuzzi has coordinated all of the research that takes place there, and since 1992 he has done the same for the Aldo e Cele Daccò Clinical Research Centre for Rare Diseases in Ranica, Bergamo. Since July 1st Professor Remuzzi has also taken on the role of Director of the the Mario Negri Institute. His main research interests include the causes of glomerulonephritis and the mechanisms of progression of kidney diseases. He has also conducted many studies in the field of transplant rejection. With an innovative approach (transplanting two kidneys from older donors into one recipient, after carefully evaluating the condition of the organs), his research has facilitated an increase in the number of transplants conducted. His most recent research concerns the possibility of regenerating tissues and creating organs in the laboratory using stem cells.*

*Prof. Remuzzi serves on editorial boards of numerous journals and is member of the International Advisory Board of The Lancet. He served as Editorial Board member of the New England Journal of Medicine from 1998-2013. In recognition of his achievements, he has been awarded in 1998 honorary memberships of the Association of American Physicians and the British Royal College of Physicians. In 2005 during the World Congress of Nephrology in Singapore he received the ISN Jean Hamburger Award. In 2007 he received during the annual American Society of Nephrology Congress in San Francisco the prestigious ASN John P. Peters Award and in 2011 he was awarded with the ISN AMGEN Award (World Congress of Nephrology: WCN 2011, Vancouver). In November 2011 he received the Third Edition of the International Award "Luis Hernando" assigned by the Iñigo Alvarez de Toledo Renal Foundation (FRIAT) in Madrid, Spain.*

*From June 2013 until March 2015 he was President of the International Society of Nephrology (ISN). During his tenure he created and launched the global Oby25 project, the goal of which is that "Nobody should die of preventable and treatable Acute Kidney Injury (AKI) by 2025".*

*In April 2018 he was awarded the "Lennox K. Black International Prize for Excellence in Medicine" at the Thomas Jefferson University in Philadelphia.*

*Prof. Remuzzi is the author of over 1450 publications in International medical journals and has written 16 books. He also regularly writes editorials for the Corriere della Sera newspaper.*

## **Mesenchymal Stromal Cells for Transplant Tolerance**

Manuel Alfredo Podestà, Giuseppe Remuzzi, Federica Casiraghi

*Front Immunol. 2019 Jun 4;10:1287*

## **Abstract**

In solid organ transplantation lifelong immunosuppression exposes transplant recipients to life-threatening complications, such as infections and malignancies, and to severe side effects. Cellular therapy with mesenchymal stromal cells (MSC) has recently emerged as a promising strategy to regulate anti-donor immune responses, allowing immunosuppressive drug minimization and tolerance induction. In this review we summarize preclinical data on MSC in solid organ transplant models, focusing on potential mechanisms of action of MSC, including down-regulation of effector T-cell response and activation of regulatory pathways. We will also provide an overview of available data on safety and feasibility of MSC therapy in solid organ transplant patients, highlighting the issues that still need to be addressed before establishing MSC as a safe and effective tolerogenic cell therapy in transplantation.

### **Octreotide-LAR in later-stage autosomal dominant polycystic kidney disease (ALADIN 2): A randomized, double-blind, placebo-controlled, multicenter trial**

Norberto Perico, Piero Ruggenti, Annalisa Perna, Anna Caroli, Matias Trillini, Sandro Sironi, Antonio Pisani, Eleonora Riccio, Massimo Imbriaco, Mauro Dugo, Giovanni Morana 8, Antonio Granata 9, Michele Figuera 10, Flavio Gaspari 1, Fabiola Carrara, Nadia Rubis, Alessandro Villa, Sara Gamba, Silvia Prandini, Monica Cortinovis, Andrea Remuzzi, Giuseppe Remuzzi  
*PLoS Med* 2019 Apr 5;16(4):e1002777

#### **Abstract**

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent genetically determined renal disease. In affected patients, renal function may progressively decline up to end-stage renal disease (ESRD), and approximately 10% of those with ESRD are affected by ADPKD. The somatostatin analog octreotide long-acting release (octreotide-LAR) slows renal function deterioration in patients in early stages of the disease. We evaluated the renoprotective effect of octreotide-LAR in ADPKD patients at high risk of ESRD because of later-stage ADPKD.

**Methods and findings:** We did an internally funded, parallel-group, double-blind, placebo-controlled phase III trial to assess octreotide-LAR in adults with ADPKD with glomerular filtration rate (GFR) 15-40 ml/min/1.73 m<sup>2</sup>. Participants were randomized to receive 2 intramuscular injections of 20 mg octreotide-LAR (n = 51) or 0.9% sodium chloride solution (placebo; n = 49) every 28 days for 3 years. Central randomization was 1:1 using a computerized list stratified by center and presence or absence of diabetes or proteinuria. Co-primary short- and long-term outcomes were 1-year total kidney volume (TKV) (computed tomography scan) growth and 3-year GFR (iohexol plasma clearance) decline. Analyses were by modified intention-to-treat. Patients were recruited from 4 Italian nephrology units between October 11, 2011, and March 20, 2014, and followed up to April 14, 2017. Baseline characteristics were similar between groups. Compared to placebo, octreotide-LAR reduced median (95% CI) TKV growth from baseline by 96.8 (10.8 to 182.7) ml at 1 year (p = 0.027) and 422.6 (150.3 to 695.0) ml at 3 years (p = 0.002). Reduction in the median (95% CI) rate of GFR decline (0.56 [-0.63 to 1.75] ml/min/1.73 m<sup>2</sup> per year) was not significant (p = 0.295). TKV analyses were adjusted for age, sex, and baseline TKV. Over a median (IQR) 36 (24 to 37) months of follow-up, 9

patients on octreotide-LAR and 21 patients on placebo progressed to a doubling of serum creatinine or ESRD (composite endpoint) (hazard ratio [HR] [95% CI] adjusted for age, sex, baseline serum creatinine, and baseline TKV: 0.307 [0.127 to 0.742],  $p = 0.009$ ). One composite endpoint was prevented for every 4 treated patients. Among 63 patients with chronic kidney disease (CKD) stage 4, 3 on octreotide-LAR and 8 on placebo progressed to ESRD (adjusted HR [95% CI]: 0.121 [0.017 to 0.866],  $p = 0.036$ ). Three patients on placebo had a serious renal cyst rupture/infection and 1 patient had a serious urinary tract infection/obstruction, versus 1 patient on octreotide-LAR with a serious renal cyst infection. The main study limitation was the small sample size.

**Conclusions:** In this study we observed that in later-stage ADPKD, octreotide-LAR slowed kidney growth and delayed progression to ESRD, in particular in CKD stage 4.

### **The role of B7-1 in proteinuria of glomerular origin**

Rubina Novelli 1, Ariela Benigni 1, Giuseppe Remuzzi

*Nat Rev Nephrol* 2018 Sep;14(9):589-596.

#### **Abstract**

The damage and loss of podocytes is a primary hallmark of nephrotic syndrome. In the pursuit of targetable molecules that are involved in podocyte pathophysiology, some studies have identified B7-1 (also known as CD80) as a potential biomarker. Furthermore, B7-1 blockade has been proposed as a podocyte-specific treatment for patients with nephrotic syndrome who have limited therapeutic options, such as those with focal segmental glomerulosclerosis, minimal change disease, diabetic nephropathy and lupus nephritis. In this Perspectives article, we describe and compare supporting and contradicting data on the role of podocyte B7-1 in the pathogenesis of various podocytopathies. Moreover, we highlight crucial issues that should be addressed urgently - such as standardization of sample processing time, material conservation and antibody usage in immunohistochemical protocols - as a clinical trial that is investigating the efficacy of B7-1 blockade in treatment-resistant nephrotic syndrome is ongoing.

### **Experimental Evaluation of Kidney Regeneration by Organ Scaffold Recellularization**

Andrea Remuzzi, Marina Figliuzzi, Barbara Bonandrini, Sara Silvani, Nadia

Azzollini, Roberta Nossa, Ariela Benigni, Giuseppe Remuzzi

*Sci Rep* 2017 Mar 7;7:43502

#### **Abstract**

The rising number of patients needing renal replacement therapy, alongside the significant clinical and economic limitations of current therapies, creates an imperative need for new strategies to treat kidney diseases. Kidney bioengineering through the production of acellular scaffolds and recellularization with stem cells is one potential strategy. While protocols for obtaining organ scaffolds have been developed successfully, scaffold recellularization is more challenging. We evaluated the potential of in vivo and in vitro kidney scaffold recellularization procedures. Our results show that acellular scaffolds implanted in rats cannot be repopulated with host cells, and in vitro recellularization is necessary. However, we obtained very limited and inconsistent cell seeding when using different infusion protocols, regardless of injection site. We also obtained experimental and theoretical data indicating that uniform cell delivery into the kidney scaffolds cannot be

obtained using these infusion protocols, due to the permeability of the extracellular matrix of the scaffold. Our results highlight the major physical barriers that limit in vitro recellularization of acellular kidney scaffolds and the obstacles that must be investigated to effectively advance this strategy for regenerative medicine.

### **Liver transplantation for aHUS: still needed in the eculizumab era?**

Rosanna Coppo, Roberto Bonaudo, R Licia Peruzzi, Alessandro Amore, Andrea Brunati, Renato Romagnoli, Mauro Salizzoni, Miriam Galbusera, Eliana Gotti, Erica Daina, Marina Noris, Giuseppe Remuzzi  
*Pediatr Nephrol* 2016 May;31(5):759-68

#### **Abstract**

**Background:** The risk of disease recurrence after a kidney transplant is high in patients with atypical hemolytic uremic syndrome (aHUS) and mutations in the complement factor H (FH) gene (CFH). Since FH is mostly produced by the liver, a kidney transplant does not correct the genetic defect. The anti-C5 antibody eculizumab prevents post-transplant aHUS recurrence, but it does not cure the disease. Combined liver-kidney transplantation has been performed in few patients with CFH mutations based on the rationale that liver replacement provides a source of normal FH.

**Methods:** We report the 9-year follow-up of a child with aHUS and a CFH mutation, including clinical data, extensive genetic characterization, and complement profile in the circulation and at endothelial level. The outcome of kidney and liver transplants performed separately 3 years apart are reported.

**Results:** The patient showed incomplete response to plasma, with relapsing episodes, progression to end-stage renal disease, and endothelial-restricted complement dysregulation. Eculizumab prophylaxis post-kidney transplant did not achieve sustained remission, leaving the child at risk of disease recurrence. A liver graft given 3 years after the kidney transplant completely abrogated endothelial complement activation and allowed eculizumab withdrawal.

**Conclusions:** Liver transplant may definitely cure aHUS and represents an option for patients with suboptimal response to eculizumab.

### **Rituximab in idiopathic membranous nephropathy**

Piero Ruggenti, Paolo Cravedi, Antonietta Chianca, Annalisa Perna, Barbara Ruggiero, Flavio Gaspari, Alessandro Rambaldi, Maddalena Marasà, Giuseppe Remuzzi  
*J Am Soc Nephrol* . 2012 Aug;23(8):1416-25

#### **Abstract**

Selective depletion of B cells with the mAb rituximab may benefit the autoimmune glomerular disease idiopathic membranous nephropathy (IMN). Here, we describe our experience treating 100 consecutive IMN patients with persistent nephrotic syndrome with rituximab. We defined complete remission as persistent proteinuria <0.3 g/24 h and partial remission as persistent proteinuria <3 g/24 h, each also having >50% reduction in proteinuria from baseline. During a median follow-up of 29 months after rituximab

administration, 65 patients achieved complete or partial remission. The median time to remission was 7.1 months. All 24 patients who had at least 4 years of follow-up achieved complete or partial remission. Rates of remission were similar between patients with or without previous immunosuppressive treatment. Four patients died and four progressed to ESRD. Measured GFR increased by a mean 13.2 (SD 19.6) ml/min per 1.73 m<sup>2</sup> among those who achieved complete remission. Serum albumin significantly increased and albumin fractional clearance decreased among those achieving complete or partial remission. Proteinuria at baseline and the follow-up duration each independently predicted the decline of proteinuria. Furthermore, the magnitude of proteinuria reduction significantly correlated with slower GFR decline (P=0.0001). No treatment-related serious adverse events occurred. In summary, rituximab achieved disease remission and stabilized or improved renal function in a large cohort of high-risk patients with IMN.

### **Long-term outcome of renal transplantation from older donors**

Giuseppe Remuzzi, Paolo Cravedi, Annalisa Perna, Borislav D Dimitrov, Marta Turturro, Giuseppe Locatelli, Paolo Rigotti, Nicola Baldan, Marco Beatini, Umberto Valente, Mario Scalamogna, Piero Ruggenenti, Dual Kidney Transplant Group  
*N Engl J Med 2006 Jan 26;354(4):343-52*

#### **Abstract**

**Background:** Long-term survival of kidney grafts from older donors is inferior to that of grafts from younger donors. We sought to determine whether selecting older kidneys according to their histologic characteristics before implantation would positively influence long-term outcome.

**Methods:** In a prospective cohort study, we assessed outcomes among 62 patients who received one or two histologically evaluated kidneys from donors older than 60 years of age. These outcomes were compared with outcomes among 248 matched recipients of single kidney grafts that had not been histologically evaluated and were either from donors 60 years of age or younger (124 positive-reference recipients who, according to available data, were expected to have an optimal outcome) or from those older than 60 years (124 negative-reference recipients, expected to have a worse outcome). The primary end point was graft survival.

**Results:** During a median period of 23 months, 4 recipients (6 percent) of histologically evaluated kidneys progressed to dialysis, as compared with 7 positive-reference recipients (6 percent) and 29 negative-reference recipients (23 percent). Graft survival in recipients of histologically evaluated kidneys did not differ significantly from that of grafts in positive-reference recipients but was superior to that of grafts in negative-reference recipients (hazard ratio for graft failure in the negative-reference recipients relative to the recipients of histologically evaluated kidneys, 3.68; 95 percent confidence interval, 1.29 to 10.52; P=0.02). The performance of preimplantation histologic evaluation predicted better survival both in the whole study group (P=0.02) and among recipients of kidneys from older donors (P=0.01).

**Conclusions:** The long-term survival of single or dual kidney grafts from donors older than 60 years of age is excellent, provided that the grafts are evaluated histologically before implantation. This approach may help to expand the donor-organ pool for kidney

transplantation.

### **Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial**

Giuseppe Remuzzi, Mariadomenica Lesti, Eliana Gotti, Maria Ganeva, Borislav D Dimitrov, Bogdan Ene-Iordache, Giulia Gherardi, Donato Donati, Maurizio Salvadori, Silvio Sandrini, Umberto Valente, Giuseppe Segoloni, Georges Mourad, Stefano Federico, Paolo Rigotti, Vito Sparacino, Jean-Louis Bosmans, Norberto Perico, Piero Ruggenenti

*Lancet* 2004 Aug 7-13;364(9433):503-12.

#### **Abstract**

**Background:** Mycophenolate mofetil has replaced azathioprine in immunosuppression regimens worldwide to prevent graft rejection. However, evidence that its antirejection activity is better than that of azathioprine has been provided only by registration trials with an old formulation of ciclosporin and steroid. We aimed to compare the antirejection activity of these two drugs with a new formulation of ciclosporin.

**Methods:** The mycophenolate steroids sparing multicentre, prospective, randomised, parallel-group trial compared acute rejections and adverse events in recipients of cadaver-kidney transplants over 6-month treatment with mycophenolate mofetil or azathioprine along with ciclosporin microemulsion (Neoral) and steroids (phase A), and over 15 more months without steroids (phase B). The primary endpoint was occurrence of acute rejection episodes. Analysis was by intention to treat.

**Findings:** 168 patients per group entered phase A. 56 (34%) assigned mycophenolate mofetil and 58 (35%) assigned azathioprine had clinical rejections (risk reduction [RR] on mycophenolate mofetil compared with azathioprine 13.7% [95% CI -25.7% to 40.7%],  $p=0.44$ ). 88 patients in the mycophenolate mofetil group and 89 in the azathioprine group entered phase B. 14 (16%) taking mycophenolate mofetil and 11 (12%) taking azathioprine had clinical rejections (RR -16.2%, [-157.5% to 47.5%],  $p=0.71$ ). Average per-patient costs of mycophenolate mofetil treatment greatly exceeded those of azathioprine (phase A 2665 Euros [SD 586] vs Euros 184 [62]; phase B 5095 Euros [2658] vs 322 Euros [170],  $p<0.0001$  for both).

**Interpretation:** In recipients of cadaver kidney-transplants given ciclosporin microemulsion, mycophenolate mofetil offers no advantages over azathioprine in preventing acute rejections and is about 15 times more expensive. Standard immunosuppression regimens for transplantation should perhaps include azathioprine rather than mycophenolate mofetil, at least for kidney grafts.

### **Preventing microalbuminuria in type 2 diabetes**

Piero Ruggenenti, Anna Fassi, Anelja Parvanova Ilieva, Simona Bruno, Ilian Petrov Iliev, Varusca Brusegan, Nadia Rubis, Giulia Gherardi, Federica Arnoldi, Maria Ganeva, Bogdan Ene-Iordache, Flavio Gaspari, Annalisa Perna, Antonio Bossi, Roberto Trevisan, Alessandro R Dodesini, Giuseppe Remuzzi, Bergamo Nephrologic Diabetes

Complications Trial (BENEDICT) Investigators  
*N Engl J Med* 2004 Nov 4;351(19):1941-51

#### Abstract

**Background:** The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether angiotensin-converting-enzyme inhibitors and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion.

**Methods:** We studied 1204 subjects, who were randomly assigned to receive at least three years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day), or placebo. The target blood pressure was 120/80 mm Hg. The primary end point was the development of persistent microalbuminuria (overnight albumin excretion,  $>$  or  $=20$  microg per minute at two consecutive visits).

**Results:** The primary outcome was reached in 5.7 percent of the subjects receiving trandolapril plus verapamil, 6.0 percent of the subjects receiving trandolapril, 11.9 percent of the subjects receiving verapamil, and 10.0 percent of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo ( $P=0.01$ ), 0.47 for the comparison between trandolapril and placebo ( $P=0.01$ ), and 0.83 for the comparison between verapamil and placebo ( $P=0.54$ ). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Serious adverse events were similar in all treatment groups.

**Conclusions:** In subjects with type 2 diabetes and hypertension but with normoalbuminuria, the use of trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. The effect of verapamil alone was similar to that of placebo.

#### Progression, remission, regression of chronic renal diseases

P. Ruggenenti, A. Schieppati, G. Remuzzi  
*Lancet* 2001 May 19;357(9268):1601-8

#### Abstract

The prevalence of chronic renal disease is increasing worldwide. Most chronic nephropathies lack a specific treatment and progress relentlessly to end-stage renal disease. However, research in animals and people has helped our understanding of the mechanisms of this progression and has indicated possible preventive methods. The notion of renoprotection is developing into a combined approach to renal diseases, the main measures being pharmacological control of blood pressure and reduction of proteinuria. Lowering of blood lipids, smoking cessation, and tight glucose control for diabetes also form part of the multimodal protocol for management of renal patients. With available treatments, dialysis can be postponed for many patients with chronic nephropathies, but the real goal has to be less dialysis—in other words remission of disease and regression of

structural damage to the kidney. Experimental and clinical data lend support to the notion that less dialysis (and maybe none for some patients) is at least possible.

**Kidney graft survival in rats without immunosuppressants after intrathymic glomerular transplantation**

G Remuzzi, M Rossini, O Imberti, N Perico

*Lancet. 1991 Mar 30;337(8744):750-2*

**Abstract**

Isolated glomeruli from Brown-Norway (RT1n) rat kidney were inoculated into the thymus of 6 incompatible Lewis (RT1(1)) rats pretreated for 2 days with 40 mg/kg oral cyclosporin daily and given 2.5 mg/kg subcutaneous dexamethasone at inoculation. 10 days later the left kidney from the Brown-Norway donor used to prepare glomeruli was transplanted orthotopically to the Lewis (RT1(1)) rat that had received intrathymic glomeruli. Donor-specific unresponsiveness allowed the renal allograft to survive indefinitely without further immunosuppression. 6 control Lewis rats treated as above except that medium alone was injected intrathymically rejected a renal allograft within 7-9 days.

# Optimal Control Computation -- A Brief Introduction

by Kok Lay Teo, Member EUAS

## Short Biography

Professor Teo obtained his PhD degree in electrical engineering, University of Ottawa, Canada in 1974. From 1974 to 1998, he held a regular, fulltime teaching and research position at The University of New South Wales, National University of Singapore, and The University of Western Australia in respective periods of time. From January 1997 to December 1998, he was Professor of Applied Mathematics at Curtin University of Technology. From January, 1999 to December 2004, he was the Chair Professor of Applied Mathematics and Head of the Department of Applied Mathematics at The Hong Kong Polytechnic University. From January, 2005 to December 2010, he was the Professor of Applied Mathematics and Head of the Department of Mathematics and Statistics at Curtin University. He was John Curtin Distinguished Professor, the highest rank professor at Curtin University from January 2011 until he retired from Curtin University in November 2019. While waiting for the award of John Curtin Distinguished Emeritus Professor, he was given the title of Adjunct Professor so that he could use the facility at Curtin University during this waiting period. Since December 2021, he has been a John Curtin Distinguished Emeritus Professor. Professor Teo has taken up the position as a Professor and Associate Dean (Research & Postgraduate Studies) in the School of Sunway University, Sunway University in May 2021.

## **Achievements**

- Professor Teo was the Head of Applied Mathematics Department in the Hong Kong Polytechnic University, Hong Kong from 1999 to 2004, and under the foundation build through his leadership, the Department is now a world leading Mathematics Department ranked within top 100 by ARWU in a number of years. He was also the Head of Curtin's Department of Maths & Stats from 2005 to 2010 and set a strong foundation for Curtin's Mathematics & Statistics to become a nationally and internationally highly ranked discipline today (equal top 3 in Australia according to ARWU's 2021 result). Professor Teo has also shown strong leadership in external professional activities. He is currently the Chair of Pacific Optimization Research Activity Group (POP) and has been a major player for several international conference series. Professor Teo has established a strong research group specializing in optimal control, and numerical optimization and their practical applications. This group consists of leading researchers in the US, UK, China, Hong Kong, Malaysia and Thailand.
- He successfully supervised over 40 PhD students to completion, and he was the supervisor of over 45 postdoctoral fellows/research fellow/visiting research fellows.

## **Awards/Honours received include**

- Professor Teo was awarded the title of John Curtin Distinguished Professorship, Curtin University from January 2011 until he retired from Curtin University in November 2019. John Curtin Distinguished Professor is the highest ranked Professor at Curtin University. He is now John Curtin Distinguished Emeritus Professor.
- He was the winner of the 2013 John de Laeter Research Leadership Award, Curtin University. This award is the most prestigious award for research achievement at Curtin University.
- He was the winner of the "Senior Researcher of the Year Award 2010" from the Faculty of Science and Engineering at Curtin University.
- He is a Fellow of the Australian Mathematical Society.
- His paper, entitled "The control parameterization method for nonlinear optimal control: A survey", by Lin, Loxton and Teo, *Journal of Industrial and Management Optimization*, 2014, was a winning paper in the prestigious Emerald Citations of Excellence for 2017.

## **Contributions in Research**

### **COMPUTATIONAL OPTIMAL CONTROL**

Professor Teo's important contributions to this field include numerous highly effective computational methods for solving many practically important optimal control problems. The control parameterization technique and constraint transcription method are described in Professor Teo's 1991 monograph "A Unified Computational Approach to Optimal Control Problems" (over 911 citations in Google Scholar). This book

was praised by Sethi and Thompson, who in their own book wrote: "Needless to say, computational methods are required to solve problems with general inequality constraints in all but the simplest of cases. The reader should consult the excellent book by Teo, Goh, and Wong (1991)" (see page 108 of "Optimal Control Theory: Applications to Management Science and Economics," 2nd Edition, 2000). The software package called MISER was developed under his leadership based on the numerical techniques in his 1991 monograph. MISER (version 3.3) was released in 2004. MISER is now used by researchers around the world. A search for "MISER optimal control software" using Google Scholar reveals dozens of papers in which MISER has been used to solve real world problems in applications as diverse as robotics, fishery harvesting, and spacecraft control. Professor Teo has also published a book on solution techniques for optimal control problems arising in cancer chemotherapy: "Optimal Control of Drug Administration in Cancer Chemotherapy" (with R. Martin, published in 1994, over 258 citations in Google Scholar). These techniques have been found indispensable in the development of computational methods for optimal control problems governed by various dynamical systems, such as time delayed systems, switched systems, and stochastic systems. For further details, see the list of publications given.

#### **OPTIMAL CONTROL OF DISTRIBUTED PARAMETER SYSTEMS**

Professor Teo has written two books in this area: "Optimal Control of Distributed Parameter Systems" (with N. U. Ahmed, published in 1981, over 478 citations in Google Scholar) and "Computational Methods for Optimizing Distributed Parameter Systems" (with Z. S. Wu, published in 1984, 65 citations in Google Scholar). These books describe optimality and existence theorems that are now known to be closely related to option pricing in financial mathematics.

#### **DIGITAL FILTER DESIGN and MANAGEMENT SCIENCE**

Professor Teo has developed efficient optimization methods for a number of filter design problems arising in communications engineering. These problems are typically formulated as nonlinear programming problems, semi-infinite and/or semi-definite programming problems, or nonlinear discrete optimization problems. The different formulations are designed to incorporate specific engineering requirements and practical specifications. Professor Teo has developed reliable solution methods based on dual parameterization and constraint transcription for semi-infinite optimization problems, interior-point methods for combined semi-infinite and semi-definite optimization problems, and filled function methods for discrete optimization problems. These results have been published in top international journals, including *IEEE Transactions on Signal Processing*, *IEEE Transactions on Wireless Communications*, *IEEE Transactions on Circuits and Systems*, and *IEEE Communications Letters*.

He has also published numerous high impact papers in prestigious journals such as, *Management Science*, and *European Journal of Operations Research* and *Journal of Global Optimization*, addressing important problems arising in portfolio optimization and supply chain.

## **Optimal Control Computation -- A Brief Introduction**

### **Abstract**

This article is a brief introduction to computation methods for solving optimal control problems. For details including the relevant references, see the recent monograph, titled "Applied and Computational Optimal Control: A Control Parameterization Approach", by Teo, Li, Yu and Rehbock, Springer, 2021

### **1. Introduction**

Broadly speaking, an optimal control problem seeks to optimize a performance measure subject to a dynamical system and a set of algebraic constraints on the state and control variables. Optimal control has many practical applications, such as aquaculture operation, cancer chemotherapy, switched power converters, spacecraft control, ship steering, automobiles or trains, and crystallization process and management sciences. For details,

see the reference section of [2].

The famous Pontryagin maximum principle is a set of necessary conditions of optimality for a constrained optimal control problem. It provides the means to solve many practical problems in various disciplines. Dynamic Programming Principle developed by Bellman has been used to determine optimal feedback controls for a range of practical optimal control problems. However, its application typically requires the solution of a highly nonlinear partial differential equation known as the Hamilton-Jacobi-Bellman (HJB) equation.

For many practical real-life optimal control problems, the underlying dynamical systems are often large scale and highly complex. These optimal control problems are also subject to rigid algebraic constraints arising naturally due to practical limitations and engineering specifications. Thus, it is often not possible to obtain their analytical solutions using Pontryagin maximum principle or dynamic programming. Therefore, we can only depend on computational methods for solving these real-world problems. For this reason, many successful computational methods have been developed to solve many different classes of optimal control problems with various types of constraints in the literature.

In this article, we shall only discuss briefly three families of computation methods.

## 2. Collocation Methods

For a direct local collocation method, the state and control are approximated using a specified functional form. The time interval  $[t_0, T]$  is partitioned into  $N$  subintervals  $[t_{i-1}, t_i]$ ,  $i=1, \dots, N$ , where  $t_N = T$ . Since the state is required to be continuous across intervals, the following condition is imposed for each  $i=1, \dots, N$ :

$$x(t_i^-) = x(t_i^+), \quad i = 2, \dots, N-1,$$

where  $x(t_i^-) = \lim_{t \uparrow t_i} x(t)$  and  $x(t_i^+) = \lim_{t \downarrow t_i} x(t)$ .

Two types of discretization schemes are normally used in the development of algorithms for solving optimal control problems: (i) Runge-Kutta methods; and (ii) orthogonal collocation methods. Runge-Kutta discretization schemes are normally in implicit form. This is because they have better stability properties than those of explicit methods. An algorithm is available in the literature to solve optimal control problems based on orthogonal collocation method, where Legendre-Gauss points, which are chosen as discretized points, are used together with cubic splines over each subinterval. For another algorithm, Lagrange polynomials are used, instead of cubic spline. Note that the application of a direct local collocation to an optimal control problem will give rise to a nonlinear programming problem of very high dimension containing thousands to tens of thousands of variables and a similar number of constraints. However, the nonlinear programming problem will tend to be very sparse with many of the derivatives of the constraint Jacobian being zero. Thus, it can be solved efficiently using nonlinear programming solvers.

A pseudospectral is a global orthogonal collocation method. It approximates the state using a global polynomial, and the collocation is carried out at appropriately chosen discretized points. Typically, the basis functions used are Chebyshev or Lagrange polynomials. For local collocation, the degree of the polynomial is fixed while the number of meshes is varied. On the other hand, for a pseudospectral method, the number of meshes is fixed while the degree of the polynomial is varied. Pseudospectral methods have been used to develop numerical algorithms for solving optimal control problems, where

appropriate discretized points (with the basis functions being Lagrange polynomials) are to be chosen. For example, the Legendre-Gauss-Lobatto points or Chebyshev-Gauss-Lobatto points are chosen as the discretized points for the Gauss-Lobatto pseudospectral method, the Legendre-Gauss points are used as discretized points in the Gauss pseudospectral method, and for the Radau pseudospectral method, Legendre-Gauss-Radau Points are used as discretized points.

### **3. Full Parametrization**

Full parametrization (discretization) is a popular approach for solving optimal control problems, where an optimal control problem is discretized as a finite dimensional optimization problem by using Euler, midpoint, trapezoid or, in general, Runge-Kutta discretization schemes. Among these discretization schemes, Euler discretization scheme is the simplest but most popular one, for which the optimality conditions can be expressed easily. The full discretization approximates an optimal control problem as a nonlinear constrained optimization problems. Then, Sequential Quadratic Programming (SQP) optimization method is utilized to find an optimal (local) control. In addition, SQP optimization method is used again to check numerically whether the obtained control satisfies the second order sufficient conditions, and the post-optimal calculation of the adjoint variables. The Inexact Restoration (IR) method is an iterative finite dimensional optimization method. Each IR iteration consists of two phases---the feasibility phase and optimality phase. They are solved separately as two separate subproblems. It has been shown that if feasibility is improved, while the magnitude of the update in control variables is kept small, then the magnitude of the update in state variables is also small. A local convergence analysis and an associated algorithm for the Inexact Restoration (IR) method have been obtained. Note that the (IR) method is an iterative finite dimensional optimization method. It has been applied to the discretization of optimal control problems such as the application of Euler discretization of state and control to a constrained optimal control problem, where the convergence of the discretized (finite dimensional optimization) problem to an approximate solution using the Inexact Restoration method, and the convergence of the approximate solution to a solution of the original continuous time optimal control problem are established. A practical algorithm is available in the literature developed for the IR method. By using the modeling language AMPL, the adapted version of the algorithm is coded for constrained optimal control problems, where the optimization software Ipopt is used. The convergence of the solution of the Euler discretized problem to a continuous time solution of the original constrained optimal control problem has also been established, where the time derivative of the pure state constraints is adjoined to the Hamiltonian function. This approach is known as the indirect adjoining approach. The adjoint (or costate) variables so obtained differ from those obtained by using the direct adjoining approach. Four discretization methods for ordinary differential equations and differential algebraic equations are proposed in [1], which are discretized by one-step method, backward differentiation formula, linearized implicit Runge-Kutta method and automatic step-size selection.

### **4. Control Parametrization**

The control parametrization method relies on the discretization of the control variables using a finite set of parameters. This is most commonly done by partitioning the time horizon of a given problem into several subintervals such that each control can be

approximated by a piecewise constant function that is consistent with the corresponding partition. The approximating piecewise constant function can be defined in terms of a finite set of parameters, known as control parameters. Upon such an approximation, an optimal control problem becomes a finite dimensional optimal parameter selection problem. In real world, optimal control problems are often subject to constraints on the state and/or control. These constraints can be point constraints and/or continuous inequality constraints. The point constraints are expressed as functions of the states at the end point or some intermediate interior points of the time horizon. These point constraints can be handled without much difficulty. However, for the continuous state inequality constraints, they are expressed as functions of the states and/or controls over the entire time horizon and hence are very difficult to handle. Through the control parametrization, a constrained optimal control problem is approximated as a constrained optimal parameter selection problem, where the continuous state inequality constraints are functions of control parameters rather than control functions. Thus, the approximate optimal parameter selection problem with the continuous state inequality constraints can be viewed as a semi-infinite programming (SIP) problem involving dynamic system. A popular approach to deal with the continuous state inequality constraints is known as the constraint transcription (see, Section 4.3 of [2]). Another effective method to handle continuous state inequality constraints is the exact penalty functions method (see, Section 4.4 of [2]).

After the use of the constraint transcription method or the exact penalty function method, the continuous state inequality constrained optimal parameter selection problem becomes an optimal parameter selection problem subject to constraints in the form of the objective functional, and these constraints are referred to as canonical constraints. Each of these optimal parameter selection problems with canonical constraints can be regarded as a mathematical programming problem, and hence is solvable using existing efficient constrained optimization techniques. The control parametrization technique has been used in conjunction with the constraint transcription or the exact penalty function extensively in the literature. The technique has been proven to be very efficient in solving a wide range of optimal control problems. In particular, several computational algorithms to deal with a variety of different classes of problems together with a sound theoretical convergence analysis are reported in the literature. Under some mild assumptions, convergence of the sequence of approximate optimal costs obtained from a corresponding sequence of partition refinements of the time horizon to the optimal cost of the original optimal control problem has been demonstrated. Furthermore, the solution obtained for each approximate optimal control problem, which is regarded as a constrained optimization problem, is such that the KKT conditions are satisfied. However, there is no proof of the convergence of the approximate optimal controls to true optimal control. Therefore, the approximate optimal control obtained is likely to be not identically the same as the true optimal control, but the difference in the approximate optimal cost and the true optimal cost is insignificant. This is sufficient in real-world applications. Finally, note that the standard control parametrization approach assumes a fixed partition for the piecewise constant (or polynomial) approximation of the control. In many practical problems, it is desirable to allow the knot points of the partition to be variable as well. For this, the Control Parametrization Enhancing Transform (CPET) is introduced in the literature. It is now called the time scaling transformation to better reflect the actual meaning of the transformation. It is now widely used in the literature. As mentioned above, the control parameterization technique approximates the control function by a piecewise constant function for which the heights and the partition points of each subsection of the piecewise constant function are decision variables to be optimized. Thus, the optimal control problem concerned becomes an

optimal parameter selection problem. The variable partition points of the piecewise constant function may cause some difficulties in actual numerical implementation. Thus, the time scaling transformation is used to map these variable partition points of the piecewise constant control into fixed partition points in a new time horizon through the introduction of an additional piecewise constant control with the same set of fixed partition points. The transformed problem is in the same form of the optimal parameter selection problem obtained using standard control parametrization approach.

## 5. Optimal Control Software Packages

Several general-purpose software packages are available in the literature for solving constrained optimal control problems. Recursive Integration Optimal Trajectory Solver (RIOTS) is a collection of programs for solving optimal control problems, designed as a MATLAB toolbox. The method underlying the program is the representation of controls by finite dimensional B-splines to discretize the optimal control problems. In this sense, it is an example of the control parametrization approach. The integration of the system dynamics is carried out using fixed step-size Runge-Kutta integration. The use of Runge-Kutta method to numerically integrate the system dynamics leads to approximations of the optimal control problem. The software can solve a large class of finite time optimal control problems involving path and terminal time constraints, control bounds, variable initial conditions and problems with integral as well as endpoint cost functionals. It also has a special feature for dealing with singular optimal control problems. However, RIOTS comes with some limitations on the type of problems it can effectively solve. Among those, it has difficulty in solving problems with inequality state constraints that require a very high level of discretization. Another disadvantage is associated with the consistent approximations, which require that the approximating problems be defined on finite dimensional subspaces of the control space to which Runge-Kutta methods can be extended. The selection of the control subspaces affects both the accuracy of numerical integration and the accuracy of the approximate solutions to the original problem.

A general-purpose MATLAB software program called GPOPS-II is now available for solving multiple-phase optimal control problems using variable-order Gaussian quadrature collocation methods. In this software, a Legendre-Gauss-Radau quadrature orthogonal collocation method is used to approximate the continuous time optimal control problem by a large sparse nonlinear programming (NLP) problem. Then, an adaptive mesh refinement scheme is utilized to determine the number of mesh intervals and the degree of the approximating polynomial within each mesh interval such that a specified accuracy is achieved. The optimization solver with the software is NLP solver, which can either be quasi-Newton or Newton solver. The derivatives of the functions involved in the optimal control problem, which are required by the NLP solver, are calculated using sparse finite differencing.

The optimal control software package MISER3.3 is an implementation of the control parametrization technique. It has considerable flexibility in the range of features that can be handled. A large variety of constraints is catered for by allowing a general canonical constraint formulation as well as several special types of constraints. In particular, the constraint transcription technique or exact penalty function method can be incorporated in the software to handle continuous time inequality constraints on the state. MISER3.3 has been successfully used to solve a significantly large number of practical optimal control problems. MISER3.3 is written in the FORTRAN programming language as well as in the MATLAB environment. Recently, a new version known as Visual MISER was developed

with the Visual FORTRAN compiler within the Microsoft Visual Studio environment. It provides an easy-to-use interface while retaining the computational efficiency of the MISER3.3 software.

**References**

1. M. Gerds, Optimal Control of ODEs and DAEs. De Gruyter, Berlin (2012)
2. K.L. Teo, B. Li, C.J. Yu and V. Rehbock, Applied and Computational Optimal Control: A Control Parameterization Approach, Springer, 2021.

# Double Wall Cooling Research Investigations

by Phil Ligrani, Member EUAS

## Short Biography

*Eminent Scholar in Propulsion, Professor of Mechanical and Aerospace Engineering, Department of Mechanical and Aerospace Engineering, Propulsion Research Center, 5000 Technology Drive, University of Alabama at Huntsville*

## **PROFESSIONAL PREPARATION**

University of Texas at Austin	Mechanical Engineering	Bachelor of Science, 1974
Stanford University	Mechanical Engineering	Master of Science, 1975
Stanford University	Mechanical Engineering	Doctor of Philosophy, 1980

## **APPOINTMENTS**

2014 – present	<i>Eminent Scholar in Propulsion, Professor of Mechanical and Aerospace Engineering, Department of Mechanical and Aerospace Engineering, University of Alabama</i>
2010 – 2014	<i>Professor of Aerospace &amp; Mechanical Eng, Saint Louis University</i>
2010 – 2013	<i>Director of Graduate Programs, Parks College, Saint Louis University</i>
2006 – 2009	<i>Statutory Professor, Department of Engineering Science, University of Oxford</i>
2006 – 2009	<i>Director, Rolls-Royce UTC (University Technology Centre)</i>
1997 – 2006	<i>Professor, Department of Mechanical Engineering, University of Utah</i>
2002 – 2006	<i>Adjunct Professor, Department of Bioengineering, University of Utah</i>
1992 – 1997	<i>Associate Professor, Department of Mechanical Engineering, University of Utah</i>

## **ARCHIVAL JOURNAL PUBLICATIONS AND RELATED ITEMS.**

*As of December 2021, Dr. Ligrani is author or co-author of more than 207 publications in archival journals, including the International Journal of Heat and Mass Transfer, the ASME Transactions-Journal of Turbomachinery, the ASME Transactions-Journal of Engineering for Gas Turbines and Power, the ASME Transactions-Journal of Heat Transfer, the ASME Transactions-Journal of Fluids Engineering, Nature - Scientific Reports, the Journal of Fluid Mechanics, the AIAA Journal, Experiments in Fluids, Physics of Fluids, the AIAA Journal of Heat Transfer and Thermophysics, the International Journal of Rotating Machinery, Separation Science and Technology, Sensors and Actuators A: Physical, and the Journal of Microcolumn Separations. He is also author of 10 book chapters, and about 155 conference presentations and publications. A number of these are invited conference presentations at international meetings, at locations which include Korea, France, the Ukraine, Croatia, Germany, England-United Kingdom, and Belgium. From 1994 to 2021, he has also presented approximately 191 lectures at different institutions and establishments, including many invited lectures. From 2006 to 2022, he presented or is scheduled to present 9 Invited Keynote Papers, 12 Invited Papers, and 10 Invited Plenary Keynote Papers at different international conferences. Current SCOPUS Reference Citation H-INDEX is 45. Current GOOGLE SCHOLAR Reference Citation H-INDEX is 50.*

## **EDITOR ACTIVITIES.**

*From 1998 to 2000, Dr. Ligrani served as Guest Editor for a Special Topical Issue for Measurement Science and Technology. He has also served as Associate Editor for the ASME Transactions-Journal of Heat Transfer from 2003 to 2006, and from 2010 to 2014, and as Associate Editor for the ASME Transactions-Journal of Fluids Engineering from 2005 to 2008. Present editor duties include: (i) Member of the Distinguished Editorial Review Board for the Advances in Transport Phenomena, Book Series with Springer Publishing Corporation (since 2006), (ii) Editorial Board Member, Power and Thermal Engineering Processes and Equipment Journal, Published by the National Technical University “Kharkov Polytechnic Institute”, Russia and Ukraine (since 2015), (iii) Editorial Board Member, International Journal of Innovative Works in Engineering and Technology (IJIWET) (since 2015), (iv) Associate Editor, Journal of Propulsion Technology (JPT) Journal, Published by CNPIEC, P. R. China (since 2015), (v) International Editorial Board Member, Industrial Thermal Engineering Journal, Published by Thermogasdynamics Department, National Academy of Sciences of Ukraine, Kiev, Ukraine (since 2018), (vi) Editorial Board Member, Advances in Aerodynamics (AIA) Journal. Published by the Chinese Society of Aerodynamics (CSA), and the China Aerodynamics Research and Development Center (CARD), P. R. China (since 2018), (vii) Associate Editor, Energies Journal (since 2018), (viii) Associate Editor, ASME Transactions-Journal of*

*Journal of Engineering for Gas Turbines and Power (2018-2021).*

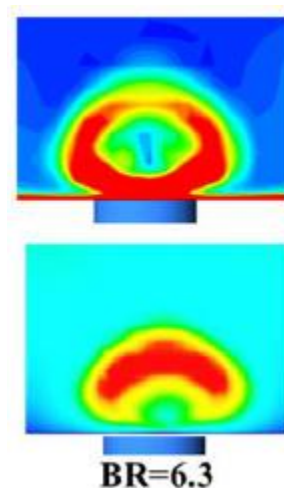
**SELECTED RECENT HONORS, AWARDS, ACADEMIC RECOGNITIONS**

• 2020 College of Engineering Outstanding Faculty Member Award. University Award, University of Alabama in Huntsville, Huntsville, Alabama, USA. • 2020 Undergraduate Research and Creative Activity Mentor Award. University of Alabama in Huntsville, Huntsville, Alabama, USA. • May 2020. Hermann Oberth Award in recognition of outstanding individual scientific achievement in the field of astronautics and advancement of the aeronautical sciences. AIAA – American Institute of Aeronautics and Astronautics. Greater Huntsville Section of the AIAA, Huntsville, Alabama, USA. • March 2020. Employee Service Award, Five Years of Service. University of Alabama in Huntsville, Huntsville, Alabama, USA. • ASME IGTI Outstanding Service Award 2019. • 2019 University Distinguished Research Award for Excellence. University of Alabama in Huntsville, Huntsville, Alabama, USA. • Outstanding Senior Faculty Member Award for 2019. College Award, College of Engineering, University of Alabama in Huntsville, Huntsville, Alabama, USA. • Member. European Union Academy of Sciences (EUAS). 2019 to present. • Guest Professor. School of Mechanical Engineering, Shanghai Jiao Tong University, Shanghai, P. R. China. 2019 to 2022. • Outstanding Mechanical Engineer of the Year Award 2016, ASME – American Society of Mechanical Engineers, NAS - North Alabama Section, USA. • Marquis Lifetime Achievement Award, Marquis Who's Who, New Providence, New Jersey, USA, 2016. • Distinguished Advisory Professor, Inje University, South Korea, 2010 to 2022. • Distinguished Lecture Award, 2011, CEAS Distinguished Lecture Series, College of Engineering, University of Wisconsin, Milwaukee, Wisconsin, USA. • Distinguished Editorial Review Board membership for Springer Publishing Corporation. • Carl E. and Jessie W. Menneken Faculty Award for Excellence in Scientific Research. • NASA Space Act Tech Brief Award for "Development of Subminiature Multi-Sensor Hot-Wire Probes." • Silver Winner for the Annual 26<sup>th</sup> Educational Advertising Awards for the Higher Education Marketing Report.

Dr. Ligrani has a strong past and present record of working with many different collaborators and co-workers, from many locations throughout the world. Additional information on selected, currently active research projects is provided within sections which follow. (i) **Traditional Heat Transfer and Fluid Mechanics Investigations** involving electronics cooling, heat transfer augmentation, drag reduction, turbulent boundary layers, flows in channels with dimpled surfaces, flows in curved channels, elastic turbulence, slot impingement cooling, and macro-scale pumps and pump flows. Also included are **aerodynamics investigations with high-speed, compressible flows at transonic and supersonic Mach numbers**, including SWBLI – Shock Wave Boundary Layer Interactions. Related projects involve **transonic and supersonic experimental testing**. Research interests also include experimental diagnostics in high speed flows, and air breathing propulsion. (ii) **Air Breathing Engines - Gas Turbine Heat Transfer, Cooling, and Aerodynamics Losses**, including internal cooling, film cooling, impingement cooling, cooling of extremities, aerodynamic performance including aerodynamic losses, and transonic turbine flows and heat transfer. This subject area includes the effects of uses of bio-fuels, synthetic fuels, and renewable energy sources in relation to gas turbines and gas turbine heat transfer and cooling technologies. Note that an important area of turbomachinery research interest involves heat transfer and aerodynamics investigations with *high-speed, compressible flows at transonic and supersonic Mach numbers*, including linear cascade studies. (iii) **Micro-Fluidics and Millimeter-Scale-Fluidics**, including micro-pump flows, and the effects of slip phenomena on gas and liquid flows in micro-scale passage flows with and without surface roughness, including the effects of hydrophobic surfaces and elastic turbulence. (iv) **Experimental Techniques**, including development of millimeter-scale multiple-hole pressure probes, subminiature hot-wire anemometry, and infrared thermography.

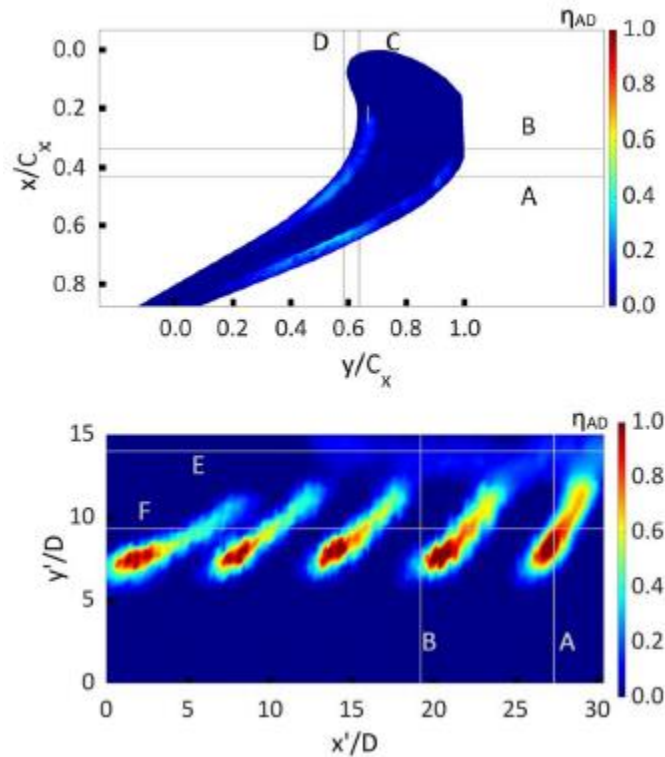
**DOUBLE WALL COOLING RESEARCH INVESTIGATIONS**

Provided are new data for both surfaces of full coverage effusion cooling plate. For the effusion cooled hot-side surface, measured and predicted are spatially-resolved distributions of surface adiabatic film cooling effectiveness, and surface heat transfer coefficients (measured using transient techniques and infrared thermography). For the impingement cooled cold-side surface, measured and predicted are spatially-resolved distributions of surface Nusselt numbers (measured using steady-state liquid crystal thermography). The ANSYS FLUENT Version 19.1 numerical code, with a  $k-\omega$  SST turbulence model is employed to predict flow and heat transfer characteristics with coolant supplied by an impingement jet array. Considered are the effects of effusion blowing ratio, impingement jet Reynolds number, and streamwise development on flow structure, and on hot-side and cold-side surface heat transfer characteristics. Of particular importance are horseshoe-shaped vortices, which form upstream and around each effusion jet, which then result in two horseshoe-originated vortex legs which advect downstream along coolant trajectories. Resulting variations of local flow structural characteristics, such as streamwise vorticity and turbulence kinetic energy distributions downstream of a single effusion cooling hole, are shown at right.

**TRANSONIC TURBINE BLADE TIP HEAT TRANSFER WITH UPPER PRESSURE SIDE FILM COOLING.**

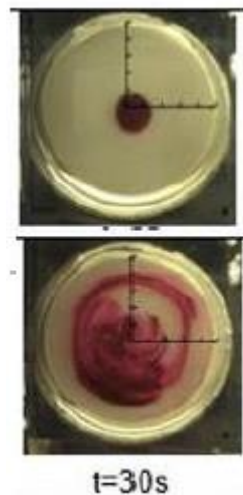
Investigated are spatially-resolved distributions of surface adiabatic film cooling effectiveness and surface heat transfer coefficients for a transonic turbine blade tip, with unique and innovative film cooling arrangements, wherein a single row of five film cooling holes, located on the pressure-side of the blade very near to the blade tip, provides thermal protection to the blade tip. The blade tip contains a squealer rim, and a squealer recess region. The present tip gap magnitude is 1.2 percent of the true blade span. When blade upper pressure side data are considered, heat transfer coefficient ratio variations are due, in part, to a horseshoe-shaped vortex structure, which forms around each film cooling jet, and then advects downstream. Spatially-resolved distributions of surface adiabatic film cooling effectiveness show that the coolant advects to the upper edge of the blade pressure surface, along the pressure side rim, over the squealer recess region, and then sometimes collects in a substantial manner along portions of the suction side rim. As a result, local effectiveness values are generally higher on the suction side rim relative to pressure side rim values when compared at a particular value of blowing ratio. Such local surface variations of adiabatic film cooling effectiveness are thus important as they evidence paths and trajectories of the film

coolant as it advects along blade tip surfaces and along upper pressure sides of turbine blades, with examples for one blowing ratio shown at left.



### CHARACTERIZATION OF EFFECTIVE DIFFUSION WITHIN VISCOELASTIC FLUIDS WITH ELASTIC INSTABILITIES

The remarkable ability of viscoelastic fluids to augment local and global mass species transport characteristics is demonstrated by experimental results. Considered is effective diffusion, characterized by magnitudes of effective diffusion coefficients, in order to quantify mass transport due to the onset and development of elastic instabilities. Effective diffusion coefficient magnitudes are determined using different analytic approaches, as they are applied to tracked visualizations of fluorescein dye front variations, as circumferential advection is imposed upon a flow environment produced using a rotating Couette flow arrangement. To visualize flow behavior within the rotating Couette flow environment, minute amounts of fluorescein dye are injected into the flow. This dye is then redistributed within the flow by radial diffusion only when no disk rotation is used, and by radial diffusion and by circumferential advection when disk rotation is present. Associated effective diffusion coefficient values, for the latter arrangement, are compared to coefficients values with no disk rotation, which are to molecular diffusion alone, in order to quantify enhancements due to elastic instabilities. With no elastic instabilities present, dye distributions, shown at right (above), continue to be concentrated near the center of the disk flow passage, even for extended testing times. Here, the dye moves radially outward only very slowly and smoothly, always with an approximately circular distribution, which evidences pure laminar flow. With elastic instabilities present, dye distributions, shown at right (below), are then dispersed over a much larger area, relative to the center of the flow passage, with progressively increased spatial distributions, which are increasingly irregular and dispersed, as time increases. With this arrangement, the effective radial diffusion rate of the dye is notably enhanced by the presence of elastic instabilities, as flow advects through the rotating Couette flow passage.



### **SPATIAL COHERENCE OF LOW-FREQUENCY UNSTEADINESS ASSOCIATED WITH A NORMAL SHOCK WAVE.**

New experimental data illustrate a unique analysis approach to explore the physics of shock-wave-flow interactions, based upon correlation and spectral analysis of digitized shadowgraph visualization time-sequence data. The shadowgraph system is employed to visualize time-varying, shock wave flow features within the test section of one leg of the transonic/supersonic wind tunnel (which is also referred to as the SS/TS/WT or SuperSonic/TranSonic/WindTunnel), located within the Propulsion Research Center of the University of Alabama in Huntsville. Of interest is a flow field with a well-defined normal shock wave, lambda foot, and separated turbulent boundary layer near the entrance of the lower flow passage (which is part of the test section), produced with a test section inlet Mach number of 1.54. Shadowgraph flow visualization image data associated with two separate pixel region locations, each from a different flow region, are employed to determine magnitude squared coherence values, and associated time lag magnitudes. The data associated with lower Strouhal numbers in vicinity of 0.0013 and 0.0039 illustrate important and pronounced interactions between the normal shock wave and the boundary layer separation zone. As this zone breathes and oscillates, additional flow locations are affected in a subsequent and significant manner. With Strouhal numbers in the vicinity of 0.0091, 0.0104, and 0.0260, the most pronounced and significant interactions between the normal shock wave occur with respect to the downstream boundary layer. When Str equals 0.0091, spatially-varying time lag data show events with significant coherence propagate from a range of locations within the downstream boundary layer to the normal shock wave location. As such, events which originate within the downstream boundary layer at these experimental conditions are far more important (compared to events which originate with the upstream boundary layer) in regard to their effects on shock wave unsteadiness and associated flow motions.

### **TURBULENT HEAT TRANSFER IN CHANNELS WITH MICRO-DEPTH DIMPLES.**

Experimentally-measured heat transfer and pressure loss characteristics are considered for dimpled surfaces, placed along one surface of a channel, with different ratios of dimple depth to channel height, and for Reynolds numbers ranging from 10,000 to 70,000. With the same relative dimple spacing, relative to dimple print diameter, and the same ratio dimple depth to dimple print diameter of 0.20, results for spherical indentation dimples with micro depths of 0.03 and 0.05 (relative to channel height) are compared with thermal and flow characteristics for larger dimples with a ratio of dimple depth to channel height of 0.20. Results indicate that Nusselt number ratios and friction factor ratios are dependent upon the ratio of dimple depth to channel height. As such, the present data for dimples with ratios of dimple depth to channel height between 0.03 and 0.20

are different from previous studies with ratios of dimple depth to channel height between 0.10 and 0.78. The importance of a critical Reynolds number is also demonstrated by the results, which is determined when the ratio of viscous sublayer layer thickness to the dimple depth is equal to unity. Nusselt number enhancements for the micro dimples are generally lower at lower Reynolds numbers, but increase as the Reynolds number becomes larger and approaches the critical Reynolds number. Nusselt number enhancements are then approximately invariant with Reynolds number, when Reynolds number then exceed the critical value.

#### **SECOND LAW ANALYSIS OF AERODYNAMIC GAINS ASSOCIATED WITH SIMPLE ANGLE AND COMPOUND ANGLE FULL COVERAGE FILM COOLING.**

Entropy generation is employed to quantify second law losses, and aerodynamic gains, which are associated with a film cooled boundary layer produced by a unique full-coverage compound angle hole configuration. With this arrangement, an alternating sign for the compound angle is employed from one streamwise row of holes to another, such that compound angle is +30 degrees in one row of holes, followed by -30 degrees in the next row of holes. Results from this arrangement are compared to simple angle arrangement with a compound angle of 0 degrees. Determined from isothermal flow field measurements of local total pressure variations from film cooling, are the entropy change, entropy generation, and mass-averaged overall exergy destruction, relative to the freestream flow outside of the boundary layer. Because stagnation pressure values, associated with film cooling in the boundary layer, are higher than freestream stagnation pressure values, the present film arrangements and conditions produce aerodynamic gains relative to the freestream flow. Film cooling blowing ratio values range from 2.9 to 6.0, and mainstream Reynolds numbers range from 89,000 to 141,000. Variations of entropy generation and exergy destruction, for the compound and simple angle full-coverage film cooling arrangements, are evident with boundary layer location, and as the blowing ratio, streamwise development location, and main flow Reynolds number vary. Differences for the two film cooling configurations, as these parameters vary, are a consequence of significantly different film cooling behavior and characteristics, as related to entropy generation and exergy destruction distributions.

# Some Recent Progress on Graph Drawing and Network Visualization

by Giuseppe Liotta, Member EUAS

## Short Biography

*Giuseppe Liotta is a professor of computer science at the Department of Engineering of the University of Perugia, Italy. He received his PhD degree from “Sapienza”, University of Rome. His post-doc appointment was at Brown University, US. He also spent long term research visits at McGill University, Canada, and at the University of Sydney, Australia. His research interests are mainly directed at the analysis and design of algorithms and systems that have applications in the fields of information visualization and visual analytics, computational geometry, network analysis, and graph drawing. On these topics he edited special issues, wrote surveys papers, book chapters, published more than 280 research papers, in distinguished journals and conference proceedings, and gave lectures worldwide. He regularly serves in scientific boards, program committees, and is the editor in chief of two international journals: Computer Science Review and Journal of Graph Algorithms and Applications. During the years, Giuseppe has been the PI of several grants issued by public and private research sponsors.*

## **Abstract**

This short note shortly introduces graph drawing and network visualization and gives examples of two research directions in this field.

## **1. Introduction**

Data are the elementary, yet unexpressive, components of information. For example, ‘Alice’, ‘’ and ‘3’ are individual data which may be meaningless if considered isolated. They form an information only when related with one another: for example, “Alice 3” can be an information given as an answer to the question “what is the office of Alice?”. Note that the meaning, therefore the information, is context sensitive and subject to interpretation: In a different context the same two data may form a completely different information (for example the number of university degrees of Alice). Since interpreting data gives rise to information, managing large amounts of elementary data and making sense of them is at the heart of computer science and engineering. Human Centered Computing and in particular Visual Analytics (VA) is establishing itself as a core technology of Data Science. VA is aimed at supporting the analysis of data sets and the extraction of the associated information. It puts the data analyst at the center of a loop in which the information is derived as the result of a continuous interaction process between human and machine: The analyst (aka the policy maker) explores effective visualizations through an easy-to-use visual interface, asks questions, sets parameters; in turn, the computer returns new visualizations and/or highlights relevant patterns in the data to support the information extraction process.

Graph Drawing and Network Visualization is a well-established sub-discipline of VA. It finds its motivation in the observation that in most applications data present a networked structure, which, depending on the domain, can be explicitly represented, such as in social or biological networks, or implicitly defined, such as in financial markets. A common characteristic of many of these networks is that they are heterogeneous, with different types of feature-rich nodes and edges annotated with various labels and weights. Heterogeneity also arises at the topological level, with many real-world networks exhibiting a mix of sparsely connected and densely connected regions. In this scenario, analyzing the network while accounting for its heterogeneity is of the utmost importance for several applications in science and industry. Moreover, in many applications, the data sources are extremely dynamic, producing information evolving over time at high rates, so that their processing must take into account this temporal dimension, specifically, the staleness of older data and/or the inability to store and operate on the entire stream of data due to the finiteness of the computational resources available for the processing. These characteristics, combined with the sheer scale and high noise of the data in many domains, demand effective computational tools for exploratory analyses that allow the user to gauge the multitude of patterns and trends appearing in such multi-faceted datasets.

At a very high level, Graph Drawing and Network Visualization aims at designing algorithms and systems that receive as input a networked data set, conveniently modeled as an algebraic graph with labeled edges and vertices, and it computes a representation of such a graph in a 2D or 3D Euclidean space. Graph Drawing and Network Visualization is at the intersection of different disciplines, combining aspects of more applied fields like HCI (Human-Computer-Interaction) and SE (Software Engineering) with aspects of more theoretical fields like Graph Algorithms, Computational Geometry, and Graph Theory. As a consequence, several books, conferences, and book chapters with either a more applied focus or a more methodological focus are devoted to Graph Drawing and Network Visualization. In this note I will briefly discuss examples for each of the two aspects of this discipline. Namely, Section 2 shortly describes a case study in a particular applicative scenario, while Section 3 gives an example of a more fundamental graph drawing question.

## **2. Contrasting Financial Frauds with Network Visualization**

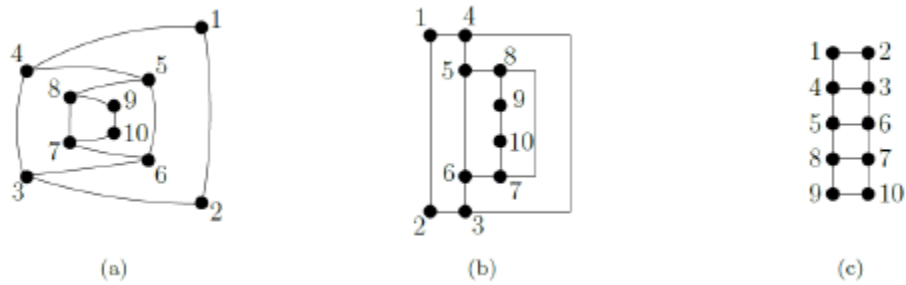
Tax noncompliance is a serious economic problem for many countries. It consists of a range of activities, such as tax evasion and tax avoidance, that undermine the government's tax system. Just to be concrete, In the period 2007–2013, the Italian government estimated an annual average of tax evasion of about 91.4 billion EUR. As a consequence, the Italian Revenue Agency (Agenzia delle Entrate), abbreviated as AdE in the following, has put in place various strategies to reduce the tax gap, that is the difference between the tax amount that should be collected and the actually collected amount. A key one is building an effective law enforcement policy based on an accurate assessment of the so-called taxpayers' tax risk. The main purpose of the tax risk assessment is to identify those taxpayers who are more likely to be involved in relevant tax evasion activities; such taxpayers are then subject to fiscal audits. Discovering such taxpayers is however not an easy task: Italian tax officers have to continuously deal with an overwhelming number of heterogeneous data sources, which causes information redundancy and makes it extremely difficult for the analysts to preserve their mental map during the fiscal audit process.

We exploited Graph Drawing and Visual Analytics to support the work of tax officers in their investigative activities. The main idea is to model the set of data as a unified network, whose nodes represent taxpayers and whose edges are different types of economic and social relationships between them, such as economic transactions, shareholdings, and corporate offices. Namely, many real cases of tax evasion are implemented through the interaction of various subjects which are more easily detected by modeling such interactions with a graph. Examples include carousel VAT frauds, exchange of false invoices, and tax avoidance implemented through transfer pricing between corporate groups. The analyst can visually define classes of suspicious patterns, based both on topological properties and on node/edge attributes. Also, the analyst can take advantage of sophisticated algorithms that combine stochastic methods of information diffusion with machine learning approaches for tax risk forecasting. See [4,5,6] for papers that describe the achieved results. These papers, which describe experimental research conducted in collaboration with the Italian Revenue Agency, were partly based on a previous research with the Central Bank of S. Marino, where Visual Analytics had been used to discover financial frauds [8].

### 3. Computing Orthogonal Drawings with the Minimum Number of Bends

An orthogonal drawing is a representation of a graph where edges are chains of horizontal and vertical segments and vertices are polygons (typically rectangles) that contain textual labels. Orthogonal drawings are among the earliest and most studied graph representation standards because of their applications in several domains, including software engineering, database design, circuit design, and visual interfaces. Since the readability of an orthogonal drawing is affected by the crossings and the bends along its edges, a classical research subject in graph drawing studies planar (i.e. crossing-free) orthogonal drawings with the minimum number of bends along the edges. From a theoretical point of view, the problem can be studied assuming that the vertices are points on a integer 2D grid and that the edges follow the grid lines.

The problem can be studied both in the *fixed embedding setting*, that is when the graph is given together with a circular order of the edges incident to the vertices and a given external boundary for the representation, or in the *variable embedding setting*, when the algorithm is allowed to choose the circular order and external boundary that leads to a bend-minimum solution. Figure 1 (a) depicts a graph  $G$  with a given planar embedding. Figure 1 (b) depicts a bend-minimum orthogonal drawing of  $G$  that preserves its embedding (i.e. in the fixed embedding setting); the drawing has four bends. Figure 1(c) depicts a bend-minimum orthogonal drawing of  $G$  where the circular order of the edges around the vertices and the external face have been chosen by the drawing algorithm to minimize the number of bends.



**Figure 1:** (a) A graph  $G$  with a given planar embedding. (b) A bend-minimum orthogonal drawing of  $G$  in the fixed embedding setting. (c) A bend-minimum orthogonal drawing of  $G$  in the variable embedding setting.

A seminal paper by Storer [13] conjectured that computing a planar orthogonal drawing with the minimum number of bends is computationally hard. The conjecture was proved incorrect in fixed embedding setting by Tamassia [14], who showed that, by using an elegant min-cost flow reduction, a polynomial time algorithm exists to compute an orthogonal drawing with the minimum number of bends. Conversely, Garg and Tamassia [12] proved the conjecture of Storer to be correct in the variable embedding setting that is, computing an orthogonal drawing with the minimum number of bends in this setting is NP-complete.

These seminal results motivated a rich body of graph drawing literature dedicated to the bend-minimization problem for orthogonal drawings both in the fixed and in the variable embedding setting. In the fixed embedding setting, the solution of Tamassia, while polynomial in the input size, is relatively expensive in a computational terms and it is not yet known whether a linear time (hence computationally optimal) solution can be designed. In the variable embedding setting, the NP-completeness leads to the study of special instances for which the problem can be solved in polynomial time on one hand and on designing general approaches which may be efficient in practice.

We remark that deciding whether the bend-minimization problem in the fixed embedding setting can be solved in linear time remains an elusive goal. Recently, a linear-time solution has been proposed for the family of series-parallel graphs in the fixed-embedding setting [7].

Concerning the bend-minimization problem in the variable embedding setting, [1] shows that the problem can be solved in polynomial time for those graphs whose vertex degree is at most three and for those graphs that are series-parallel. While polynomial, the time complexities in [1] are sub-optimal and it has been a long-standing open problem deciding whether more efficient solutions existed for these graph families. Recently, significant progress has been made in this direction: In [9] a linear-time algorithm has been presented which computes a bend minimum orthogonal drawing of a planar graph with maximum degree three in the variable embedding setting. This algorithm introduces a new data structure and builds upon the quadratic-time technique of [10]. As for general graphs, it has been proved that the problem of computing a planar orthogonal drawing with the minimum number of bends in the variable embedding setting belongs to the XP-class when parameterized by treewidth [2], and it is FPT tractable when parameterized by the number

of degree-4 vertices [3]. Finally, variants of the above problems, where the edges of the input are labeled “horizontal” or “vertical” and one asks to compute a no-bend drawing where the edges have the slope defined by the label have been studied in [11].

## References

- [1] G. Di Battista, G. Liotta, F. Vargiu, “Spirality and Optimal Orthogonal Drawings,” *SIAM Journal on Computing*, vol. 27, no. 6, pp. 1764–1811, 1998.
- [2] E. Di Giacomo, G. Liotta, F. Montecchiani, “Orthogonal Planarity Testing of Bounded Treewidth Graphs”, *Journal of Computer and System Sciences*, in print.
- [3] W. Didimo, G. Liotta. “Computing orthogonal drawings in a variable embedding setting”. *International Symposium on Algorithms and Complexity*, vol. 1533 of Lecture Notes in Computer Science, pp. 79–88.200, Springer, 1998
- [4] W. Didimo, L. Giamminonni, G. Liotta, F. Montecchiani, D. Pagliuca, “A Visual Analytics System to Support Tax Evasion Discovery”, *Decision Support Systems*, vol. 110, pp. 71-83, 2018.
- [5] W. Didimo, L. Grill, G. Liotta, F. Montecchiani, D. Pagliuca “Visual Querying and Analysis of Temporal Fiscal Networks”, *Information Sciences*, vol. 505, pp. 406-421, 2019.
- [6] W. Didimo, L. Grilli, G. Liotta, L. Menconi, F. Montecchiani, D. Pagliuca, “Combining Network Visualization and Data Mining for Tax Risk Assessment”, *IEEE Access*, vol. 8, pp. 16073-16086, 2020.
- [7] W. Didimo, M. Kaufmann, G., G. Ortali, “Rectilinear Planarity Testing of Plane Series-Parallel Graphs in Linear Time”, *International Symposium on Graph Drawing and Network Visualization, GD’20*, Lecture Notes in Computer Science, Springer-Verlag, vol. 12590, pp. 436-449, 2020.
- [8] W. Didimo, G. Liotta, F. Montecchiani, “Network Visualization for Financial Crime Detection,” *Journal of Visual Languages and Computing*, Special Issue on Representation Environments for User-driven Development of Service Applications, vol. 25, pp. 433-451, 2014.
- [9] W. Didimo, G. Liotta, G. Ortali, M. Patrignani, “Optimal Orthogonal Drawings of Planar 3-Graphs in Linear Time”, *ACM-SIAM Symposium on Discrete Algorithms SODA 2020*, SIAM, pp. 806-825, 2020.
- [10] W. Didimo, G. Liotta, M. Patrignani, “Bend-Minimum Orthogonal Drawings in Quadratic Time”, *International Symposium on Graph Drawing and Network Visualization, GD’18*, Lecture Notes in Computer Science, Springer-Verlag, vol. 11282, pp. 481-494, 2018.
- [11] W. Didimo, G. Liotta, M. Patrignani, “HV-Planarity: Algorithms and Complexity”, *Journal of Computer and System Sciences*, vol. 90, pp. 72-90, 2019.
- [12] A. Garg, R. Tamassia, “On the computational complexity of upward and rectilinear planarity testing”, *SIAM Journal on Computing*, vol. 31, no.2, pp. 601–625, 2001.
- [13] J. A. Storer, “The node cost measure for embedding graphs on the planar grid”, *ACM Symposium on Theory of Computing*, 1980,
- [14] Roberto Tamassia. On embedding a graph in the grid with the minimum number of bends.864 *SIAM Journal on Computing*, vol,16, no 3, pp. 421–444, 1987.

# Modelling Rough and Fuzzy Sets in Interactive Granular Computing (IGrC)

by Andrzej Skowron, Member EUAS



## Short Biography

*Andrzej Skowron, EurAi (ECCAI) and IRSS Fellow, Member EU Academy of Sciences, received the Ph. D. and D. Sci. (habilitation) from the University of Warsaw in Poland. In 1991 he received the Scientific Title of Professor. He is Full Professor in the Systems Research Institute, Polish Academy of Sciences as well as in Digital Research Center of Cardinal Stefan Wyszyński University in Warsaw. He is Emeritus Professor in Faculty of Mathematics, Computer Science and Mechanics at the University of Warsaw. He is currently affiliated at Systems Research Institute, Polish Academy of Sciences and Digital Science and Technology Centre, UKSW. Andrzej Skowron is the (co)author of more than 400 scientific publications and editor of many books and volumes of conference proceedings. His areas of expertise include reasoning with incomplete information, approximate reasoning, soft computing methods and applications, rough sets, rough mereology, granular computing, intelligent systems, knowledge discovery and data mining, decision support systems, adaptive and autonomous systems, perception based computing, and interactive computational systems. He was the supervisor of more than 20 PhD Theses. In the period 1995-2009 he was the Editor-in-Chief of Fundamenta Informaticae journal. He is on Editorial Boards of many others international journals. Andrzej Skowron was the President of the International Rough Set Society from 1996 to 2000. He has delivered numerous invited talks at international conferences including a plenary talk at the 16th IFIP World Computer Congress (Beijing, 2000), a keynote talk at the 8th Joint Conference on Information Sciences (JCIS 2005) (encompassing 12 individual conferences and workshops) (USA, 2005), an invited talk at the 2006 IEEE/WIC/ACM International Conference on Intelligent Agent Technology (IAT 2006) and on Web Intelligence (WI 2006) (Hong Kong, 2006), and a plenary talk at the 2nd World Congress on Biologically Inspired Computing (Japan, 2010). He was serving as (co-)program chair or PC member of more than 200 international conferences. He was involved in numerous research and commercial projects including dialog-based search engine (Nutech), fraud detection for Bank of America (Nutech), logistic project for General Motors (Nutech), algorithmic trading (Adgam), control of UAV (Linköping University), and medical decision support (e.g., in Polish-American Pediatric Clinic in Cracow). Andrzej Skowron was on the ICI Thomson Reuters/ Clarivate Analytics lists of the most cited researchers in Computer Science (globally) in 2012, 2016, 2017.*

## **Abstract**

In this article, we emphasize that linking rough sets or fuzzy sets with Interactive Granular Computing Model (IGrC) requires substantial changes in the basic definitions of these approaches.

## 1. Motivation

Existing approaches to soft computing, such as rough sets, fuzzy sets, and other tools used in machine learning lack in considering the perception and interaction with the physical world. There are two prevalent traditions of mathematical modelling. One is *purely mathematical* where it is considered that the sets are given. For example, in the case of the rough set approach, the starting point is the universe of objects and an indiscernibility or similarity relation(s); further developments on approximating concepts are made on this basis. In the context of fuzzy sets, the universe of objects and some basic fuzzy membership functions, relative to some concepts, are assumed as given; based on that fuzzy membership functions for other complex concepts are induced. The second tradition of modelling may be called *constructive*, where it is assumed that objects are partially perceived by means of some features or attributes, and only a partial information about these objects in the form of vectors of attribute values is available. On this basis indiscernibility or similarity relations are defined and further developments are carried out (assuming often that information about sets of objects is also partial). This approach is often followed in rough sets. In the context of fuzzy sets also often this approach is used, i.e., the fuzzy membership functions are constructed based on a set of attributes and then they are ascribed over the universe of objects. Both the traditional modelling do not take into account *how* the process of perceiving attribute values is realised, *where* and *how* to access the concerned objects in the physical space, and *why* those attributes are selected. Hence, clearly the perception and action are out of the scope of such practices of modelling. However, this is crucial for many tasks, especially, when we are dealing with complex phenomena in the real physical world. As a result, characterization of the state of the complex physical phenomena by a fixed set, or a priori set of attributes becomes irrelevant. From a similar concern, the researchers (see *AI Magazine* 37, 2016) proposed to extend Turing test by embedding into it the challenges related to action and perception.

So, how a function representing a particular vague concept is learned from the uses of the community, as well as which parameters to be considered crucial in (approximate) defining a vague concept and how the values for these parameters are observed or measured, incorporating such information in the model is important for an intelligent agent; otherwise a non-human system cannot derive the relevant information about unseen so far cases. Hence, we need an extension of the existing approaches where apart from the information about a physical object, a specification of how the information label of a physical object is physically linked to the actual object also can be incorporated.

## 2. From complex granules (c-granules) and informational complex granules (ic-granules) to control of c-granules

In IGrC it was recognised (see papers on interactive computations on <https://dblp.uni-trier.de/pers/hd/s/Skowron:Andrzej>) the necessity of introducing *complex granules* (*c-granules*, for short). The computations in the IGrC model are realized on the interactive complex granules and the progress of the computation process is based on the consequences of the interactions occurring in the physical world. Hence, the computational models in IGrC can't be constructed solely in an abstract mathematical space. The proposed model of computation based on complex granules seems to be of fundamental importance for developing intelligent systems dealing with complex phenomena, in particular in such areas as Data Science, Internet of Things, Wisdom Web of Things,

Cyber Physical Systems, Complex Adaptive Systems, Natural Computing, Software Engineering, and applications based on Blockchain Technology, etc .

In the discussed approach, we assume that physical objects exist in the physical space and are embedded into its parts. Physical objects are interacting in the physical space, and thus some collections of physical objects may create dynamical systems in the physical space. It is important to explain how properties of these objects and interactions among them can be perceived by c-granules. In our attempt, to design c-granules with the ability of perceiving physical objects and their interactions, this is realised by the control mechanism of c-granule based on *informational complex granules (ic-granules)* and a special kind of reasoning over them, called judgment. Informational complex granules (ic-granules) are constructed over two basic ingredients: abstract and physical; we may count these two ingredients respectively as informational and physical objects. Abstract ingredients of ic-granules consists of families of formal specifications of spatio-temporal windows labelled by information, expressed in a formal or natural language, specific for a given c-granule or a family of c-granules. The information layer of an ic-granule may contain formulas and their (expected or real) degrees of satisfiability at a given moment of time on some physical objects, as well as the formal specifications of the spatio-temporal windows indicating the location and (perception) time of those physical objects. It can be a Boolean formula over atomic formulas of the form  $a = v$  specifying the value of attribute  $a$  is  $v$  at a given moment of time  $t$ , or can be a more compound expression, encoded in an information system containing results of measurements in time for vectors of attributes of the objects related to the given (in informational layer) formal specifications of spatio-temporal windows.

The physical layer of any ic-granule is called c-granule and is divided into three parts: *soft\_suit*, *link\_suit* and *hard\_suit*. Each of these parts is a collection of physical objects.

The behavior of the control of a given c-granule can be divided into cycles. Each cycle of the control of a given c-granule starts from a current configuration (family) of ic-granules. This configuration contains a distinguished ic-granule with information representing the perception status of the current situation. Each cycle consists of several steps such as modification, deletion, suspension of ic-granules or generation of some new ic-granules from the current configuration. It should be noted that a special kind of ic-granule, called *implementation ic-granule*, is used for generation of new ic-granules from their formal specifications. Once a new configuration of ic-granules is created the control measures features of some new physical objects in the scope of the newly developed ic-granules and/or matches or aggregates information with that of the previous ic-granules using its judgment mechanism. The cycle ends when the control gathers perception, to a satisfactory degree, about the current configuration, and becomes able to take a relevant decision with respect to the goal of the computation process.

Formal specification of many complex tasks or formal specification of c-granule needs may be thought of as a *complex game* consisting of a family of complex vague concepts, labeled by actions or plans (represented by the relevant formal specification ic-granules) that to be performed when the concepts are satisfied to a satisfactory degree. These complex vague concepts may describe, e.g., invariants which should be preserved to a satisfactory degree, conditions representing degrees of risk of disaster in the environment perceived by the system, safety properties of trajectory of granular computations, conditions representing the quality of the current path from the point of view of carried out computation toward the target goals, or risk concerning a possibility that the current needs are no longer achievable. It should be noted that these complex vague concepts (usually described in a fragment of a natural language) should be learned from data and domain

knowledge with the use of physical laws. During perception of the current situation in the physical world the control uses its judgment tools over information gathered from information layers of dynamically changing (by control and the environment) configurations of the ic-granules. Moreover, the concepts as well as their labels, involved in a complex game, are evolving in time. Hence, the control should have some adaptive strategies allowing relevant modification of the complex game.

We would like to emphasize the role of reasoning, called judgment, for the control of a c-granule. The further development of judgment methods will play the principal role in further development of intelligent systems. These reasoning methods are far beyond the existing deductive methods so well already developed in mathematical logic or even inductive reasoning (e.g., in Machine Learning). They should take into account, e.g., experience as well as explanation of behaviour. These reasoning methods should be grounded on a new computing model making it possible to perform reasoning from sensory measurement to perception (i.e., understanding the perceived situation). We propose to base such a model on interactive complex granules (c-granules) having their informational parts grounded in the physical world.

### 3. Rough sets and fuzzy sets in IGrC

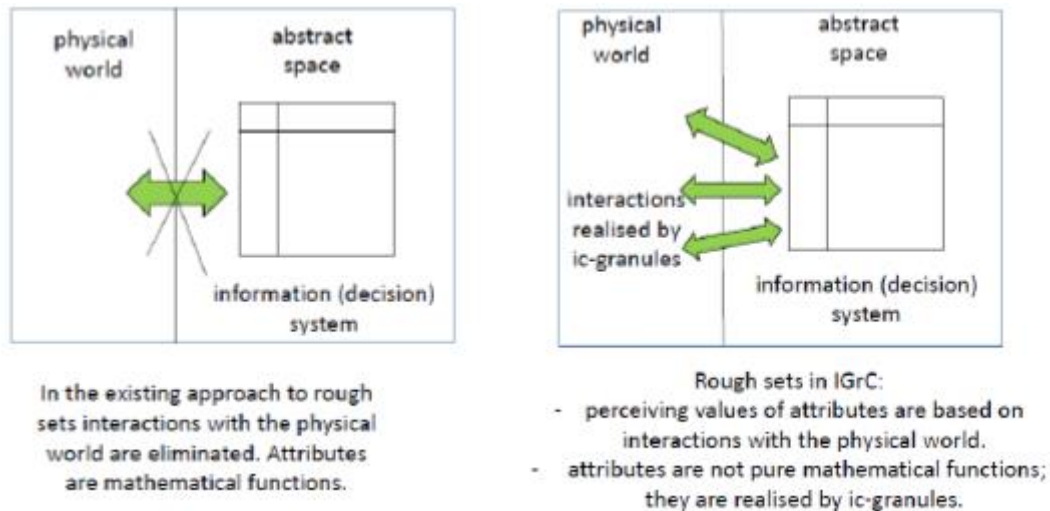
Modelling of rough sets and fuzzy sets in The IGrC framework requires some substantial changes in the fuzzy and rough set approaches.

For example, a fuzzy set is defined by a membership function  $f$  from a given set  $X$  of objects into the interval  $[0,1]$  of reals. In this way, fuzzy sets are completely embedded in the "mathematical manifold." However, fuzzy concepts are embedded in the real world where humans are using fuzzy concepts and from this world their semantics should be perceived by c-granule control<sup>1</sup>. The perception of real situations (objects) by control of c-granules should create the base for estimation of membership functions (and their values) by c-granules. One should be aware that physical situations (objects) can't be omitted in the perception. Hence, instead of pure mathematical objects such as functions some non-pure mathematical constructs should be also used in modeling of c-granule control. Partial information about the perceived situations is used by control of c-granules as input for estimation of mathematical membership functions which can be only treated as temporary models. These estimated functions should be adapted by the relevant strategies according to changes in the perceived data recorded by c-granule. Before the control of c-granule is constructing an estimation of membership function it gradually strives to better understand the perceived situations in order to make the right decision regarding construction of the estimated membership functions, taking into account different constraints concerning, e.g., time or other resources. Control of c-granule should provide mechanisms deciding how c-granule should behave in perceiving the situation to obtain the relevant data, in particular by answering queries related to *what, where, when, how*, etc. to do. On the basis of perceived data by c-granule estimations of membership functions are constructed and adapted according to observed changes in perceived data.

Analogous comments can be made about rough sets. An attempt to link rough sets and IGrC for developing the *perceptual rough set approach*, requires introducing changes in definitions of the basic concepts of the existing rough set approach. In particular, this concerns the definition of attributes in information systems (decision systems) (see Fig. 1).

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<sup>1</sup> The discussed approach is consistent with the idea of perception presented in the book *Action in perception* (MIT Press, Cambridge, MA (2004)) by Alva Nöe.



**Figure 1.** Differences in construction of information (decision) systems in the existing approach to rough sets and the approach to rough sets in IGrC.

Attributes are now grounded in the physical world and their values are perceived using constructs which are not purely mathematical functions as it is in the existing rough set approach. These constructs are called ic-granules in IGrC. They are, like physical pointers, linking the abstract objects and the physical objects from the real-physical world. They are making it possible to perceive the relevant fragments of current situation in the physical world. The mentioned fragments are pointed out using formal specifications of spatio-temporal windows from the abstract layers of ic-granules. The semantics of ic-granules is defined by implementation in the physical world of formal transformations of ic-granules (from the abstract layers of ic-granules) communicate to their physical layers. Data perceived in informational layers of ic-granules generated after implementation of submitted by control transformations of ic-granules are used to define values of attributes.

The issues related to developing the rough set approach in IGrC will be discussed in more detail in the full version of our paper concerning the rough set approach in IGrC.

From the above considerations it follows an important conclusion concerning the control of c-granule architecture. The c-granule control should contain an implementation module enabling to generate from the, provided by control, specification some relevant configurations of interacting physical objects. Perceived (by control) properties of these objects and their interactions should satisfy the given specification, if only unexpected interactions caused by the environment are not too high.

# Novel Nanomaterials for Optical and Environmental Applications

by Yoshio Bando, Member EUAS



## Short Biography

*Prof. Yoshio Bando has been leading the communities of nanomaterials and electron microscopy for many years. Holding a PhD degree from Osaka University, he joined the National Institute for Research in Inorganic Materials (NIRIM) in 1975. In 2001, NIRIM was merged with the National Research Institute for Metals to form the National Institute for Materials Science (NIMS), and he was appointed as Director of the Advanced Beam Analysis Group, followed by being appointed Director-General of International Center for Young Scientist. He became a NIMS Fellow in 2004. From 2008 to March 2017, he was responsible for the operation of MANA with the appointed position of Chief Operating Officer (COO). In addition, he was adjunct professor at the University of Tokyo (2009-2012) and guest professor of Waseda University (2008-2016). After retirement of NIMS in 2017, he has been appointed as Distinguished Professor at the University of Wollongong, Australia, and Emeritus NIMS Fellow. He was also Professor at Institute for Molecular Plus, Tianjin University China from 2018 to 2021. He has received many prestigious awards and fellowships, including the "Sacred Treasure" given from the Japanese Emperor in 2017, The 3rd Thomson Reuters Research Front Award in 2012, The Tsukuba Prize in 2005, Academician, The Commendation Award by the Minister of State for Science and Technology in 1998, The Academic Award of the Ceramic Society of Japan in 1997, The Seto Award of Electron Microscopy Society of Japan in 1994 and others. He was appointed as adjunct member of the Science Council of Japan in 2006. He is also a Fellow of the American Ceramic Society and the Royal Society of Chemistry. He served as Editor-in-Chief of Journal of Electron Microscopy and Editorial Board Members of "Nano Energy", "Small", "Nanotechnology", "Materials Horizon", "Nanomaterials" and others. He has been selected as ISI Highly Cited Researcher in Materials Science in 2014, 2015, 2016, 2017, 2018, 2019, 2020 and 2021. To date, he has authored 925 original research papers that have been cited more than 63,400 times with h-index of 133 (Web of Science in 2021). He has registered 43 foreign patents and 70 Japanese patents.*

## **Research Activities**

- 1. A New Path in Lighting and Display: White Light Emitting Diode with A Single Active Layer<sup>1)</sup>**

Despite the rapid growth in availability of WLED materials, current white light technologies use the same principle of operation. White light is synthesized by mixing colours originating from two or three emitters contained in vertically stacked or horizontally integrated devices. Unfortunately, the manufacture of these devices involves complex and expensive processes making it difficult to obtain a standard light source (similar to sunlight with a continuous spectrum in the visible band) using two or three monochromatic emitters. In addition, the properties of emitter materials, such as emission lifetime, are not uniform, which can be detrimental to the long-term stabilities and efficiencies of WLEDs. A viable strategy to overcome these shortcomings is to achieve white electroluminescence using a single light emitting layer. Many researchers are working in this field and several visible spectrum-wide emitters have been successfully developed in the form of single layer films. [6–9] However, there are limits to imitating sunlight and/or photoelectric performance when preparing WLEDs, especially considering the luminous performance indicators required for marketization.

Recently, Professor H. Zeng and colleagues at Nanjing University of Science and Technology have succeeded in developing a highly efficient and stable WLED using the phase transition of halide perovskite quantum dots. This WLED contains as an active layer a uniformly distributed monolayer CsPbI<sub>3</sub> perovskite film formed as a two-phase mixed system of  $\alpha$ -CsPbI<sub>3</sub> /  $\delta$ -CsPbI<sub>3</sub>. This film exhibits continuous spectrum emission characteristics over the entire visible light region where  $\delta$ -CsPbI<sub>3</sub> emits white light in the 400-750 nm range due to self-trapped exciton emission. The  $\alpha$ -CsPbI<sub>3</sub> component also plays an essential role due to its excellent carrier transport capacity while it also promotes carrier injection to  $\delta$ -CsPbI<sub>3</sub> and realizes balanced exciton recombination in the WLED. The synergistic photoelectric effect of this phase transition material leads to an extremely high performance for CsPbI<sub>3</sub> QD as a WLED. A maximum brightness of more than 10,000 cd m<sup>-2</sup> has been achieved at a low voltage of 6.6 V with a maximum EQE of 6.5%. These characteristics of the devices are appropriate for their application in lighting and displays. This result was published in Nature Photonics as a research article “Efficient and bright white light-emitting diodes based on single-layer heterophase halide perovskites”.

This WLED has been constructed based on a single light-emitting layer with device structure and light-emitting principle which differ substantially from the currently used white light sources. Thus this work opens a new route in the development of future lighting and display technologies. The additional advantages of ultra-slimness and high transparency also make these WLEDs of great value for the next generation of flexible and wearable devices.

## **2. Programmed design of selectively-functionalized wood aerogel: Affordable and mildew-resistant solar-driven evaporator<sup>2)</sup>**

The wood-based solar-driven interfacial evaporators are inexpensive for generating potable water. Previous research has focused on improving the light absorption capacity of wood-based devices rather than optimizing manufacturing costs, energy consumption, and internal structure. Here, a thermally stable wood-derived aerogel (TWA) with hierarchically ordered microchannels is programmatically designed via delignification and selective thermal treatment. The structural features of the TWA facilitate efficient thermal management during the solar-driven interfacial evaporation process. These features enable controlled hydrophilicity, low thermal conductivity, and good light absorption. By reducing the heat loss of the system, TWA has a high evaporation efficiency of 85.9% under 3 sun irradiation. In addition, TWA can operate in complicated water environments for long periods due to excellent mildew resistance and chemical stability. More importantly, TWA can be used to remove organic dyes and heavy metals in sewage, highlighting the significance of programmable-designed wood aerogel for the solar-driven interfacial evaporator.

### **References**

- 1) Yoshio Bando, "A new path in lighting and display: white light emitting diode with a single active layer", *Science Bulletin*, Volume 66, Issue 9, 15 May 2021, Pages 860-861.
- 2) Taotao Meng, Bo Jiang, Zhengtong Li, Xingtao Xu, Dagang Li, Joel Henzie, Ashok Kumar Nanjundan, Yusuke Yamauchi, Yoshio Bando, "Programmed design of selectively-functionalized wood aerogel: Affordable and mildew-resistant solar-driven evaporator", *Nano Energy*, Volume 87, September 2021, Pages 106146.

# Pen portraits of Presidents – Professor Raymond Hide

by Chris Folland, Member EUAS

## Short Biography

*Retired Met Office Hadley Centre Science Fellow (1990-2017) and former Head. of Climate Variability and Forecasting Research (1990-2008). Currently retired unpaid Climate Expert for the Met Office.*

*Chris has had a varied career in meteorology after a spell in oceanography in 1966-68. He joined the UK Met Office in 1968, becoming a **Fellow of the Royal Meteorological Society** in 1967. After a spell at the Met Office Training School, he joined the Operational Instrumentation Branch in 1969. He led a small group researching the development of surface meteorological instruments, particularly those measuring temperature and humidity on land and at sea on buoys and was soon promoted. Chris had his first involvement with the World Meteorological Organisation (WMO), providing scientific input to the WMO Working Group on Reference Psychrometry.*

*Chris joined the Met Office Synoptic Climatology Branch in 1974, working on observed climate change and taking part operational statistical UK monthly weather forecasts. Here he co-authored his first Nature paper in 1974 on the emerging Sahel drought. Promoted again in 1976, Chris led a group of about 15 staff working on hydrometeorological research and consultancy. His most important role was working with hydrologists, hydraulics experts and prominent civil engineers, leading the meteorological input to a pioneering computerised model and manual for the Hydraulic Design of Storm Sewers in 1976-1981, sponsored by the UK National Water Council and the Department of the Environment (DOE). Chris also joined the WMO working group on Precipitation Evaporation and Soil Moisture mainly to develop a physical model (which remains unique) to quantitatively explain the long-standing problem of the systematic losses of rainfall from conventional raingauges, and to test his ideas in the field. This he did working with prominent hydrologists at the UK Institute of Hydrology. The model led to a new raingauge design to minimise rainfall and snowfall losses, initially marketed as the Folland Sevruk Strangeways (FSS)100 tipping bucket raingauge, now the ARG100 raingauge, marketed by several companies. This activity led to membership of the Royal Society sub-group on Hydrology (1979-82). For both research activities Chris was awarded the **Royal Met Soc. Hugh Robert Mill Medal and Prize in 1985**, fully publishing details of the raingauge research soon afterwards. Chris was also involved with hydrologists in the Institute of Civil Engineers on follow up research to the landmark 1975 UK Flood Studies Report and carried out hydrometeorological consultancy jobs for clients (e.g. for parts of Africa and Brazil) in connection with the commercial consultancy work of his group.*

*Chris gained his first major post in climate research (1980-88) when he re-joined the Met Office Synoptic Climatology Branch. Here he was in charge of global climate data set development, UK monthly forecasting and aspects of climate change research. A key task was to develop the emerging global SST data set, extended by Chris to include night marine air temperature (NMAT), for the first time in climate research, to check problems with SST data. This led to the publication of the first global SST and NMAT data sets in Nature in 1984 and what they showed about climate variability and change. This paper was the first to identify interhemispheric variations in SST, later largely identified with the Atlantic Multidecadal Oscillation. The SST data set allowed identification of several influences of SST on Sahel rainfall, changing the then dominant paradigm that the key influence was regional soil moisture. The work, including dynamical climate modelling, was published in Nature in 1986. It led to the first, successful, forecast of Sahel rainfall in 1986 for which Chris was awarded a **Ministry of Defence prize**. Chris was invited to present his Sahel and SST research at a special climate conference at the Vatican Pontifical Academy in 1986, published in their scientific journal. Rainfall forecasts were extended to several regions of West Africa and to North East Brazil in 1987, a region also dominated by SST variations. This introduced real-time tropical seasonal forecasting into the Met Office, which has developed since then. The work was made well-known through Chris' membership of the WMO Working Group on Long Range Forecasting Research (1986-90).*

*A key part of Chris's job was to develop a mixed statistical and dynamical real-time monthly forecasting system for UK, likely the first partly dynamical such system in the world. Signs of progress were published in 1986 where some skill was shown to exist, particularly for temperature, helped by utilising observed regional SST anomalies using the new global SST data set. Chris first involvement with politicians occurred in August 1984 when a Minister for Drought was created and his advice (fortunately correct!) on whether the drought*

might soon end was sought in a conversation with the Minister. A further key task for this period was Chris' development of the first version of physically based SST bias correction models, accelerated by a short spell as a visiting scientist at the Massachusetts Institute of Technology (MIT). This led to a jointly published 300-page SST Atlas, largely funded by DOE, as a major background document for the 1990 IPCC Report. Here Met Office bias corrected SST data were the main SST data used by IPCC. The method remains unique, though he improved it in the 1990s. Published wind tunnel tests in publications by Southampton Oceanography Centre show the models to be accurate.

As part of an exchange scientist scheme, Chris over a year at the then NOAA Climate Analysis Center (CAC) in Washington DC (1988-89). There he became a Convening Lead Author for the Observed Climate Variability and Change chapter in the 1990 IPCC Report and organised an early IPCC Workshop in summer 1989 in USA. He also co-authored two Nature papers and was commissioned by the CAC Director to write a strategy paper for the future directions of CAC. These activities gained him an "outstanding" visiting scientist report from the Director. Soon after returning to the Met Office, Chris was promoted to what is now a Science Fellow and completed his IPCC work.

In April 1990 the Met Office Hadley Centre was created, and Chris also became Head of Climate Variability, later Climate Variability and Forecasting, from 1990-2008. In 2008 he stepped down from being Head, retaining his Fellowship until retirement in 2017. Soon after becoming Head, Chris shared the main Met Office scientific prize for his SST research, the **1991 L.G. Groves Memorial Prize for Meteorology**. His key responsibility was to develop a wide range of global climate data sets. These ranged from SST, NMAT and sea ice, radiosonde temperatures to surface pressure and later, global temperature and rainfall extremes. They were applied to understanding climate variability and seasonal to interannual forecasting, partly using climate models, as well as to a prominent involvement in IPCC. His group, which grew to about 35 observational and modelling posts in 2008, gained a reputation a leading world developer of global climate data sets and their applications to climate change and variability research. In addition, Chris led development of the first daily Central England temperature data set, the longest daily data in the world. The HadISST SST and sea ice data set published in 2003, together with what it showed about marine climate change, was identified by the Carbon Brief blog in 2015 as the fifth most highly cited paper in climate change/ This now has over 6,800 Web of Science citations (all data bases) and is believed to be the most cited Met Office lead authored paper. Chris shared a **Met Office Achiever Award** for this work in 2008.

The tropical seasonal forecasts for West Africa and North east Brazil were further improved and for these Chris shared with colleagues the **1996 WMO Norbert Gerbier-Mumm International Award (Medal and Prize)**. Additionally, he created real-time forecasts a year ahead of global mean surface temperature, initially statistical, but since 2008 working with dynamical climatologists, both dynamical and statistical. These have had high skill, the 22 forecasts issued for 2000-2021 having a correlation with observations of 0.95. Chris became a **Meteorological Fellow of the Link Foundation of New Zealand** in 1993 and had two visiting scientist awards (1994 and 2000) to work at the New Zealand National Institute of Water and Atmospheric Research to test the SST data sets in the relatively remote South Pacific. This resulted in four published papers and successful tests of the SST data. Related work also led to his published identification of the Interdecadal Pacific Oscillation (IPO) SST and NMAT patterns in 1999. This led to a highly cited paper with the Australian Bureau of Meteorology on the IPO in 1999, and a lead authored paper detecting its influence on the South Pacific Convergence Zone in 2002.

A key strategy, developed by Chris from the mid-1990s, was to work towards operational integrated monthly and seasonal forecasts for UK and Europe with selected forecasts globally Through dynamical and observational papers, most prominently in Nature in 1999, it became clear that there was some predictability of the North Atlantic Oscillation, opening the way for potentially useful winter UK and European forecasts. The first operational winter forecast was published for winter 2005-6. Since Chris started working part time in 2008, he has continued publishing in this area and to help with practical aspects of the now entirely dynamical winter long range forecasts, In 2009, Chris published details of the now widely accepted Summer North Atlantic Oscillation mode in a well cited paper in 2009, leading to a new area of research.

Chris' international involvement in climate change and variability accelerated during this period, partly through being Convening Lead Author of Climate Variability and Change Chapters in the 1990, 1992 Supplementary and 2001 Working Group 1 Reports and Lead Author of the Climate Models - Evaluation Chapter in the 1996 Report, as well as contributions as a Contributing Author and reviewer in later IPCC reports. Chris was also awarded a **Nobel Peace Prize certificate in 2007** given to all IPCC Lead authors. In addition, Chris created and co-chaired the CLIVAR Climate of the Twentieth Century (C20C) project (1999-2014) which has published a number of papers. It continues, as planned by Chris in 2013, as the C20C+ Detection and Attribution project whose new activities were published in 2019, Chris being a co-author. He also became Deputy Chair of the WMO Working Group on Climate Change Detection and Indices (1998-2007) which led to key papers on changing temperature and rainfall extremes in the 2001 and 2007 IPCC

*Reports. He also led Met Office climate variability and change research in four European Union Projects (1990-2008). Chris was invited to give Plenary Presentations to WMO Congress in 1999 on the problems of climate data and on observed climate change to the World Climate Congress in Moscow in 2003, opened by President Putin, and which led to Russia signing the Kyoto Protocol. Especially through the 1990s, the Met Office was developing its relationship with UK politicians on climate change issues. Thus, Chris gave 11 presentations on observed climate change to visiting politicians and a Lords Science and Technology Committee. This included the Prime Minister, Mrs Thatcher, when she opened the Met Office Hadley Centre in 1990.*

*Besides his academic interests, Chris has carried out many media interviews since 1976 and given several talks to local societies on climate change. He was a member of Council of the Royal Met. Soc. in 1978-81, its Education Committee (1976-81) and recently its History of Meteorology and Physical Oceanography Committee (2015-now) where he contributed to two recent Royal Met Soc climate documents. As a member of the Climate Variability and Change Committee of the American Met. Soc. (AMS) (2010-16) he was awarded an AMS Outstanding Service Certificate in 2016.*

*Chris's long period as a climate scientist has also been rewarded by Fellowship of the Institute of Physics (1996), Fellowship of the American Met. Soc. (2003), a Met Office Career Achievement Award (2007), Fellowship of the American Geophysical Union (FAGU, 2011), Honorary Professor at the University of East Anglia (2003), Adjunct Professor at the University of Southern Queensland (USQ) (2009, who also fund Met Office modelling posts) and Guest Professor of Climatology at the University of Gothenburg (2011). The Swedish Research Council partly funded Chris in 2013-16 to research Summer North Atlantic Oscillation mechanisms. In 2016 the Korean Meteorological Administration awarded Chris a Gray Expert Scientist Honorarium to give a lecture course in South Korea on seasonal to decadal forecasting, climate variability and climate change. Recently, he received the USQ 2019 Research Giant Award of \$A8,000 and gave several filmed climate change lectures in early 2020 at USQ for future university courses. Chris was listed in 2021 in the top 20% of the Reuters Hot List of scientists who have contributed most to climate change issues over the last few decades Chris has a Web of Science h Index of 58 with over 24,000 citations, and over 55,000 Google Scholar citations.*

## **Chris K. Folland and Peter L. Read**

### **Introduction**

Professor Raymond Hide was a supreme example of a geophysicist who was much honoured in his lifetime. He covered a very wide area of geophysics from geo- magnetism, meteorology, geodesy, ocean- ography and related aspects of planetary physics. A full appreciation of his life and achievements can be found at Read (2019) and a brief Weather obituary at Read (2017). Raymond Hide was born to relatively hum- ble beginnings on 17 May 1929 in Bentley, a mining village in South Yorkshire and now part of Doncaster. His father, Stephen Hide, had various jobs, particularly after World War I, selling and maintaining miners' lamps at the local pithead. His mother, Edna (née Cartlidge) worked after World War I as a council warden looking after old people living alone in Bentley.

Raymond showed much ability from a very early age. His grandmother taught him to read, write and do addition before he was three. Despite this, Raymond had a difficult younger childhood, largely because his father suffered greatly from the effects of poison gas in World War I for the

remainder of his life. The family then broke up after his father's suicide in 1940. Remarkably, this spurred Raymond on to achieve his potential, gaining a place at the Doncaster Percy Jackson Grammar School. Here he thrived greatly, becoming head boy and securing a state scholarship to Manchester University. He went on to graduate in Physics in 1950 with first class honours.

Reference: Folland C.K and P. Read, 2021: Pen Portraits of Presidents – Professor Raymond Hide CBE FRS. *Weather*, (*on line*).

# Increasing HPV Vaccination Coverage on Preventing Oropharyngeal Cancer: A Cost-Effectiveness Analysis

by Stephen Sonis, Member EUAS

## Short Biography

*Dr. Sonis is Professor of Oral Medicine at Harvard, a designated member of the Distinguished Faculty of the Dana-Farber Cancer Institute and a Senior Surgeon at Brigham and Women's Hospital in Boston, MA, USA. In addition, he is the Chief Scientific Officer at Biomodels, LLC and Chief Medical Officer at Primary Endpoint Solutions, LLC, both in Waltham, MA, USA. Dr. Sonis has published extensively on the clinical, biological, and health economic aspects of cancer and complications associated with its treatment. He holds several patents and is the author of more than 300 original publications, reviews, and chapters and 11 books. Dr. Sonis received his DMD from Tufts, completed his DMSc and residency at Harvard and his postdoctoral training at Oxford where he was a Knox Fellow.*

## 2021 Publications Abstracts

**Choi SE, Choudhary A, Huang J, Sonis S, Giuliano AR, Villa A. Increasing HPV Vaccination Coverage on Preventing Oropharyngeal Cancer: A Cost-Effectiveness Analysis. Tumour Virus Res. 2021 Dec 30:200234. doi: 10.1016/j.tvr.2021.200234**

### **Abstract**

The incidence of oropharyngeal cancer (OPC) has been rising, especially among middle-aged men. While Human Papillomavirus (HPV) has been irrevocably implicated in the pathogenesis of oropharyngeal cancer (OPC), the current HPV vaccination uptake rate remains low in the US. The aim of our study was to evaluate the impact of increased HPV vaccination coverage on HPV-associated OPC incidence and costs. A decision analytic model was constructed for hypothetical cohorts of 9-year-old boys and girls. Two strategies were compared: 1) Maintaining the current vaccination uptake rates; 2) Increasing HPV vaccination uptake rates to the Healthy People 2030 target (80%) for both sexes. Increasing HPV vaccination coverage rates to 80% would be expected to prevent 5,339 OPC cases at a cost of \$0.57 billion USD. Increased HPV vaccination coverage would result in 7,430 quality-adjusted life year (QALY) gains in the overall population, and it is estimated to be cost-effective for males with an incremental cost-effectiveness ratio of \$86,940 per QALY gained under certain conditions. Expanding HPV vaccination rates would likely provide a cost-effective way to reduce the OPC incidence, particularly among males.

**Yaroslavsky AN, Juliano AF, Adnan A, Selting WJ, Iorizzo TW, Carroll JD, Sonis ST, Duncan CN, London WB, Treister NS. Validation of a**

**Monte Carlo modeling based dosimetry of extraoral photobiomodulation. *Diagnostics* 2021. Nov 26;11(12):2207.****Abstract**

An in vivo validation study was performed to confirm the accuracy of extraoral photobiomodulation therapy (PBMT) dosimetry determined by modelling. The Monte Carlo technique was utilized to calculate the fluence rate and absorbed power of light delivered through multi-layered tissue. Optical properties used during Monte Carlo simulations were taken from the literature. Morphological data of four study volunteers were acquired using magnetic resonance imaging (MRI) scans. Light emitting diode (LED) coupled to a power meter were utilized to measure transmitted power through each volunteer's cheek, in vivo. The transmitted power determined by Monte Carlo modelling was compared to the in vivo measurements to determine the accuracy of the simulations. Experimental and simulation results were in good agreement for all four subjects. The difference between the mean values of the measured transmission was within 12% from the respective transmission obtained using Monte Carlo simulations. The results of the study indicate that Monte Carlo modelling is a robust and reliable method for light dosimetry.

**Elad S, Yarom N, Zadik Y, Kuten-Shorrer M, Sonis S. The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anti-cancer therapies. *CA Cancer J Clin* 2021; doi: 10.3322/caac.21704****Abstract**

Oral mucositis (OM) is a common, highly symptomatic complication of cancer therapy that affects patients' function, quality of life, and ability to tolerate treatment. In certain patients with cancer, OM is associated with increased mortality. Research on the management of OM is ongoing. Oral mucosal toxicities are also reported in targeted and immune checkpoint inhibitor therapies. The objective of this article is to present current knowledge about the epidemiology, pathogenesis, assessment, risk prediction, and current and developing intervention strategies for OM and other ulcerative mucosal toxicities caused by both conventional and evolving forms of cancer therapy.

**Klein BA, Alves FA, de Santana Rodrigues Velho J, Vacharotayangul P, Hanna GJ, LeBoeuf NR, Shazib MA, Villa A, Woo SB, Sroussi H, Sonis S, Treister NS. Oral manifestations of immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. *Oral Dis.* 2021 Jul 15. doi: 10.1111/odi.1396****Abstract**

Immunotherapy with immune checkpoint inhibitors (ICIs) has transformed cancer treatment over the past decade, improving survival rates in numerous advanced cancers. Immune-related adverse events (irAEs) are common and can affect any organ system, with many of these toxicities being well-characterized with clear grading criteria and management approaches. There has been less emphasis on oral manifestations of irAEs. This review provides an overview of oral manifestations of irAEs, including mucosal and salivary gland toxicities, and proposes a grading system and management guidelines. irAEs

are common treatment-related toxicities in patients treated with ICIs. Oral irAEs can range from asymptomatic white reticulations to life-threatening mucocutaneous reactions requiring aggressive management with corticosteroids and/or permanent discontinuation of ICIs. Oral healthcare providers should be prepared to identify and manage oral irAEs in collaboration with oncologists and other specialists.

**Lee WY, Pulsipher A, Savage JR, Kennedy TP, Gupta K, Cuiffo BG, Sonis ST. GM-1111 reduces radiation-induced oral mucositis in mice by targeting pattern recognition receptor-mediated inflammatory signaling. PLOS One 2021 Mar 26;16(3):e0249343.**

#### **Abstract**

**Purpose:** Oral mucositis (OM) is a common, painful side effect of radiation therapy used for the treatment of head and neck cancer (HNC). Activation of the innate immune system upon irradiation has been identified as a key precipitating event of OM. To better understand OM's pathogenesis, we studied pattern recognition receptors (PRRs) and their downstream pro-inflammatory cytokines in a mouse model of radiation-induced OM. We also tested therapeutic efficacy of GM-1111 that targets innate immune system to reduce radiation-induced OM.

**Methods and materials:** The pathogenesis of OM was studied in a single X-ray induced mouse model. The severity of OM was measured by visual and microscopical examinations. The irradiation-induced changes of PRRs and their downstream effector cytokine gene expression levels were determined. The efficacy of GM-1111 to reduce OM was tested in single and fractionated irradiation mouse models. The impact of the drug on tumor response to radiation therapy was also tested in a mouse model of human HNC.

**Results:** Radiation-induced tissue ulcerations were radiation-dosage and -time dependent. The lesions showed selective increases in PRR and pro-inflammatory cytokine gene expression levels. Once daily administration of GM-1111 ( $\geq 30$  mg/kg, s.c.) significantly reduced the severity and the incidence of OM. The drug had little effect on PRRs but significantly inhibited downstream pro-inflammatory cytokine genes. GM-1111 did not interfere radiation therapy to induce HNC SCC-25 tumor regression. Instead, we observed significant drug-induced tumor regression.

**Conclusions:** Radiation induces tissue damages. The increased expression levels of PRRs and their downstream pro-inflammatory cytokine genes in the damaged tissues suggest their important contribution to the pathogenesis of OM. Drug GM-1111 that targets these innate immune molecules may be a potential drug candidate as an intervention for OM.

**Villa A, Vollemans M, De Moraes A, Sonis S. Concordance of the WHO, RTOG, and CTCAE v4.0 grading scales for the evaluation of oral mucositis associated with chemoradiation therapy for the treatment of oral and oropharyngeal cancers. Support Care Cancer 2021 Mar 31. doi: 10.1007/s00520-021-06177.**

#### **Abstract**

**Background:** The ability to consistently and accurately assess oral mucositis (OM) is critical to descriptions of its incidence and severity and in evaluating the effectiveness of potential interventions. The lack of a single grading scale compounds outcome

interpretation. Consequently, we assessed the concordance of three of the most commonly used OM grading criteria (World Health Organization (WHO), Radiation Therapy Oncology Group (RTOG), and the common terminology criteria for adverse events (CTCAE).

**Methods:** Data was evaluated from two hundred patients with oropharyngeal or oral cavity cancers who underwent chemoradiation therapy and were enrolled in a double-blind, randomized, placebo-controlled trial in which trained assessors evaluated patients twice weekly. WHO, RTOG, and CTCAE scores were assigned centrally by independent evaluators blinded to the study group. Concordance among the three scales for all OM scores and severe OM scores (score  $\geq 3$ ) was defined as the percentage agreement and measured using Cohen's weighted Kappa.

**Results:** Of 3,578 OM assessments, 57% had identical scores for all three scales. When any score was considered, the concordance between WHO and RTOG scales was 71% (kappa 0.58; 95%CI: 0.56-0.60), 62% for the WHO and CTCAE scales (kappa 0.46; 95%CI: 0.44-0.48) and 78% for the CTCAE and RTOG scales (kappa 0.69; 95%CI: 0.68-0.71). When patients had severe OM (WHO score  $\geq 3$ ), 99.6% (521/523) of the CTCAE OM assessments had scores of 3 or 4 (kappa 0.98; 95%CI: 0.98-0.999) and 97.7% of the RTOG ones (511/523) had scores of 3 or 4 (kappa 0.69; 95%CI: 0.62-0.75). Among patients who had a WHO score of 4, 31.7% (63/199) and 96.0% (196/199) of patients had RTOG or CTCAE scores of 2 or 3, respectively.

**Conclusions:** Discordance was seen with patients who exhibited mild to moderate OM or most severe OM (grade 4) as described by WHO criteria. Whereas scale selection seems less critical in studies in which general "severe mucositis" is the primary outcome, it is particularly important in accurately describing OM's clinical trajectory and the frequency and impact in its most severe forms.

**Sonis ST. Superoxide Dismutase as an Intervention for Radiation Therapy-Associated Toxicities: Review and Profile of Avasopasem Manganese as a Treatment Option for Radiation-Induced Mucositis. Drug Design Develop Ther 2021 Mar 5;15:1021-1029. doi: 10.2147/DDDT.S267400**

#### **Abstract**

Toxicities associated with radiation therapy are common, symptomatically devastating, and costly. The best chance to effectively mitigate radiation-associated normal tissue side effects are interventions aimed at disrupting the biological cascade, which is the basis for toxicity development, while simultaneously not reducing the beneficial impact of radiation on tumor. Oxidative stress is a key initiator of radiation-associated normal tissue injury as physiologic antioxidant mechanisms are overwhelmed by the accumulation of effects produced by fractionated treatment regimens. And fundamental to this is the generation of superoxide, which is normally removed by superoxide dismutases (SODs). Attempts to supplement the activity of endogenous SOD to prevent radiation-induced normal tissue injury have included the administration of bovine-derived SOD and increasing SOD production using gene transfer, neither of which has resulted in a clinically acceptable therapy. A third approach has been to develop synthetic small molecule dismutase mimetics. This approach has led to the creation and development of avasopasem manganese, a unique and specific dismutase mimetic that, in clinical trials, has shown promising potential to reduce the incidence, severity and duration of severe oral mucositis

amongst patients being treated with concomitant chemoradiation for cancers of the head and neck. Further, avasopasem and related analogues have demonstrated mechanism-related antitumor synergy in combination with high dose per fraction radiotherapy, an observation that is also being tested in clinical trials. An ongoing Phase 3 trial seeks to confirm avasopasem manganese as an effective intervention for severe oral mucositis associated with chemoradiation in head and neck cancer patients.

**Sonis ST. A hypothesis for the pathogenesis of radiation-induced oral mucositis: when biological challenges exceed physiologic protective mechanisms. Implications for pharmacological prevention and treatment. J Support Care Cancer 2021 Sep;29(9):4939-4947**

#### **Abstract**

Oral mucositis (OM) remains a significant unmet need for patients being treated with standard concomitant chemoradiation (CRT) regimens for head and neck cancers (HNC). OM's pathogenesis is complex and includes both direct and indirect damage pathways. In this paper, the field is reviewed with emphasis on the initiating and sustaining role of oxidative stress on OM's pathobiology. A hypothesis is presented which suggests that based on OM's clinical and biological trajectory, mucosal damage is largely the consequence of cumulative CRT-induced biological changes overwhelming physiologic self-protective mechanisms. Furthermore, an individual's ability to mount and maintain a protective response is dependent on interacting pathways which are primarily determined by a multiplex consisting of genomics, epigenomics, and microbiomics. Effective biologic or pharmacologic OM interventions are likely to supplement or stimulate existing physiologic damage-control mechanisms.

**Satheeshkumar PS, Sonis ST. Network meta-analysis from a pairwise meta-analysis design--to assess the comparative effectiveness of oral care interventions in preventing ventilator associated pneumonia in critically ill patients. Clinical Oral Invest 2021 May;25(5):2439-2447**

#### **Abstract**

**Objective:** In this research, we assessed the usefulness of network meta-analysis (NMA), in creating a hierarchy to define the most effective oral care intervention for the prevention and management of ventilation-associated pneumonia (VAP).

**Materials and methods:** We applied NMA to a previously published robust pairwise meta-analysis. Statistical analyses were based on comparing rates of total VAP events between intervention groups and placebo-usual care groups. We synthesized a netgraph, reported the ranking order of the interventions, and summarized output by a forest plot with a reference treatment placebo/usual care.

**Results:** The results of this NMA are from the low and high risk of bias studies, and hence, we strongly recommend not to use findings of this NMA for clinical treatment needs, but based on results of the NMA, we highly recommend for future clinical trials. With our inclusion and exclusion criteria for the NMA, we extracted 25 studies (4473 subjects). The NMA included 16 treatments, 29 pairwise comparisons, and 15 designs. Based on results of NMA frequentist-ranking P scores, tooth brushing (P fixed-0.94, P random-0.89), tooth brushing with povidone-iodine (P fixed-0.90, P random-0.88), and furacillin (P fixed-0.88, P random-0.84) were the best three interventions for preventing VAP.

**Conclusions:** Any conclusion drawn from this NMA should be taken with caution and recommend future clinical trials with the results.

**Clinical relevance:** NMA appeared to be an effective platform from which multiple interventions reported in disparate clinical trials could be compared to derive a hierarchical assessment of efficacy in VAP intervention.

**Choi SE, Choudhary A, Sonis S, Villa A. Benefits of the involvement of dentists in managing Oral Complications among Oral Cavity and Oropharyngeal Cancer Patients: An Analysis of Claims Data; JCO Oncology Practice 2021 Nov;17(11):e1668-e1677**

**Abstract**

**Purpose:** Patients with oral cancer and oropharyngeal cancer frequently develop treatment-related oral complications that negatively affect patients' quality-of-life, cost, and health outcomes. We investigated whether the provider specialty affected the costs and treatment duration of managing oral complications.

**Methods:** Using deidentified claims from a commercial insurer from 2008 to 2019, we compared costs and duration of common oral complication management between patients whose care included a dentist, with those whose care did not include a dentist. Our primary outcomes were treatment cost and duration. Multivariate linear regression models were used to evaluate the relationship between the primary outcomes and involvement of dentists. Separate analyses were conducted for acute and chronic oral complications.

**Results:** Involvement of dentists in oral complications management resulted in lower costs and shorter treatment duration for acute complications on average. For chronic complications, when dentists were involved, the average cost was higher by \$1,672 (USD) (95% CI, 1,124 to 2,219), but the average treatment duration was shorter by 74 days (95% CI, 62 to 84). When complications were acute, dentists' intervention was beneficial for dentofacial functional abnormalities, disorders of teeth and supporting structures, stomatitis and mucositis (ulcerative), and thrush, in terms of both costs and duration. Among chronic complications, dental caries was the only complication type that resulted in lower cost and shorter treatment duration with dentists' involvement.

**Conclusion:** Oral complications of cancer therapy incur a significant financial and clinical burden. Involvement of dentists results in shorter treatment duration, while lowering the financial burden of care for certain complication types.

**Sankaran SP, Villa A, Sonis ST. Healthcare-associated infections among patients hospitalized for cancers of the lip, oral cavity and pharynx. Infection Prevention in Practice 2021, 13:3(1):100115**

**Abstract**

**Introduction:** The negative consequences of healthcare-associated infections (HAI) on the burden of illness (BOI) of cancer patients are well-established. However, there is a paucity of research on HAI among cancers of the lip, oral cavity and pharynx (CLOCP), and whether HAI-related BOI differed for other common solid tumors-malignant neoplasm of the colon (MNC) and malignant neoplasm of the lung (MNL).

**Methods:** We utilized the United States' National Inpatient Sample database 2017 to study longitudinal inpatient hospital stay of CLOCP, MNC and MNL. Patient demographics and hospital characteristics of patients were assessed, and the impact of HAI-related BOI

compared based on differences in length of hospital stays (LOS), total charges during hospitalization and mortality were compared.

**Findings:** In 2017, of the 54,934 patients with CLOCP, 1.2% had HAI, compared to MNC (n=64,470) with 2% HAI and MNL (n=154,685) with 1.2% HAI. In adjusted multivariable regression analysis, we determined CLOCP patients with HAI had LOS of 5.6 days longer (95% CIs, 3.0-8.2 days,  $P < 0.001$ ), and hospitalization charges of \$40,341 higher (95% CIs 15,715-64,967,  $P < 0.01$ ) than the non-HAI CLOCP patients. Mortality was not significantly different among HAI and non-HAI CLOCP patients (odds ratio: 0.80; 95% CIs 0.35-1.87,  $P = 0.6$ ). In unadjusted analysis, LOS and total charges were higher for CLOCP-HAI patients vs. MNC-HAI or MNL-HAI patients.

**Conclusion:** HAI in patients with CLOCP patients were associated with an increased BOI, and this is considerably higher than observed in patients with MNC or MNL patients who had HAI.

**Xu Y, Wen N, Sonis S, Villa A. Oral side effects of immune checkpoint inhibitor therapy (ICIT): An analysis of 4,683 patients receiving ICIT for malignancies at Mass General Brigham and the Dana-Farber Cancer Institute 2011-2019. Cancer 2021 Jun 1;127(11):1796-1804**

**Abstract**

**Background:** Immune checkpoint inhibitors (ICIs) are increasingly accepted as a treatment option for several cancers. Although various systemic immune-related adverse events (irAEs) have been characterized, the effect of ICIs on the oral cavity and contiguous structures is still poorly understood.

**Methods:** Electronic medical records of 4683 patients in the Mass General Brigham Registered Patient Data Registry who received ICI therapy (ICIT) between December 2011 and September 2019 were reviewed. Reports of oral conditions were categorized into oral mucosal disorders, xerostomia, and dysgeusia. After applying exclusion criteria, demographic characteristics and clinical features were summarized for the patients who had oral irAEs.

**Results:** In total, 317 patients developed oral conditions that were associated with ICIT (incidence, 6.8%; 317 of 4683 patients). These conditions included xerostomia (68.5%), oral mucosal disorders (33.4%), and dysgeusia (24.0%). In patients with oral irAEs, respiratory cancer (28.4%) was the most common primary cancer, followed by melanoma (26.2%), and head and neck cancer (14.8%). Oral mucosal disorders developed after the initiation of ICIT between 2 and 851 days (between 1 and 1332 days in patients with xerostomia and between 1 and 1455 days in patients with dysgeusia). Of all oral irAEs, 50.9% developed within 3 months, and 85.5% developed within 12 months.

**Conclusions:** Oral side effects appear to be more common among patients who receive ICIT than has been previously reported. Concomitant cytotoxic regimens may exacerbate the risk of oral adverse events, perhaps representing the sum of the effects of different, but simultaneous or sequential, pathogenic mechanisms. Additional studies are warranted to better characterize oral irAEs and their biologic basis.

## Activities in Materials Science and Engineering

by Derek O. Northwood, Member EUAS

### Short Biography

*Professor Derek O. Northwood is a Distinguished University Professor Emeritus and Professor of Engineering Materials in the Department of Mechanical, Automotive and Materials Engineering at the University of Windsor, Windsor, Ontario, Canada. Professor Northwood has an earned doctorate in Chemical Physics (Crystallography) from the University of Surrey (UK) and a BSc (Eng) in Engineering Metallurgy from the Imperial College, University of London (UK). He is a licensed Professional Engineer in Ontario, Canada (PEng) and is a Chartered Professional Engineer (CPEng; NER), APEC Engineer, and International Professional Engineer (IntPE(AUS), in Australia. In the 40+ years as an academic, Professor Northwood has held various administrative positions including Department Head, Dean, Associate Dean of Research, Director of the Office of Research Services, President of the Industrial Research Institute, and, Research Leadership Chair, both at the University of Windsor and Ryerson University, Toronto, Canada. Professor Northwood has taught, researched and facilitated joint research and educational programs at 14 universities worldwide, including the UK, the USA, Australia, Taiwan, China, Singapore and Canada. He has published 703 papers in refereed international journals and conference proceedings, 9 chapters in books and has edited 10 books, on a wide range of topics including materials and their applications, and engineering and technology education. He has been elected Fellow of six international professional societies in Australia, Canada, the UK and the USA; namely, Fellow of the Royal Society of Canada (FRSC); Fellow of the Institution of Engineers Australia (FIEAust); Fellow of the World Institute for Engineering and Technology Education (FWIETE); Fellow of the Institute of Materials, Minerals and Mining (FIMMM); and Fellow of ASM International (FASM); and Fellow of Alpha Sigma Mu (FAΣM), The International Professional Honor Society for Materials Science and Engineering. Professor Northwood is recognized as being among the world's top 100,000 - or top 2% of scientists - according to the database published by Stanford University. The database recognizes the long-term career performance of scientists around the world, living or deceased, who are the most cited authors in their disciplines. It reflects six citation metrics, including total citations and number of citations to papers as single or first author between 1965 and 2019. The data was collected from the Scopus database of nearly 7 million authors out of which the top 100,000/2% were analysed.*

*As noted in the Short Biography, my title at the University of Windsor changed in 2021 from Distinguished University Professor to Distinguished University Professor Emeritus. My decision to retire effective March 1, 2021 was predicated by the ongoing pandemic, on-line teaching and little, or no, access to laboratories or in-person interactions.*

*I intend to remain relatively active in 2022 with my ongoing research activities both with Professor Cheng Liu at Yangzhou University in China on steels and ductile irons and with Associate Professor Daniela Pusca at the University of Windsor on matters relating to engineering education. I am also continuing my paper review activities for both the World Institute of Engineering and Technology Education (WIETE), Australia, and to the Wessex Institute, UK.*

### **RESEARCH ACTIVITIES AND PUBLICATIONS 2021**

As was the case for 2020, Covid-19 restrictions have had a negative impact on our ability to conduct research both in my home university and with my partners across the globe.

Limited research activities have continued in two areas.

1. Developing the potential properties of traditional materials.
2. Innovation in Engineering Education.

### 1. Developing the potential properties of traditional materials

This is part of my ongoing collaboration with Professor Cheng Liu, College of Mechanical Engineering, Yangzhou University, Yangzhou, China which has resulted in 32 publications on steels, cast irons, aluminum alloys and zirconia ceramics. Research in 2021 was concentrated on the development of heat treatments for enhancing the properties of both disc springs made from 60Si2Mn/55Mn2SiCr steel and unalloyed ductile iron.

The work on the spring steels in 2021 built on the work reported in 2020 where application of a multi-step austempering process produced a multi-phase nanostructure microstructure which improved both the hardness and strength of a conventional 60Si2Mn disc spring, and allowed for applications involving higher loads and fatigue conditions. In 2021, guided by the work on advances high-strength steels, the quenching and partitioning process (Q & P), and the transformation of a nano-scaled bainite, a novel quenching-partitioning-austempering process (Q-P-A) was developed and applied to a 55Mn2SiCr steel. Ultimate tensile strengths (UTS) of over 2 GPa and elongations of 3% were obtained. Mouth-like cracks were observed on the fracture surface and superior crack resistance was obtained. This has been shown to be due to a multi-phase microstructure comprising prior martensite (PM), bainitic ferrite (BF), retained austenite (RA) and a nanoscaled structure ((BF+RA(+C))nano). RA(+C) is carbon-enriched retained austenite.

Li, J., Hang, Y., Zhou, S., Wang, X., Liang, Z., Zhou, W., Northwood, D.O., Liu, C.

**Multi-phase nanostructured 60Si2Mn disc spring by a novel austempering process**  
(2020) WIT Transactions on The Built Environment. 196, pp. 11-18

#### Abstract

A disc spring, also known as a Belleville spring, is a conical shell which can be loaded along its axis either statically or dynamically. It can generate a high force in a very short spring length with minimal movement when compressed. A novel multi-step austempering heat treatment process is developed to improve both the hardness and strength of a conventional 60Si2Mn disc spring. In this case, the disc spring is austenitized at 900°C for 0.5 h, control-quenched to a temperature below Ms (the starting temperature of martensite transformation) for a very short time, subsequently heated to the Ms point and holding for a specific time, and finally air cooled to the room temperature. It is found that the resulting multiphase microstructure consists mainly of prior lenticular martensite formed during controlled quenching (PM), needle bainitic ferrite (BF), and high carbon enriched retained austenite (RA). Further observation shows that a nanostructured (BF+RA) nano phase including lath BF and film RA with a width of about 100 nm nucleates around the PM. Such a microstructure results in uniform compression behavior, and significantly higher strength and hardness than for a conventional 60Si2Mn disc spring. This controlled multi-step austempering process is a promising solution for enhancing the disc spring properties for those applications involving higher loading and fatigue conditions

Wang, X., Gao, J., Hang, Y., Zheng, Y., Northwood, D.O., Liu, C.

**Mouth-like cracking in a high-strength multiphase steel and its relationship to fracture toughness**

(2021) *WIT Transactions on Engineering Sciences*, 133, pp. 3-14.

#### Abstract

The effect of microstructure on crack growth behaviour in steels has always been a subject of considerable research interest. Based on a quenching and partitioning process (Q&P), and the transformation of a nano-scaled bainite in advanced high-strength steels, a novel quenching-partitioning-austempering process (Q-P-A) has been developed for manufacturing a multiphase microstructure in a medium carbon steel (55Mn2SiCr). The processing sequence consists of the following steps: austenitizing at 900°C for 0.5 h; controlled quenching and cooling to 200°C, i.e. slightly below  $M_s$  (the start temperature for martensite transformation) for 5 s; austempering at 170°C for 5 min; up-heating to 250°C for 120 min; final air cooling to room temperature. An ultimate tensile strength (UTS) above 2 GPa, as well as an acceptable elongation of 3%, is obtained due to a multiphase formation comprising prior martensite (PM), bainitic ferrite (BF), retained austenite (RA) and nano-scaled structure ((BF + RA(+C))nano). Mouth-like cracks are observed on the fracture surface and the crack arrest behavior is investigated. When a microstructural cluster with (BF + RA(+C))nano fully covered PM is formed, a mouth-like crack can be formed and a superior crack resistance can be obtained. The crack initiates from the PM boundary and propagates along the interface between the PM and (BF + RA(+C))nano over a distance of a few millimeters and before being arrested in the (BF + RA(+C))nano. This behaviour is mainly attributed to the uniform distribution of film RA and needle BF with nano-level spacing in the (BF + RA) nano. The stress concentration energy at the crack tip can be absorbed by the martensitic transformation of the film RA. The results are important when designing a multiphase microstructure for a commercial high-strength steel.

Austempered ductile iron (ADI) has found wide usage in various structural applications due to its attractive combination of properties including high strength and toughness, good design flexibility and low production cost. However, since ADI is increasingly being examined as a substitute for forged steels, there is a need to develop ductile irons that can perform well when subjected to heavy loading. One approach to developing these high-performance ductile irons is to use a quenching and partitioning process (Q&PDI), similar to that used to produce ultra-high strength steels (as in our work on the 55Mn2SiCr spring steel). We have developed a quenching and partitioning process for an unalloyed ductile iron. Initial work on the wear resistance, showed that the multiphase microstructure that is produced, led to a comprehensive strengthening and toughening effect at high loads, and improved the wear resistance for situations without lubrication. Further investigations demonstrated that using a Q&PDI process, an unalloyed ductile iron can be produced with mechanical properties comparable to those of a high strength carbon alloy steel.

Dong, K., Lu, C., Zhou, W., Northwood, D.O., Liu, C.

#### **Wear behavior of a multiphase ductile iron produced by quenching and partitioning process**

(2021) *Engineering Failure Analysis*, 123, art. no. 105290, .

#### Abstract

A quenching and partitioning process has been developed for an unalloyed ductile iron. The process includes austenitizing at 890 °C for 0.5 h, quenching to 180 °C below the  $M_s$  (the starting temperature of martensite transformation) for 5 s, with a controlled speed, then followed by a partitioning at 190 °C (10 °C lower than the  $M_s$ ) for 8 h, and finally air cooling to the room temperature. A multiphase microstructure consisting of prior martensite (PM), bainitic ferrite (BF), and fresh martensite formed on final quenching (FM) with retained austenite (RA) is obtained through the microstructural evolution on quenching and partitioning steps. Further observation shows that a unique nano structure including lath BF and film RA with a width less than 100 nm nucleates around the PM. A strong influence of RA content and stability on both the tensile strength and the elongation is observed. In addition, the wear behavior is investigated under various loads without lubrication. A combined wear mechanism of abrasion and oxidation is found in a case of a low load. With increasing the load, the wear behavior

correlates to a comprehensive strengthening and toughening effect of the multiphase microstructure in the matrix.

Zhou, W., Northwood, D.O., Liu, C.

**A steel-like unalloyed multiphase ductile iron**

(2021) *Journal of Materials Research and Technology*, 15, pp. 3836-3849.

**Abstract**

This work highlights a new process for direct manufacturing of ductile iron that is based on the innovative combined technology of quenching and partitioning, and low-temperature-transformation of nano bainite as used for high strength steels. In this process, a commercial unalloyed ductile iron is austenitized at 890 °C for 20 min, then rapidly quenched to 180 °C for 5 s, and finally partitioned at 220 °C for 240 min. A maximum tensile strength of more than 1600 MPa, a hardness of 55 HRC at an elongation in excess of 5%, and the number of repeat tensile fatigue failure of  $2.5 \times 10^4$  cycles at a stress amplitude of 600 MPa, are achieved. This is comparable to those of a high strength carbon alloy steel. These properties are due to the synergistic strengthening and toughening effects of a multiphase structure comprising tempered martensite, bainitic ferrite and retained austenite in the matrix, and a spherical graphite morphology. This work provides a guidance on how to produce unique steel-like ductile iron with a high level of strength and acceptable toughness.

## 2. Innovation in Engineering Education

In 2021, I have continued working with Associate Professor Daniela Pusca, University of Windsor, on the challenges we face as educators in an engineering faculty. As was the case in 2020, COVID-19 continues to present its own challenges and has highlighted the need for change.

These changes are related to both teaching and learning. COVID concerns have moved us to remote life participation (RLP) where students are expected to be in the virtual classroom and participate actively for all synchronous activities.. Using a First-Year Engineering Design course as our "framework", we have addressed three basic questions with respect to the move towards RLP. These are: How much change is needed?; Do Ed-Tech tools help solve education problems/challenges?; What is the impact on students' learning?

The guiding vision for the changes was "effectivity", namely "effective learning". From the perspective of the student, we chose to use the description of "effective" that was put forward by Ilkovicova et al (Ways of rationality and effectivity in architectural education, *World Trans. on Engng. and Technol. Educ.*, 15(4), 331-337, 2017), namely: "What does the student use, creatively develop and apply in practice and, then, use in a successful profession?"

The first step in the course design process was to answer the question as to what graduate attributes/skills needed to be addressed. In this course they were identified as: Graphical Communication; Use of Engineering Tools; Design and Creativity; Critical Thinking; Communication. The next step was to answer "What teaching activities are to be employed?", followed by "What learning activities are to be used?" and "What methods of assessment will be used?". The final question "What EdTech tools would be used for

teaching and learning?" The choice of EdTech tools was not easy, since they vary in their effectiveness and there are high costs associated with new cutting-edge EdTech tools. We have included Multimedia, Transmedia, CAD, Augmented Reality, and Virtual Reality.

Our experience has shown that EdTech tools have the potential to transform the teaching and learning experience for all participants in the educational process - faculty, teaching assistants and students. Students became more familiar with the use of multimedia and transmedia, and were more engaged and more interested in the process with the implementation of AR and VR.

Pusca, D., Northwood, D.O.

**Teaching and learning engineering design: creative methods for remote education**

(2021) *World Transactions on Engineering and Technology Education*, 19 (3), pp. 306-312.

**Abstract**

The traditional engineering design class was created for integrated lecture-laboratory sessions in a face-to-face environment. With the move towards remote teaching and learning at the University of Windsor, Windsor, Canada, there was a need to make changes related to both, teaching and learning. In this article, the authors discuss issues on How much change is needed; Does tech solve education problems?; What is the impact on students' learning?; and present innovative course design strategies for remote education, based on identified problems and challenges associated with using an e-learning platform. It is the authors' opinion that both teaching and learning should be done creatively, regardless of the environment - face-to-face or remotely. In times of rapid technological changes, instructors and students should be able to use different tools associated with the learning management system (LMS) and also course-related digital tools to achieve the desired student-centred results. The purpose of this article is to present digital tools and new technology that have the potential to transform the teaching and learning experience, regardless of the learning spaces.

# New Trends in Covid-19

by Kari C. Nadeau, Member EUAS

## Short Biography

### **Certifications**

- 2021: Certificate in Public Policy (Harvard Kennedy School of Government)
- 2021: Executive Course on Sr Executive Fellows on Leadership (Harvard Kennedy School of Government)
- 2021: Executive Course on Climate Change, Economics and Public Policy (Harvard Kennedy School of Government)
- 2008: Elected Fellow of the American Academy of Allergy, Asthma, and Immunology
- 2007: Board Certification in Allergy and Immunology
- 2006: Board Certification in Pediatrics

### **Educational Background**

1. 2003-2006: Fellow, Stanford-UCSF Allergy, Asthma, and Immunology Program
2. 1995-1997: Pediatric Internship and Residency, Pediatrics, Children's Hospital of Boston Special Alternative Pathway
3. 1988-1995: MD and PhD at Harvard Medical School, Medical Scientist Training Program Doctoral work completed in Biochemistry and Immunology, Boston, MA
4. 1984-1988: BS in Biology, Haverford College, Summa cum Laude, Haverford, PA

### **Professional Appointments (Stanford University School of Medicine)**

- April 2021-present Affiliated faculty member. Wu Tsai Neurosciences Institute
- Jul. 2020 -present: Professor of Epidemiology, Department of Epidemiology and Population Health (courtesy appointment)
- May 2019-present Medical Director, Precision Medicine in Allergy, Stanford University
- March 2020-present Sr. Director, Clinical Research, Division of Hospital Medicine, Stanford Hospitals and Clinics
- Jun. 2015-present: Professor of Otolaryngology, Department of Otolaryngology (courtesy appointment)
- Jun. 2015-present: Professor of Pediatrics, Division of Allergy, Immuno Rheumatology (joint appointment) • Jun. 2015-present: Professor of Medicine. Division of Pulmonary and Critical Care Medicine
- June 2016-present Section Chief, Allergy and Asthma, Stanford Hospital and Clinics
- Jan. 2015-present Director, Sean N. Parker Center for Allergy and Asthma Research at Stanford University
- 2010-present: Member, Children's Health Research Institute, Stanford
- 2007-present: Faculty Member, Multidisciplinary Program in Immunology (MPI), Stanford University School of Medicine, Stanford, CA
- 2007-present: Faculty Member, Stanford Institute of Immunity, Transplantation, and Infectious Disease
- June 2015-Sept. 2015: Associate Professor of Pediatrics (MCL), Division of Allergy, Immunology, and Rheumatology (joint appointment)
- June 2015-Sept. 2015: Associate Professor of Medicine (MCL), Division of Pulmonary and Critical Care Medicine
- Aug. 2011-Sept. 2015: Associate Professor of Otolaryngology (MCL), Courtesy Appointment
- Aug. 2011-May 2015: Associate Professor of Pediatrics (MCL), Division of Allergy, Immunology, and Rheumatology
- June 2008-July 2011: Assistant Professor of Otolaryngology (MCL), Courtesy Appointment
- June 2008-July 2011: Assistant Professor of Pediatrics (MCL), Division of Immunology and Allergy
- July 2006-May 2008: Instructor, Department of Pediatrics
- Nov. 2005-June 2006: Post-doctoral fellow, Laboratory of Dr. Alan Krensky, Clinical Fellow, Allergy and Immunology
- Nov. 2002-Oct. 2005: Clinical Instructor, General Pediatrics

### **Honors and Awards**

1. Member, International Women's Forum (IWF) (2021-present)
2. Member, Stanford Center for Precision Mental Health & Wellness (PMHW) (2021 -present)
3. Distinguished Member. World Society for Virology (2021-present)
4. Member, European Union Academy of Sciences (EUAS) (2021-present)
5. Advisory Board for the EAACI Research and Outreach Committee (2020 – present)
6. Member, Association of American Physicians (2020)
7. American Academy of Allergy, Asthma and Immunology (AAAAI) National Distinguished Scientist Award (2020)
8. Nominee from Stanford Medical School for Warren Alpert Award (2020)

9. *Stanford Cardiovascular Institute Seed Grant Award, "Single-cell Sequencing to Identify Air Pollution-Induced Cardiac Risks."* (2019)
10. *Senior Fellow, Stanford Woods Institute for the Environment* (2019-current)
11. *Chief Innovation Officer, Food Allergy Research & Education (FARE)* (2018-present)
12. *Food Allergy Research & Education (FARE), Distinguished Research Award* (2018)
13. *Chair, Board of Scientific Counselors of NIH Clinical Centers (CCBSC)* (2018-current)
14. *White House Medical Unit Consultant* (2015- 2016)
15. *National Scientific Advisory Board Environmental Protection Agency* (2015-2016)
16. *Member, National Scientific Committee, Immune Tolerance Network, NIAID* (2015-present)
17. *Institute of Medicine, National Academy of Sciences (U.S.), Consultant and Panel Participant* (2014)
18. *Faculty Fellow, Stanford Center for Innovation in Global Health* (2015-Present)
19. *United Nations Annual Innovations Lecture "An Allergy Free World For Every Child"* (2015)
20. *University of Washington Grand Rounds and Pierson Lectureship* (2015)
21. *Texas Children's Hospital Visiting Professorship Lecture* (2015)
22. *Distinguished Lecture Award, NIEHS Annual Distinguished Lecture* (2014)
23. *Member, The American Society of Clinical Investigation* (2014)
24. *American Academy of Asthma, Allergy, and Immunology Research Award* (2014)
25. *Helen F. Cserr Memorial Lecture Award* (2014)
26. *Canadian Allergy and Clinical Immunology Society Plenary Speaker Award* (2013)
27. *Member and Alain L. de Weck Travel Grant Awardee, Collegium Internationale Allergologicum* (2012)
28. *Faculty Fellows Program Award, Stanford University School of Medicine* (2012-2013)
29. *EPA Star Grant Award* (2011-2013)
30. *Clinical Immunological Society (CIS) Junior Faculty Award* (2010)
31. *Council for Collegium Internationale Allergologicum* (2010-present)
32. *American Lung Association National Junior Faculty Award* (2009)
33. *Fellow of the American Academy of Asthma, Allergy and Immunology* (2008-present)
34. *ART trust American Academy of Allergy, Asthma and Immunology Award* (2008)
35. *International CIS Immunodeficiency School for Fellows (faculty member)* (2008- 2011)
36. *Speaker Award, La Entrada Inspirational Speaker Series* (2007)
37. *Teaching Award, Stanford Cardinal Free Clinic* (2007)
38. *Speaker Awardee, American Society of Transplantation* (5/97, 5/98, 5/99)
39. *Von Mayer Scholarship Awardee, Children's Hospital* (1995-1998)
40. *Soma Weiss Speaker for Harvard Medical School* (1993)
41. *Medical Student Teaching Award, Harvard Medical School* (6/91, 6/92, 6/93)

#### **Awards and International/ European Committees**

- *Member, International Women's Forum (IWF)* (2021-present)
- *Distinguished Member. World Society for Virology* (2021-present)
- *Council for Collegium Internationale Allergologicum* (2010-present)
- *Member, Annual Meeting Program Committee for the American Academy of Asthma, Allergy, and Immunology (AAAAI)*
- *Member, Board of Scientific Counselors of the NIH Clinical Center*
- *Member, European Academy of Allergy and Clinical Immunology*
- *International Society of Global Health (ISoGH)*

Dr. Nadeau is a Naddisy Foundation Professor in the Department of Medicine and Pediatrics (and by courtesy, Otolaryngology and Population Health/Epidemiology) at the Stanford University School of Medicine. She is a physician-scientist board certified in allergy, asthma, and immunology with over 30 years of experience. She is also the Director of the Sean N. Parker Center for Allergy and Asthma Research at Stanford University and is a member of the Woods Institute at Stanford University, Stanford Lane Center for the West, and the Stanford Center for Innovation and Global Health. **She has successfully worked with global leaders, NIH, FDA, EPA, and policy makers to apply scientific evidence towards making sustained impacts in human and planetary health.**

Her clinical team has overseen over 40 clinical trials and cohort studies in air pollution, immunology, asthma, allergy, and COVID 19, and have overseen 4 birth and 2 pregnancy cohorts and enrolled over 6,000 patients in longitudinal studies. She **was part of the Children's Environmental Health Studies through the NIEHS and EPA.** Her

**accomplishments to date include over 320 peer-reviewed publications, many in high-impact journals.**

Her laboratory focuses mainly on basic science mechanistic research on environmental exposures to air and water pollution by studying immune cells and their function. The lab also studies antigen-specific T cells, immune cell responses to viral and food antigens, and host responses to toxicant exposures in air pollution and wildfires.

The goals of her research can be broadly classified into four main areas: 1) Climate change/pollution/wildfire, 2) Food allergy and other atopic diseases 3) Prevention, 4) Asthma, and 5) COVID-19.

Her lab has dedicated, collaborative teams examining plasma, cellular, and epigenetic markers that are affected by air pollution in children, adolescents, and adults. Using well characterized cohorts in the Bay Area (for acute pollution exposure—i.e. wildfire) and in the Central Valley (for chronic exposure—i.e. Fresno is one of the highest ranked cities in the country for PM<sub>2.5</sub> air pollution), her lab has been able to perform innovative and impactful research that has helped shape public policy towards mitigating pollution and its effects on the public, (especially those at risk populations (like children) and the underserved (like Hispanic populations in the Central Valley of California)).

Her group was the first to treat patients with multi-food allergen immunotherapy and demonstrate that oral immunotherapy can simultaneously and successfully achieve desensitization for multiple allergens and that adjunct use of omalizumab facilitates and decreases time to desensitization. Multi-allergen oral immunotherapy has also enabled determination of associations and cross-reactivities between different food allergens and has also enabled epitope mapping, identification, and characterization of allergenic components of foods. The data from her clinical trials have provided initial evidence for the safety and feasibility of oral immunotherapy for simultaneously treating multiple food allergies and has paved the way for further innovative research in this field. Her lab is also working on diagnostic techniques that aim to replace food challenge as a diagnostic technique. Other novel trials for food allergy in her clinic include the use of skin patches for delivering allergens, DNA vaccines and novel immunoglobulins such as anti-IL-4R $\alpha$ , anti-IL-13, and anti-IL-33. Clinical research on atopic dermatitis, eosinophilic esophagitis, and allergic rhinitis are also underway. Using high throughput omic technologies, her team is evaluating and determining epigenetic, mRNA, immune, and humoral differences between healthy and allergic individuals. The role of T cells is of particular interest to her lab. Using state-of-the-art techniques, such as allergen-specific T-cell sorting and single-cell gene expression, her team has successfully demonstrated T cell differences between healthy, allergic and asthmatic individuals. Her research team was also the first to show that epigenetics, and high dimensional immunophenotyping of epitope-, allergen-, or asthma-specific T cells involved in allergy could be used to impact patient management in real time.

She has focused on tolerogenic mechanisms in the immune system for almost 30 years. With the rising rates of allergy and asthma, her group is also looking at ways to prevent these diseases. They are evaluating both aspects of the dual allergen exposure hypothesis which states that exposure to food allergens through the skin leads to allergy, while consumption of these foods at an early age can result in tolerance. They are determining whether early oral exposure to food allergens and diverse foods can prevent food allergy. Another line of research is to determine whether the use of moisturizers can prevent development of atopic dermatitis and food allergies in those at high risk of developing allergies. Her lab continues translational work (through conducting novel and innovative

clinical studies to induce tolerance through immunotherapy) on Treg function and epigenetic changes of pivotal loci in Foxp3, IL-10, IFN- $\gamma$ , and IL-4.

Her lab is also evaluating biomarkers associated with “immune monitoring” in asthma. Using high dimensional immunophenotyping technology, they were able to detect differences between immune cell subsets from previously frozen peripheral blood mononuclear cells from those obtained from patients with asthma, food allergy, and healthy controls. Another novel method that we have developed is the Isotype-specific agglutination-PCR (ISAP), which is a sensitive and multiplex method for measuring allergen-specific IgE.

During the COVID-19 pandemic, her lab has joined global efforts to treat patients with COVID-19 and to understand the effects of SARS-CoV-2 on the immune system, including those with cancer, autoimmune disease, or allergic diseases. They have focused on understanding the alterations in immune cell populations in patients with COVID-19 and have identified a number of immune changes that can assist with diagnosis, prognosis, and development of targeted therapy. The Center has conducted clinical trials on novel drugs for SARS-CoV-2 and assessed predictive factors for disease severity. They have also focused our efforts on understanding the effect of allergy and asthma on SARS-CoV-2 and management of patients with allergy, asthma, and COVID-19.

**Below, are some of her recent manuscripts. A Complete List of her Published Works can be found at**

<https://www.ncbi.nlm.nih.gov/myncbi/kari.nadeau.1/bibliography/public/>

[https://cap.stanford.edu/profiles/viewCV?facultyId=7485&name=Kari\\_Nadeau](https://cap.stanford.edu/profiles/viewCV?facultyId=7485&name=Kari_Nadeau)

## CLIMATE CHANGE/POLLUTION/WILDFIRE

- **Nadeau KC**, Agache I, Jutel M, Annesi Maesano I, Akdis M, Sampath V, D'Amato G, Cecchi L, Traidl-Hoffmann C, Akdis CA. Climate change: A call to action for the United Nations. *Allergy*. 2021 Sep 3. [Online ahead of Print].
- Mann JK, Lutzker L, Holm SM, Margolis HG, Neophytou AM, Eisen EA, Costello S, Tyner T, Holland N, Tindula G, Prunicki M, **Nadeau K**, Noth EM, Lurmann F, Hammond SK, Balmes JR. Traffic-related air pollution is associated with glucose dysregulation, blood pressure, and oxidative stress in children. *Environ Res*. 2021 Apr;195:110870.
- Prunicki M, Cauwenberghs N, Lee J, Zhou X, Movassagh H, Noth E, Lurmann F, Hammond SK, Balmes JR, Desai M, Wu JC, **Nadeau KC**. Air pollution exposure is linked with methylation of immunoregulatory genes, altered immune cell profiles, and increased blood pressure in children. *Nature Sci Rep*. 2021 Feb 18;11(1):4067.
- Prunicki M, Cauwenberghs N, Ataam JA, Movassagh H, Kim JB, Kuznetsova T, Wu JC, Maecker H, Haddad F, **Nadeau K**. Immune biomarkers link air pollution exposure to blood pressure in adolescents. *Environ Health*. 2020 Oct 16;19(1):108.
- Kim JB, Prunicki M, Haddad F, Dant C, Sampath V, Patel R, Smith E, Akdis C, Balmes J, Snyder MP, Wu JC, **Nadeau KC**. Cumulative Lifetime Burden of Cardiovascular Disease From Early Exposure to Air Pollution. *J Am Heart Assoc*. 2020 Mar 17;9(6):e014944.

## COVID-19

- Jiang SY, Smith EM, Vo V, Akdis C, **Nadeau KC**. Non-immunoglobulin E-mediated allergy associated with Pfizer-BioNTech coronavirus disease 2019 vaccine excipient polyethylene glycol. *Ann Allergy Asthma Immunol*. 2021 Dec;127(6):694-696.
- Warren CM, Snow TT, Lee AS, Shah MM, Heider A, Blomkalns A, Betts B, Buzzanco AS, Gonzalez J, Chinthrajah RS, Do E, Chang I, Dunham D, Lee G, O'Hara R, Park H, Shamji MH, Schilling L, Sindher SB, Sisodiya D, Smith E, Tsai M, Galli SJ, Akdis C, **Nadeau KC**. Assessment of allergic and anaphylactic reactions to mRNA COVID-19 vaccines with confirmatory testing in a US regional health

- system. *JAMA Open Network*. 2021 Sep 1;4(9):e2125524.
- Arunachalam PS, Scott MKD, Hagan T, ..., **Nadeau KC\***, Pulendran B\*. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. *Nature*. 2021 Aug;596(7872):410-416. (\*- co senior authors)
  - Mallajosyula V, Ganjavi C, Chakraborty S, McSween AM, Pavlovitch-Bedzyk AJ, Wilhelmy J, Nau A, Manohar M, **Nadeau KC**, Davis MM. CD8+ T cells specific for conserved coronavirus epitopes correlate with milder disease in COVID-19 patients. *Sci Immunol*. 2021 Jul 1;6(61).
  - Sampath V, Rabinowitz G, Shah M, ..., **Nadeau KC**. Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives. *Allergy*. 2021 Jun;76(6):1640-1660.
  - Yang F, Nielsen SCA, Hoh RA, Röltgen K, Wirz OF, Haraguchi E, Jean GH, Lee JY, Pham TD, Jackson KJL, Roskin KM, Liu Y, Nguyen K, Ohgami RS, Osborne EM, **Nadeau KC**, Niemann CU, Parsonnet J, Boyd SD. Shared B cell memory to coronaviruses and other pathogens varies in human age groups and tissues. *Science*. 2021 May 14;372(6543):738-741.
  - Skevaki C, Karsonova A, Karaulov A, Fomina D, Xie M, Chinthrajah S, **Nadeau KC**, Renz H. SARS-CoV-2 infection and COVID-19 in asthmatics: a complex relationship. *Nat Rev Immunol*. 2021 Apr;21(4):202-203.

## PREVENTION

- Sharif H, Acharya S, Dhondalay GKR, Varricchi G, Krasner-Macleod S, Laisuan W, Switzer A, Lenormand M, Kashe E, Parkin RV, Yi Y, Koc M, Fedina O, Vilà-Nadal G, Marone G, Eifan A, Scadding GW, Fear DJ, **Nadeau KC**, Durham SR, Shamji MH. Altered chromatin landscape in circulating T follicular helper and regulatory cells following grass pollen subcutaneous and sublingual immunotherapy. *J Allergy Clin Immunol*. 2021 Feb;147(2):663-676. d.
- Yu W, Zhou X, Lyu SC, Davis MM, **Nadeau KC**. Regulation of peanut-specific CD8+ T cells from nonallergic individuals. *J Allergy Clin Immunol*. 2021 Jan;147(1):385-387.e1.
- Bao R, Hesser LA, He Z, Zhou X, **Nadeau KC\***, Nagler CR\*. Fecal microbiome and metabolome differ in healthy and food-allergic twins. *J Clin Invest*. 2021 Jan 19;131(2):141935. (\*- co senior authors)
- Alkotob SS, Cannedy C, Harter K, Movassagh H, Paudel B, Prunicki M, Sampath V, Schikowski T, Smith E, Zhao Q, Traidl-Hoffmann C, **Nadeau KC**. Advances and novel developments in environmental influences on the development of atopic diseases. *Allergy*. 2020 Dec;75(12):3077-3086.

## ASTHMA

- Paudel B, Chu T, Chen M, Sampath V, Prunicki M, **Nadeau KC**. Increased duration of pollen and mold exposure are linked to asthma and climate change. *Nature Sci Rep*. 2021 Jun 17;11(1):12816.
- Eggert LE, He Z, Collins W, Lee AS, Dhondalay G, Jiang SY, Fitzpatrick J, Snow TT, Pinsky BA, Artandi M, Barman L, Puri R, Wittman R, Ahuja N, Blomkalns A, O'Hara R, Cao S, Desai M, Sindher SB, **Nadeau K**, Chinthrajah RS. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19. *Allergy*. 2021 Jun 3. [Online ahead of Print].
- Dhondalay GKR, Bunning B, Bauer RN, Barnathan ES, Maniscalco C, Baribaud F, **Nadeau KC**, Andorf S. Transcriptomic and methylomic features in asthmatic and nonasthmatic twins. *Allergy*. 2020 Apr;75(4):989-992.
- Camiolo MJ, Zhou X, Oriss TB, Yan Q, Gorry M, Horne W, Trudeau JB, Scholl K, Chen W, Kolls JK, Ray P, Weisel FJ, Weisel NM, Aghaeepour N, **Nadeau K**, Wenzel SE, Ray A. High-dimensional profiling clusters asthma severity by lymphoid and non-lymphoid status. *Cell Rep*. 2021 Apr 13;35(2):108974.

## FOOD ALLERGY

- Sampath V, Abrams EM, Adlou B, Akdis C, Akdis M, Brough HA, Chan S, Chatchatee P, Chinthrajah RS, Cocco RR, Deschildre A, Eigenmann P, Galvan C, Gupta R, Hossny E, Koplin JJ, Lack G, Levin M, Shek LP, Makela M, Mendoza-Hernandez D, Muraro A, Papadopoulous NG, Pawankar R, Perrett KP, Roberts G, Sackesen C, Sampson H, Tang MLK, Togias A, Venter C, Warren CM, Wheatley LM, Wong GWK, Beyer K, **Nadeau KC**, Renz H. Food allergy across the globe. *J Allergy Clin Immunol*. 2021 Dec;148(6):1347-1364.

- Manohar M, Dunham D, Gupta S, Yan Z, Zhang W, Minnicozzi S, Kirkey M, Bunning B, Roy Chowdhury R, Galli SJ, Boyd SD, Kost LE, Chinthrajah RS, Desai M, Oettgen HC, Maecker HT, Yu W, DeKruyff RH, Andorf S, **Nadeau KC**. Immune changes beyond Th2 pathways during rapid multifoed immunotherapy enabled with omalizumab. *Allergy*. 2021 Sep;76(9):2809-2826.
- Zhou X, Yu W, Lyu SC, Macaubas C, Bunning B, He Z, Mellins ED, **Nadeau KC**. A positive feedback loop reinforces the allergic immune response in human peanut allergy. *J Exp Med*. 2021 Jul 5;218(7):e20201793.
- Andorf S, Bunning B, Tupa D, Cao S, Long AJ, Borres MP, Galli SJ, Chinthrajah RS, **Nadeau KC**. Trends in egg specific immunoglobulin levels during natural tolerance and oral immunotherapy. *Allergy*. 2020 Jun;75(6):1454-1456.
- Sindher S, Alkotob SS, Shojinaga MN, Hamilton R, Chan S, Cao S, Bahnson HT, Brough HA, Lack G, Leung DYM, **Nadeau KC**. Increases in plasma IgG4/IgE with trilipid vs paraffin/petrolatum-based emollients for dry skin/eczema. *Pediatr Allergy Immunol*. 2020 Aug;31(6):699-703.
- Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC, Manohar M, Boyd SD, Tibshirani R, Maecker H, Plaut M, Mukai K, Tsai M, Desai M, Galli SJ, **Nadeau KC**. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2019 Oct 19;394(10207):1437-1449.

# Structure – Property Correlations in Metastable Materials

by Jürgen Eckert, Member EUAS

## Short Biography

*Jürgen Eckert obtained his Ph.D. in Materials Science and Engineering at the Friedrich-Alexander-University Erlangen-Nuremberg, Germany in 1990. After his Ph.D. he worked for two and a half years as postdoc at the California Institute of Technology. After a short break in industry, he moved to the Leibniz-Institute for Solid State and Materials Research (IFW) Dresden, one of the leading Materials Research Science Centers in Germany. From 1996 until 2003 he was Head of the Department Metastable and Nanostructured Materials at IFW Dresden, before moving to TU Darmstadt as Full Professor for Physical Metallurgy. In 2006 he moved back to Dresden as Director of the Institute for Complex Materials at IFW Dresden and Chair for Synthesis and Analysis of Materials at Dresden University of Technology (TU) Dresden. He also served as Scientific Director of IFW Dresden (2013/2014). In 2015 he became Chair Professor of Materials Physics at Montanuniversität Leoben, and Director of the Erich Schmid Institute of Materials Science of the Austrian Academy of Sciences. He held an Adjunct Professor Position at Michigan Technological University, Houghton, USA (2002-2005), was a Visiting Professor at University of Vienna, Austria (2009/2010/2012) and was appointed Honorary Professor at Shenzhen University, PR China (2021).*

*He is an international expert in the field of metastable materials and has published more than 1250 papers in archival journals (h-index: 95 (WoSci), more than 43.800 citations), as well as more than 150 conference papers, 18 book chapters, 6 edited books, conference proceedings and journal issues, holds more than 20 patents, and delivered so far more than 235 plenary, keynote and invited presentations.*

*Jürgen Eckert was honored as Dr. honoris causa (Dr. h.c.) by the Slovak University of Technology in Bratislava, Slovak Republic (2012), and received the Gottfried Wilhelm Leibniz Award of the German Research Foundation (2009), the highest Science Prize and scientific honor in Germany. Other honors include the THERMEC 2021 Distinguished Award (2021), the European Advanced Materials Award of the International Association of Advanced Materials, Sweden (2021), an ERC-Proof of Concept Grant of the European Research Council (2019), the DGM-Prize 2014 of the German Materials Research Society, an ERC Advanced Grant of the European Research Council (2013), the ISMANAM Senior Scientist Award (2012), the Hsun Lee Lecture Award of the Chinese Academy of Sciences (2006), the Georg-Sachs-Prize of the German Materials Research Society and the Austrian Metal Industry (1997), and the FEMS Materials Science and Technology Prize of the Federation of European Materials Science Societies (FEMS) in 1997. He received the Young Scientist Award of the German Materials Research Society (1994), and the ISMANAM Young Scientist Award (1997). He is corresponding Member of the Section Mathematics-Natural Sciences of the Austrian Academy of Sciences (2017), Member of the European Academy of Sciences (2018), MRS Fellow of the Materials Research Society, USA (2018), Honorary Member of The Indian Institute of Metals, corresponding Member of the Section Technical Sciences of the Saxon Academy of Sciences and Humanities in Leipzig, Germany (2020) and Foreign Fellow of the Indian National Academy of Engineering, India (2021).*

Jürgen Eckert's research activities focus on phase formation and structure-property correlations of metastable materials processed under non-equilibrium conditions; structural and functional materials with particular emphasis on fundamentals of solidification and solid state reactions; additive manufacturing

techniques; high strength, biocompatible and magnetic alloys, and materials for sustainable energy applications (e.g. next generation batteries, supercapacitors, carbon materials, materials for hydrogen production and storage) and thin film systems for flexible electronics; mechanical and electrochemical properties of bulk materials, coatings and surfaces; biologically inspired far-from-equilibrium materials and architected structures; mathematical modelling of advanced materials and processes.

Over the years, Jürgen Eckert and his team have provided seminal contributions in developing metastable advanced high-performance materials. Early work focused on amorphization and quasicrystal formation in metallic systems, and fundamental observations on establishing nanoscale grain sizes in metallic materials. The interest shifted later on to the development and property optimization of bulk metallic glasses and composites, high entropy alloys and structurally modulated systems with hierarchically tuned microstructure for creating plastically deformable and tough engineering materials. This work followed a synergistic approach by understanding how atomic scale structures, microstructural features and stress, along with processing-induced heterogeneities determine the mechanisms of plastic deformation on different length scales such as to overcome the otherwise unavoidable brittleness of glassy or nanoscale materials, and evolved into a comprehensive approach using disorder and heterogeneity concepts for creating new strategies to tailor the properties of advanced materials under non-equilibrium conditions. This allowed to create new high-strength lightweight alloys, hard and soft magnetic materials, porous bulk materials and hybrid structures for biomedical applications, materials for energy applications, and also touched on surface modification and development of architected gradient structures.

Jürgen Eckert's recent research activities focus on in-depth *in situ* and *in operando* investigations of phase transformations and structure-property correlations using local probes and high-resolution techniques for structure characterization and imaging of local structures, chemical compositions and interaction of nanoscale objects with external fields and stimuli (e.g. mechanical, thermal, electrical, magnetic fields) for creating tailored biologically inspired metastable materials with hierarchical structure and tuned disorder. This can be realized in a microscope or through flash annealing at extreme heating and cooling rates. An example for such materials is the *in situ* design and testing of glassy or nanostructured metallic alloys containing heterogeneities on different length-scales to overcome their intrinsic brittleness. The heterogeneities can be triggered through local chemical variations, modulation of short- or medium-range order or via creating locally tuned stress/strain states. The concept of *in situ* design and testing is applicable to bulk materials, granular or thin film systems and to a variety of materials, and thus opens new research avenues for designing materials with unique properties. Some of the key publications in this area include:

- Z. Wang, S.Y. Tang, S. Scudino, Yu.P. Ivanov, R.T. Qu, D. Wang, C. Yang, W.W. Zhang, A.L. Greer, J. Eckert, K.G. Prashanth, "Additive Manufacturing

- of a Martensitic Co-Cr-Mo Alloy: Towards Circumventing the Strength-Ductility Tradeoff", *Addit. Manuf.* **37**, 101725 (2021).
- M. Stoica, B. Sarac, F. Spieckermann, J. Wright, C. Gammer, J.H. Han, P.F. Gostin, J. Eckert, J.F. Löffler, "X-Ray Diffraction Computed Nanotomography Applied to Solve the Structure of Hierarchically Phase-separated Metallic Glass", *ACS Nano* **15**, 2386 (2021).
  - D. Şopu, X. Yuan, F. Moitzi, F. Spieckermann, X. Bian, J. Eckert, "From Elastic Excitations to Macroscopic Plasticity in Metallic Glasses", *Appl. Mater. Today* **22**, 100958 (2021).
  - B. Sarac, T. Karazehir, E. Yüce, M. Mühlbacher, A.S. Sarac, J. Eckert, "Nanoporous Pd-Cu-Si Amorphous Thin Films for Electrochemical Hydrogen Storage and Sensing", *ACS Appl. Energy Mater.* **4**, 2672 (2021).
  - K. Nomoto, A.V. Ceguerra, C. Gammer, B.S. Li, H. Bilal, A. Hohenwarter, B. Gludovatz, J. Eckert, S.P. Ringer, J.J. Kruzic, "Medium-Range Order Dictates Local Hardness in Bulk Metallic Glasses", *Mater. Today* **44**, 48 (2021).
  - O. Glushko, C. Gammer, L.-M. Weniger, H.P. Sheng, C. Mitterer, J. Eckert, "Morphology of Cracks and Shear Bands in Polymer-Supported Thin Film Metallic Glasses", *Mater. Today Commun.* **28**, 102547 (2021).
  - B. Sarac, T. Karazehir, E. Yüce, M. Mühlbacher, A.S. Sarac, J. Eckert, "Porosity and Thickness Effect of Pd-Cu-Si Metallic Glasses on Electrocatalytic Hydrogen Production and Storage", *Mater. Des.* **210**, 110099 (2021).

The long-term perspective of this research is to advance the understanding of structure-property correlations for hierarchically modulated structures and disordered systems over a variety of different length-scales under highly non-equilibrium thermodynamic and kinetic conditions. This allows to obtain a comprehensive description of phase formation, transformation, dynamics and property design under extreme conditions, such as ultra-fast heating and cooling on extremely short time scales with or without external mechanical, electrical or magnetic stimuli. Some of these approaches are already followed for crystalline materials, whereas research on disordered and granular heterogeneous solids along these lines touches almost unknown grounds: The structural diversity introduced through disorder and local heterogeneity fluctuations opens up new avenues for overcoming the structure and property constraints of conventional crystalline materials. The ability to predict and tune disorder in architected materials with unique functionality provides vast opportunities for new property-optimized materials including high-strength-lightweight systems, biomedical implants, micromechanical components or modulated thin film systems for energy applications with unique performance characteristics. For this not only the fundamental mechanisms of structure formation and property tuning have to be considered, but it is also essential to understand how the findings can be transferred into devices and systems for high performance structural and functional applications. For example, new flexible microelectronic systems and sensing devices, novel materials for energy storage and harvesting, or biocompatible as well

as biodegradable materials, porous structures, coatings and surfaces can be created and tuned for property optimization, e.g., for use as tailored orthopedic implants, personalized medical devices, miniaturized hydrogen storage systems or functional membranes.

For creating such materials and structures, state-of-the-art techniques of materials physics, structure analysis, *in situ* structure investigations under different applied fields (e.g. mechanical, electrical, magnetic), and also structure-biological mimetic and 3d printing techniques are used to generate hierarchically modulated and architected heterogeneous materials. Multi-scale modelling techniques based on hierarchies of overlapping scales including quantum mechanics-based structure modelling, atomistic modelling and numerical methods supplement the experiments and derive guidelines for structure and property optimization. Machine learning algorithms and artificial intelligence approaches for characterizing and exploiting (local) property statistics not assessable with direct measurements are employed for determining materials with tailored properties or property combinations. This is vital for property-directed material design of disordered systems, promising to open new routes for nanoscale structure formation in architected materials with unique functionality through generating an atomic structural – functional understanding of properties, performance and correlation of hierarchical bulk materials, thin films, tailored interface structures, nano- and multiscale hybrid systems and heterogeneous materials with locally modulated structure and properties.

# Analysis of Elementary Chemical and Physical Processes in Proteins

by Peter Hildebrandt, Member EUAS

## Short Biography

### **University education**

- 1981: Diploma Degree in Chemistry at the Universität Göttingen  
 1981 -1984: PhD, Max-Planck-Institut für Biophysikalische Chemie (A. Weller), Göttingen: "Surface Enhanced Resonance Raman Spectroscopy and its Application to Biological Molecules"  
 1985: PhD Degree in Chemistry at the Universität Göttingen  
 1987 - 1992: Habilitation in Physical Chemistry at the Universität GHS Essen: "Resonance Raman Spectroscopic Study of Structure-Function-Relationships of the Heme Proteins Cytochrome c und Cytochrome P-450"  
 1998: apl. Professor for Physical Chemistry at the Universität GHS Essen  
 2000: Agregação no Grupo e Disciplina Química e Biológica, pelo Instituto de Tecnologia Química e Biológica da Universidade Nova de Lisboa

### **Scientific employments**

- 1985: Post-doc fellow, Max-Planck-Institut für Biophysikalische Chemie, Göttingen  
 1986: Research associate, Department of Chemistry (T. G. Spiro), Princeton University, USA  
 1987 - 1989: Research associate, Max-Planck-Institut für Biophysikalische Chemie, Göttingen  
 1989 – 2001: Research group leader, Max-Planck-Institut für Strahlenchemie, Mülheim  
 1995 - 2000 : Heisenberg-Fellowship  
 2001- 2002: Investigador Coordenador (Full Professor) at the Instituto de Tecnologia Química e Biológica der Universidade Nova de Lisboa.  
 2002 -: Professor for Physical Chemistry and Biophysical Chemistry, Technische Universität Berlin  
 2010: Call for the Professorship "Analytical Sciences" at the TU Dortmund/ISAS, declined.

### **Awards and Honours**

- 1985: Otto-Hahn-medal of the Max-Planck-Gesellschaft  
 1989: ADUC-Award für Habilitanden der Arbeitsgemeinschaft der Lehrstuhlinhaber von Unterrichtsinstituten für Chemie an Hochschulen der Bundesrepublik Deutschland  
 1990: Bennisgen-Foerder-Research-Award des Landes Nordrhein-Westfalen  
 1993: Heisenberg-Fellowship  
 1998: Visiting Professor at the Universidad Nacional de LaPlata  
 2003-: Visiting Professor at the Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa.

### **Research fields**

- Structure-dynamics-function relationships of proteins in solution and at interfaces with static, time-resolved, and spatially resolved spectroscopic methods, specifically Raman and IR spectroscopies.
- Electron transfer reactions of redox proteins and model compounds.
- Molecular processes of immobilised proteins in structural and functional membrane models.
- Reaction mechanisms of metalloenzymes.
- Chromophore structure and dynamics in photoreceptors
- Quantum chemical calculations of molecular structures and spectra
- Methodological developments in vibrational spectroscopy
- Applications of vibrational spectroscopy in biotechnology and food analysis

### **Scientific publications:**

450 publications (H-factor 58 WoS, 69 GS), including 1 textbook, 19 review articles, 14 book chapters, 333 peer-reviewed articles (6 submitted), and 83 short communications.

### **Edited publications:**

Co-editor: *Journal of Molecular Structure* Vol. 347, 348, 349 - Special Issues "Molecular Spectroscopy and Molecular Structure - Proceedings of the XXIIInd European Congress on Molecular Spectroscopy", (Schrader, B., Korte, H., Hildebrandt, P., Barnes, A., Orville-Thomas, W. J., Eds.), Elsevier, Amsterdam, 1995.

Guest editor: *Special issue of Chem.Phys.Chem.* "Protein-Cofactor Interactions", Vol. 11, issue 6, 2010.

**Funded projects (since 2012):**

1. Einstein Center of Catalysis (Principal applicant), 2019 – 2025, 8400 T€.
2. DFG, Cluster of Excellence „Unifying Systems in Catalysis“ (Principal applicant with M. Driess, A. Thomas), 2019-2025, ca. 42000 T€.
3. TIMB3 – Horizon2020: “Twin to Illuminate Metals in Biology and Biocatalysis through biospectroscopy” 2018 – 2021, ca. 165 T€
4. Einstein Visiting Fellow Katrina Forest, 2019 – 2022, ca. 360 T€
5. Einstein Visiting Fellow Stephen P. Cramer, 2017 – 2019, ca. 450 T€
6. DFG, Sfb1078 (B6):” Proton-coupled conformational changes in photoreceptors” (with P. Scheerer), 2013 – 2016, ca. 700 T€; 2017 – 2020, ca. 450 T€; 2021 – 2024, ca. 380 T€
7. Einstein Foundation Berlin, Einstein Center of Catalysis, (Principal applicant with M. Driess), 2016 - 2018, ca. 900 T€
8. DFG, Cluster of Excellence „Unifying Concepts in Catalysis“, (Principal applicant with M. Driess) 2007-2011, ca. 34242 T€, renewal 2011 – 2017, ca. 30000 T€.
9. DFG, SALSA Graduate School, 2013 – 2017, ca. 300 T€.
10. DFG, IRTG1524, „Self-assembled soft matter nanostructures at interfaces”, 2009-2017, ca. 180 T€. Further funding refers to stipends and fellowships and bilateral scientific exchange with Portugal (AvH, DFG, DAAD).

**Current and previous scientific and academic functions:**

Chair of the Einstein Center of Catalysis, since 2016

Deputy chair of the Sfb1078 „Protonation dynamics in protein function“, 2013 - 2017.

Deputy chair of the „Cluster of Excellence initiative: Unifying Systems in Catalysis“, 2016 - 2018.

Deputy chair of the „Cluster of Excellence: Unifying Concepts in Catalysis“, since 2007.

Reviewer for various scientific journals and institutions.

Elected member of the Academic Senate of the TU Berlin, since 2007.

Member of the Advisory Board of The Journal of Raman Spectroscopy, since 2000.

Our research is focused on the analysis of elementary chemical and physical processes in proteins aiming at the elucidation of structure-dynamics-function relationships. We are mainly employing spectroscopic techniques, particularly vibrational spectroscopies, which are complemented by theoretical methods, protein engineering, and protein crystallography. We are particularly interested to understand the

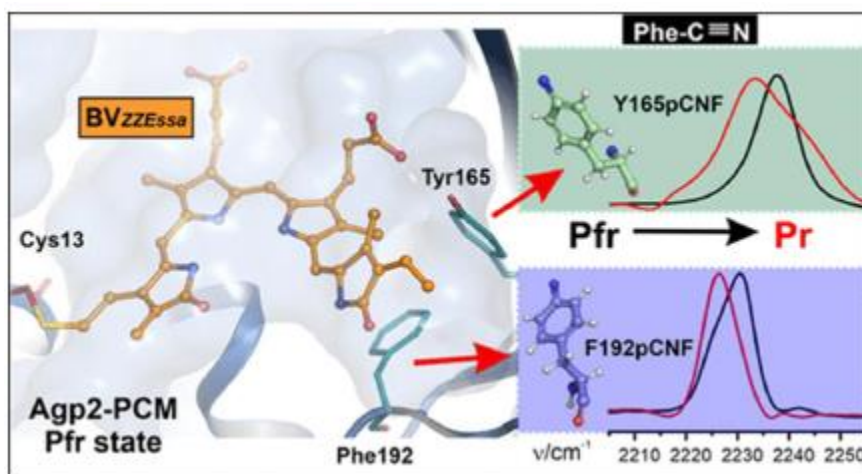
- translation of photoinduced chromophore structural changes into functional conformational changes of the protein in biological photoreceptors (1, 2)
- role electric field changes in coupling fundamental processes in proteins (2, 3)
- parameters that control biophysical and biochemical processes at membranes (3, 4)

Our research is exemplified on the basis of four selected papers, the abstracts of which given below.

**(1) Kraskov A, von Sass J, Nguyen DA, Hoang TO, Buhrke D, Katz S, Michael N, Kozuch J, Zebger I, Siebert F, Scheerer P, Mroginski MA, Budisa N, Hildebrandt P (2021). Local Electric Field Changes during the Photoconversion of the Bathy Phytochrome Agp2. *Biochemistry*, 60, 2967–2977.**

Phytochromes switch between a physiologically inactive and active state via a light-induced reaction cascade, which is initiated by isomerization of the tetrapyrrole chromophore and leads to the functionally relevant secondary structure transition of a

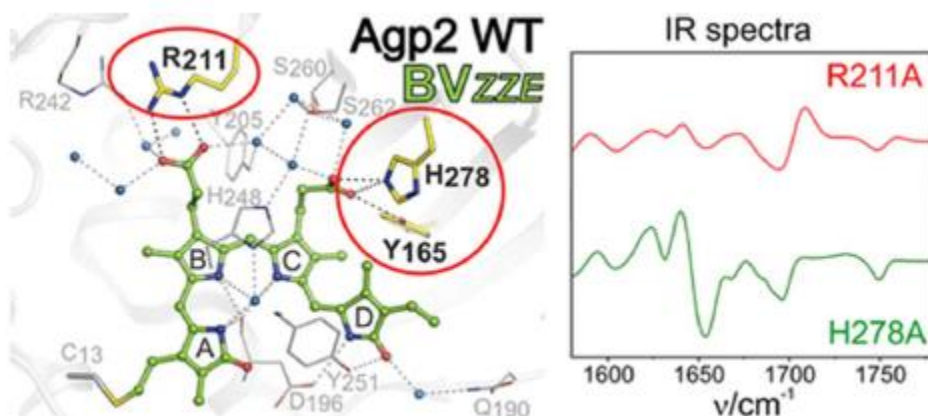
protein segment (tongue). Although details of the underlying cause–effect relationships are not known, electrostatic fields are likely to play a crucial role in coupling chromophores and protein structural changes. Here, we studied local electric field changes during the photoconversion of the dark state Pfr to the photoactivated state Pr of the bathy phytochrome Agp2. Substituting Tyr165 and Phe192 in the chromophore pocket by para-cyanophenylalanine (pCNF), we monitored the respective nitrile stretching modes in the various states of photoconversion (vibrational Stark effect). Resonance Raman and IR spectroscopic analyses revealed that both pCNF-substituted variants undergo the same photoinduced structural changes as wild-type Agp2. Based on a structural model for the Pfr state of F192pCNF, a molecular mechanical–quantum mechanical approach was employed to calculate the electric field at the nitrile group and the respective stretching frequency, in excellent agreement with the experiment. These calculations serve as a reference for determining the electric field changes in the photoinduced states of F192pCNF. Unlike F192pCNF, the nitrile group in Y165pCNF is strongly hydrogen bonded such that the theoretical approach is not applicable. However, in both variants, the largest changes of the nitrile stretching modes occur in the last step of the photoconversion, supporting the view that the proton-coupled restructuring of the tongue is accompanied by a change of the electric field.



(2) Kraskov A, Nguyen DA, Buhrke D, Velasquez Escobar F, Fernandez Lopez M, Michael N, Sauthof L, Schmidt A, Piwowarski P, Yang Y, Stensitzki T, Adam S, Bartl F, Schapiro I, Heyne K, Siebert F, Scheerer P, Mroginski MA, Hildebrandt P (2020) **Intramolecular Proton Transfer Controls Protein Structural Changes in Phytochrome.** *Biochemistry*, 59, 1023-1037.

Phytochromes are biological photoswitches that interconvert between two parent states (Pr and Pfr). The transformation is initiated by photoisomerization of the tetrapyrrole chromophore, followed by a sequence of chromophore and protein structural changes. In the last step, a phytochrome-specific peptide segment (tongue) undergoes a secondary structure change, which in prokaryotic phytochromes is associated with the (de)activation of the output module. The focus of this work is the Pfr-to-Pr photoconversion of the bathy

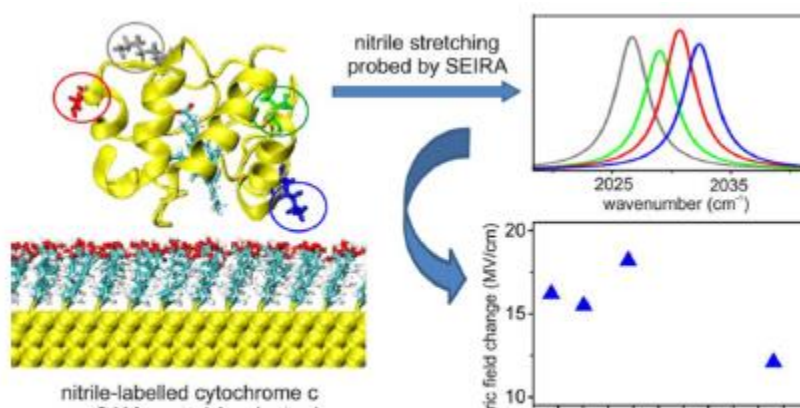
bacteriophytochrome Agp2 in which Pfr is the thermodynamically stable state. Using spectroscopic techniques, we studied the structural and functional consequences of substituting Arg211, Tyr165, His278, and Phe192 close to the biliverdin (BV) chromophore. In Pfr, substitutions of these residues do not affect the BV structure. The characteristic Pfr properties of bathy phytochromes, including the protonated propionic side chain of ring C (propC) of BV, are preserved. However, replacing Arg211 or Tyr165 blocks the photoconversion in the Meta-F state, prior to the secondary structure transition of the tongue and without deprotonation of propC. The Meta-F state of these variants displays low photochemical activity, but electronic excitation causes ultrafast alterations of the hydrogen bond network surrounding the chromophore. In all variants studied here, thermal back conversion from the photoproducts to Pfr is decelerated but substitution of His278 or Phe192 is not critical for the Pfr-to-Pr photoconversion. These variants do not impair deprotonation of propC or the  $\alpha$ -helix/ $\beta$ -sheet transformation of the tongue during the Meta-F-to-Pr decay. Thus, we conclude that propC deprotonation is essential for restructuring of the tongue.



(3) Biava H, Schreiber T, Katz S, Völler JS, Stolarski M, Schulz C, Michael N, Budisa N, Kozuch M, Utesch T, Hildebrandt P (2018) **Long-Range Modulations of Electric Fields in Proteins.** *J. Phys. Chem. B.* 122, 8330–8342.

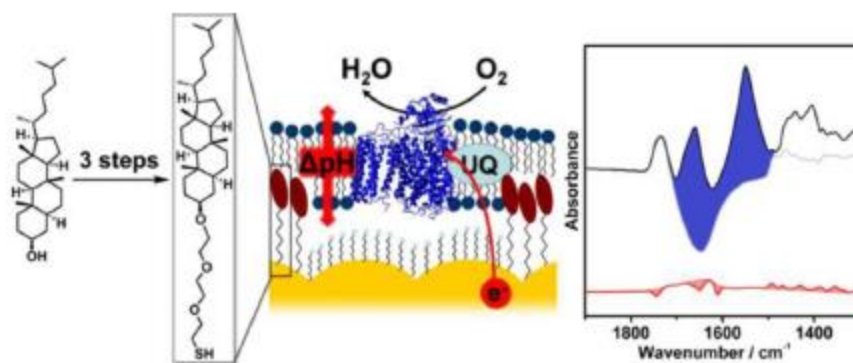
Electrostatic interactions are essential for controlling the protein structure and function. Whereas so far experimental and theoretical efforts focused on the effect of local electrostatics, this work aims at elucidating the long range modulation of electric fields in proteins upon binding to charged surfaces. The study is based on cytochrome c (Cyt c) variants carrying nitrile reporters for the vibrational Stark effect that are incorporated into the protein via genetic engineering and chemical modification. The Cyt c variants were thoroughly characterized with respect to possible structural perturbations due to labeling. For the proteins in solution, the relative hydrogen bond occupancy and the calculated electric fields, both obtained from molecular dynamics (MD) simulations, and the experimental nitrile stretching frequencies were used to develop a relationship for separating hydrogen-bonding and non-hydrogen-bonding electric field effects. This relationship provides an excellent description for the stable Cyt c variants in solution. For the proteins bound to Au electrodes coated with charged self-assembled monolayers (SAMs), the underlying MD simulations can only account for the electric field changes

$\Delta E_{\text{ads}}$  due to the formation of the electrostatic SAM–Cyt<sub>c</sub> complexes but not for the additional contribution,  $\Delta E_{\text{int}}$ , representing the consequences of the potential drops over the electrode/SAM/protein interfaces. Both  $\Delta E_{\text{ads}}$  and  $\Delta E_{\text{int}}$ , determined at distances between 20 and 30 Å with respect to the SAM surface, are comparable in magnitude to the non-hydrogen-bonding electric field in the unbound protein. This long-range modulation of the internal electric field may be of functional relevance for proteins in complexes with partner proteins ( $\Delta E_{\text{ads}}$ ) and attached to membranes ( $\Delta E_{\text{ads}} + \Delta E_{\text{int}}$ ).



(4) Wiebalck S, Kozuch J, Tzschucke C, Jeuken LIC, Hildebrandt P (2016) **A novel tethered bilayer lipid membrane tailored for the IR spectroscopic investigation of membrane proteins: monitoring catalysis of cytochrome c<sub>bo3</sub>**, *J. Phys. Chem. B* **120**, 2249-2256.

Membrane proteins act as biocatalysts or ion/proton pumps to convert and store energy from ubiquitous environmental sources. Interfacing these proteins to electrodes allows utilizing the energy for enzymatic biofuel cells or other auspicious biotechnological applications. To optimize the efficiency of these devices, appropriate membrane models are required that ensure structural and functional integrity of the embedded enzymes and provide structural insight. We present a spectroelectrochemical surface-enhanced infrared absorption (SEIRA) and electrical impedance spectroscopy (EIS) study of the bacterial respiratory ubiquinol/cytochrome bo<sub>3</sub> (cyt bo<sub>3</sub>) couple incorporated into a tethered bilayer lipid membrane (tBLM). Here, we employed a new lipid tether (WK3SH, dihydrocholesteryl (2-(2-(2-ethoxy)ethoxy)ethanethiol), which was synthesized using a three-step procedure with very good yield and allowed measuring IR spectra without significant spectral interference of the tBLM. The functional integrity of the incorporated cyt bo<sub>3</sub> was demonstrated by monitoring the enzymatic O<sub>2</sub> reduction current and the formation of the transmembrane proton gradient. Based on a SEIRA-spectroscopic redox titration, a shift of the pH-dependent redox potential of the ubiquinones under turnover conditions was correlated with an alkalization of the submembrane reservoir by +0.8 pH units. This study demonstrates the high potential of tBLMs and the SEIRA spectroscopic approach to study bioenergetic processes.



# Methods for Fire Risk Assessment & Safety Design of Buildings & Urban Areas

by Jinhua Sun, Member EUAS



## Short Biography

### **Education and Positions**

- 2019~ Chairman, Sub-Committee on Fire Science, University of Science & Technology of China
- 2004~2019 Vice Director of State Key Laboratory of Fire Science of China, CHINA
- 2014~ Director of Energy Fire Safety Institute, SKLFS, CHINA
- 2002~ Professor, University of Science & Technology of China, CHINA
- 1999~2002 Research Professor, Japan Science and Technology Agency, JAPAN
- 1996~1999 Ph.D., The University of Tokyo, JAPAN
- 1988~1996 Associate Professor, Anhui University of Science & Technology, CHINA
- 1986~1988 M. Sc., Nanjing University of Science and Technology, CHINA
- 1983~1986 Assistant Professor, Anhui University of Science & Technology, CHINA
- 1979~1983 B. Sc., Nanjing University of Science and Technology, CHINA

### **Professional Activities**

- Vice-Presidents of Asia-Oceania Association for Fire Science and Technology (2007~2020)
- Committee Member of the International Association for Fire Safety Science (2008~2017)
- Committee Member of the National Science and Technology Award (2010~)
- Vice-chairman of Chemical Safety Committee, CIESC (2017~)
- Vice-chairman of Building Fire Protection Committee, CFPA (2008~)
- Experts of the first national emergency response expert group for work safety (2015~)
- Experts of the fifth national work safety expert group (2014~)
- Academic Committee Member of University of Science and Technology of China (2009~)
- Safety expert committee Anhui Province, Civil blasting group leader (2009~)
- Member of Science and Technology Award Committee, Ministry of Public Security (2007~)
- Member of Academic Committee of urban safety and disaster prevention, Urban Planning Society of China (2005~2015)
- Evaluation expert in international scientific and technological cooperation program, Ministry of Science and Technology of China (2005~)
- Executive director of Anhui Fire Protection Association (2005~)
- Associate Editorial or Editorial Board of five International Journals (2010~)
- Editorial Board of nine national Journals (2003~)
- Academic Committee Member of China Fire Protection Association (2003~)

### **Honors and Awards**

- Lifetime Contribution Award, Asia-Oceania Association for Fire Science and Technology (2021)
- Science and Technology Progress Award, First-class Award, the China Association for Public Safety (2021)
- Special government allowance of the State Council, The State Council of the People's Republic of China (2019)

*Science and Technology Innovation Award, First-class Award, China Fire Protection Association (2018)*

*Science and Technology Progress Award, First-class Award, China Highway and Transportation Society (2018)*

*Zhu Li Yuehua excellent teacher Award, Chinese Academy of Sciences (2017)*

*Excellent graduate student supervisor Award, Chinese Academy of Sciences (2017)*

*Zhu Li Yuehua excellent teacher Award, Chinese Academy of Sciences (2014)*

*Excellent graduate student supervisor Award, Chinese Academy of Sciences (2014)*

*Teaching Award of Anhui Province, First-class Award, Anhui Province (2010)*

*Beijing Science and Technology Award, Third-class Award, Beijing (2008)*

*Science and Technology Award for Young Scientist, Anhui Province (2006)*

*Safety Science and Technology Award of State Administration of Work Safety, Second-class Award (2006)*

*National Science and Technology Progress Award, Second-class Award, China (2006)*

*Outstanding Member Hundred Talent Program, Chinese Academy of Sciences (2005)*

*Member of Hundred Talent Program, Chinese Academy of Sciences (2001)*

*National Science and Technology Progress Award, First-class Award, China (1993)*

Professor Sun Jinhua has long been devoted to academic research and education in the area of fire science and fire protection. He has made substantial accomplishments in a number of fields in fire safety science and engineering, including fire risk assessment, performance-based fire protection design, building fire safety, industrial fire safety, fire safety in new energies. He led as a PI more than 20 important national research projects, such as the National “973 Program”, key projects funded by National Natural Science Foundation of China (NSFC), the “11th Five-Year plan” and the “13th Five-Year Plan” national key R&D program, the sixth Framework Project of the EU International Cooperation Program in Science and Technology, NSFC general projects, and “Outstanding Talents” project funded by the Chinese Academy of Sciences.

Prof. Sun has published more than 400 papers in peer-reviewed journals, including Progress in Energy and Combustion Science, Combustion and Flame, Renewable and Sustainable Energy Reviews, et al, which have been cited more than 10,000 times (Web of Science). Contributions have also been recorded in 11 academic books or book chapters and over 40 keynote or invited talks at national or international conferences. In addition, Prof. Sun has supervised more than 50 PhD students.

### Major Research Areas

1. Theories and methods of fire prevention for new energies.
2. Methods for fire risk assessment and safety design of buildings and urban areas.
3. Theory of fire dynamics, fire prevention and control for buildings.
4. Industry fire dynamics and fire prevention.

### Selected Publications in 2021

1. **Jinhua Sun\*, Binbin Mao, Qingsong Wang, Progress on the research of fire behavior and fire protection of lithium ion battery, Fire Safety Journal, 120(2021) 103119**

Progress on the research of fire behavior and safe protection of lithium ion batteries (LIBs) is reviewed in this paper. Thermal runaway (TR) mechanism of LIB is revealed

from the aspects of chemical reactions and heat accumulation. The fire behavior of high energy LIB is exhibited, and the TR propagations between cells and modules are discussed. This paper introduces the warning parameters and strategies of the fire prediction and early warning of LIB. Improving the inherent safety and suppressing the LIB fire effectively are still challenges at present. Some perspectives and outlooks on the future LIB safety researches are given.

**2. Huiqi Cao, Xiaoxi Li, Kaiqiang Jin, Qiangling Duan\*, Hua Chai, Jinhua Sun\*, Experimental and theoretical study of the effect of typical halides on thermal decomposition products and energy release of ammonium nitrate based on microcalorimetry and FTIR, Chemical Engineering Journal 410 (2021) 128405**

Ammonium nitrate (AN) is widely used as a raw material in industry and agriculture. However, the Beirut explosion in Lebanon once again shows that AN has a risk of thermal runaway during storage, especially long-term storage or when some possible substances are mixed therein. This paper focuses on the effect of halides additives, such as sodium fluoride, sodium chloride, sodium bromide and sodium iodide, on the thermal decomposition products and energy release of AN. Especially, the thermal decomposition of AN added with 5% sodium halide and the evolved gases in the thermal decomposition process are investigated by C80 microcalorimetry and FTIR. The results show that all kinds of sodium halides have an effect on the thermal decomposition of AN, although these effects are different. The addition of the halide not only changes the timing of the formation of the AN thermal decomposition characteristic product, but also reduces the heat of the reaction. Combined with optimized kinetic parameters, the engineering prediction of thermal safety was carried out for each type of sample. It is found that sodium iodide is beneficial to the safety of large-scale storage of AN. The research results can provide a reference and guidance for revealing the thermal decomposition mechanism of halide-containing AN and thermal decomposition simulation of AN with additives.

**3. Peiyu Duan, Huahua Xiao, Zhaoyu Wang, Qingkui Peng, Kaiqiang Jin\*, Jinhua Sun\* Hydrogen sensing properties of Pd/SnO<sub>2</sub> nano-spherical composites under UV enhancement, Sensors and Actuators: B. Chemical, 346(2021)130557**

The rapid and efficient detection of hydrogen plays an important role in the development of hydrogen energy. The response and selectivity of typical metal oxide semiconductor (MOS) sensors to low concentration hydrogen detection still need to be improved to meet the application of hydrogen. In this work, Pure SnO<sub>2</sub> hollow spheres and different molar ratio of Pd decorated SnO<sub>2</sub> spherical composites were synthesized by a facile template-free hydrothermal method. High response of 14.5 and fast response/recovery time of 2.2/22.4 s to 200 ppm hydrogen were achieved by 5.0 mol% Pd/SnO<sub>2</sub> at 330 °C. The response to 200 ppm hydrogen was enhanced to 18.1 and the recovery time was also improved to 17.4 s with 10 mW/cm<sup>2</sup> UV irradiation. Especially, the response to interfering gases was inhibited with UV irradiation, which improved the selectivity of as-prepared sensors to hydrogen molecules. Linear dependence of the responses of as-prepared sensors on the hydrogen concentration was observed, indicating the great potential for quantitative detection of H<sub>2</sub> at ppm level. This work provides a facile route to synthesize porous spherical Pd/SnO<sub>2</sub> for hydrogen detection and a reference for the future design of hydrogen detectors with UV irradiation.

- 4. Binbin Mao, Chaoqun Liu, Kai Yang, Shi Li, Pengjie Liu, Mingjie Zhang, Xiangdong Meng, Fei Gao, Qiangling Duan, Qingsong Wang \*, Jinhua Sun, Thermal runaway and fire behaviors of a 300 Ah lithium ion battery with LiFePO<sub>4</sub> as cathode, Renewable and Sustainable Energy Reviews 139(2021)110717**

A series of thermal runaway (TR) tests are conducted on the 300 Ah large-scale lithium iron phosphate (LiFePO<sub>4</sub>) batteries under external heating. The combustion process of the battery can be divided into four stages, and the aggressive cylindrical flame is observed. Due to the battery's large size, the TR expanding process within the battery body is clearly observed based on the temperature rate curves of different surfaces. The flaming combustion accelerates the occurrence of TR but has little influence on the peak surface temperature. The cooling effect of safety valve opening on each thermocouple is influenced by the electrolyte distribution inside the cell. A real-scale scenario is considered to evaluate the fire-induced toxicity of an electric bus that a 10 cell pack combusts in a garage with fresh air renewal. The fractional effective dose is much greater than the critical value of 1, indicating the catastrophic toxicity. The air renewal rate required for safety is calculated to provide advice for the ventilation management of garage. The battery fire is compared with the pool and gas fires of common fuels. It is found that this large-scale LiFePO<sub>4</sub> battery has the higher specific capacity and superior safety performance in the aspect of heat release features after comparing with previous LIB samples.

# Recent Developments Regarding Painting Robots for Research in Automatic Painting, Artificial Creativity, and Machine Learning

by Oliver Deussen, Member EUAS



## Short Biography

### **Education and Professional Experience**

Mar 2003 – now	<b>Full Professor</b> Visual Computing, Konstanz University, Germany
Jun 2010 – Dec 2020	<b>Visiting Professor</b> Shenzhen Institute of Applied Technologies, Chinese Academy of Science, China
Jul – Sep 2006	<b>Visiting Researcher</b> Computer Graphics Group, Microsoft Research, Redmond
Mar 2004 – Sep 2005	<b>Head of Department</b> Computer and Information Science, Konstanz University, Germany
Sep 2000 – Feb 2003	<b>Associate Professor (C3)</b> Dresden University of Technology, Germany
Apr 1996 – Aug 2000	<b>Postdoctoral Researcher</b> Otto-von-Guericke University of Magdeburg, Germany
Mar 1996	<b>Graduation</b> Dr. rer nat, Karlsruhe Institute of Technology (KIT), Germany

### **Professional Activities**

Jan 2019 – now	<b>Speaker</b> Excellence Cluster “Centre for the Advanced Study of Collective Behaviour”, University of Konstanz (with Iain Couzin and Urs Fischbacher)
Jan 2019 – Dec 2020	<b>President</b> Eurographics Association
Jan 2012 – Dec 2015	<b>Editor in Chief</b> Computer Graphics Forum, Journal for Computer Graphics
Jul 2015 – now	<b>Vice Speaker</b> DFG Collaborative Research Center 161 Quantitative Methods for Visual Computing with Daniel Weiskopf, University of Stuttgart
March 2020 – now	<b>DFG Review Board</b> DFG Review Board 409-05 “Interactive and Intelligent Systems, Image and Language Processing, Computer Graphics and Visualization”
Ongoing	<b>Associated Editor, IPC-Member, Papers Chair etc.</b> ACM SIGGRAPH; IEEE Visualization; Eurographics; Pacific

*Graphics; Workshop on Computational Aesthetics in Graphics, Visualization and Imaging; Symposium on Non-Photorealistic Animation and Rendering; Vision Modelling Visualization; Informatik Spektrum; Sibgrapi; Sino-German Symposium on Visualization, Selection committees for Studienstiftung des Deutschen Volkes*

#### **Honors, Awards, Patents, Scientific Achievements**

2022	<i>Member of the Heidelberg Academy of Science</i>
2021	<i>Fellow of the German Association for Informatics</i>
2020	<i>Member EU Academy of Sciences</i>
2016	<i>awarded within the Guangdong leading Talents Plan (China)</i>
2014	<i>awarded within the 1000 Talents Plan (China)</i>
2014	<i>Nomination Technical Achievement Award for Xfrog Modelling Software</i>
2013	<i>Eurographics Fellow</i>
2007	<i>awarded Virtual earth academic collaboration of Microsoft Research, 35k USD</i>

#### **Ten important Publications**

1. Mariana Rodriguez-Santiago, Paul Nührenberg, James Derry, Oliver Deussen, Fritz A Francisco, Linda K Garrison, Sylvia F Garza, Hans A Hofmann, and Alex Jordan. **Behavioral traits that define social dominance are the same that reduce social influence in a consensus task.** *Proceedings of the National Academy of Sciences (PNAS)*, 117(31):18566–18573, 2020

A first high-profile paper within our Excellence Cluster. We contributed tracking methods and visual analysis. The paper shows that fish swarms learn less from dominant males than from less dominant and more social exemplars

2. Jörg Marvin Gülzow, Patrick Paetzold, and Oliver Deussen. **Recent developments regarding painting robots for research in automatic painting, artificial creativity, and machine learning.** *Applied Sciences*, 10(10):3396, 2020

The latest paper of our e-david project in which we develop a painting robot that, like human painters, uses visual feedback to create its paintings. The machine is able to paint with acrylic colors and handle a variety of brushes.

3. Spicker M., F. Götz-Hahn, T. Lindemeier, D. Saupe, O. Deussen: **Quantifying Visual Abstraction Quality for Computer-Generated Illustrations**, *ACM Transactions on Applied Perception* 16.1 (2019), P. 5:1-20

This paper is the first that quantitatively measures visual abstraction, here for the case of stippling, a dot-oriented abstraction method. We show that

the Weber-Fechtner law applies here and can be used to quantify the perceived visual abstraction of a stipple drawing.

4. Deussen O., M. Spicker, Q. Zheng: **Weighted Linde-Buzo-Gray Stippling**, ACM Transactions on Graphics 36.6 (2017), P. 233:1-12

We present an improvement of a popular algorithm for automatic abstraction (stippling) that enables to create abstractions automatically based on some simple optimization criteria.

5. Ahmed, G., Perrier, H., Coeurjolly, D., Ostromoukhov, V., Guo, J., Yan, D., Huang, H., and Deussen, O.: **Low-Discrepancy Blue Noise Sampling**, ACM Transactions on Graphics (TOG) 35 (6), 247, 2016

We present the first method to create Blue Noise point distributions (very important for sampling in Computer Graphics) based on discrete, easy and fast to produce processes with low discrepancy.

6. Liangliang Nan, Andrei Sharf, Ke Xie, Tien-Tsin Wong, Oliver Deussen, Daniel Cohen-Or, and Baoquan Chen. **Conjoining gestalt rules for abstraction of architectural drawings**. ACM Transactions on Graphics (TOG), 30(6):1–10, 2011.

Gestalt laws are very popular in psychology, but they are not real laws since they cannot predict much. Some of these laws, however, can be mathematically formulated and be used for visual abstraction. This paper is the first that allows this by using multi-graph cuts to deal with conflicting laws.

7. Heino Hellwig, Ralph Engelmann, and Oliver Deussen. **Contact pressure models for spiral phyllotaxis and their computer simulation**. Journal of Theoretical Biology, 240(3):489–500, 2006

My most underrated paper. We present the first simulation method for complex seed arrangements in sun flowers and other plants that, based on Voronoi Diagrams, exhibit the Golden Section arrangement including existing statistical deviations based on simple biological start conditions. This method explains the beauty of seed (and petal arrangements) in nature.

8. Michael Balzer and Oliver Deussen. **Voronoi treemaps**. In IEEE Symposium on Information Visualization (INFOVIS 2005), PP 49–56. IEEE Association, 2005

We developed a popular Visualization Technique called Voronoi Treemaps, which today is widely used in science and also popular media for displaying hierarchical data sets.

9. Michael F Cohen, Jonathan Shade, Stefan Hiller, and Oliver Deussen. **Wang tiles for image and texture generation**. ACM Transactions on Graphics (TOG), 22(3):287–294, 2003

Placing objects in Computer Graphics suffers from repetition artifacts, especially when large scenes are shown in perspective projection. We introduce Wang Tiles, a simple non-repetitive arrangement method known from mathematics, for placing objects and for texture synthesis.

10. Bernd Lintermann and Oliver Deussen. **Interactive modeling of plants**. IEEE Computer Graphics and Applications, 19(1):56–65, 1999.

An interactive modelling method that for the first time combines rule-based modelling with parameterized components and this way allows to create complex plant models efficiently. The approach initiated the development of companies such as Xfrog, Inc. and Laubwerk (a Berlin-based company) and was nominated for the technical achievement award (technical Oscar of the Academy for Motion Picture Arts).

### Further Activities

- A Together with Iain Couzin and Urs Fischbacher I initiated the excellence cluster for **Collective Behaviour** at University of Konstanz. As one of the speakers I represent computer science in the excellence cluster. We were able to acquire funding for a new research building (§91b). I helped with the institutional proposal for renewing the excellence status of my university. The successful prolongation enables the university now to build an entirely new campus center.
- As a member of the Executive Committee, as Editor-in-Chief of the associated journal and President I helped the **Eurographics Association** to develop in a critical time in which publishers (due to Open Access) and associations (due to Covid-19) are threatened. I was responsible for making paper archives Open Access and for developing author-based income schemes for virtual conferences that enable the association to survive in a post-Covid time.
- Since 2008 I am very active in China. In 2010 I was appointed a visiting professor at SIAT, the **Shenzhen Institute for Advanced Technologies**, a member of the Chinese Academy of Sciences. My collaboration and efforts for building up high-quality research in China led to the 1000 Talents Award in 2014 and the Guangdong Talents award in 2016, both came along with substantial funding for research groups. Besides being co-author of dozens of joint papers, I was involved in activities initiated by SAFEA, the State Administration of Foreign Experts Affairs. In these activities I advised several politicians up to Li Keqian, the prime

minister. With John Hopcroft I proposed to change teaching incentives for young university teachers in China which lead to a prestigious teaching award.

- In my involvement as an associate editor for **Informatik Spektrum** (organ of the Gesellschaft für Informatik) I contributed to the recognition of visual computing in Germany, but also tried to highlight political responsibilities of computer science. In 2017, after the American presidential election I edited (together with Katharina Zweig) a special issue on political responsibility of computer science and the influence of algorithms.
- In 2009 I established the e-David ([www.e-david.org](http://www.e-david.org)) project, a painting robot that, like human painters, uses visual feedback to create its paintings. Besides the scientific aspects, where I try to apply our methods of abstraction and non-photorealistic rendering, we use the project to collaborate intensively with artists. We gave a number of exhibitions, the project was widely discussed in media, we received two prizes in the robotart competition.

# Stratification of the Risk of Developing Severe or Lethal Covid-19 using a new score from a Large Italian Population

by Giuseppe Mancia, Member EUAS

## Short Biography

**PRESENT POSITION.** GM is Professor Emeritus of the University Milano.-Bicocca. He is also Head of the Hypertension Center, University Institute, Verano, Policlinico di Monza, President of the Italian Foundation on “Ricerca e Innovazione su Ipertensione e Protezione Cardiovascolare” and Chairman of the Foundation of the European Society of Hypertension (ESH, Zurig,Switzerland). He serves since 2008 as Chairman of the Joint Board of the Italian Scientific Societies operating in the area of cardiovascular prevention.

**DEGREES/DIPLOMAS.** He trained at the University of Siena, Medical School, where he graduated in 1964 cum laude. He obtained in 1967 the Post-graduate Diploma (cum laude) of Specialist in Cardiology and Rheumatology while working at the Istituto di Patologia Medica of the University of Siena with a fellowship of the National Research Council. He obtained the Ph.D. (Libera Docenza) in Physiology in 1970 and worked as Post-graduate Fellow of the US Public Health Service and Associate Researcher at the Mayo Clinic (1972-1974).He has been Resident in the Postgraduate School of Cardiology of the Virginia Commonwealth University(1974)

**ACADEMIC/HOSPITAL POSITIONS.**GM has been Assistant and Associate Professor of Internal Medicine at the University of Milan from 1969 to 1985.From 1985 he has been appointed full Professor of Internal Medicine at the University of Milano first and the Milano-Bicocca University later. Between 1992 and 2012 he has been Head of the Division of Internal Medicine and Chairman of the University and Hospital Departments of Clinical Medicine at the S. Gerardo Hospital, Monza.He has also been Director of several Postgraduate Schools of Medicine (Cardiology, Internal Medicine, Emergency Medicine and Endocrinology),University Masters (Transplant Medicine, Electrophysiology and Cardiac Electro-Stimulation),and the Research Doctorate in Hypertension and Cardiovascular Risk of the Milano-Bicocca University. He has chaired the Interuniversity (Universities of Milano, Milano-Bicocca and Pavia) Center of Clinical Physiology and Hypertension from 2001 to 2012 .

**SCIENTIFIC SOCIETES/TASK FORCES/COMMITTEES.** GM has served as Member of the Scientific Council, Secretary and President of the International Society of Hypertension (ISH) between 1982 and 1992, President of the European Society of Clinical Investigation (1980-1982), Chairman of the Working Group on Hypertension and the Heart of the European Society of Cardiology (ESC,1994-1996), member of the Executive Scientific Committee of ESC (1986-1991), President of the Italian Society of Hypertension (1997-1999) and member of the Scientific Council of ESH between 1989 and 2003 (President, 1999-2001). He has been member ex-officio (only European) of the Executive Council of the American Society of Hypertension (1996-2008), Officer for the ISH Forum of National Societies, member of the Committee on Cardiovascular Drugs and Therapy of the World Heart Federation and member of the Writing Committee of the ESC guidelines on Prevention of Cardiovascular Diseases (1993, 1998, 2003),the WHO/ISH Guidelines on Hypertension (1993, 1999) and the Guidelines on Hypertension in the Elderly of the American College of Cardiology (2011).He has co-chaired the Task Force on the ESH-ESC guidelines on Hypertension (2003,2007,2009 and 2013 and 2018) and the WHO/ISH Liaison Committee. He has chaired the Scientific and Organising Committees of various ESH Meetings (2001, 2003, 2005, 2007, 2009, 2011, 2013,2015,2017 and 2019). He has been Chairman of the Scientific Committee of the ISH Congresses in Prague (2002) and San Paulo (2004), and Honorary President of the ISH Meeting in Montreal (1990), Athens (ESH/ISH meeting,2014) and Glasgow (ESH/ISH Meeting, 2020).He is currently Chairman of the Educational Board of ESH.

**AWARDS/HONORS.**GM has received several Awards, among which the AHA Award of the Hypertension Council for Excellence in Hypertension Research, the Heymans Award of the International Society of Pharmacology, the Wright International Award of the High Blood Pressure Council of Australia, the ISH Volhard and the Tigersted (MSD) Awards, the ESH Folkow Award, the Life Achievement Award of the Italian Society of Hypertension, the Sleight Award of the World Hypertension League and the Zanchetti Life Achievement Award of ESH. He was appointed Lecturer of the Year by the Belgian Universities and Hypertension Leagues (1992) and was conferred the Talal Zein Foundation Award, the International

Recordati Prize (2000), the 2001 Invernizzi Award for Medicine, the Gold Medal of the Lorenzini Foundation (2008), the Hariri Memorial Award (2009) and the Spinoza Award of the Amsterdam University. He has been appointed Honorary Member of ESH, the High Blood Pressure Council of Australia, the Latino-American Hypertension Society, the Japanese Circulation Society, the British Hypertension Society, the German Hypertension League and many other Scientific Academies or Societies in the area of hypertension, Cardiology or Internal Medicine. He has received the highest Award of the Lombardy Region (Rosa Camuna) and the title of Commander of the Order of the Italian Republic. He has been awarded (2014) as one of the 100 Italian excellences in various areas of human activities. He is member of the European Academy of Sciences

He has been invited to give state-of-the-art, keynote, debates or special and plenary lectures in more than 700 international meetings. He has also been guest lecturer at meetings of many national societies of hypertension, cardiology and internal medicine. In addition to his lectures as Awardee, to be mentioned are the Pickering Lecture (British Hypertension Society), the Tigersted Lecture (Finnish Hypertension Society), the Merck Frosst Lecture (Canadian Society of Cardiology), the Saeb Salam Memorial Lecture (Beirut University), the Brian Bronte Steward Memorial Lecture (Glasgow University) the Leloir Nobel Laureate Lecture (Buenos Aires), the Gavras Lecture (Athens) the Population Health Lecture (Mac Master University, Hamilton) and the Kasperzac Lecture (Cleveland Clinic)

**HONORARY DEGREES/ACADEMIC RECOGNITIONS.** GM has received the Honorary Professorship of the University of Cordoba. He is Honorary member of the Academy of Science of Cordoba, and has been conferred the Degree Honoris Causa in Medicine from the University of Gdansk and the Carol Davila University of Bucharest. He has received the Degree Honoris Causa from the University of Glasgow.

**EDITORIAL ACTIVITY.** GM has edited more than 90 Special issues or Supplements to international cardiovascular and internal medicine Journals. He has written or edited more than 20 books on hypertension, metabolic diseases and cardiovascular diseases edited by international Publishers, among which several Manuals, including the three official ones Manuals of ESH. He is or has been member of the Editorial Board, Guest Editor and Reviewer of many important international journal on hypertension, cardiovascular disease and internal medicine. He has served as Deputy Editor and Editor-in-Chief of the Journal of Hypertension, (the official ISH/ESH Journal) from 1995 to 2021

**SCIENTIFIC ACTIVITY.** GM's research interests focus on epidemiology pathophysiology, diagnosis and treatment of hypertension, heart failure, and coronary disease, as well as on the clinical aspects of diabetes, obesity and other metabolic abnormalities. His expertise includes ambulatory blood pressure monitoring, neurohumoral control of the circulation, large artery mechanics, cardiac damage in hypertension, hemodynamic changes of cardiovascular drugs, cardiovascular regulation during stress and sleep as well as epidemiology and intervention trials in hypertension and diabetes. He has been member or chairman of the steering committees of several clinical trials. He has published more than 2000 original papers, reviews and editorials in peer-review journals.

**BIBLIOMETRIC DATA.** GM has been for several years in the list of the Highly Cited scientists (Clarivate Analytics, formerly Thomson Reuters). One of his papers (2003 ESH/ESC Guidelines) was reported to be the most highly cited article in the world medical literature in the years 2004-2005 (Ref. The Scientist) and three were mentioned among the most widely quoted hypertension papers ever (Ref. Hypertension, 2014). In 1995 he was ranked as the most widely quoted cardiologist in Italy and, from the 1996-2011 publications, in 2013 he was included among the 400 most influential biomedical investigators (45 cardiologists and 12 hypertensiologists, Ref. Eur J Clin Inv, Scopus database). From the 2008-2018 publications, in 2019 he was ranked as the 1st expert in Europe (2nd in the world) for the hypertension area (ref. Expertscape). In 2018 and 2020, a screening of 7 million papers by 6 million scientists from 22 research areas (Ref. Plos Biology) has ranked him among the first 300 scientists (of which 15 cardiologists and 3 hypertensiologists) in the world. GM's publications have received, up to September 2021, more than 241.000 citations (>2400 papers) in the international medical literature, with a H-index of 182 (Ref. Microsoft Academy), the highest among Italian cardiologists and internists.

### **Elevated heart rate and cardiovascular risk in hypertension.**

Mancia G, Masi S, Palatini P, Tsioufis C, Grassi G.  
J Hypertens 2021;39:1060-1069.

Epidemiological studies have shown that chronically elevated resting heart rate (HR) is significantly associated with organ damage, morbidity and mortality in a wide range of

patients including hypertensive patients. Evidence is also available that an increased HR reflects sympathetic nervous system overdrive which is also known to adversely affect organ structure and function and to increase the risk of unfavourable outcomes in several diseases. The causal relationship between elevated HR, organ damage, and cardiovascular outcomes can thus be explained by its relationship with sympathetic cardiovascular influences although evidence of sympathetically-independent adverse effect of HR increases per se makes it more complex. Interventions that target HR by modulating the sympathetic nervous system have therefore a strong pathophysiological and clinical rationale. As most clinical guidelines now recommend the use of combination therapies in patients with hypertension, it might be desirable to consider as combination components drugs which lower HR, if HR is elevated such as, according to guidelines, when it is above 80 b/min.

### **Adding Home and/or Ambulatory Blood Pressure to Office Blood Pressure for Cardiovascular Risk Prediction**

Giuseppe Mancia, Rita Facchetti, Gino Seravalle , Cesare Cuspidi , Giovanni Corrao, Guido Grassi

Hypertension. 2021;77:640–649

**ABSTRACT:** Home and 24-hour blood pressure (BP<sub>Home</sub> and BP<sub>24h</sub>) are believed to improve the prognostic value of office BP (BP<sub>Office</sub>) alone, but the evidence has limitations such as that (1) these 3 BPs are characterized by multicollinearity and (2) the procedures adopted do not allow quantification of the prognostic advantage. One thousand eight hundred thirtythree individuals belonging to the PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) were followed for 16 years. Prediction of cardiovascular and all-cause mortality was determined via the goodness of fit of individual data (Cox model), the area underlying the receiving operator curves and the net reclassification improvement of cardiovascular and all-cause mortality risk. Calculations were made for BP<sub>Office</sub> alone and after addition of BP<sub>Home</sub>, BP<sub>24h</sub>, or both, limited to their residual portion which was found to be unexplained by, and thus independent on, BP<sub>Office</sub>. With all methods addition of residual out-of-office systolic or diastolic BP to BP<sub>Office</sub> significantly improved cardiovascular and all-cause mortality prediction. The improvement was more consistent when BP<sub>Home</sub> rather than BP<sub>24h</sub> was added to BP<sub>Office</sub> and, compared with BP<sub>Office</sub> plus BP<sub>Home</sub>, no better prediction was found when addition was extended to BP<sub>24h</sub>. With all additions, however, the improvement was quantitatively modest, which was the case also when data were separately analyzed in younger and older individuals or in dippers and nondippers. Thus, addition of out-of-office to BP<sub>Office</sub> improves prediction of cardiovascular risk, even when data analysis avoids previous limitations. The improvement appears to be limited, however, which raises the question of the advantage to recommend their extended use in clinical practice.

### **Short- and Long-Term Reproducibility of Nighttime Blood Pressure Phenotypes and Nocturnal Blood Pressure Reduction**

Giuseppe Mancia , Rita Facchetti, Michele Bombelli, Fosca Quarti-Trevano, Cesare Cuspidi , Guido Grassi

Hypertension. 021;77:1745–1755

**ABSTRACT:** In 1722 hypertensives recruited for the European Lacidipine Study on Atherosclerosis and treated with atenolol or lacidipine ( $\pm$ additional drugs) during 4 years, we evaluated the long-term reproducibility of dipping, nondipping, extreme dipping, and reverse dipping, an information of key relevance for defining the prognostic impact of these blood pressure (BP) phenotypes. Ambulatory BP was measured at baseline and every year during treatment, allowing repeated classifications of these conditions. Based on systolic BP, at baseline 50.1%, 37.5 %, 4.5 %, and 7.9 % were dippers, nondippers, extreme dippers, and reverse dippers, respectively. Antihypertensive drug treatment reduced the number of dippers and extreme dippers in favor of nondippers and reverse dippers. During treatment, the dipping and nondipping phenotypes were markedly unstable and shifts from one to other phenotypes were even more common in reverse and extreme dippers. In only a very small fraction of patients, a given nighttime BP phenotype was persistently found throughout the 4 years. Data were similar for diastolic BP and in subgroups differing for the type of treatment, the treatment complexity, and the achieved on-treatment BP value. Poor reproducibility characterized also the absolute nighttime BP reduction as measured by the nighttime BP fall and the night/day BP ratio. Thus nighttime BP phenotypes are all largely inconsistent, their detection over the entire treatment period involving just a minute fraction of the entire patients' cohort.

### **Adherence to Treatment by Initial Antihypertensive Mono and Combination Therapies**

Federico Rea, Laura Savaré, Matteo Franchi, Giovanni Corrao, and Giuseppe Mancia

#### **BACKGROUND**

Aim of our study was to compare adherence to antihypertensive drug therapy between newly treated patients in whom monotherapy or a 2-drug single-pill combination (SPC) was initially dispensed.

#### **METHODS**

The 63,448 residents of Lombardy Region (Italy), aged 40–80 years, who were newly treated with antihypertensive drugs during 2016, were identified and followed for 1 year after the first prescription. The outcome of interest was adherence to drug therapy that was measured

according to the “proportion of days covered” (PDC) criterion, i.e., the ratio between the number of days in which the drug was available and the days of follow-up. Patients who had a PDC  $>75\%$  and  $<25\%$  were defined as highly and poorly adherent to drug therapy, respectively. Log-binomial regression models were fitted to compare the propensity to treatment adherence between the initial therapeutic strategies, after adjusting for baseline demographic and clinical covariates.

#### **RESULTS**

About 46% and 17% of patients showed high and poor adherence, respectively. Compared with patients under initial monotherapy (85%), those who were initially treated with a SPC (15%) had higher propensity to be highly adherent and a lower propensity to be poorly adherent to antihypertensive treatment (risk ratio: 1.18, 95% confidence interval 1.16–1.21; 0.42, 0.39–0.45, respectively). This was the case regardless the sex, the age, the patient clinical status, and with almost any type of SPC.

**CONCLUSIONS**

In a real-life setting, patients who were initially prescribed a 2-drug SPC exhibited more frequently a good adherence to antihypertensive treatment than those starting with a single drug.

**Sympathetic Neural Mechanisms Underlying Attended and Unattended Blood Pressure Measurement**

Guido Grassi, Fosca Quarti-Trevano, Gino Seravalle, Raffaella Dell'Oro, Jennifer Vanoli, Gianluca Perseghin, Giuseppe Mancia

Hypertension. 2021;78:1126–1133

**ABSTRACT:** Whether blood pressure (BP) values differ when BP is measured with or without the presence of a doctor (attended and unattended BP measurements) is controversial, and no information exists on whether and to what extent neurogenic mechanisms participate at the possible BP differences between these measurements. In this study, we assessed continuous beat-to-beat finger systolic BP and diastolic BP, heart rate, muscle, and skin sympathetic nerve traffic (microneurography) before and during BP measurement by an automatic device in the presence or absence of a doctor. This was done in 18 untreated mild-to-moderate essential hypertensive patients (age, 40.2±2.8 years, mean±SEM). During attended BP measurement, there was an increase in systolic BP, diastolic BP, heart rate, and skin sympathetic nerve traffic and a muscle sympathetic nerve traffic decrease, the peak changes being +5.3%,+8.4%,+9.4%,+30.9%, and -15.2%, respectively (P<0.05 for all). In contrast, during unattended BP measurement, systolic BP, diastolic BP, heart rate, and skin sympathetic nerve traffic were modestly, albeit in most instances significantly, reduced, whereas muscle sympathetic nerve traffic remained almost unchanged. During unattended BP measurement, peak systolic BP was 14.1 mm Hg lower, peak heart rate was 10.6 bpm lower, and peak skin sympathetic nerve traffic was 8.5 bursts/min lower than the peak values detected during attended BP measurement. Thus the cardiovascular and neural sympathetic responses to the alerting reaction elicited by BP measurement in the presence of a doctor are almost absent during unattended BP measurement, during which, if anything, a modest cardiovascular sympathoinhibition occurs. This has important implications for comparison of studies using these different BP measurement approaches as well as for decision concerning threshold and target BP values for treatment.

**White-Coat Hypertension: Pathophysiological and Clinical Aspects Excellence Award for Hypertension Research 2020**

Giuseppe Mancia , Rita Facchetti, Michele Bombelli, Cesare Cuspidi , Guido Grassi  
Hypertension 2021,78,1677-1688

**ABSTRACT:** Few issues of modern cardiovascular medicine have been as controversial as the relationship between whitecoat hypertension (WCH), that is, a common condition in which office blood pressure is elevated while out-of-office blood pressure (ambulatory blood pressure or home blood pressure) is normal. While earlier studies showed no increased risk of cardiovascular events in WCH compared with the normotensive state,

more recent studies have changed this conclusion by showing that an increased cardiovascular risk represents a trait of this hypertensive phenotype. The present article will review a number of issues related to WCH, that is, its definition, pathophysiological background, clinical alterations, and prognostic significance. This will be done by considering the available evidence published during the last decades, with special focus on the data collected in PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni)—a research project performed with a cross-sectional and longitudinal design, which has provided a series of novel clinical information on WCH throughout the years. The final part of the article will discuss the therapeutic implications of the abovementioned evidence, as well as some controversial or still undefined issues related to WCH, whose investigation will be an important goal to pursue by future research.

### **Stratification of the risk of developing severe or lethal Covid-19 using a new score from a large Italian population: a population-based cohort study**

Giovanni Corrao, Federico Rea, Flavia Carle, Salvatore Scondotto, Alessandra Allotta, Vito Lepore, Antonio D'Etto, Cinzia Tanzarella, Patrizia Vittori, Sabrina Abena, Marica Iommi, Liana Spazzafumo, Michele Ercolanoni, Roberto Blaco, Simona Carbone, Cristina Giordani, Dario Manfellotto, Massimo Galli, Giuseppe Mancina, On behalf of the 'Monitoring and Assessing care Pathways (MAP)' working group of the Italian Ministry of Health

#### **ABSTRACT**

**Objectives** To develop a population-based risk stratification model (COVID-19 Vulnerability Score) for predicting severe/fatal clinical manifestations of SARS-CoV-2 infection, using the multiple source information provided by the healthcare utilisation databases of the Italian National Health Service. **Design** Retrospective observational cohort study. **Setting** Population-based study using the healthcare utilisation database from five Italian regions. **Participants** Beneficiaries of the National Health Service, aged 18–79 years, who had the residency in the five participating regions. Residents in a nursing home were not included. The model was built from the 7 655 502 residents of Lombardy region. **Main outcome measure** The score included gender, age and 29 conditions/diseases selected from a list of 61 conditions which independently predicted the primary outcome, that is, severe (intensive care unit admission) or fatal manifestation of COVID-19 experienced during the first epidemic wave (until June 2020). The score performance was validated by applying the model to several validation sets, that is, Lombardy population (second epidemic wave), and the other four Italian regions (entire 2020) for a total of about 15.4 million individuals and 7031 outcomes. Predictive performance was assessed by discrimination (areas under the receiver operating characteristic curve) and calibration (plot of observed vs predicted outcomes). **Results** We observed a clear positive trend towards increasing outcome incidence as the score increased. The areas under the receiver operating characteristic curve of the COVID-19 Vulnerability Score ranged from 0.85 to 0.88, which compared favourably with the areas of generic scores such as the Charlson Comorbidity Score (0.60). A remarkable performance of the score on the calibration of observed and predicted outcome probability was also observed. **Conclusions** A score based on data used for public health management accurately predicted the occurrence of severe/fatal manifestations of COVID-19. Use of this score may help health decision-makers to more accurately identify high-risk citizens who need early preventive or treatment interventions.

# Conclusions regarding the Quantitative Assessment of Ground Deformations for the Risk Management of Petroleum and Gas Pipelines using Radar Interferometry

by Manfred F. Buchroithner EUAS

## Short Biography

*Manfred Ferdinand Buchroithner (\*17-12-1950) studied Geology & Palaeontology at the University of Graz/Austria and both Remote Sensing and Cartography at ITC/Netherlands. He obtained his PhD in 1977 in Graz. In 1982 he went as Fulbright Scholar to the USA (Fort Worth/Texas, Boulder/Colorado and Stanford University/California). During the following years at the Institute for Cartography of the Austrian Academy of Sciences in Vienna and as Director of the Joanneum Research Institute of Digital Image Processing and Computer Graphics in Graz he spent several months of postdoctoral research at the Finnish National Research Center/VTT in Espoo near Helsinki and at the Jet Propulsion Laboratory/JPL of NASA in Pasadena. In 1985 he obtained his habilitation (venia legendi) for both General Geology and Remote Sensing. From 1992 to 2016 he was Full Professor, holding the Chair of Cartography at TU Dresden, Germany. Subsequently he held the position of a Senior Professor for two years. M. F. Buchroithner led many expeditions to high mountain regions in the Andes, Alps, Balkan mountain ranges, Kilimanjaro Massif, Altai mountains, most of the regions of High Asia (Tian Shan, Pamir, Hindu Kush, Karakorum, Himalaya, Tibet incl. Nyenchen Tanglha Mountains and Kailash) and to Borneo/Malaysia. He spent semesters as Invited Professor at the Universities of Munich/Germany, Salzburg/Austria (twice), Bergamo/Italy, COMSATS/Islamabad, and the École Nationale Supérieure des Mines des Paris in Sophia Antipolis/France and also gave invited guest lectures at various Chinese universities. He supervised and successfully graduated more than 50 doctoral students. Buchroithner both authored and edited several books on cartographic, GIT and remote sensing issues and has nearly 500 publications incl. maps and several educational films to his credit. He holds international patents in 3D cartography, is member of several learned societies and obtained a series of national and international scientific awards, i.a. the Friedrich Hopfner Medal (A) and the Denny Medal (UK).*

The following report represents a portion of the following comprehensive publication:

***Bayramov, E., Manfred Buchroithner, M.F. & Kada, M. (2020): Quantitative Assessment of Ground Deformations for the Risk Management of Petroleum and Gas Pipelines Using Radar Interferometry. Geomatics, Natural Hazards and Risk, 11, 1: 2540 – 2568.***

The corridor of BTC oil, SCP gas, WREP oil and SCPX gas pipelines starts at the Sangachal Terminal in Azerbaijan, crosses Georgia and terminates at the Turkey Ceyhan Marine Terminal. The BTC pipeline is 1768 km long (443 km in Azerbaijan, 249 km in Georgia and 1076 km in Turkey). SCP pipeline is a 692 km long (443 km in Azerbaijan and 249 km in Georgia), WREP pipeline is 829 km long (455 km in Azerbaijan and 374 km in Georgia) and SCPX pipeline is 489 km long (424 km in

Azerbaijan, 63 km in Georgia and 2 km in Trans-Anatolian Natural Gas Pipeline (TANAP) interconnection). The pipelines pass through areas of active seismic faults in Azerbaijan, Georgia and Turkey (Bayramov 2013). BTC, SCP and SCPX pipelines are properly earthquake engineered through the design of trapezoidal trenches to reduce soil resistance either side of the pipe to allow it to move more freely in case of significant ground movements whereas WREP pipeline is quite old and was designed based on lower protection principles against ground movements.

Measurements carried out in the above study area demonstrated the practical values for the measurements of ground deformation velocity and rates using PS-InSAR along the corridor of underground oil and gas pipelines. The outcomes of this research suggests that the PS-InSAR technique can have a high potential for the optimized and simplified monitoring and risk management of ground deformations along pipelines, but the use of only this technique for the assessment of ground movement risks to petroleum and gas infrastructure needs to be carefully evaluated (Tofani et al. 2013). Since the BTC, SCP, SCPX and WREP pipelines are underground, for the present studies it was obviously impossible to judge about the conditions of the pipelines in terms of any kind of deformations but it was only feasible to analyze the status of ground movements. Even if the PSI technique can be used as the predictor for the prioritization of potential risky sites, it cannot fully replace in-situ measurements based on the visual inspections and geodetic measurements. The justification of remediation costs requires detailed geotechnical assessments on the ground with the consideration of geodetic measurements, readings from piezometers, inclinometers, pipeline in-line inspections like different types of piggings, direct current voltage gradient (dcvg) and close interval potential surveys, depth of pipelines, existing trapezoidal trench standards etc. to understand how seriously pipelines are affected. If there are no specific changes in the shape of pipelines and other conditions, then this will raise a number of questions in terms of probability of failure for the evaluation prior to the investment into the geotechnical remediation activities. It is also necessary to emphasize the availability of historical recordings of actual pipelines incidents caused by the ground deformation processes.

However, very often for the sites of interest, there are no historical records from geodetic measurements to set-up a baseline for the continuous site monitoring. In this case time-series of space satellite observations are irreplaceable. It is also necessary to emphasize that the single-point measurements using ground-based geodetic techniques are not sufficient to analyze broader spatial patterns of ground movements. Even though there are many studies focused on PS-InSAR, the present research demonstrated the combined PS-InSAR and the geospatial machine learning – based interpolation and concentration analysis which contributed to the development and understanding of the broader picture of ground deformation processes along petroleum and gas pipelines. Majority of PS-InSAR studies primarily analyzed and summarized produced results using generated point clouds of ground movement velocity and rates. However this research clearly demonstrated that running of advanced spatial interpolation and concentration statistics would significantly contribute to more comprehensive research results.

PS-InSAR studies showed the prevailing and continuous subsidence patterns in the KP13-70 range of pipelines crossing two active seismic faults. The ground uplift deformations were observed in the pipeline range of KP0-KP13. The spatial distribution of sites with ground deformation velocity less than  $\pm 15$  mm/y and more than 15 mm/y was

diverse and random all along 70km of pipelines without any cumulative spatial patterns. This means that it would be complicated to find all of these locations using purely ground-based expeditions and visual inspections.

Even though PS-InSAR demonstrated a reliable approach for the detection of ground deformation processes along petroleum and gas pipelines, it is highly recommended to advance these studies with the integration of other geological, geotechnical, seismic, thermal and climatic information to better understand controlling natural and man-made factors. Besides, it is crucial to also use other techniques like Small Baseline Subset (SBAS), Intermittent Small Baseline Subset (ISBAS) and SqueeSAR and cross-validate measured results (Sowter et al. 2013; Gee et al. 2016; Sowter et al. 2016; Gee et al. 2017; Sowter et al. 2018).

To the extent of our awareness, for the present study area of BTC, SCP, SCPX and WREP pipelines, these studies of public accessibility is the first in a sequence of works that seeks to answer whether or not PS-InSAR-based technique holds practical value for the pipeline operators to highlight areas of ground deformations at seismic faults and also along entire range of pipelines. However, the erosion vulnerability of these pipelines was well studied by Bayramov 2013 using the optical multi-temporal remote sensing. These studies concluded that first 70km of BTC, SCP, SCPX and WREP pipelines are most vulnerable to erosion occurrences which create risks of pipeline damage by natural and anthropogenic factors. In particular this was related to the soil types with high silt content, low vegetation cover and hilly terrain. This means that there is obviously an impact from ground deformation processes which should also be investigated in the spatial relationship to naturally occurred erosion processes along petroleum and gas pipelines. Based on the pipeline related studies by Hole et al. 2011, it is recommended to run PS-InSAR in both ascending and descending acquisition models to resolve the LOS measurements into vertical deformation. Vertical displacement can only be estimated from a single LOS measurement if motion azimuth and the angle between slope motion and a level plane are assumed for the area of interest (Hole et al. 2011). As it was mentioned before in the present studies it was not feasible to perform computations for both ascending and descending acquisitions because of nonsufficient computing power and storage space. Therefore single LOS measurements were obtained from the descending flight direction and approximated to the vertical movement as proposed by Dai et al. (2015), Gee et al. (2016) and Hole et al. (2011). Singhroy et al. (2018) used the corner reflectors along buried oil pipelines to detect subtle ground and pipeline movements, thereby reduced the need for frequent ground based survey campaigns and increased the reliability, precision and confidence level of measurements. Sharma et al. (2016) coupled the InSAR displacements, GIS analyses, field data and geomechanical modelling to optimize understanding of landslide geohazards along pipelines. Ianoschi et al. (2013) determined the feasibility of gas pipeline monitoring by PS-InSAR using TerraSAR-X (3\_3m) radar satellite images and application of high resolution images added significant amount of information and details in terms of point density. Considering fore-mentioned InSAR studies along pipelines, it is possible to conclude that for the best performance of PS-InSAR techniques along petroleum and gas pipelines, it is necessary: to process both ascending and descending passes for the computation of precise vertical movement; install permanent corner reflectors along vulnerable areas of pipeline movements and also areas with a lack of objects of high scattering properties for the reliability, precision and confidence of measurements; apply both high and low resolution radar images; collect all possible

geological and geotechnical contextual information from ground-based surveys and other sources to perform combined analysis; run other SAR ground deformation techniques to cross-validate the results. Another limitation is to automate separation of natural - and manmade - caused ground changes which can be mistakenly reflected as the subsidence or uplift, e.g., development of petroleum and gas infrastructure or excavation activities etc. Ianoschi et al. 2013 performed PS-InSAR with further classification and characterization of persistent scatterers (PS) in terms of ground or building reflections. The thresholding approach was used to perform this classification (Dheenathayalan and Hanssen 2011; Dheenathayalan et al. 2011). This is crucial to effectively prioritize critical points for further field investigations along petroleum and gas pipelines. Therefore, it is necessary to proceed with the present studies by applying of other advanced ground movement measurement techniques. It is also necessary to integrate more geospatial information to understand natural and man-made controlling factors of ground movement processes and improve the reliability of produced results.

We performed PS-InSAR analysis along petroleum and gas pipelines to identify the spatial patterns of ground surface deformations with respect to the location of active seismic faults. Our conclusions are as follows:

1. As a primary factor of ground deformations, the influence of tectonic movements was observed in the broad-scale analysis along 70km long and 10 km wide section of petroleum and gas pipelines with the prevailing and continuous subsidence in the KP13-70 range of pipelines crossing two active seismic faults. However the largest subsidence rates were observed in the areas of croplands, where agricultural activities like overuse of groundwater, irrigation and ploughing etc. also negatively affect to the ground movement processes along pipelines as the secondary factor. The ground uplift deformations were observed in the pipeline range of KP0-KP13. The largest spatial distribution of subsidence velocity class (-25 - - 15) was prevailing within the agricultural landcover class along oil and gas pipelines.
2. Local-scale analyses were performed along 70km section of pipelines with 250 m buffer zone for the detailed quantitative ground movement assessment of two seismic faults. The minimum and maximum vertical ground movement velocities were observed to be -21.3 mm/y and 14.1 mm/y. The minimum and maximum ground movement rates in December 27, 2019 since January 6, 2018 were observed to be -46.09mm and 33.46 mm, respectively. Both of them were observed within the buffer zones of two seismic faults. However, the spatial distribution of sites with ground deformation velocity less than - 15mm/y and more than 15mm/y was diverse and random all along 70 km of pipelines without any cumulative spatial patterns.
3. Seismic Fault KP21-31 revealed its higher vulnerability to subsidence processes rather than the Seismic Fault KP46-54 and this was reflected in lower mean, variation and standard deviation of pixel values the buffer zones of seismic faults with 250m width. The ground deformation velocities within the range of Seismic Fault KP21-31 revealed the minimum and maximum values of -19.74 mm/y and 14.1mm/y, respectively. The minimum and maximum ground movement rates in December 27, 2019 since January 6, 2018, were observed to be - 46.07mm and 33.46mm. The ground deformation velocities within the Seismic Fault KP46-54 revealed the minimum and maximum values of - 17.07mm/y and 9.29mm/y. The minimum and maximum ground movement rates in

December 27, 2019 since January 6, 2018, were observed to be -46.09mm and 22.24mm.

4. Encouraging level of agreement with the regression coefficients of 0.92 and 0.96 for known subsiding sites at KP28p500 and KP52p750 respectively was observed between the high-precision GPS and PS-InSAR measurements. It was also possible to observe the encouraging level of correlation between the high-precision GPS and PS-InSAR measurements with the regression coefficients of 0.97 and 0.96 for known uplifting sites at KP04p900 and KP35p050, respectively. Although the GPS measurements showed minor variations in comparison to PS-InSAR (RMSE of 2.7mm and 2.5mm for KP28p500 and KP52p750 respectively; the RMSE of 1.7mm and 1.9mm for KP04p900 and KP35p050) the achieved accuracy allows to state without any doubts that the deformation trends clearly confirms the presence of subsidence processes at the seismic faults. This means that the PS-InSAR – based approach outlined in this paper is a significant improvement over current ground-based monitoring practices.

5. The spatial distribution and variation of ground movement processes along pipelines demonstrated that general geological and geotechnical understanding of the study area is not sufficient to find and mitigate all the critical areas of subsidence and uplifts for the pipeline operators. The prediction of the potential subsidence or uplift locations based on the field visual verifications holds a lot of uncertainties without broad and detailed scale airborne, satellite or unmanned aerial vehicle space observation technologies. The justification of the budget for the geotechnical maintenance activities along long-range oil and gas pipelines requires sophisticated prioritization and planning of the remediation sites and clear quantitative and qualitative risk assessment proving the activeness of these sites and effectiveness of the remediation measures.

6. Even though PS-InSAR demonstrated a reliable approach for the detection of ground deformation processes along petroleum and gas pipelines, it is highly recommended to advance these studies with the integration of other geological, geotechnical, thermal and climatic information to better understand controlling natural and man-made factors. Besides, it is crucial to also use other techniques like Small Baseline Subset (SBAS), Intermittent Small Baseline Subset (ISBAS) and SqueeSAR and cross-validate the results.

Literature references can be obtained from the afore mentioned publication which contains a detailed description of the complete study.

# Engineering Brain: Metaverse for Future Engineering

by Xiangyu Wang, Member EUAS



## Short Biography

### **WORK EXPERIENCE**

*Professor (Personal Chair) (2011 to presence), Curtin University, Australia*

*Curtin-Woodside Chair Professor for Oil, Gas & LNG Construction and Project Management (July 2013- July 2018), Curtin University, Australia*

*College of Experts, ARC (Australian Research Council) (January 2016 – Dec 2018), Australian Government*  
*Acting Woodside Chair Professor of LNG Construction (February 2012 – July 2013), Curtin University, Australia*

*Curtin Director of Australasian Research Centre for Building Information Modelling (BIM) (March 2012 - presence), Curtin University, Australia*

*Editor-in-Chief, Visualization in Engineering: an International Journal, Springer-Verlag (2012 - presence)*

### **EDUCATION**

*Ph.D., Purdue University, 2005*

*Master, University of Washington, 2002*

*Bachelor, Tongji University, 2000*

### **RECOGNITIONS**

- *Member, EU Academy of Sciences, since 2018*
- *Have published 18+ Web of Science Hi-Cite Papers, and 8+ Hot Papers.*
- *In terms of the number of Hi-Cite Papers, he is ranked top 3 scholars among the areas of civil engineering, building/construction, and transportation in the entire world.*
- *Keynote and Plenary Speakers for over 70 International conferences/forums*
- *World Top 100 Engineers, 2014*
- *External judge for Innovation and Technology award, 2013 Woodside Awards*
- *The impact of his work was reported over 40 times by a wide range of international and domestic prestigious media. His work with his industry partners was featured twice in the Australian newspaper, Energynewsbulletin.net, ScienceWAmagazine, LNG World News, Business News, Western Australian Energy Research Alliance, CNN, the Conversation, and Energy Publications*

## **Abstract**

The past decade has witnessed a notable transformation of the Architecture, Engineering and Construction (AEC) industry. Efforts both in the academia and industry have been made to facilitate improved efficiency, safety, sustainability, and automation in civil projects. To integrate all the achievements made so far and further step up, this paper proposes a novel theory, Engineering Brain, to effectively adapt the metaverse concept in the field of civil engineering. Specifically, the concept of metaverse is first introduced and the Engineering Brain theory is presented. Their relationships are illustrated and outlooks

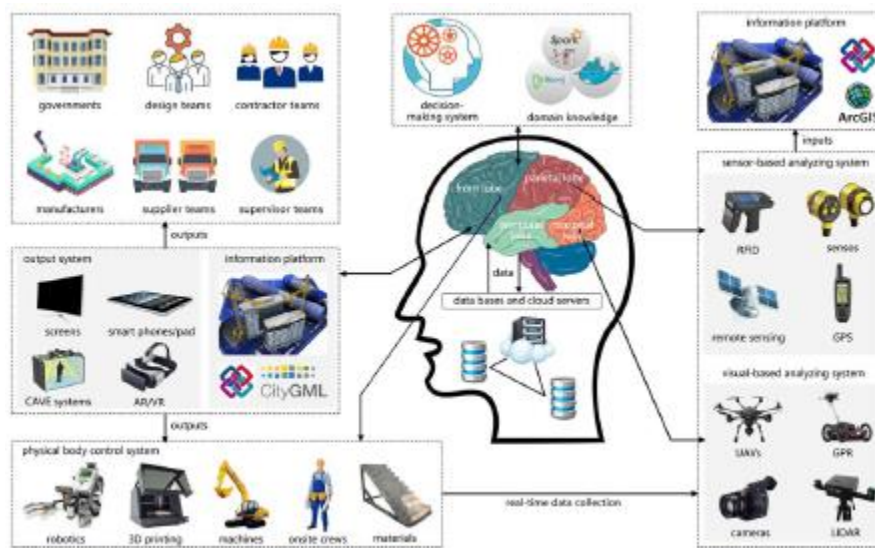
are indicated. This paper provides an innovative insight into the future engineering sector and potentially guides the entire industry towards its new era within the Metaverse environment.

### **1. Introduction to the Metaverse**

In early phases of evolution, similar concepts of metaverse under various names can be originated back to 1980s in a range of fiction novels and massively multiplayer online role-playing games (MMORPG). Metaverse was first coined in Neal Stephenson's 1992 science fiction *Snow Crash* (Stephenson 1992). A few well-known examples of the metaverse in the field of entertainment include *Fortnite* by Epic Games and *Second Life* by Linden Lab, where players can create an avatar for themselves and explore the world in a virtual environment. In a sense, metaverse resembles a parallel world where human activities currently in physical world take place in a digital environment. Recently, the heated discussion was brought about by Facebook's CEO, Mark Zuckerberg, in the developer conference (Zuckerberg 2021), and joined by Microsoft CEO Satya Nadella (Microsoft 2021), chipmaker Nvidia, video game platforms like Epic and Roblox, and even consumer brands like Gucci. Until today, the concept is still in the progress of evolving and no authoritative definition can be given at this stage. Yet, key elements in a metaverse can be identified, including videoconferencing, games, email, live streaming, social media, e-commerce, virtual reality, etc. And to realise such activities, the assets within the metaverse ecosystem (e.g., avatar and items of value) should be compatible, interoperable, and transferable among a variety of providers and competing products (Lanxon; et al. 2021). In addition, the developing metaverse concerns more and more on elements that are centred on users, ranging from avatar identity, content creation, virtual economy, social acceptability, presence, security and privacy, and trust and accountability (Lee et al. 2021). Nonetheless, All the components of a metaverse have readily existed yet moving from the proprietary ecosystem used by different competing businesses and creators to a universal and integrated ecosystem is key to the ultimate construction of metaverse. Integration of the scattered research findings and technology into an interoperable "universe" would be the next step. To facilitate the transition from current Internet to the metaverse, key technologies like Mixed Reality, User Interactivity (Human-Computer Interaction), Artificial Intelligence, Computer Vision, Edge and Cloud computing, and Future Mobile Networks, e.g., 5G, are required.

### **2. Engineering Brain**

The underlying theories of the proposed Engineering Brain cover neuroscience and neural engineering, bionics, and the cyber-physical system in the computer science field. The Engineering Brain is defined as an efficient and intelligent cyber-physical system for realizing optimized decision-making in construction projects based on heterogeneous, multi-modal and life-cycle data and state-of-the-art cross-domain technologies. Figure 1 presents the four key components in the Engineering Brain, i.e., 1) the frontal lobe, 2) the occipital lobe, 3) the parietal lobe, and 4) the temporal lobe.



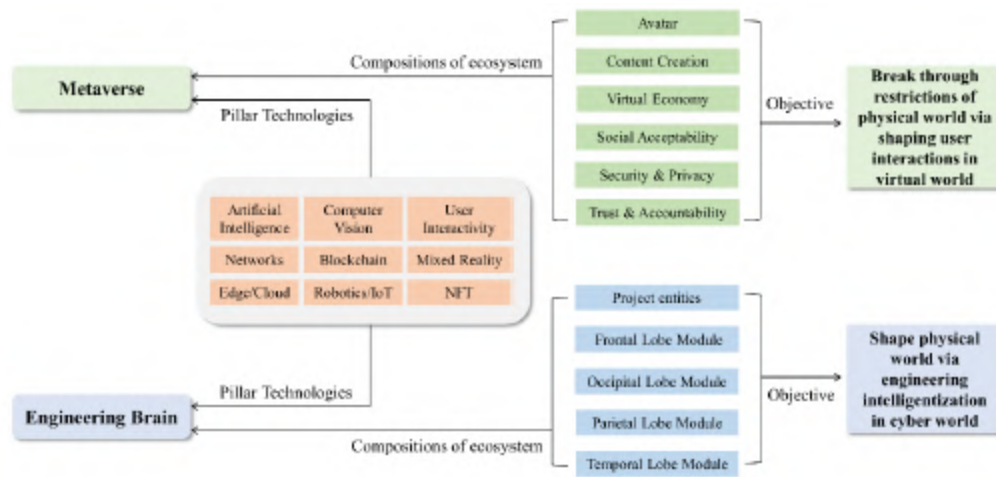
**Fig. 1** The conceptual framework of Engineering Brain

The working mechanism of Engineering Brain is similar to a real person. Specifically,

- The parietal lobe is responsible for the sense of smell and touch of people. Therefore, it to-some-extent corresponds to IoT systems that collect real-time readings of various types of sensors, such as status of machines (e.g., mounted sensors), workers (e.g., wearable sensors), and environment (e.g., fixed sensors) (Gamil et al. 2020). Also, data fusion methods including conventional filtering methods and cutting-edge encoding methods can be adopted to pre-process and integrate data.
- The occipital lobe handles visual signals in a human brain so that people can see things. Therefore, in Engineering Brain, it corresponds to collecting site images using RGB and depth cameras and implementing analysing methods that belong to the computer vision (CV) sector to process images (Xu et al. 2020). The methods include traditional image processing techniques and advanced deep neural networks. Also, the lobe obtains knowledge by 'reading' project documents stored in file systems using naive natural language pre-processing methods (Ayhan et al. 2019; Denny et al. 2018; İlal et al. 2017).
- The temporal lobe is where the hippocampus lies, which deals with memory. Thus, it corresponds to information storage. Structured data can be easily stored using typical relational databases (e.g., Oracle and DB2) and NoSQL databases (e.g., MongoDB and Apache Cassandra). For unstructured data, graph databases, e.g., Neo4j and Protégé, can be adopted (Jeong et al. 2019; Wu et al. 2021).
- The frontal lobe involves three gyri, where (a) the superior frontal gyrus is the part for convergent thinking (i.e., prediction and decision-making), (b) the middle frontal gyrus deal with speaking and corresponds to the information/knowledge exchanging function in Engineering Brain, and (c) the inferior frontal gyrus refers to the task execution module. Information platforms, e.g., BIM and CIM, can serve as the front-end that access to users for information searching, whereas modern human-machine interaction techniques, such as mobile computing, AR, and VR, can be used to increase the communication efficiency (Li et al. 2018).

Collectively, the workflow in the Engineering Brain is as follows. The parietal and occipital lobes collect, pre-process, and analyze data collected by sensors and image and text data, respectively. All data, information, and knowledge formed by information analysis (i.e., divergent thinking) are sent and stored in the temporal lobe. It then sends information and knowledge to the superior frontal gyrus for making predictions and decisions and enabling exchanging between the parietal and occipital lobe. The temporal lobe sends instructions to the middle frontal gyrus which can inform entities in the physical world to take actions.

**3. Engineering Brain: Metaverse for Future Engineering**



**Fig. 2** Pillar technologies, compositions of ecosystem, and objectives of Metaverse and Engineering Brian.

Figure 2 presents a comparison between the Metaverse and Engineering Brain. Development of Metaverse and Engineering Brain both strongly rely on similar modern technologies (Lee et al., 2021). Although the compositions and objectives of these two systems differ, the Engineering Brain is seen as the metaverse for future engineering. Both of Engineering Brain and Metaverse equip physical entities or users with interfaces to connect with the virtual world and eventually influence their behaviour and performance in the physical world by shaping their participation and interaction in the virtual environment. The virtual worlds of Engineering Brain and Metaverse are not only simple duplications or mappings of the realities, but also feature to remedy and surpass the defects of the physical world.

Considering the importance of the proposed Engineering Brain in future engineering, outlooks are multi-folded. Given the advances in various technologies and inter-related research areas, the development of project demands-oriented intelligent selection and combination of smart technologies is promising. Other potential developments including knowledge graph based intelligent recognition reasoning and decision-making, multi-machine collaboration and human-machine collaboration can be expected in the near future.

#### 4. Conclusions

Given the heated discussion of metaverse and current advances towards digitalization and automation in the construction industry, this paper proposes a theoretical system, Engineering Brain, functioning as the metaverse in future engineering. Outlooks into the future construction industry fueled by the metaverse and relevant technologies is promising.

#### References

- Ayhan, B. U., and Tokdemir, O. B. 2019. "Safety assessment in megaprojects using artificial intelligence." *Safety science*, 118, 273-287.
- Denny, M. J., and Spirling, A. 2018. "Text preprocessing for unsupervised learning: Why it matters, when it misleads, and what to do about it." *Political Analysis*, 26(2), 168-189.
- Epic Games. "Fortnite." Accessed Nov 10, 2021.
- Gamil, Y., Abdullah, M. A., Abd Rahman, I., and Asad, M. M. 2020. "Internet of things in construction industry revolution 4.0: Recent trends and challenges in the Malaysian context." *Journal of Engineering, Design and Technology*, 18(5), 1091-1102.
- İlal, S. M., and Günaydın, H. M. 2017. "Computer representation of building codes for automated compliance checking." *Automation in Construction*, 82, 43-58.
- Jeong, S., Hou, R., Lynch, J. P., Sohn, H., and Law, K. H. 2019. "A scalable cloud-based cyberinfrastructure platform for bridge monitoring." *Structure and Infrastructure Engineering*, 15(1), 82-102.
- Lanxon, N., and Bloomberg. 2021. "Welcome to the Metaverse: What it is, who's behind it, and why it matters." Fortune. Accessed Nov 3, 2021.
- Lee, P., Braud, T., Zhou, P., Wang, L., Xu, D., Lin, Z., Kumar, A., Bermejo, C., and Hui, P. 2021. *All One Needs to Know about Metaverse: A Complete Survey on Technological Singularity, Virtual Ecosystem, and Research Agenda*.
- Li, X., Yi, W., Chi, H.-L., Wang, X., and Chan, A. P. 2018. "A critical review of virtual and augmented reality (VR/AR) applications in construction safety." *Automation in Construction*, 86, 150-162.
- Linden Lab. "Second Life." Accessed Nov 10, 2021.
- Microsoft. 2021. "Microsoft Inspire 2021."
- Stephenson, N. 1992. *Snow Crash*. Bantam Books (US).
- Wu, C., Wu, P., Wang, J., Jiang, R., Chen, M., and Wang, X. 2021. "Ontological knowledge base for concrete bridge rehabilitation project management." *Automation in Construction*, 121, 103428.
- Xu, S., Wang, J., Shou, W., Ngo, T., Sadick, A. M., and Wang, X. 2020. "Computer Vision Techniques in Construction: A Critical Review." *Archives of Computational Methods in Engineering*, 1-15.
- Zuckerberg, M. (2021). *Connect 2021*.

# Discovery of a New Class of Materials: Nanoglass Alloys

by Herbert Gleiter, Member EUAS

## Short Biography

*Herbert Gleiter received his Ph.D. in Physics and was a Post Doctoral Fellow at Harvard University and MIT. In 1973, Gleiter became Chair Professor of Materials Science and founded in 1988 today's Leibniz Institute of New Materials at Saarbruecken, Germany. In 1994, he was appointed President of Research and Technology of the Research Center Karlsruhe, Germany, and 4 years later, he became the Founding Director of the Center's Institute of Nanotechnology. In 2012 the University of Nanjing founded the "Herbert Gleiter Institute of Nanoscience" and appointed him as the Institute's Founding Director. In 2019 the Chinese Academy of Science decided to set up a new research laboratory at Shenyang working on Nanomaterials. This laboratory - named Herbert Gleiter International Laboratory - will be managed and guided by scientists from China, Germany and the US.*

*Prof. Gleiter received more than 40 prizes. Among them, the most highly reputed awards in Germany, the Leibniz and the Max Planck Research Prize and the Cothenius Medal, the most prestigious award of the German National Academy of Sciences. The Alexander von Humboldt Foundation honored him by selecting him in 2006 for the Humboldt Medal and in 1999 for Werner Heisenberg Medal. Seven Universities from Germany, Hong Kong, Switzerland and China awarded him Honorary Doctor degrees. He is a Member of 12 Academies/National Academies of Science and/or Engineering: Three Academies in the US, one in Germany, in UK, in Belgium, in Austria, in Greece, and three Academies/National Academies in India. Among them are the National Academy of Engineering, the American Academy of Arts and Sciences, the National Academy of Inventors, the European Academy of Arts and Sciences, the Academia Europaea, the EU Academy of Sciences, the Indian National Academy of Sciences and the Indian National Academy of Engineering..*

*By the end of the 70's he and his research group pioneered to a new kind of materials, called today nano-crystalline materials. In fact, the first publication on nanocrystalline materials has been cited today more than 3400 times and this area of Materials Science has been cited up to now in total over 150 000 times and about 6 to 8 international conferences on nano-materials are organized every year. His first paper pioneering nano-crystalline materials has been cited so far more than 3500 times.*

*In recent years, Herbert Gleiter expanded the field of Materials Science by developing nanostructured non-crystalline materials. They are called today nano-glasses. Nano-glasses opened the door to non-crystalline materials with new atomic and electronic structures and/or with chemical compositions that cannot be generated in the form of the glassy materials we have today. For example, they permit the production of new kinds of alloys (e.g. alloys of silica and metals), new magnetic materials, new medical applications etc. In other words, nano-glasses may open the way into a "glass age" that would be based on the new properties of nano-glasses.. The significance of this contribution was recently acknowledged by electing him (together with the Nobel Laureates Haensch and zur Hausen) as the first member from Germany in the US National Academy of Inventors and by appointing him to be the "Researcher of the Year 2020.*

In recent time, the new option was revealed of alloying components in nanoglasses that are immiscible in all of the crystalline materials (metals, semiconductors, ceramic material) we have today.. The motivation for the attention to be focused on these new alloys was of historical origin. In fact, history teaches us

the following lesson: In the past, the discovery of materials with new kinds of chemical compositions resulted in new cultural developments. Well known examples are the discovery of the Cu-Sn alloys resulting in the Bronze Age or the discovery of iron and its alloys resulting in the Iron Age. In fact, today's technologies are based to a large extent on alloys of metallic, ionic or covalent components. However, almost all of these alloys have crystalline structures. On the other hand, recent studies have shown that in non-crystalline materials components may be alloyed that are immiscible in the crystalline state.

Hence, this observation suggests the following concept for the production of new kinds of materials: If one could produce in nanoglasses alloys of components that are immiscible in all of today's crystalline materials, these new alloys are likely to open the door to new technological developments. These new developments would be similar to the developments following the discovery of the CuSn alloys or the iron and its alloys during the Bronze or the Iron Age. In fact, it was this idea that motivated us to find out if we could find ways of producing alloys of components that are immiscible in all of today's crystalline materials by means of nanoglasses.

The first example of a nanoglass alloy of components that are immiscible in today's crystalline materials is displayed in Fig. 2 (This figure is taken from the publication by Chen Na et al in *Nanotechnology* **24** (2013) 045610). It shows the alloying of Cu and Fe in nanoglasses. In the crystalline state Cu and Fe are nearly immiscible (Fig. 1) whereas in the amorphous state, i.e., in nanoglasses, a non-crystalline solid solution is formed at all chemical compositions (Fig.2).

In fact, this conclusion seems to apply even if the nature of the chemical bonds of both components are different: Indeed, even in those cases alloying seems possible in nanoglasses. As an example, the formation of an amorphous solid solution of SiO<sub>2</sub> (covalent chemical bonds) and a metallic glass with the chemical composition Pd<sub>70</sub>Si<sub>27</sub>Fe<sub>3</sub> is shown in Fig. 3. As may be seen from Fig. 3, annealing of the nanoglass mixture of both components results in the formation of an amorphous solid solution of PdFeSiO.

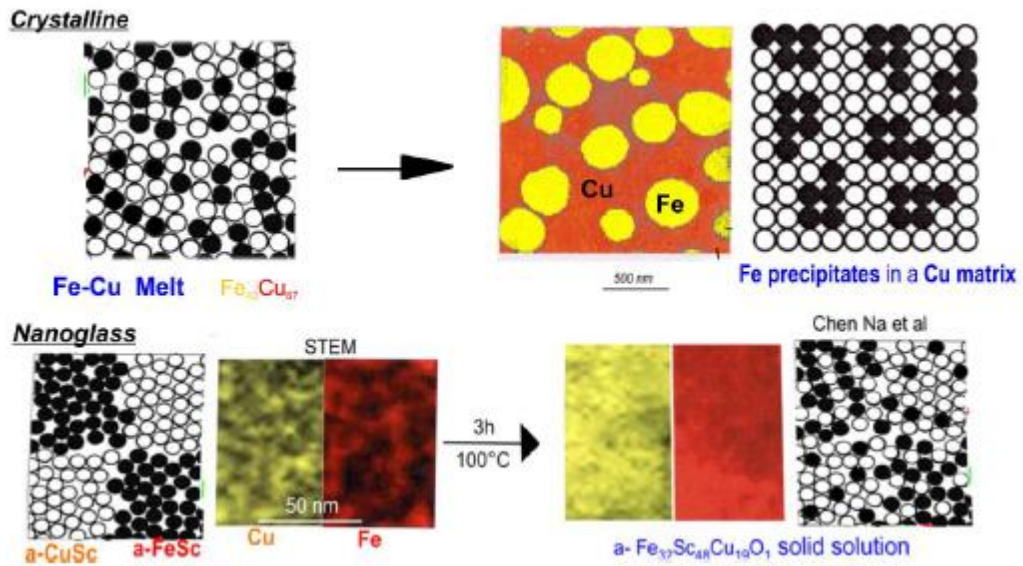


Fig. 1 (upper Figure) and Fig. 2 (lower Figure)

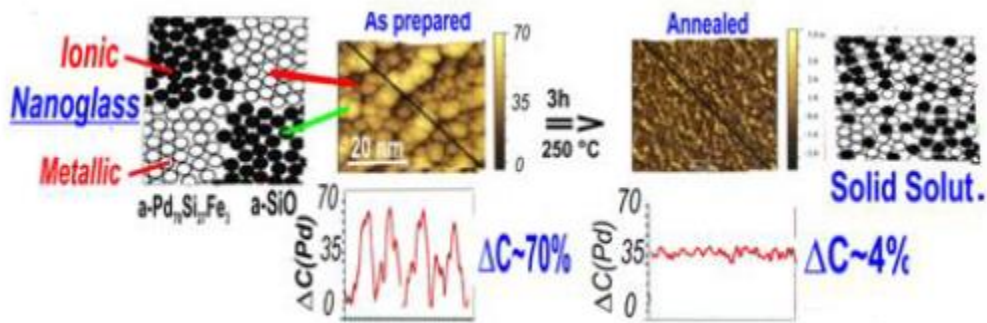


Fig. 3

Clearly, such alloys open the door to a new class of solids. They differ composition-wise from all of the solids we have so far. The historically attractive perspective of these new alloys was already pointed out above: If in the past, materials with new kinds of chemical compositions were discovered to result in new technological developments. Well known examples were already pointed out above: the discovery of the Cu-Sn alloys resulting in the Bronze Age or the discovery of iron and its alloys resulting in the Iron Age. However, the same applies e.g. to the discovery of the semiconductors. The discovery of the semiconductors and the modification of their electric properties by alloying (doping) opened the way to today’s electronic devices. Hence, by analogy to all of these developments, it might be expected that the opening of the way to the new kind of alloys in the form of nanoglass alloys might result in a new age, a “Glass Age”.

## Discovery of Transcription Factor RGPR-p117

by Masayoshi Yamaguchi, Member EUAS



### Short Biography

Masayoshi Yamaguchi, Ph.D., IOM, FAOE, DDG, DG, is Full Professor, University of Hawaii Cancer Center, University of Hawaii at Manoa, Honolulu, USA (2021-); Adjunct Professor, University of Hawaii Cancer Center, University of Hawaii at Manoa (2019-); Visiting Professor, David Geffen School of Medicine, University of California, Los Angeles (UCLA) (2017-2019); Adjunct Professor, Emory University School of Medicine, Atlanta,, USA (2013~2016); Visiting Professor in Department of Medicine, Baylor College of Medicine, Houston, USA (2012–2013); Visiting Professor, Department of Medicine, Emory University School of Medicine, GA, USA (2007~2011); Full Professor in Graduate School of Nutritional Sciences, University of Shizuoka, Shizuoka, Japan (1993 ~ 2007); Associate Professor in Graduate School of Nutritional Sciences, University of Shizuoka, Shizuoka, Japan (1991~1993); Assistant Professor in School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan (1987~1991); Research Associate in Shizuoka College of Pharmacy, Shizuoka, Japan (1973 ~ 1986). He received a Ph.D. in Pharmaceutical Sciences from Shizuoka College of Pharmacy Shizuoka, Japan (1976). He has completed his M.S. (1973) and B.S. (1971) in Pharmaceutical Sciences, Shizuoka College of Pharmacy, Shizuoka, Japan).

**Professional membership.** Editorial Academy Member in *International Journal of Molecular Medicine* (2001-2019); Editorial Board Member in *Molecular and Cellular Biochemistry* (2010-2013); Editorial Academy Member in *International Journal of Oncology* (2015-2019); Editorial Board Member in *Current Molecular Medicine* (2019 -); Section Editor in *Current Nutraceuticals* (2019-); Editorial Board Member in *Cancers* (2020-); Editorial Board Member in *Translational Oncology* (2021-); Co-Editors in *Current Cancer Drug Targets* (2021 -), Editorial Board Member of *Nutraceuticals* (2021-).

**Membership in professional organizations.** Dr. Yamaguchi serviced with the membership in Professional Organizations, including Japan Society for Pharmaceutical Sciences (1971 – 2011), Japan Society for Biochemistry, Councilor (1973 – 2011), Endocrine Society for Japan, Councilor (1977 – 2010), International Society of Bone and Mineral (1984 – 2007), Japan Society for Pharmacology, Councilor (1987 – 2007), Japan Society for Bone and Mineral Metabolism, Councilor (1988 – 2007), Japan Society for Biomedical Research on Trace Elements, Councilor (1990 – 2011), Japan Society for Hepatocyte Research, Councilor (1995 – 2006), European Society of Calcium (1997 – 2004), Japan Society for Osteoporosis, Councilor (1999 – 2008), American Society for Cell Biology (2001 – 2007), The New York Academy of Sciences (1996 – 2012), American Society for Bone and Mineral Research (1999 – 2017), American Society for Biochemistry and Molecular

*Biology (2005 -), Member of European Union (EU) Academy of Sciences (2021 -). Advisory Board Member of The USERN (Universal Science Education and Research Network) (2021-)*

**Awards and Honors.** *Dr. Yamaguchi received many honors and awards, including Prize for Sato Memorial Foundation (1992, Japan/USA); Senji Miyata Foundation Award 2005, Japan; Japan Society for Biomedical Research on Trace Elements Award, Japan, 2007; The Lifetime Achievement Award from International Biographical Centre (IBC), Cambridge, UK (2004); The World Lifetime Achievement Award from American Biographical Institute, USA (2004); The Distinguished Service to Science Award IBC, Cambridge, UK (2007) and many others. Dr. Yamaguchi is listed in various biographies; Who's Who in the World (2005-, Marquis Who's Who, USA), Who's Who in Sciences and Engineering (2004-, Marquis Who's Who, USA), International Biographical Dictionary (2006, IBC, UK), Who's Who in America (2009-, Marquis Who's Who, USA), and Who's Who in Asia (2007-, Marquis Who's Who, USA). Notably, Dr. Yamaguchi received "The 2017 Albert Nelson Marquis Lifetime Achievement Award (Marquis Who's Who, USA) .*

## Discovery of RGPR-p117

RGPR-p117 (gene symbol; *rgpr*), which was identified as the regucalcin gene promoter region-related protein, was originally discovered as a novel transcription factor in 2001 [1-4]. The RGPR-p117 gene is consisted of 26 exons spanning approximately 4.1 kbp, and is present on human chromosome 1q25.2 [3]. RGPR-p117 conserves a leucine zipper motif [3, 4]. Thereby, RGPR-p117 was also named as the leucine zipper transcription regulator 2 (*Lztr2*) (in PubMed). Phosphorylated RGPR-p117 in the nucleus specifically binds to a nuclear factor I (NFI) consensus motif TTGGC(N)<sub>6</sub>CC that is located on the 5'-flanking region of the regucalcin gene (*rgn*) [3, 4]. Regucalcin is demonstrated to play a pivotal role as a repressor in manifold cell signaling pathways and transcriptional activity in maintaining cell homeostasis and disorder in various types of cells and tissues [5-7]. RGPR-p117 was proposed to rename as Sec16 homologues B (SEC16B) that plays a putative role as an endoplasmic reticulum export (ER) factor implicated in the transports of protein and lipid in the ER in 2007 [8, 9]. In recent years, the RGPR-p117/SEC16B gene is suggested to involve in human obesity and type 2 diabetes [10]. However, the role of RGPR-p117/SEC16B as an ER export factor implicated to lipid metabolism is poorly understood. This review introduces the role of RGPR-p117 as a novel transcription factor.

## RGPR-p117 Gene in Various Species

The RGPR-p117 gene is identified in various biological species, including human, rat, mouse, dog, cow, pig, rabbit, chicken, frog (*Xenopus*), fish (*Zebrafish*), *C. elegance*, and yeast [3, 4]. The highly homologous human genomic sequence (HTG clone RP11-6501; DDBJ/EMBL/GenBank accession number AL356279) that encodes human RGPR-p117 gene was found from the result in BLAST search of rat RGPR [3]. The structure of the human RGPR-p117 gene was predicted from the RP11-6501 sequence. We identified that human RGPR-p117 gene consisted of at least 26 exons spanning approximately 4.1 kbp [3]. The human RGPR-p117 gene is located on human chromosome 1q25.2 [3].

We succeeded in cloning RGPR-p117 in human, rat, mouse, bovine, rabbit and chicken livers, which consisted of 1060, 1058, 1051, 1052, 1045, and 929 amino acid residues with the calculated molecular mass of 117, 115, 117, 117, 114, and 103 kDa, and the estimated *pI* of 5.71, 5.70, 5.69, 5.64, 5.84, and 5.59, respectively [3, 4]. Comparison analysis

showed that the nucleotide sequences of the RGPR-p117 in mammalian species consisted of 1045-1060 amino acids which have 63.1 - 90.2% identity, and that of chicken RGPR-p117 have at least 36.4 and 43.7 % identities, respectively. The sequence analysis demonstrated that the 423 amino acids of the central protein (269-693) of human RGPR-p117 are clearly well-conserved in vertebrate species including chicken as compared to the parts of the proteins in other animals; the homology was at least 70% [3, 4]. Thus, RGPR-p117 in mammalian species was highly homologous. The central conserved region of RGPR-p117 may be functionally important in vertebrate species.

The secondary structure of human RGPR-p117 protein is predicted by the PSIPRED program [3]. The predicted structure of RGPR-p117 has 29%  $\alpha$ -helix content in the region 269-693 in amino acid sequence and the  $\alpha$ -strand is slight. The  $\alpha$ -helix content in the region 269-693 in amino acid sequence, which showed a comparatively higher homology in six vertebrates RGPR-p117, is at least 50% [3]. Phylogenetic tree constructed from aligned amino acid sequences suggests that RGPR-p117 is descended from a common ancestral gene [3, 4]. RGPR-p117 may play a crucial role in vertebrate species as a gene regulatory protein.

Using PSORT II, which is a program to predict the subcellular localization of proteins from their amino acid sequences, RGPR-p117 from six vertebrates are nuclear proteins [3, 4]. The probability of nuclear localization of RGPR-p117 is 78.3% in rat and mouse models [3, 4]. Moreover, analysis of the subcellular localization of RGPR-p117 from six vertebrates shows that the probability of nuclear localization is >52.2%, indicating a great conservation of RGPR-p117 genes through evolution.

Mammalian RGPR-p117 conserves a leucine zipper motif. PROSITE search reveals that RGPR-p117 has a leucine zipper motif [L(X)<sub>6</sub>L(X)<sub>6</sub>L(X)<sub>6</sub>L], and that its location is highly conserved among RGPR-p117 in rats, mice, and humans [3, 4]. Therefore, RGPR-p117 is also called as the leucine zipper transcription regulator 2 (*Lztr2*). The leucine side chains extending from one  $\alpha$  helix may interact with those from a similar  $\alpha$  helix of a second polypeptide, facilitating dimerization. The structure formed by cooperation of these two regions may form a short coiled-coil [3, 4]. The leucine zipper pattern is present in many gene regulatory proteins such as CCATT-box and enhancer binding protein (C/EBP), nuclear oncogene *fos* and *jun*, cAMP response element (CRE) binding proteins (CREB, CRE-BP1, ATFs), *c-myc*, *L-myc* and *N-myc* oncogenes, and octamer-binding transcription factor 2 (Oct-2/OTF-2) [3, 4].

## Regulation of RGPR-p117 Gene Expression

The nucleotide sequence of the *Eco* RV-*Hind* III fragment of rat RGPR-p117, with cDNA used as the probe, shows homologies of 95% and 90% for the corresponding region of mouse and human RGPR-p117 cDNAs, respectively [11]. The rabbit RGPR-p117 gene is more related to the rodent gene than that of humans. The frog or fish RGPR-p117 gene is only detected slightly using both “Zoo blot” and Northern blot analyses. RGPR-p117 gene has less homology in frog or fish. Clear bands are detected in *C. elegans* and yeast genomic DNA using the rat cDNA probe [11].

The expression of RGPR-p117 mRNA is found to be different in various species [11]. Rat and mouse RGPR-p117 mRNAs are clearly detected in the liver, while RGPR-p117 mRNA levels in rabbits are comparatively low. Human liver RGPR-p117 mRNA is detected as a faint band. The expression of RGPR-p117 mRNA in the liver was found to be stimulated by calcium administration in rats *in vivo* [11]. The effect of calcium administration that stimulates RGPR-p117 mRNA expression in rat liver was seen at

within 5 hours of the administration [11]. This suggests that the liver RGPR-p117 mRNA expression is partly mediated through calcium administration-induced secondary factor(s) rather than a direct effect of calcium on the gene expression. Of note, the expression of RGPR-p117 mRNA in the cloned rat hepatoma cells (H4-II-E) was found to be stimulated by various intracellular signaling factors [11], supporting the view that the H4-II-E cells may be a good tool to explore a possible regulatory mechanism of RGPR-p117 mRNA expression. Moreover, the expression of RGPR-p117 mRNA in the cloned rat hepatoma H4-II-E cells was found to be stimulated by the addition of serum (10% fetal bovine serum) in culture medium, suggesting that the gene expression is regulated through signaling factors in the serum [11]. Interestingly, RGPR-p117 mRNA expression was increased by the presence of dibutyl cAMP, phorbol 12-myristate 13-acetate (PMA), insulin or 17 $\beta$ -estradiol in culture medium without serum addition [11]. This result demonstrates that RGPR-p117 mRNA expression is regulated via various signaling factors. RGPR-p117 protein may have an important role in signaling system of cells.

In addition, RGPR-p117 mRNA was shown to be expressed in the kidney, heart, spleen, and brain of rats [12]. The role of RGPR-p117 in these tissues is unknown at present. However, RGPR-p117 has a leucine zipper motif, which is conserved among RGPR-p117 in human, rat, and mouse. RGPR-p117 may have a role as transcriptional factor for gene expression in many tissues and cells. The expression of RGPR-p117 mRNA in the liver of rats under physiologic conditions is also demonstrated [12]. The expression of RGPR-p117 mRNA was not changed with increasing age (1- 50 weeks old) and was not altered with fasting or refeeding [12]. The expression of RGPR-p117 mRNA in the liver of rats may be stable with physiologic change.

### **Nuclear Localization of RGPR-p117**

The computer analysis of subcellular localization of RGPR-p117 from six vertebrates shows a higher probability of nuclear localization especially in rats and mice (78.3%) [3]. The nuclear localization of RGPR-p117 was elucidated using the cloned normal rat kidney proximal tubular epithelial NRK52E cells *in vitro* [13]. RGPR-p117 mRNA was expressed in the kidney cortex, and the protein was also found in NRK52E cells [13]. The expression of RGPR-p117 mRNA in NRK52E cells was stimulated by culturing with parathyroid hormone (PTH) which affects kidney proximal tubular epithelial cells [13]. 1, 25-dihydroxyvitamin D<sub>3</sub> [1, 25-(OH)<sub>2</sub>D<sub>3</sub>] or aldosterone, which targets kidney cells, did not have an effect on RGPR-p117 mRNA expression in NRK52E cells [13]. Of various factors involved in intracellular signaling, PMA was found to have a potential stimulatory effect on RGPR-p117 mRNA expression in NRK52E cells [13]. PMA can activate protein kinase C [14], and the action of PTH is mediated via the activation of protein kinase C [15]. RGPR-p117 mRNA expression in the cells may be stimulated by PTH, which regulates the reabsorption of calcium ion (Ca<sup>2+</sup>) in the kidney proximal tubular cells [16], suggesting a role of RGPR-p117 in the kidney.

RGPR-p117 was found to localize in the cytoplasm and nucleus of NRK52E cells with immunocytochemical analysis using transient HA-RGPR-p117/phCMV2-transfected cells [13]. This localization was also enhanced by culturing with FBS, PTH, or PMA. Moreover, we generated the transfectants that HA-RGPR-p117 is stably overexpressed in NRK52E cells [13]. Results of Western blot analysis demonstrated that HA-RGPR-p117 was markedly localized in the cytoplasm and nucleus of NRK52E cells. This finding may support the view that RGPR-p117 in the cytoplasm of NRK52E cells is translocated into the nucleus.

Effect of RGPR-p117 on transcriptional activity was examined using stable HA-RGPR-p117/phCMV2-transfected NRK52E cells [17]. Overexpression of HA-RGPR-p117 stimulated regucalcin mRNA expression in NRK52E cells [17], supporting the view that RGPR-p117 plays a role as a transcription factor in regucalcin gene expression. RGPR-p117 binds to the TTGGC(N)<sub>6</sub>CC motif [1-4]. There are many genes that contain the TTGGC motif in the promoter region, including regucalcin, albumin, glucokinase,  $\alpha$ -fetoprotein, adenylate cyclase, phosphoenolpyruvate carboxy kinase and others. RGPR-p117 may regulate transcriptional activity of various genes.

### **Role of RGPR-p117 in Regucalcin Gene Expression**

We investigated whether overexpression of RGPR-p117 regulated gene expression of various proteins, which contains the TTGGC motif in the promoter region of their genes. We used stably HA-RGPR-p117/phCMV2-transfected cells [17]. Overexpression of RGPR-p117 was found to stimulate both regucalcin mRNA expression and its protein level in NRK52E cells. Albumin,  $\alpha$ -fetoprotein, glucokinase, 11 $\beta$ -hydroxysteroid dehydrogenase, phosphoenolpyruvate carboxykinase, p21 and glyceraldehyde-3-phosphate dehydrogenase mRNA contain the TTGGC motif in the promoter region in their genes. Gene expression of these proteins was not changed by overexpression of RGPR-p117 [17]. Thus, among the various genes that contain the TTGGC motif in the promoter region, regucalcin gene expression was uniquely enhanced with overexpression of RGPR-p117 [17]. TTGGC motif may be important in the enhancement of transcriptional activity in regucalcin gene expression.

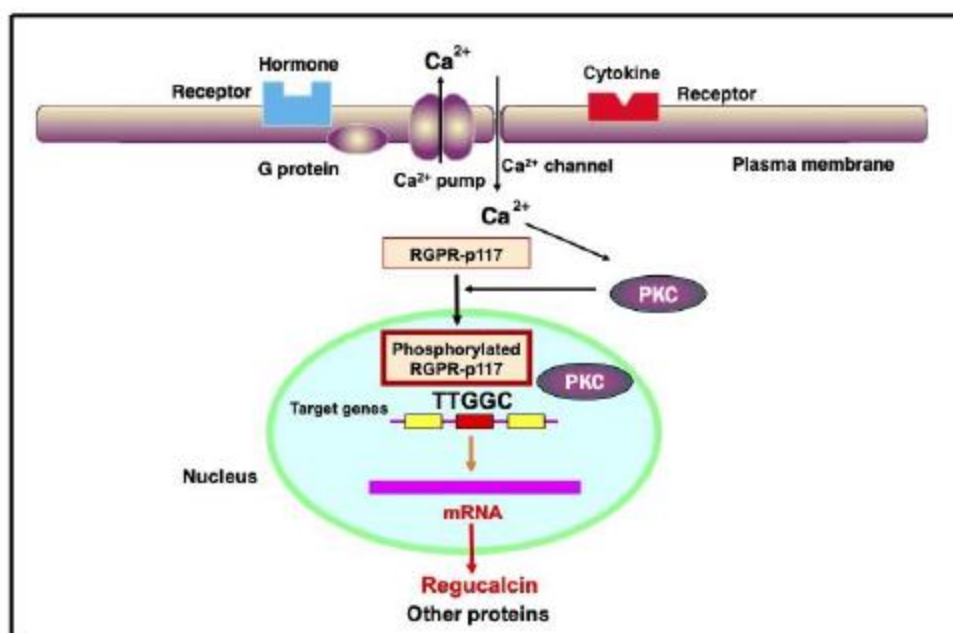
NRK52E cells were cultured in a medium without bovine serum that contains various hormones and cytokines. Regucalcin mRNA expression was not enhanced by overexpression of RGPR-p117 [17]. This result suggests that regucalcin mRNA expression in the RGPR-p117-overexpressing NRK52E cells is stimulated by hormones and cytokines [17]. Moreover, the enhancement of regucalcin mRNA expression in RGPR-p117-overexpressing NRK52E cells was blocked by the presence of staurosporine, an inhibitor of protein kinase C, [17]. This enhancement was not blocked by the presence of dibucaine, an inhibitor of Ca<sup>2+</sup>/calmodulin-dependent protein kinase, or PD98059, an inhibitor of MAP kinase [17]. Stimulatory effect of RGPR-p117 on regucalcin mRNA expression may be mainly mediated via protein kinase C-dependent signaling pathway in NRK52E cells. Of note, regucalcin mRNA expression is found to be stimulated via Ca<sup>2+</sup> signaling factors that are involved in protein kinase C in the cloned rat hepatoma H4-II-E cells [18] and cloned rat kidney proximately tubular epithelial NRK52E cells [13]. Thus, Ca<sup>2+</sup> signaling factor may be important in the mechanism by which RGPR-p117 enhances regucalcin mRNA expression.

Next, we investigated whether overexpression of RGPR-p117 could enhance the regucalcin promoter activity using the -710/+18 LUC construct (wild-type; WT) or -710/+18 LUC construct (mutant; Mut 1 - 3) with deletion of -523/-435 including TTGGC motif [20]. The regucalcin gene promoter activity was enhanced in the RGPR-p117-overexpressing NRK52E cells with the -710/+18 LUC constructs (WT) which contains TTGGC sequence [20]. This enhancement was found to be disappeared in the NRK52E cells transfected with the regucalcin promoter -710/+18 LUC construct with deletion of the -523/-435 (Mut 1) or -523/-503 sequences (Mut 2) [20]. The effect of RGPR-p117 in enhancing the promoter activity was also found in NRK52E cells which are transfected the -710/+18 LUC construct with deletion of -504/-435 sequence (Mut 3). These results demonstrate that the TTGGC motif is essential in the enhancement of the regucalcin

promoter activity in the RGPR-p117-overexpressing cells [20].

Interestingly, the regucalcin gene promoter activity in NRK52E cells (wild type) is increased by culturing with bovine serum, PTH, or PMA. Such an increase was not observed in NRK52E cells which are transfected with the regucalcin promoter -710/+18 LUC construct with the deletion of -523/-435 sequence (Mut 1) [20]. Moreover, the effects of bovine serum or PTH on the regucalcin gene promoter activity in NRK52E cells (wild-type) were inhibited by culturing with protein kinase inhibitors. These findings support the view that the regucalcin gene promoter activity with -523/-503 LUC construct was enhanced via intracellular signaling mechanism. Notably, regucalcin gene promoter activity in the NRK52E cells (wild-type) transfected the regucalcin promoter -710/+18 LUC construct with the deletion of the -523/-435 (Mut 1) or -523/-503 sequences (Mut 2) was not inhibited by culturing with dibucaine, an inhibitor of  $Ca^{2+}$ /calmodulin-dependent protein kinase; staurosporine, an inhibitor of protein kinase C; PD 98059, an inhibitor of mitogen activating protein (MAP) kinase; wortmannin, an inhibitor of  $PI_3$  kinase, or genistein, an inhibitor of protein tyrosine kinase [20]. Meanwhile, regucalcin gene promoter activity in the RGPRp117-overexpressing NRK52E cells transfected with the -710/+18 LUC construct (wild-type) was found to decrease in culture with their inhibitors [21]. Thus, the effect of RGPR-p117 in enhancing the regucalcin promoter activity may be clearly mediated via phosphorylation with various protein kinases, including protein kinase C.

Vanadate and okadaic acid are inhibitors of protein phosphatases [21]. The enhancement of regucalcin gene promoter activity in the RGPR-p117-overexpressing NRK52E cells was inhibited by culturing with vanadate [20]. Such an effect was not observed in the case of okadaic acid, an inhibitor of protein serine/threonine phosphatase. Thus, the participation of protein tyrosine phosphatases was also suggested in the enhancing effect of RGPR-p117 on regucalcin promoter activity.



**Fig. 1.** The role of RGPR-p117 as a transcriptional factor

The role of RGPR-p117 as a transcriptional factor was illustrated in Fig. 1 [23, Yamaguchi M]. RGPR-p117 translocates from the cytoplasm to nucleus, which is enhanced via  $\text{Ca}^{2+}$  signaling-dependent protein kinase C in NRK52E cells. RGPR-p117 in the nucleus may be phosphorylated by various protein kinases, including protein kinase C. Phosphorylated RGPR-p117 in the nucleus may bind to TTGGC motif in the promoter region of regucalcin gene, and this binding enhances regucalcin mRNA expression in the cells. Thus, RGPR-p117 plays a pivotal role as a transcriptional factor in the enhancement of regucalcin mRNA expression in the cells.

### Role of RGPR-p117 in Cell Regulation

RGPR-p117 is demonstrated to protect of apoptotic cell death in NRK52E cells *in vitro* [22]. Overexpression of RGPR-p117 protected apoptotic cell death induced by culturing with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), lipopolysaccharide (LPS) or Bay K 8644 in NRK52E cells [22]. Mechanically, overexpression of RGPR-p117 decreased the mRNA levels of Fas-associating death domain protein (FADD), caspase-8, caspase-9, or caspase-3 that are implicated in the promotion of apoptotic cell death in NRK52E cells [22]. RGPR-p117 may protect apoptosis by suppressing the gene expression of various proteins implicated in the promotion of apoptosis [22]. Importantly, the TTGGC motif, which is found in the regucalcin gene promoter region, is found in the promoter region of the genes of caspase-3, caspase-8 or FADD as analyzed using the Databases. RGPR-p117, which binds to the TTGGC motif in the promoter region of these genes, may repress the gene expressions of caspase-3, caspase-8 or FADD in the nucleus of NRK52E cells. This further supports the view that RGPR-p117 plays a crucial role as a transcriptional factor in gene expression of many proteins involved in the regulation of various types of cells and tissues.

### Prospect

RGPR-p117 was originally discovered as a novel protein that binds to a nuclear factor I consensus motif TTGGC(N)<sub>6</sub>CC in the promoter region of the regucalcin gene in 2001 [1-4]. RGPR-p117, which possesses leucine zipper motif, plays a crucial role as a transcriptional factor in the expression of various target genes, including regucalcin gene [17]. Moreover, RGPR-p117 distributes to the plasma membranes, mitochondria and endoplasmic reticulum (ER) in modeled kidney cells [20], suggesting a role in the regulation of cellular functions. Of note, RGPR-p117 was shown to play a protective role in apoptotic cell death evoked by various stimulatory factors *in vitro* [22]. RGPR-p117 may play a multifunctional role in cell regulation [23, 24]. Further studies are expected to elucidate the role of RGPR-p117 in cell regulation.

### References

1. Miasawa H, Yamaguchi M (2000) Involvement of hepatic nuclear factor I binding motif in transcriptional regulation of  $\text{Ca}^{2+}$ -binding protein regucalcin gene. *Biochem Biophys Res Commun* 269: 270-278.
2. Misawa H, Yamaguchi M (2000) Intracellular signaling factors-enhanced hepatic nuclear protein binding to TTGGC sequence in the rat regucalcin gene promoter: involvement of protein phosphorylation. *Biochem Biophys Res Commun* 279: 275-281.
3. Misawa H, Yamaguchi M (2001) Molecular cloning and sequencing of the cDNA coding for a novel regucalcin gene promoter region-related protein in rat, mouse and human liver. *Int J Mol Med* 8: 513-520.
4. Sawada N, Yamaguchi M (2005) A novel regucalcin gene promoter region-related protein: Comparison of nucleotide and amino acid sequences in vertebrate species. *Int J Mol Med* 15: 97-104.
5. Yamaguchi M (2000) Role of regucalcin in calcium signaling. *Life Sci* 66: 1769-1780.

6. Yamaguchi M (2005) Role of regucalcin in maintaining cell homeostasis and function. *Int J Mol Med* 15: 372-389.
7. Yamaguchi M (2001) Regucalcin and cell regulation: role as a suppressor in cell signaling. *Mol Cell Biochem* 223:101-137
8. Bhattacharyya D, Glick BS (2007) Two mammalian Sec16 homologues have nonredundant functions in endoplasmic reticulum (ER) export and transitional ER organization. *Mol Biol Cell* 18: 839-849.
9. Budnik A, Stephens DJ (2009) ER exit sites-Localization and control of COPII vesicle formation. *FEBS Lett* 583:3796-3803.
10. Ng MCY, Tam CHT, So WY, Ho JSK, Chan AW, Lee HM, Wang Y, Lam VKL, Chan JCN, Ma RCW (2010) Implication of genetic variants near NEGR1, SEC16B, TMEM18, ETV5/DGKG, GNPDA2, LIN7C/BDNF, MTCH2, BCDIN3D/FAIM2, SH3B1, FTO, MC4R, and KCTD15 with obesity and type 2 diabetes in 7705 Chinese. *J Clin Endocrinol Metab* 95:2418-2425.
11. Misawa H, Yamaguchi M (2002) Gene expression for a novel protein RGPR-p117 in various species: The stimulation by intracellular signaling factors. *J Cell Biochem* 87: 188-193.
12. Yamaguchi M, Misawa H, Ma ZJ (2003) Novel protein RGPR-p117: The gene expression in physiologic state and the binding activity to regucalcin gene promoter region in rat liver. *J Cell Biochem* 88: 1092-1100.
13. Sawada N, Nakagawa T, Murata T, Yamaguchi M (2005) Nuclear localization of a novel protein, RGPR-p117, in cloned normal rat kidney proximal tubular epithelial cells. *Int J Mol Med* 16: 809-814.
14. Nishizuka Y (1986) Studies and perspectives of protein kinase C. *Science* 233: 305-312.
15. Verheijen MHG, Defize LHK (1997) Parathyroid hormone activates mitogen-activated protein kinase via a cAMP-mediated pathway independent of rats. *J Biol Chem* 272: 3423-3429.
16. Agus ZS, Chiu PJ, Goldberg M (1997) Regulation of urinary calcium excretion in the rat. *Am J Physiol* 272: F545-F549.
17. Sawada N, Yamaguchi M (2005) Overexpression of RGPR-p117 enhances regucalcin gene expression in cloned normal rat kidney proximal tubular epithelial cells. *Int J Mol Med* 16: 1049-1055.
18. Yamaguchi M, Nakajima M (1999) Involvement of intracellular signaling factors in the serum-enhanced Ca<sup>2+</sup>-binding protein regucalcin mRNA expression in the cloned rat hepatoma cells (H4-II-E). *J Cell Biochem* 74: 81-89.
19. Tamaoki T, Nomoto H, Takahashi I, Kato Y, Morimoto M, Tomita E (1986) Staurosporine, a potent inhibitor of phospholipid/Ca<sup>2+</sup> dependent protein kinase. *Biochem Biophys Res Commun* 135: 397-402.
20. Sawada N, Yamaguchi M (2006) Overexpression of RGPR-p117 enhances regucalcin gene promoter activity in cloned normal rat kidney proximal tubular epithelial cells: Involvement of TTGGC motif. *J Cell Biochem* 99: 589-597.
21. Hunter T (1995) Protein kinases and phosphatases: The Yin and yang of protein phosphorylation and signaling. *Cell* 80: 225-236.
22. Tomono S, Sawada N, Yamaguchi M (2007) Overexpression of RGPR-p117 induces the decrease in protein and DNA contents in cloned normal rat kidney proximal tubular epithelial NRK52E cells. *Int J Mol Med* 20: 79-83.
23. Yamaguchi M (2009) Novel protein RGPR-p117: its role as theregucalcin gene transcription factor. *Mol Cell Biochem* 327:53-63.
24. Yamaguchi M, Murata T (2017) Involvement of regucalcin gene promoter region-related protein-117, a transcription factor, in human obesity (Review). *Biomed Rep* 6:374-378

# iCAS and iCISCF for Strongly Correlated Electrons

by Wenjian Liu, Member EUAS

## Short Biography

### Education Background:

1. Sept., 1992-July, 1995, Ph. D, Peking University, Beijing
2. Sept., 1989-July, 1992, M. Sc., Shandong University, Jinan
3. Sept., 1985-July, 1989, B. Sc., Shandong University, Jinan

### Work Experience:

1. Dec., 2018-present, Shandong University, Chair Professor, inaugural director of Qingdao Institute for Theoretical and Computational Sciences
2. Dec., 2001-Dec., 2018, Cheung Kong Professor, Peking University
3. Jan., 1998-Dec., 2001, postdoc, Ruhr-Universität Bochum, Germany
4. Sept., 1995-Dec., 1997, postdoc, Max-Planck-Institut für Physik komplexer Systeme, Germany

### Academic Distinctions:

1. Fellow of International Association of Advanced Materials (2020)
2. Vebleo fellow of molecular science (2020)
3. Fellow of Royal Society of Chemistry (2019)
4. Member of European Academy of Sciences (2019)
5. Fellow of Asia-Pacific Association of Theoretical and Computational Chemists (2017)
6. Fukui Medal of Asia-Pacific Association of Theoretical and Computational Chemists (2017)
7. Member of International Academy of Quantum Molecular Science (2014)
8. Bessel Award of the Humboldt Foundation (2007)
9. Annual Medal of International Academy of Quantum Molecular Science (2006)
10. Pople Medal of Asia-Pacific Association of Theoretical and Computational Chemists (2006)
11. Outstanding Young Scientist Award of National Natural Science Foundation (2006)
12. Cheung Kong Scholarship, State Education Ministry of China (2001)
13. QSCP (Quantum Systems in Chemistry and Physics) Promising Scientist Prize of CMOA (Centre de Mécanique Ondulatoire Appliquée), Europe, 2001

### Academic Services:

1. Co-editor of *Current Chinese Science* (2020.7-present)
2. Editorial board member of *Advances in Chemical Research* (2020.4-present)
3. Member of board of directors of International Society of Theoretical Chemical Physics (2019.7-present)
4. Associate editor, *Molecular Physics* (Taylor & Francis; 2016.6-present)
5. Advisory editorial board member, *Journal of Chemical Theory and Computation* (ACS; 2015.1-present)
6. National representative of International Society of Theoretical Chemical Physics (2013.8-2019.7)
7. Advisory editorial board member, *Molecular Physics* (Taylor & Francis; 2013.1-2016.6)
8. Advisory editorial board member, *International Journal of Quantum Chemistry* (Wiley; 2013.1-present)
9. Editorial board member, *Chemical Physics* (Elsevier; 2010.7-present)
10. Editorial board member, *Acta Physico-Chimica Sinica* (2009.10-2015.6)
11. Editorial board member, *Interdisciplinary Sciences: Computational Life Sciences* (Springer; 2009.3-present)

12. Scientific board member, Asia-Pacific Association of Theoretical and Computational Chemists (2007.6-present)
13. Editorial board member, Journal of Theoretical and Computational Chemistry (World Scientific, Singapore; 2007.3-present)

#### Specializations

*quantum electrodynamics, relativistic quantum chemistry, relativistic electronic structure theory, relativistic many-electron Hamiltonians, relativistic many-electron wave functions, relativistic time-dependent density functional theory, relativistic theories of magnetic properties, relativistic energy band theory, time-dependent density functional theory for nonadiabatic couplings between excited states, many-body theory for strongly correlated electrons, solvers for exterior/interior solutions of large eigenvalue problems*

### **Scientific Achievements**

Dr. Liu has long been working in the field of relativistic quantum chemistry, focusing mainly on methodological developments and programming. His achievements include (1) a series of relativistic many-electron Hamiltonians (eQED, Q4C, X2C, spf-X2C+soc-DKHn/BSSn/X2Cn) for electronic structure calculations of heavy elements; (2) a body-fixed four-component relativistic molecular Hamiltonian for spectroscopies involving the nuclear degrees of freedom; (3) four-component and exact two-component relativistic theories of nuclear magnetic shieldings (4C/X2C-NMR) that capture naturally the diamagnetism missed in the standard relativistic linear response theory; (4) several variants of time-dependent density functional theory (4C/X2C-TD-DFT, spin-adapted open-shell TD-DFT, linear scaling TD-DFT, NAC-TD-DFT for nonadiabatic couplings between excited states); (5) a series of novel wave function-based correlation methods (SDSPT2, SDSCI, iCI, iCIPT2, iCAS, iCISCF) for strongly correlated electrons; (6) an exact two-component relativistic energy band theory that provides absolute positions of energy bands; (7) a very efficient and robust solver, iVI (iterative vector interaction), for exterior or interior solutions of large eigenvalue problems; (8) the BDF program package for electronic structure calculations.

### **iCAS and iCISCF for Strongly Correlated Electrons**

The so-called complete active space self-consistent field (CASSCF) theory [1] is the very first step towards an accurate description of a strongly correlated system of electrons. It has widely been used because of its operational simplicity: one needs to just specify the numbers of active electrons ( $n_e$ ) and orbitals ( $n_o$ ) and then generate all possible determinants (or equivalently configuration state functions). However, CASSCF has been plagued by several factors: (1) it is by no means trivial to select which and how many orbitals as active orbitals. (2) It is often the case that some desired active orbitals run out of the CAS during the SCF iterations, thereby resulting in undesired solutions or no convergence. (3) It is particularly difficult to maintain the same CAS when scanning potential energy surfaces. (4) The size of CAS grows combinatorially with respect to  $n_o$  and  $n_e$ . To handle the first three issues, we proposed 'imposed automatic selection and localization of complete active spaces' (iCAS) [2], which proceeds as follows: 1) a set of valence atomic orbitals (VAO) is first chosen according to chemical intuition and is converted to an equivalent set of pre-LMO (localized molecular orbitals). The pre-LMOs are then taken as probe to select precisely the same number of guess orbitals for

subsequent CASSCF calculations. 2) The doubly, active, and virtual subspaces are enforced to match between adjacent iterations to make the converged CASSCF orbitals as close as possible to the guess orbitals. 3) Localized CASSCF orbitals can be generated for free. Since the VAOs (and hence pre-LMOs) do not change along the geometry, the same CAS is guaranteed for the whole geometry. In short, iCAS can be regarded as a driver of any CASSCF calculation. To handle the cost issue, we employed selected iCI (iterative configuration interaction) [3-5] as the CAS solver. The resulting near-exact CASSCF approach, iCISCF [6], can handle 60 electrons in 60 orbitals, far beyond the standard CASSCF calculations (18 electrons in 18 orbitals). Further combined with SDSPT2 [7,8], SDSCI [7] or iCIPT2 [4,5] for dynamic correlation, highly accurate results can be obtained for strongly correlated systems of electrons[9]. Relativistic effects can also be accounted for efficiently by making use of double group and time reversal symmetries [10].

## References

1. B. O. Roos, P. R. Taylor, and P. E. M. A. Sigbahn, complete active space SCF method (CASSCF) using a density matrix formulated super-CI approach. *Chem. Phys.* 48 (1980) 157–173
2. Y. Lei, B. Suo, and W. Liu, iCAS: Imposed automatic selection and localization of complete active spaces, *J. Chem. Theory Comput.* 17 (2021) 4846–4859.
3. W. Liu and M. R. Hoffmann, iCI: iterative configuration interaction toward full CI, *J. Chem. Theory Comput.* 12 (2016) 1169.
4. N. Zhang, W. Liu, and M. R. Hoffmann, Iterative configuration interaction with selection, *J. Chem. Theory Comput.* 16 (2020) 2296.
5. N. Zhang, W. Liu, and M. R. Hoffmann, Further development of iCIPT2 for strongly correlated electrons, *J. Chem. Theory Comput.* 17 (2021) 949-964.
6. Y. Guo, Y. Lei, N. Zhang, and W. Liu, iCISCF: An iterative configuration interaction-based multiconfigurational self-consistent field theory for large active spaces *J. Chem. Theory Comput.* 17 (2021) 7545-7561.
7. W. Liu and M. R. Hoffmann, SDS: the “static-dynamic-static” framework for strongly correlated electrons, *Theor. Chem. Acc.* 133 (2014) 1481.
8. Y. Lei, W. Liu, and M. R. Hoffmann, Further development of SDSPT2 for strongly correlated electrons, *Mol. Phys.* 15 (2017) 2696.
9. Y. Song, Y. Guo, Y. Lei, N. Zhang, and W. Liu, The static-dynamic-static family of methods for strongly correlated electrons: methodology and benchmarking, *Top. Current Chem.* 379 (2021) 43.
10. N. Zhang, Y. Xiao, and W. Liu, SOiCI and iCISO: Combining iterative configuration interaction with spin-orbit coupling in two ways. *Arxiv: 2201.10783.*

# Invariant Isogeometric Formulation for the Geometric Stiffness Matrix of Spatial Curved Kirchhoff Rods

by Yeong-Bin Yang, Member EUAS

## Short Biography

Honorary Dean, School of Civil Engineering, Chongqing University, Chongqing 400045, China

Dr. Yeong-Bin Yang received his Ph.D. degree from Cornell University in 1984. He is a member of Chinese Academy of Engineering, foreign member of Austrian Academy of Sciences, and member of EU Academy of Sciences. Currently, he is Honorary Dean of Civil Engineering, Chongqing University, and Professor Emeritus of National Taiwan University (NTU). Also, he is Editor-in-Chief of *International Journal of Structural Stability and Dynamics*, former President of Asian-Pacific Association of Computational Mechanics, and former Chairman of International Steering Committee of East Asia-Pacific Conference on Structural Engineering and Construction.

Previously, he was President of National Yunlin University of Science and Technology (Yuntech), Dean of NTU College of Engineering, Chairman of NTU Civil Engineering Department, and President of four societies in Taiwan: Institute of Engineering Education Taiwan (IEET), Chinese Institute of Civil and Hydraulic Engineering (CICHE), Society of Theoretical and Applied Mechanics (TAM), and Chinese Society of Structural Engineering (CSSE). He has published over 280 referred journal papers, focused on the following areas: structural nonlinear theory and analysis, vehicle-bridge interaction dynamics, train-induced wave propagation, and vehicle scanning method for bridges. In each area he has also published a monograph. He has a Google citation of 12644 times and H index of 57.

In 2021, Dr. Yang and his group have published the following papers:

1. Yang, Y.B., Li, P.L., Chen, W., Li, J., Wu, Y.T., 2.5D formulation and analysis of a half-space subjected to internal loads moving at sub- and super-critical speeds, *Soil Dyn. and Earthquake Eng.*, 2021, 142, 106550.
2. Yang, Y.B., Chen, A. He, S., Wu, Y.T., Research on nonlinear, postbuckling and elastoplastic analyses of framed structures and curved beams, *Meccanica*, 2021, 56:1587–1612.
3. Yang, Y.B., Wang, Z.L., Shi, K., Hao, X., Yang, J.P., Adaptive amplifier for a test vehicle moving over bridges: Theoretical study, *Int. J. Struct. Stab. & Dyn.*, 2021, 21(3), 2150042.
4. Jin, N., Yang, Y.B., Dimitrakopoulos, E.G., Paraskeva, T.S., Kafatygiotis, L.S., Application of short-time stochastic subspace identification to estimate bridge frequencies from a traversing vehicle, *Eng. Struct.*, 2021, 230, 111688.
5. Yang, Y.B., Liu, Y.Z., Invariant isogeometric formulation for the geometric stiffness matrix of spatial curved Kirchhoff rods, *Comp. Meth. Appl. Eng.*, 2021, 377, 113692.
6. Yang, Y.B., Xu, H., Mo, X.Q., Wang, Z.L., Wu, Y.T., An effective procedure for extracting first few bridge frequencies from a test vehicle, *Acta Mech.*, 2021, 232, 1227–1251.

7. Yang, Y.B., Liu, S.J., Chen, W., Tan, Q., Wu, Y.T., Half-space response to trains moving along curved paths by 2.5D finite/infinite element approach, *Soil Dyn. and Earthquake Eng.*, 2021, 145, 106740.
8. Yang, Y.B., Shi, K., Wang, Z.L., Xu, H., Zhang, B., Wu, Y.T., Using a single-DOF test vehicle to simultaneously retrieve the first few frequencies and damping ratios of the bridge, *Int. J. Struct. Stab. & Dyn.*, 2021, 21(8), 2150108.
9. Xu, H., Huang, C.C., Wang, Z.L., Shi, K., Wu, Y.T., Yang, Y.B., Damped test vehicle for scanning bridge frequencies: Theory, simulation and experiment, *J. Sound & Vibr.*, 2021, 506, 116155.
10. Yang, Y.B., Wang, Z.L., Shi, K., Xu, H., Research progress on bridge indirect measurement and monitoring from moving vehicle response, *China J. Highw. Transp.*, 2021, 34(4) (in Chinese).
11. Yang, Y.B., Shi, K., Wang, Z.L., Xu, H., Wu, Y.T., Theoretical study on a dual-beam model for detection of track/bridge frequencies and track modulus by a moving vehicle, *Eng. Struct.*, 2021, 112726.
12. Yang, Y.B., Mo, X.Q., Shi, K., Wang, Z.L., Xu, H., Wu, Y.T., Contact residue for simultaneous removal of vehicle's frequency and surface roughness in scanning bridge frequencies using two connected vehicles, *Int. J. Struct. Stab. & Dyn.*, 2021, 21, 13, 2171006.
13. Yang, Y.B., Mo, X.Q., Shi, K., Wang, Z.L., Xu, H., Wu, Y.T., Scanning torsional-flexural frequencies of thin-walled box girders with rough surface from vehicles' residual contact response: theoretical study. *Thin-Walled Struct.*, 2021, 169, 108332.

Typically, the Abstract for Ref. [5] is as follows:

### **Invariant isogeometric formulation for the geometric stiffness matrix of spatial curved Kirchhoff rods**

Y.B. Yang<sup>a,b,c</sup> - Y.Z. Liu<sup>a,c</sup>

a School of Civil Engineering, Chongqing University, Chongqing 400045, China

b Department of Construction Engineering, National Yunlin University of Science and Technology, Yunlin, Taiwan, Province of China

c MOE Key Lab. of New Technology for Construction of Cities in Mountain Area, Chongqing University, China

**Abstract:** This paper presents an invariant isogeometric formulation for the geometric stiffness matrix of spatial curved Kirchhoff rods considering various end moments, i.e., the internal (member) moments and applied (conservative) moments. There are two levels of rigid-body qualification, one is on the buckling theory of the rod itself and the other on the isogeometric formulation for discretization. Both will be illustrated. Based on the updated Lagrangian formulation of three-dimensional continua, the rotational effect of end moments is naturally included in the external virtual work done by end tractions without introducing any definition of finite rotations. Both the geometric torsion and curvatures of the rod are considered closely for the centroidal axis, except with the omission of higher order terms. The geometric stiffness matrix for internal moments is consistent with that of the geometrically exact rod model with its rigid-body quality demonstrated. For structures rigorously defined for the deformed state, the geometric stiffness matrix after global assembly is always symmetric, for both the internal and external moments. By adopting the invariant isogeometric discretization following our previous work, a series of numerical

examples, including the cases of external conservative moments, angled joint and complicated spatial geometry, were solved for buckling analysis, by which the reliability of the geometric stiffness matrix derived is verified via comparison with the analytical or straight beam solutions.

**Keywords:** Buckling analysis; Curved rod; Geometric stiffness matrix; Invariance; Isogeometric analysis; Spatial Kirchhoff rod

The Abstract for Ref. [8] is:

### **Using a Single-DOF Test Vehicle to Simultaneously Retrieve the First Few Frequencies and Damping Ratios of the Bridge**

Y. B. Yang\*, K. Shi\*,<sup>‡</sup>, Z. L. Wang\*, H. Xu\*, B. Zhang\*,<sup>†</sup> and Y. T. Wu\*

\*School of Civil Engineering

Chongqing University, Chongqing, P. R. China

<sup>†</sup>CMCU Engineering Co., Ltd., Chongqing, P. R. China

<sup>‡</sup>shikang@cqu.edu.cn

**Abstract:** Bridge damping ratios are extracted via the skillful use of the single-degree-of-freedom (DOF) test vehicle for the first time in this paper. Central to the simultaneous retrieval of the first few frequencies and damping ratios from the contact (point) response of the bridge is the use of the variational mode decomposition (VMD) and random-decrement technique (RDT). Closed-form solutions are newly derived for the vehicle and contact responses of the damped bridge and validated later numerically. Using the proposed method, one calculates first the mono-component from the contact response by the VMD; then extracts the free-decay response for each mode by the RDT; and finally identifies the frequency and damping ratio by the Hilbert transform. The parametric study confirms that: (1) the contact response outperforms vehicle's response in retrieving bridge frequencies and damping ratios; (2) the first few frequencies can be identified with robustness for reasonable levels of road roughness, vehicle speed, bridge damping and noise; (1) good result is obtained for the first damping ratio, in spite of the traditional uncertainty existing with damping; and (2) ongoing traffic can enhance the proposed method for bridge identification.

**Keywords:** Bridge; damping; frequency; random-decrement technique (RDT); variational mode decomposition (VMD); vehicle scanning method (VSM).

# Upper Limit of Aerodynamic Forces for Inelastic Wind Design

by Thomas Kang, Member EUAS

## Short Biography

*Dr. Thomas Kang is a Professor of structural engineering in the Department of Architecture & Architectural Engineering and the Director for Engineering Education Innovation Center & GECE (Global Education Center for Engineers) at Seoul National University (SNU), Korea, and has served as a part of the Vice-Deans' group of the College of Engineering at SNU since 2017. Before that, he was an Assistant Professor in the School of Civil Engineering and Environmental Science at the University of Oklahoma, Norman, OK, USA. He has held various affiliated positions in the U.S. and Japan, including Adjunct Professor at the University of Illinois at Urbana-Champaign, Adjunct Professor at the University of Oklahoma, and Lecturer at UCLA, the University of Hawaii at Manoa, the University of Tokyo and the University of Cape Town. Prof. Kang received his PhD from UCLA, his MS from Michigan State University, and his BS from Seoul National University.*

*Prof. Kang is a Fellow of Post-Tensioning Institute (PTI) and a Fellow of American Concrete Institute (ACI), as well as a member of National Academy of Engineering of Korea and EU Academy of Sciences. Prof. Kang received the Kenneth B. Bondy Award for Most Meritorious Technical Paper as Lead Author from PTI in 2012, and the Wason Medal for Most Meritorious Paper as Lead Author from ACI in 2009. He regularly teaches the course of Post-Tensioned Concrete Structures at the University of Illinois at Urbana-Champaign every other summer (both on campus and online) and at the University of Hawaii at Manoa every fall and the University of Cape Town every other fall (real-time online lectures). Prof. Kang has served as an Editor-in-Chief for four journals: Wind and Structures, International Journal of Concrete Structures and Materials, Journal of Structural Integrity and Maintenance, and Advances in Computational Design; and as Associate Editor for PTI Journal of Post-Tensioning Institute. He is one of the founding and voting members of PTI DC-20 Committee, Building Design; and has been a voting member for a variety of technical committees, including: ACI Subcommittee 318-T, Structural Concrete Building Code – Post-Tensioned Concrete; ACI Committee 369, Seismic Repair and Rehabilitation; Joint ACI-PTI Committee 320, Post-Tensioned Concrete Building Code; Joint ACI-ASCE Committees 335, Composite and Hybrid Structures; 352 Joints and Connections in Monolithic Concrete Structures; and 423, Prestressed Concrete; and Joint ACI-ASME Committee 359, Concrete Containments for Nuclear Reactors.*

*Prof. Kang published more than 150 international journal papers (as of Dec. 2021), including over 50 in ACI Structural Journal and over 10 in PTI Journal, and more than 100 international conference proceedings. He has chaired numerous sessions/symposiums of structural engineering; delivered many plenary/keynote/invited speeches; and organized several international conferences/workshops as a Chair.*

*Additionally, Dr. Kang has done a lot of practices as a consulting engineer in Korea and the U.S. Prior to joining the academia, he had a working experience in California, USA (e.g., John A. Martin & Associates), and was a licensed Professor Engineer (PE) in California. He is currently working on the smart stressing system as a Consultant with EVEHX, a world-leading company in the area of post-tensioning headquartered in Brazil. Prof. Kang has also been working on the adoption of newer technologies such as artificial intelligence (AI) for the performance-based design in wind engineering, and holds over 20 registered patents in the U.S., Korea, Canada, China, EU (France, U.K., Italy, Spain, Switzerland, Germany), Thailand, and Australia.*

**Abstracts of Selected Recent Papers and Patent****Upper Limit of Aerodynamic Forces for Inelastic Wind Design (by H. Alinejad, S. Y. Jeong, C. Chang, and T. H.-K. Kang; *Journal of Structural Engineering*, V. 148, No. 2, Feb. 2022)**

Due to the increasing tendency to construct taller and more slender buildings, the need to address aerodynamic and induced dynamic forces (inertial forces) under both service and strength-level wind loads has become more important. Currently, application of performance-based wind design (PBWD) to reduce induced dynamic forces applied through the acceptance of inelastic deformation is permitted as an alternative design approach, in which wind load can be reduced with respect to the yield strength and ductility of the structure. However, reduced wind load smaller than aerodynamic forces may not ensure proper inelastic wind design. The results of this study indicate that to avoid huge ductility demand due to damage accumulation, the yield strength for structural systems with zero-to-modest post-yield stiffness must be larger than the aerodynamic forces. Moreover, due to uncertainty in the number of occurrences of peak aerodynamic loads applied to a structure during a wind event, it would be advisable for systems with large post-yield stiffness to consider upper limits of aerodynamic forces.

**Experimental Study on Restraining Headed Bars in Roof-Exterior Connection (by J.-W. Baek and T. H.-K. Kang; *ACI Structural Journal*, V. 118, No. 6, Nov. 2021)**

For roof-level exterior beam-column connections, the design requirement associated with side-face blowout failure for restraining headed bars can be alleviated by considering the concrete contribution. To evaluate concrete strength, investigation of the safety against side-face blowout failure of such knee-joint connections is deemed warranted. In this study, existing experimental tests for roof-exterior beam-column connections were reviewed and a cyclic loading test for a full-scale roof-exterior connection specimen was performed to examine concrete side-face blowout strength. In addition, the head-restraining bar area required in the current ACI 318 design provision and in the original ACI 349-97 design provision was evaluated. Results indicate that the head-restraining bar area required in ACI 349-97 was sufficient to prevent concrete side-face blowout failure for both Type 1 and 2 specimens. For conservative design, an explicit equation was also proposed for design of head-restraining bars in roof-level exterior connections.

**Performance-Based Wind Design of High-Rise Buildings Using Generated Time-History Wind Loads (by S. Y. Jeong, H. Alinejad, and T. H.-K. Kang; *Journal of Structural Engineering*, V. 147, No. 9, Sept. 2021)**

Performance-based wind design (PBWD) allowing inelastic behavior under extreme wind load has only been recently considered for design of high-rise buildings. Unlike performance-based seismic design, there are few guidelines and research on inelastic wind design. Time-history wind loads for PBWD rely on wind tunnel tests. However, conducting wind tunnel tests for preliminary structural concepts may not be practical due to changes in design and cost. To address these concerns, the following topics were studied: initial design using an RW factor to introduce inelastic behavior; generation of time-history wind loads from power spectral density (PSD) functions for inelastic analysis including vertical distribution and maximum directional load occurrence, and a case study for wind resistance performance evaluation of a reinforced concrete building design using an RW factor of 1, 2, and 3.

**Performance-Based Wind Design Framework Proposal for Tall Buildings (by H. Alinejad, T. H.-K. Kang, and S. Y. Jeong; *Wind and Structures*, V. 32, No. 4, Apr. 2021)**

Performance-based seismic design (PBSD) is currently used for retrofitting of older buildings and the design of new buildings. Whereas, application of performance-based design for wind load is still under development. The tendency has been in the codes to increase wind hazard based on recent recorded events. Since tall buildings are highly susceptible to wind load, necessity for developing a framework for performance-based wind design (PBWD) has intensified. Only a few guidelines such as ASCE (2019) provide information on using PBWD as an alternative for code prescriptive wind design. Though wind hazards, performance objectives, analysis techniques, and acceptance criteria are explained, no recommendations are provided for several aspects like how to select a proper level of wind hazard for each target performance criterion. This paper is an attempt to explain current design philosophy for wind and seismic loads and inherent connection between the components of PBSD for development of a framework for PBWD of tall buildings. Recognizing this connection, a framework for PBWD based on limits set for serviceability and strength is also proposed. Also, the potential for carrying out PBWD in line with ASCE 7-16 is investigated and proposed in this paper.

# Atomic Layer Deposition of TbF<sub>3</sub> Thin Films

by Markku Leskelä, Member EUAS

## Short Biography

**Markku Leskelä** (born 1950) received both M.Sc. (1974) and PhD (1980) degrees from Helsinki University of Technology. During 1979-1986 he worked at University of Oulu and Helsinki University of Technology as associate professor or acting professor, in 1986-1990 at University of Turku as professor and in 1990-2018 at University of Helsinki as professor of inorganic chemistry. He made visits abroad in 1983 (University of Utrecht), 1987-1988 (University of Florida) and in 1999 (University of Paris VI). During 2004-2009 he worked as Academy professor. Since 2019 he has worked as emeritus professor at University of Helsinki.

His research interests cover luminescent materials, catalytic activation of small molecules with metal compounds, and development of chemistry for Atomic Layer Deposition of thin films – the latter topic being dominating during last five years. He has worked as vice-director (2002-2007) and director (2012-2017) in two centers of excellence funded by Academy of Finland. He has published about 725 original and 60 review papers which have been cited more than 30 000 times (h-index 80; Web of Science). He holds more than 40 patents. He was nominated in 2004 as ISI Highly Cited Author in materials science. He has received several honors and awards: Magnus Ehrnrooth Foundation Award in Chemistry (2002), SVR I (2005), A.I. Virtanen award (2011), American Vacuum Society ALD award (2012), Honorary award of Finnish Academy of Sciences and Letters (2014), Honorary member (2014) and honorary chairman (2019) of Finnish Chemical Society, Honorary doctor (University of Tartu 2016). He is a member of four academies of sciences. He has and has had several positions of trust in universities (for example board of trustees of University of Helsinki 2010-2017), scientific societies, academies and foundations. He is at the present the president of the Finnish Academy of Technical Sciences 2019-2023.

**E. Atosuo, J. Ojala, M.J. Heikkilä, M. Mattinen, K. Mizohata, J. Räisänen, M. Leskelä & M. Ritala: Atomic Layer Deposition of TbF<sub>3</sub> Thin Films. Journal of Vacuum Science and Technology A 39 (2021) 022404 (7 pp.)**

Lanthanide fluoride thin films have gained interest as materials for various optical applications, including electroluminescent displays and mid-IR lasers. However, the number of atomic layer deposition (ALD) processes for lanthanide fluorides has remained low. In this work, we present an ALD process for TbF<sub>3</sub> using tris(2,2,6,6-tetramethyl-3,5-heptanedionato)terbium and TiF<sub>4</sub> as precursors. The films were grown at 175–350 °C. The process yields weakly crystalline films at the lowest deposition temperature, whereas strongly crystalline, orthorhombic TbF<sub>3</sub> films are obtained at higher temperatures. The films deposited at 275–350 °C are exceptionally pure, with low contents of C, O, and H,

and the content of titanium is below the detection limit (<0.1 at. %) of time-of-flight elastic recoil detection analysis (ToF-ERDA). Due to the lack of titanium impurities, the films show high transmittance down to short UV wavelengths.

**M. Napari, T.N. Huq, D.J. Meeth, M.J. Heikkilä, K.M. Niang, H. Wang, T. Iivonen, H. Wang, M. Leskelä, M. Ritala, A.J. Flewitt, R.L. Z. Hoye & J.L. MacManus-Driscoll: Role of ALD Al<sub>2</sub>O<sub>3</sub> Surface Passivation on the Performance of p-TypeCu<sub>2</sub>O Thin Film Transistors. ACS Applied Materials & Interfaces 13 (2021) 4516-4164.**

High-performance p-type oxide thin film transistors (TFTs) have great potential for many semiconductor applications. However, these devices typically suffer from low hole mobility and high off-state currents. We fabricated p-type TFTs with a phase-pure polycrystalline Cu<sub>2</sub>O semiconductor channel grown by atomic layer deposition (ALD). The TFT switching characteristics were improved by applying a thin ALD Al<sub>2</sub>O<sub>3</sub> passivation layer on the Cu<sub>2</sub>O channel, followed by vacuum annealing at 300 °C. Detailed characterization by transmission electron microscopy–energy dispersive X-ray analysis and X-ray photoelectron spectroscopy shows that the surface of Cu<sub>2</sub>O is reduced following Al<sub>2</sub>O<sub>3</sub> deposition and indicates the formation of a 1–2 nm thick CuAlO<sub>2</sub> interfacial layer. This, together with field-effect passivation caused by the high negative fixed charge of the ALD Al<sub>2</sub>O<sub>3</sub>, leads to an improvement in the TFT performance by reducing the density of deep trap states as well as by reducing the accumulation of electrons in the semiconducting layer in the device off-state.

**X. Li, M. Vehkamäki, M.J. Heikkilä, M. Mattinen, M. Kemell, M. Putkonen, M. Leskelä & M. Ritala: Atomic Layer Deposition of Insulating AlF<sub>3</sub>/Polyimide Nanolaminate Films. Coatings 11 (2021) 355(13 pp.)**

This article describes the deposition of AlF<sub>3</sub>/polyimide nanolaminate film by inorganic-organic atomic layer deposition (ALD) at 170 °C. AlCl<sub>3</sub> and TiF<sub>4</sub> were used as precursors for AlF<sub>3</sub>. Polyimide layers were deposited from PMDA (pyromellitic dianhydride, 1,2,3,5-benzenetetracarboxylic anhydride) and DAH (1,6-diaminohexane). With field-emission scanning electron microscopy (FE-SEM) and X-ray reflection (XRR) analysis, it was found that the topmost layer (nominally 10 nm in thickness) of the nanolaminate film (100 nm total thickness) changed when exposed to the atmosphere. After all, the effect on roughness was minimal. The length of a delay time between the AlF<sub>3</sub> and polyimide depositions was found to affect the sharpness of the nanolaminate structure. Electrical properties of AlF<sub>3</sub>/polyimide nanolaminate films were measured, indicating an increase in dielectric constant compared to single AlF<sub>3</sub> and a decrease in leakage current compared to polyimide films, respectively.

**O.G. Ossorio, G. Vinuesa, H. García, B. Sahelices, S. Duenas, H. Castán, M.**

**Ritala, M. Leskelä, M. Kemell & K. Kukli: Analysis of the Performance of Nb<sub>2</sub>O<sub>5</sub>-doped SiO<sub>2</sub>-based MIM Devices for Memory and Neural Computation Applications. *Solid State Electronics* 186 (2021) 108114 (4 pp.)**

Since two decades ago, research on resistive memories has continuously grown, gathering relevance through the variety of different technologies that fit into the non-volatile memories' area. In this study, we discuss the performance and electrical characteristics of RRAM cells constituted by MIM stacks with dielectric formed by Nb<sub>2</sub>O<sub>5</sub>-doped SiO<sub>2</sub>. We report experimental results that show a clear improvement in the resistive behavior of the devices and an excellent analogical control of the intermediate levels between high-resistance and low-resistance states.

**S. Ghafourisaleh, G. Popov, M. Leskelä, M. Putkonen & M. Ritala: Oxidative MLD of Conductive PEDOT Thin Films with EDOT and ReCl<sub>5</sub> as Precursors. *ACS Omega* 6 (2021) 17545-17554.**

Because of its high conductivity and intrinsic stability, poly(3,4-ethylenedioxythiophene (PEDOT) has gained great attention both in academic research and industry over the years. In this study, we used the oxidative molecular layer deposition (oMLD) technique to deposit PEDOT from 3,4-ethylenedioxythiophene (EDOT) and a new inorganic oxidizing agent, rhenium pentachloride (ReCl<sub>5</sub>). We extensively characterized the properties of the films by scanning electron microscopy, X-ray diffraction, X-ray photoelectron spectroscopy (XPS), energy-dispersive X-ray spectroscopy (EDS), Raman, and conductivity measurements. The oMLD of polymers is based on the sequential adsorption of the monomer and its oxidation-induced polymerization. However, oMLD has been scarcely used because of the challenge of finding a suitable combination of volatile, reactive, and stable organic monomers applicable at high temperatures. ReCl<sub>5</sub> showed promising properties in oMLD because it has high thermal stability and high oxidizing ability for EDOT. PEDOT films were deposited at temperatures of 125–200 °C. EDS and XPS measurements showed that the as-deposited films contained residues of rhenium and chlorine, which could be removed by rinsing the films with deionized water. The polymer films were transparent in the visible region and showed relatively high electrical conductivities within the 2–2000 S cm<sup>-1</sup> range.

**C. Zhang, M. Leskelä & M. Ritala: Self-aligned Thin-film Patterning by Area-Selective Etching of Polymers. *Coatings* 11 (2021) 1124 (13 pp.)**

Patterning of thin films with lithography techniques for making semiconductor devices has been facing increasing difficulties with feature sizes shrinking to the sub-10 nm range, and alternatives have been actively sought from area-selective thin film deposition processes. Here, an entirely new method is introduced to self-aligned thin-film patterning: area-selective gas-phase etching of polymers. The etching reactions are selective to the

materials underneath the polymers. Either O<sub>2</sub> or H<sub>2</sub> can be used as an etchant gas. After diffusing through the polymer film to the catalytic surfaces, the etchant gas molecules are dissociated into their respective atoms, which then readily react with the polymer, etching it away. On noncatalytic surfaces, the polymer film remains. For example, polyimide and poly(methyl methacrylate) (PMMA) were selectively oxidatively removed at 300 °C from Pt and Ru, while on SiO<sub>2</sub> they stayed. CeO<sub>2</sub> also showed a clear catalytic effect for the oxidative removal of PMMA. In H<sub>2</sub>, the most active surfaces catalysing the hydrogenolysis of PMMA were Cu and Ti. The area-selective etching of polyimide from Pt was followed by area-selective atomic layer deposition of iridium using the patterned polymer as a growth-inhibiting layer on SiO<sub>2</sub>, eventually resulting in dual side-by-side self-aligned formation of metal-on-metal and insulator (polymer)-on-insulator. This demonstrates that when innovatively combined with area-selective thin film deposition and, for example, lift-off patterning processes, self-aligned etching processes will open entirely new possibilities for the fabrication of the most advanced and challenging semiconductor devices.

**M. Mattinen, T. Hatanpää, K. Mizohata, J. Räisänen, M. Leskelä & M. Ritala: Highly Conductive and Stable Co<sub>9</sub>S<sub>8</sub> Thin Films by Atomic Layer Deposition: From Process Development and Film Characterization to Selective and Epitaxial Growth. Dalton Transactions 50 (2021) 13264-13275.**

Co<sub>9</sub>S<sub>8</sub> is an interesting sulfide material with metallic conductivity that has shown promise for various energy applications. Herein, we report a new atomic layer deposition process producing crystalline, pure, and highly conductive Co<sub>9</sub>S<sub>8</sub> thin films using CoCl<sub>2</sub>(TMEDA) (TMEDA = N,N,N',N'-tetramethylethylenediamine) and H<sub>2</sub>S as precursors at 180–300 °C. The lowest resistivity of 80 μΩ cm, best uniformity, and highest growth rate are achieved at 275 °C. Area-selective deposition is enabled by inherent substrate-dependency of film nucleation. We show that a continuous and conductive Co<sub>9</sub>S<sub>8</sub> film can be prepared on oxide-covered silicon without any growth on Si–H. Besides silicon, Co<sub>9</sub>S<sub>8</sub> films can be grown on a variety of substrates. The first example of an epitaxial Co<sub>9</sub>S<sub>8</sub> film is shown using a GaN substrate. The Co<sub>9</sub>S<sub>8</sub> films are stable up to 750 °C in N<sub>2</sub>, 400 °C in forming gas, and 225 °C in O<sub>2</sub> atmosphere. The reported ALD process offers a scalable and cost-effective route to high-quality Co<sub>9</sub>S<sub>8</sub> films, which are of interest for applications ranging from electrocatalysis and rechargeable batteries to metal barrier and liner layers in microelectronics and beyond.

**M. Mattinen, M. Leskelä & M. Ritala: Atomic Layer Deposition of 2D Metal Dichalcogenides for Electronics, Catalysis, Energy Storage, and Beyond. Advanced Materials Interfaces 8 (2021) 2001677 (47 pp.)**

2D transition metal dichalcogenides (TMDCs) are among the most exciting materials of today. Their layered crystal structures result in unique and useful electronic, optical, catalytic, and quantum properties. To realize the technological potential of TMDCs,

methods depositing uniform films of controlled thickness at low temperatures in a highly controllable, scalable, and repeatable manner are needed. Atomic layer deposition (ALD) is a chemical gas-phase thin film deposition method capable of meeting these challenges. In this review, the applications evaluated for ALD TMDCs are systematically examined, including electronics and optoelectronics, electrocatalysis and photocatalysis, energy storage, lubrication, plasmonics, solar cells, and photonics. This review focuses on understanding the interplay between ALD precursors and deposition conditions, the resulting film characteristics such as thickness, crystallinity, and morphology, and ultimately device performance. Through rational choice of precursors and conditions, ALD is observed to exhibit potential to meet the varying requirements of widely different applications. Beyond the current state of ALD TMDCs, the future prospects, opportunities, and challenges in different applications are discussed. The authors hope that the review aids in bringing together experts in the fields of ALD, TMDCs, and various applications to eventually realize industrial applications of ALD TMDCs.

## **Cross-feeding between Intestinal Pathobionts promotes their Overgrowth during Undernutrition**

**by B. Brett Finlay, Member EUAS**



### Short Biography

Dr. B. Brett Finlay is a Professor in the Michael Smith Laboratories, and the Departments of Biochemistry and Molecular Biology, and Microbiology and Immunology at the University of British Columbia. He obtained a B.Sc. (Honors) in Biochemistry at the University of Alberta, where he also did his Ph.D. (1986) in Biochemistry under Dr. William Paranchych, studying F-like plasmid conjugation. His post-doctoral studies were performed with Dr. Stanley Falkow at the Department of Medical Microbiology and Immunology at Stanford University School of Medicine, where he studied Salmonella invasion into host cells. In 1989, he joined UBC as an Assistant Professor in the Biotechnology Laboratory. Dr. Finlay's research interests are focussed on host-microbe interactions, at the molecular level. By combining cell biology with microbiology, he has been at the forefront of the field called Cellular Microbiology, making several fundamental discoveries in this area, and publishing over 525 papers (h index=140). His laboratory studies several pathogenic bacteria, including Salmonella and pathogenic E. coli, and more recently microbiota. He is well recognized internationally for his work, and has won several prestigious awards including the E.W.R. Steacie Prize, the CSM Fisher Scientific Award, CSM Roche Award, a MRC Scientist, five Howard Hughes International Research Scholar Awards, a CIHR Distinguished Investigator, BC Biotech Innovation Award, the Michael Smith Health Research Prize, the IDSA Squibb award, the Jacob Biely Prize, the prestigious Canadian Killam Health Sciences Prize, the Flavelle Medal of the Royal Society, the Queen Elizabeth II Diamond Jubilee Medal, the Prix Galien, is a Fellow of the Royal Society of Canada and the Canadian Academy of Health Sciences, is a Member of the German National Academy of Sciences, the European Union Academy of Sciences, the American Academy of Microbiology, Chair d'État, Collège de France and is the UBC Peter Wall Distinguished Professor. He is an Officer of the Order of Canada and Order of British Columbia, and inducted into the Canadian Medical Hall of Fame. He is a cofounder of Inimex Pharmaceuticals, Inc. and Microbiome Insights, scientific cofounder of Vedanta Pharmaceuticals and CommenSe, Director of the SARS Accelerated Vaccine Initiative, and Founding Director and Senior Fellow of CIFAR's Microbes and Humans. He is also the co-author of the books *Let Them Eat Dirt* and *The Whole Body Microbiome*.

### **Cross-feeding between intestinal pathobionts promotes their overgrowth during undernutrition**

Huus KE, Hoang TT, Creus-Cuadros, Vogt SL, Knuff-Janzen K, Cirstea M, Sansonetti PJ,

Vonaesch P, Finlay BB

### Abstract

Child malnutrition (undernutrition) is associated with dysbiosis of the intestinal microbiota, including overabundance of *Enterobacteriaceae* members, and with an inflammatory intestinal disease called environmental enteric dysfunction (EED). Specific communities of human-derived *Bacteroidales* spp. and *Escherichia coli* have been shown to induce EED features in undernourished mice, dependent on the combined presence of both taxonomic groups and on a low-protein diet. Here, we show that EED-inducing *Bacteroidales* spp. and *E. coli* are capable of mutually beneficial cross-feeding, resulting in synergistic growth of a mixed community *in vitro*. Growth synergy is nutrient-dependent and requires host mucin in the presence of a protein-deficient, carbohydrate-rich environment. Under these conditions, *Bacteroidales* spp. liberate sugars to benefit *E. coli* and *E. coli* improves the bioavailability of iron for *Bacteroidales* spp., leading to outgrowth of both *B. fragilis* and of *E. coli*. Analysis of fecal microbiota datasets from low- and middle-income countries reveals that the abundance of *Bacteroides* and *Escherichia* are strongly correlated in undernourished children but not in normally nourished children, consistent with a diet-dependent growth synergy in the human gut. Together these data suggest that cross-feeding among pathobionts can promote their overgrowth in the undernourished intestine.

### Quantitative proteomic screen identifies Annexin A2 as a host target for *Salmonella* pathogenicity island-2 effectors SopD2 and PipB2

Katelyn Knuff-Janzen, James McCoy, Kyung-Mee Moon, Leonard J. Foster, B. Brett Finlay

### Abstract

Intracellular pathogens need to establish an intracellular replicative niche to promote survival and replication within the hostile environment inside the host cell. *Salmonella enterica* serovar Typhimurium (*S. Typhimurium*) initiates formation of the unique *Salmonella*-containing vacuole and an extensive network of *Salmonella*-induced tubules in order to survive and thrive within host cells. At least six effectors secreted by the type III secretion system encoded within *Salmonella* pathogenicity island-2 (SPI-2), namely SifA, SopD2, PipB2, SteA, SseJ, and SseF, purportedly manipulate host cell intracellular trafficking and establish the intracellular replicative niche for *S. Typhimurium*. The phenotypes of these effectors are both subtle and complex, complicating elucidation of the mechanism underpinning host cell manipulation by *S. Typhimurium*.

In this work we use stable isotope labeling of amino acids in cell culture (SILAC) and a *S. Typhimurium* mutant that secretes increased amounts of effectors to identify cognate effector binding partners during infection. Using this method, we identified the host protein annexin A2 as a binding partner for both SopD2 and PipB2 and were able to confirm its binding to SopD2 by reciprocal pull down. This indicates that SopD2 and PipB2 likely both interact with annexin A2 through protein-protein interactions to establish the *S. Typhimurium* intracellular replicative niche. This demonstrates the value of studying effector interactions using proteomic techniques and natural effector delivery during

infection rather than transfection.

### **Composition and associations of the infant gut fungal microbiota with environmental factors and childhood allergic outcomes**

Rozlyn C.T. Boutin, Hind Sbihi, Ryan J. McLaughlin, Aria S. Hahn, Kishori M. Konwar, Rachelle S. Loo, Darlene Dai, Charisse Petersen, Fiona S.L. Brinkman, Geoffrey L. Winsor, Malcolm R. Sears, Theo J. Moraes, Allan B. Becker, Meghan B. Azad, Piush J. Mandhane, Padmaja Subbarao, Stuart E. Turvey and B. Brett Finlay

#### **Abstract**

Although often neglected in gut microbiota studies, recent evidence suggests imbalanced, or dysbiotic, gut mycobiota (fungal microbiota) communities in infancy co-associate with states of bacterial dysbiosis linked to inflammatory diseases such as asthma. In the present study, we: i) characterized the infant gut mycobiota at three months and one year of age in 343 infants from the CHILD Cohort Study; ii) defined associations amongst gut mycobiota community composition and environmental factors for the development of inhalant allergic sensitization (atopy) at age five years; and iii) built a predictive model for inhalant atopy status at age five years using these data. We show that in a Canadian population, fungal communities shift dramatically in composition over the first year of life. Early life environmental factors known to affect gut bacterial communities were associated with differences in gut fungal community alpha diversity, beta diversity, and/or the relative abundance of specific fungal taxa. Moreover, these metrics differed among healthy infants and those who developed inhalant atopy at age five years. Using a rationally selected set of early life environmental factors in combination with fungal community composition at one year of age, we developed a machine learning logistic regression model that predicted inhalant atopy status at five years of age with 81% accuracy. Together these data suggest an important role for the infant gut mycobiota in early life immune development, and indicate that early life behavioural or therapeutic interventions have the potential to modify infant gut fungal communities with implications for an infant's long-term health.

### **Gut microbes shape microglia and cognitive function during malnutrition**

K.C. Bauer, E. M. York, M. S. Cirstea, C. N. Petersen, K. E. Huus, E. M. Brown, R. Berdun, A. H. Lee, T. Bozorgmehr, Z. Krekhno, N. Radisavljevic, J. Han, S. E. Woodward, R. E. W. Hancock, V. Ayala, B. A. MacVicar, and B. B. Finlay

#### **Abstract**

Fecal-oral contamination promotes the persistence of early-life malnutrition. Lasting consequences of malnutrition include cognitive impairment, but the underlying pathology and influence of gut microbes remain largely unknown. Here we utilize an established model of malnutrition involving iterative exposure to fecal commensals (MAL-BG). We report that MAL-BG mice display altered behavioural and cognitive deficits—poor spatial

memory and learning plasticity—putatively linked to aberrant microglia, non-neuronal CNS cells that regulate neuroimmune responses and brain plasticity. Chronic fecal-oral exposures affect the morphology and transcriptional profile of MAL-BG microglia, promoting phagocytic features. Unexpectedly, these microglial alterations occurred independently from neuroinflammation or blood-brain barrier (BBB) disruption, well-studied gut-brain pathways. Metabolomic profiling of the MAL-BG cortex revealed elevated fatty acid lipoxidation, while MAL-BG microbial exposures elicit oxidative stress within *ex vivo* gut tissue. We propose that fecal microbes modulate microglia through systemic oxidative stress, exacerbating neurologic consequences of malnutrition. This work provides valued insight into systemic pathology of malnutrition identifying lipoxidative stress as a potential pathway of gut microbiota-brain interactions.

# A Human-Centered, Health-data-driven Ecosystem

by Pascal Verdonck, Member EUAS



## Short Biography

Pascal Verdonck was born in 1963 in Gent, Belgium. He graduated as Master of Science Civil Engineering in 1986 from the Ghent University. He obtained his diplomas in Master of Business Administration (1989), Master of Science Biomedical Engineering (1993) and PhD (1993) from the Ghent University. He is married with Nathalie Van Peteghem and has two children Simon (°1993) and Charlotte (°1995)

### **Professional activities and relevant experience**

- Assistant (1987-1992), post-doctoral researcher (1993-1995), assistant professor (1996-2002) and full professor "cardiovascular mechanics and biofluid dynamics "at the Ghent University since 2002
- Visiting professor University of Groningen, Groningen , the Netherlands (2001-2007)
- Visiting professor Imperial College, London (2004-2008)
- Tenured professor at the International Faculty for Artificial Organs, Bologna, Italy
- Head of the Department of Civil Engineering of the Ghent University (1998-2006)
- Ombudsman of the Faculty of Applied Sciences of the Ghent University (1993-2003)
- Chairman bachelor programs of the Faculty of Applied Sciences of the Ghent University (2003-2006)
- Scientific secretary of the Institute Biomedical Technology of the Ghent University (1997-2006)
- Visiting professor University Paris XII (1997)
- Visiting Socrates professor TU Kosice (2000-2004) and Julich (2000-2010)
- Member Board European Society for Engineering and Medicine (2002-2004)
- Member of the Board of Trustees of the International Society for Artificial Organs ISAO (1999-2003)
- Member of the Board of the ESAO European Society for Artificial Organs (2004-2011)
- Vice Chairman of the alumni of the engineers studied at the Ghent University (1995-2003)
- Vice Président "Société Biomécanique" (2000-2002) , Président "Société Biomécanique" (2002-2004)
- Member evaluation commission Belgium for " medical devices" and "active medical devices " (2001-2007)
- Chairman of the Board of Directors start-up "FluidDA" (2007- 2009)
- Member of the Board of Directors AZ Maria Middelaes hospital Gent (2000-2007)
- CEO of private hospital "AZ Maria Middelaes" Gent (2007- 2015) ([www.azmmsj.be](http://www.azmmsj.be))
- Senior full professor "MedicalTechnology" Ghent University (2007-) ([www.ugent.be](http://www.ugent.be))
- Visiting Professor "biomedical engineering" Catholic University Leuven, Belgium (2009-)
- Chairman National Committee Biomedical Engineering (2001-) ([www.ncbme.be](http://www.ncbme.be))
- Member of the Royal Flemish Academy of Belgium for sciences and arts (2009-)
- Member of the Board of Directors OLV Aalst Hospital (2012-) ([www.olvz.be](http://www.olvz.be))
- Member of the Board of Directors Acerta (2013) ([www.acerta.be](http://www.acerta.be))
- Vice chairman of the Board of Directors Artevelde University College Gent (2005-) ([www.arteveldehs.be](http://www.arteveldehs.be))
- Vice Chairman Belgian Association Hospital Directors (2013-) ([www.ziekenhuisdirecteurs.be](http://www.ziekenhuisdirecteurs.be))
- Member of the Board of Directors Voka Flanders chamber of commerce and industry (2015-)
- Chairman of the Board of Directors AZ Maria Middelaes hospital Gent (2015-) ([www.azmmsj.be](http://www.azmmsj.be))
- CEO MedTech Flanders ([www.medtech.flanders.be](http://www.medtech.flanders.be)) (2015-)

- *Member of the board of Directors Sint-Vincentius Deinze Hospital ((2017-)*
- *Member of the board of Directors Jan Yperman Hospital Ieper ((2019-)*
- *Board Member European Association Hospital Managers (2019-) (www.eahm.eu.org)*

#### **Actual academic courses**

- *“Biosystems”, 2<sup>nd</sup> year bachelor engineering sciences @Ghent University*
- *“BioFluid Mechanics”, 2nd year master biomedical engineering sciences @Leuven University*
- *“Leadership in Healthcare”, 2nd year master biomedical engineering sciences @Ghent University*
- *“Engineering project in a hospital”, 2nd year master biomedical engineering sciences @Ghent University*

#### **Research and innovation**

*His scientific research has spanned numerous fields of biomedical engineering sciences : experimental and numerical modeling of the cardiovascular system, haemodynamics and transport phenomena in extracorporeal circulation and artificial organs, computational biodesign and medical device technology. He is an active advisor for the MedTech Start & Scale-up Ecosystem.*

## **Abstract**

Value-based, connected and integrated healthcare are gaining momentum in the healthcare landscape. Industry 4.0 is transforming healthcare into a data-driven sector. Data and innovation are the foundation of future value-driven healthcare ecosystems. But how will human actors keep playing a lifelong role in this? Healthcare continuums are being created as healthcare goes beyond the reach of the traditional diagnosis and treatment, towards prevention and early detection. Health institutions are facing a new generation of 'health-conscious' consumers and 'technology-minded and -adapted' healthcare professionals. In order to accelerate innovation within healthcare institutions, it must be powered by the personal health data of an individual, independent of its location, age and health status and generated by the use of technology. Based upon these concepts and shifts, this paper describes a human-centered, health data-driven ecosystem build upon the interaction of technology, human actors and different environments. That is also influenced by international guidelines and regulations and ethical norms and values. Implementation of this health data-driven ecosystem will create future value at any time, place and location within healthcare.

## **Background**

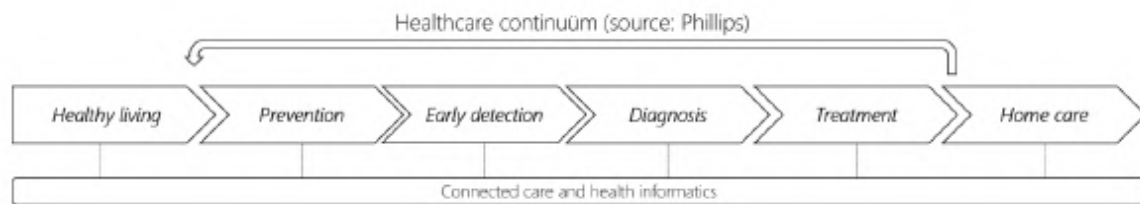
### *Value-based, integrated and connected healthcare*

Porter defined value-based healthcare as achieving the highest possible outcome and experience, that matters for the patient, for the lowest possible cost over the whole trajectory of care. K. Colorafi concluded from her review about connected care systems that being connected to care actors can only benefit your health. Therefore the willingness to use connected technology in different environments to reach patients between appointments and to ensure appropriate family support mechanisms is in place in established healthcare ecosystems. The World health organization defines integrated health services as: "health services managed and delivered in a way that they ensure people are receiving a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services, at the different levels and sites of care within the healthcare system, and according to their needs, throughout their whole life."

*Shifts in healthcare*

Novel healthcare ecosystems cover three international concepts of healthcare that gained importance over the last few years: value-based, connected and integrated healthcare. This shift becomes possible due to the rise of industry 4.0 and the parallel contextual shift towards social responsibility that is changing healthcare into health and quality into value.

As Aceto et al. mentioned, it is especially in the healthcare domain where internet of things, cloud and fog computing, and big data are transforming health into eHealth and its whole ecosystem towards a Healthcare 4.0. The rise of this Healthcare 4.0 is stimulated by evolution of the continuum thinking in healthcare. Starting from the concept of the healthcare continuum introduced by Philips, we extended this version by adding an extra phase (early detection). With this adaptation six phases can be defined starting from the phases where an individual is not yet considered as a patient (healthy living and prevention) to the phases of detecting and defining a possible pathology (early detection and diagnosis) and the phases of actual care taking (treatment and home care). In the continuum, the completion of the last phase of home care leads to the start of a new healthy living phase. This adapted healthcare continuum is visualized in figure 1. As can be seen individuals will continuously proceed from one phase to another, coming into contact with different actors and environments.



**Fig. 1** The Phillips healthcare continuum, added with the extra phase of early detection.

As Michael West showed, compassionate care is a necessary condition for successful innovation implementation. value-based care can only be implemented with multidisciplinary and integrated practice units and must be substantiated with shared and analyzed data. To unravel the road map for healthcare leaders and managers to organize their healthcare institution around their patients powered by health data, we developed a human-centered, health data-driven ecosystem. It respects a delicate equilibrium between the individual at each life stage, the technological and scientific breakthroughs and the environmental shift towards sustainability and social responsibility.

## Vision

The vision behind the human-centered, health data-driven ecosystem is oriented towards innovation to create future value. To accelerate innovation within healthcare organizations, there must be a continuous generation and inflow of an individual's data regardless the location, age and healthcare status. To be able to achieve this independency, an integrated view on how the individual, in its own environment, is using technology is required.

*Human aspect*

In every life phase (from birth till death), care is an important aspect of our daily lives. We take care, we ask for care, we receive care, we need care, etc. At every moment in our life one can jump on and off this 'care highway'. However we do often stop at the first gas station, meaning the care taking mostly stops when one's cured and recovered. Traditionally, in hospitals persons were treated as 'patients'. They were often bound to a general practitioner who referred them to a specialist or hospital to whom he/she had certain affiliations. This has shifted over the years. Hospitals nowadays do not only cover sick patients but also engage in preventive or improvement services like for example medical screenings, diet advice, sport coaching, etc. The traditional patient profile is shifting to a client- and a consumer profile. This results in clients actively participating in their own healthcare, choosing the doctors and hospitals based on the services they provide, the type of experience the patient receives and the value he/she gets. Therefore data is and will be more and more stored in different physical locations and by different actors in the healthcare ecosystem. This will only increase the need for an integrated ecosystem. Current healthcare ecosystems are not able to tackle these conceptual shifts, complexity and size of the current technological challenges in healthcare. Technology seems to have surpassed the current way of organizing healthcare and has given individuals the opportunity to arrange their healthcare around themselves.

*Environment*

Trends elsewhere have majorly contributed to a shift of the healthcare environment. Negative trends are the growing geriatric population (17% by 2050) and an increase of chronic diseases. Positive trends are new technology and innovation that can reduce the amount of hospitalizations, costs and increase patients satisfaction. Also the Covid-19 pandemic had changed the healthcare landscape drastically. Hospital managers were confronted with a more delicate balance between the inflow of patients versus the available hospital capacity (ICU beds, materials, human resources, etc.). It also initiated a change in patient behavior, including 'no shows', 'shopping-principle' and an increase in patient empowerment. Furthermore it also accelerated the need for remote and continuous data and put more emphasis on social responsibility. Shifting the in-house treatment to a more transmurals follow-up based healthcare.

*Technology*

Real tsunamis of healthcare and medical technologies are crashing into the healthcare ecosystem. Hospital managers and doctors almost need to create full-time vacancies to keep track of all these new innovations. The domains of mHealth, eHealth, data science, telemedicine, digital therapy, A.I. and virtual or augmented reality can be considered as the most promising and booming aspects of current healthcare. All of these aspects can be situated within the more total package of data science. Applied on healthcare, all of these aspects will be necessary to connect clients/patients to smart environments, wearables, smart cameras, ambient technology, connected equipment, actors, etc. in order to achieve a connected care network.

**The human-centered, health data-driven ecosystem**

The created ecosystem (see figure 2) consist out of four different data domains, the data located in each of them are generated by four different questions. Table 1 indicates the different domains and accompanied questions.

**Table 1: The four different data domains and there accompanied questions.**

<b>Question</b>	<b>Data domain</b>
Who am I?	Financial and administrative
Where am I?	Logistical and facilitary
Am I healthy?	Medical data
How do I recover?	Paramedical data

These four basic questions will continuously generate data. The quadrants are built upon the triagle of human, technology and environment. The technology will be present on the borders between two quadrants, meaning a quadrant will be influenced by two types of technology. As technology is positioned on the transition from one quadrant to another, the data generated within each of the quadrants will be transferred by this technology. The environment is placed at the top, because it has the largest impact on the changing ecosystem. For this reason the human aspect is placed the closest to the center as it influence will be lower. In the following subsections, this ecosystem will be constructed quadrant by quadrant.

#### *Who am I?*

Asking 'Who am I?' will generate administrative and financial data: individual personal info, historical medical data, medication schemes, social passports, etc. In short, it will uniquely identify who the individual is. Identification of who an individual is and the possibility to access this information by any actor within any environment will be key to deliver value-based, integrated and connected care. On the border between administrative and financial data (first quadrant) en the following quadrant the identification tools can be found.

#### *Where am I?*

The second question 'Where am I?' will generate the logistics and facility services data of the individual. This data can be related to the centered individual but also to the internal stakeholders. It will describe where a healthcare client resides and from which environment the client originates. This can range from hospitals to residential or juvenile care center, from home environment to larger communities and even hotels or public places. Caretakers and care organizations need to take into account the individual's location in order to provide personal and tailored care. On the border of the second quadrant and the third quadrant, the technology of prevention and healthy lifestyle applications or wearables can be found. Useful data can already be acquired from the individual and his/her environment before they actually become a patient.

#### *Am I healthy?*

The third questions is 'Am I healthy?'. This is where the key role of clinicians and other healthcare professionals is positioned. In this quadrant the medical data is located. It finds

its origin in exams (policlinic or technical), lab tests, imaging modalities, etc. The content of the data is related to medicotechnical, ambulant, chronic and hot floor treatments. The diagnosis and treatment phase of the client is located here. Human actors involved in this quadrant can be located in many different environments ranging from hospital to a general practitioners office or a rehabilitation center, etc. The connection between the medical data quadrant and the fourth quadrant will be defined by medical devices and applications. The devices and apps can be categorized in two categories, those used in the internal care taking (located within the third quadrant) and those used for transmural monitoring (located on the border between second and third quadrant). The latter will especially be used once an individual has been treated and he/she returns back to his or her own environment. Here the recovery and postcare are initiated. Devices or apps will capture, analyze and transmit the data from the individual in recovery and postcare to the internal stakeholder of the third quadrant so that feedback and close follow-up can be provided.

*How do I recover?*

The fourth question 'How do I recover?' and the fourth quadrant is where the paramedical data is being localized. Here all paramedic actors involved to the recovery and post-care of a client are localized. These will generate data that needs to be accessible for all internal stakeholders to close the loop of the ecosystem and lead to a full recovery. The goal of this feedback loop is to closely connect as many hospital caretakers with the follow-up of the recovery or post-hospital care of their patients. On the border between the fourth and first quadrant, new or recurrent pathologies are lurking. When they occur, the whole trajectory will restart (as we are in a continuous loop).

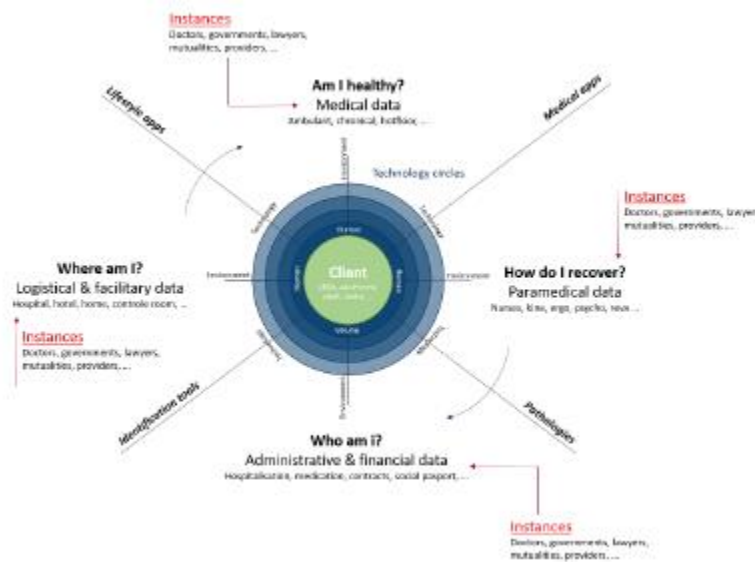


Fig. 2 Representation of the complete human-centered

**Conclusion**

A novel human-centered, health data-driven ecosystem is presented, describing a connected, integrated-care based, four quadrant model that captures all the aspects of

healthcare. This model forms the basis for the road map towards a patient, client or civilian centered healthcare with a continuously spinning ecosystem of administrative, financial, logistical, facility, medical and paramedical data around it, driven by internal and propelled by external stakeholders. The model describes the close symbiosis and permanent interaction of individuals, technological innovations and environmental shifts. Implementation of the model will create future value with a sustainable, technological, digital, qualitative, open, affordable solution in a seamless, safe, legal, efficient and effective care ecosystem and this for each individual, at anytime and anywhere.

**Acknowledgements**

This article was written together with Ir. Guylian Stevens.

# Digitization Drives Energy Efficiency

by Zhangxing (John) Chen, Member EUAS



## Short Biography

### **Education:**

- *Post-doctoral Fellow, University of Minnesota, USA, 1991-1993.*
- *Ph.D., Purdue University, USA, 1986-1991.*
- *M.S., Xi'an Jiaotong University, China, 1983-1985.*
- *B.S., Nanchang University (formerly, University of Jiangxi), China, 1979-1983.*

### **Academic Experience:**

- *Killam Professor in Engineering, University of Calgary, Canada, 2020-present.*
- *Founding Director, Global Initiative for Research in Unconventional Oil and Gas: The Beijing Site, University of Calgary, 2014-2020.*
- *Founding Director, Foundation CMG/Frank-Sarah Meyer Collaboration Centre, University of Calgary, Canada, 2012-present.*
- *Director, Schlumberger iCentre for Simulation and Visualization, University of Calgary, Canada, 2009-present.*
- *AITF (Alberta Innovates - Technology Futures, formerly iCORE) Industrial Research Chair in Reservoir Modeling, University of Calgary, Canada, 2009-present.*
- *NSERC (Natural Sciences and Engineering Research Council of Canada) / AIEES (Alberta Innovates: Energy and Environment Solutions) / Energi Simulation Industrial Research Chair in Reservoir Simulation, University of Calgary, Canada, 2008-present.*
- *Professor, Department of Chemical and Petroleum Engineering, University of Calgary, Canada, 2007-present.*
- *Professor, Southern Methodist University, Dallas, USA, 2001-2006.*
- *Associate Professor, Southern Methodist University, Dallas, USA, 1998-2001.*
- *Assistant Professor, Southern Methodist University, Dallas, USA, 1995-1998.*
- *Visiting Assistant Professor, Texas A&M University, College Station, Texas, USA, 1993-1995.*

### **Selected Academic Awards and Honors:**

- *Member, European Union Academy of Sciences (EUAS), Elected in 2022.*
- *Academician, Chinese Academy of Engineering, China, 2021.*
- *Fellow, The Parex Resources Innovation Fellowship Program, Canada, 2021.*
- *The Friendship Medal of The People's Republic of China, China, 2020.*
- *Fellow, Royal Society of Canada, Canada, 2020.*
- *Killam Professor Award, Killam Trust, Canada, 2020.*
- *Fellow, Engineering Institute of Canada, Canada, 2019.*
- *Fellow, Canadian Academy of Engineering, Canada, 2017.*
- *The Fields-CAIMS Industrial Mathematics Prize, Canadian Applied and Industrial Mathematics Society and the Fields Institute, Canada, 2017.*
- *Peak Scholar in Entrepreneurship, Innovation, and Knowledge Engagement, University of Calgary, Calgary, Canada, 2017.*

- NSERC's Synergy Award for Innovation, NSERC (Natural Sciences and Engineering Research Council of Canada), Canada, 2016.
- The President's Award, CWLS (Canadian Well Logging Society), Canada, 2015.
- NSERC (Natural Sciences and Engineering Research Council of Canada) Discovery Grant Accelerator Supplement Award, Canada, 2013.
- Outstanding Leadership in Alberta Technology Award (ASTech Award), Canada, 2012.
- IBM Faculty Award, IBM T.J. Watson Research Center, USA, 2012.
- Gerald J. Ford Research Award, The Gerald J. Ford Foundation, Dallas, USA, 2004.

### Highlighted Scholarship Contributions

Dr. Chen has authored/co-authored 600 journal articles in the most prominent journals in his research field, including *NanoToday*, *Applied Catalyst B: Environmental*, *Small Methods*, *Angewandte Chemie*, *Chemical Engineering Journal*, *Advances in Colloid and Interface Science*, and *PNAS*, and 400 conference proceedings articles. His publications have received 18,600 citations and an *H*-index of 60 (Google Scholar), ranking the most in reservoir simulation in the world in the past ten years. He has authored/co-authored 13 monographs and edited eight books with such publishers as Springer-Verlag and Elsevier. These monographs and books have been downloaded online over 600,000 times, and five of them have been used as undergraduate and graduate textbooks worldwide. Particularly, his text *Computational Methods for Multiphase Flows in Porous Media*, published in 2006 and cited 1,460 times, has been adopted extensively by many universities globally. Dr. Chen owns 30 patents and have delivered 440 invited/keynote/plenary talks. These articles, books, patents, and public talks have profoundly helped to advance many disciplines including Chemical, Petroleum, Energy, and Environmental Engineering, and engaged the public in the people and ideas shaping the future of the world. His research funding of over \$100M from private and public sponsors over the past 30 years has made him one of the highest-funded engineers and scientists worldwide.

Dr. Chen has made exceptional contributions to the fields of Chemical and Petroleum Engineering, Energy and Environmental Engineering, and particularly to the field of multidisciplinary studies in fluid flow and its applications to various industries. His original and novel research is of a fundamental and applied nature, reflected in his most significant contributions to research and practical applications in the globe. On the fundamental side, his ground-breaking research on multiphase flows in porous media has advanced the fields of *reservoir modeling*, *computational methods*, and *fluid flow in nanopores*. His comprehensive scientific models of fluid flows in porous media were the world's first in reservoir modeling in that they represent reservoirs from pore- to kilometer-scale, reflecting their real physics in terms of mass, heat, composition, kinetics and geomechanics. His models have significantly increased the energy industry's confidence in reservoir simulations, been foundational in the development of reservoir simulators, and set the stage for new directions in energy and environmental stewardship. They were foundational for the top energy company Shell's simulators to design their oil recovery projects and the world's largest independent reservoir simulator developer Computer Modelling Group (CMG) Ltd. to develop their commercial reservoir simulation software.

Dr. Chen is an international expert on the development of computational methods for fluid flows. This extraordinary research has made numerous wide-ranging contributions in

multiple areas, such as solid and fluid mechanics, groundwater modeling, and environment science. He invented a set of mixed and nonconforming finite element spaces and a suite of control volume methods for flow simulations. These novel methods generate highly accurate attributes (pressure, temperature, composition, and velocity) in complex reservoirs, and provide a three-fold improvement in accuracy and a two-fold increase in stability over earlier methods. Recognizing these outstanding achievements, the global computational method community named these spaces after me: the Chen-Douglas (his former PhD supervisor) mixed finite element spaces and Chen-rotated spaces.

Dr. Chen's fundamental research on fluid flow has significantly advanced the development and application of fluid flow mechanisms in nanopores. Unlike traditional fluid flow in porous media, fluid flow in nanopores involves more challenging mechanisms including continuum flow, slip flow, surface diffusion and adsorption. His breakthrough was a new theory that captures all these important mechanisms while detailing the variable contribution of each in nanofluid flow. This theory has significantly impacted gas production and separation, carbon capture and storage, carbon nanotube membranes, catalysis, and methane storage in vehicles. While collaborating with top service and energy companies such as CMG Ltd., ExxonMobil, and China National Petroleum Corporation (CNPC), Dr. Chen has applied this theory to studies of numerous gas production wells worldwide and guided production in nanoporous petroleum reservoirs.

Dr. Chen has developed innovative fast linear solvers and parallel simulators for reservoirs. These novel solvers and simulators have shown a thousand-fold improvement in speed over previous commercial reservoir software while their accuracy is preserved. They allow for simulations of giga-cell (billion) sizes and play a key role in increasing oil and gas recovery through a better resolution of vast disparate seismic, geologic, and field data. Moreover, they have assisted history matching methods and increased the effectiveness of field optimization. In turn, these advancements have significantly improved the modeling and simulation processes of enhanced oil recovery for conventional (light oil and natural gas), unconventional oil and gas (tight and shale oil and gas, and coalbed methane), heavy oil, and oil sands reservoirs and led to tremendous capital and operational savings for the energy industry.

In 2008, Dr. Chen created Canada's most prominent reservoir simulation consortium, which includes 15 companies who have collectively provided \$15M over 15 years to address urgent knowledge gaps in the energy industry. This consortium led to 11 patents and the spin-off technology company, ISUT Ltd. One of the most notable technologies arising from his research was the world's first patented nano-catalytic in situ upgrading technology; field tests demonstrated a 25% reduction in greenhouse gas emissions for each barrel of oil produced compared to other recovery technologies. The energy industry recognized this technology as one of 15 most promising oil and gas exploration and production technologies in the next ten years (Economics & Technology Research Institute, CNPC, 2018). Moreover, it was recognized as one of 10 most advanced technologies in petroleum in the world in 2020. In addition, Dr. Chen was a Co-founder and the Chairman of the oil production company RockEast Corp., a global leader in the provision of innovative cost-effective and environmentally friendly recovery processes for extraction and refinement of petroleum resources. These companies and initiatives have contributed to the diversification and growth of Canada's economy and quality of life through the technologies and jobs created. His multifaceted career and ability to transfer

technology have garnered national recognitions, including the NSERC Synergy Award for Innovation (2017) and two Alberta Science & Technology Foundation (ASTech) Awards (2010, 2012). The University of Calgary named Dr. Chen a Peak Scholar (2017) for his exceptional record of innovation, collaboration, knowledge engagement and technology transfer.

### Training of Highly Qualified Personnel (HQP)

Since joining the University of Calgary in 2007, Dr. Chen has successfully established a creative world-class research program, the largest multidisciplinary program on campus, composed of about 70 research associates, post-doctoral fellows (PDFs) and graduate students annually. He has trained 48 PDFs and graduated 77 PhD and 76 MSc students in his career; remarkably, 45 of these trainees are now faculty members at first-class universities in 16 countries, such as University of Calgary, University of Wyoming, University of Aberdeen, and China University of Petroleum. Some PhD students have won the most prestigious scholarships during their study including the NSERC Vanier Scholarship, Killam Laureate, and Alberta Innovates Scholarship. Furthermore, some students have won prestigious awards in their organizations, such as the SPE Reservoir Description and Dynamics Awards, Distinguished Achievement Awards, and Outstanding Young Professional Awards. Dr. Chen has twice been recognized as a top Graduate Educator in the Schulich School of Engineering, University of Calgary (2011-12 and 2014-15). Institutional equity, diversity, and inclusion (EDI) principles have been explicitly implemented in his HQP training; over 70% of his HQP are women and underrepresented people.

### Representative Books

- J. Li, X. Lin and Z. Chen, *Finite Volume Methods for the Incompressible Navier-Stokes Equations*, Springer Briefs in Mathematical Methods, Volume 11219, Springer-Verlag, 2022.
- X. Dong, H. Liu and Z. Chen, *Hybrid Enhanced Oil Recovery Processes for Heavy Oil Reservoirs*, Developments in Petroleum Science, Volume 73, Elsevier, 2021.
- L. Zhang, Z. Chen and Y. Zhao, *Well Production Performance Analysis in Shale Gas Reservoirs*. Developments in Petroleum Science, Volume 66, Elsevier, 2019.
- Z. Chen, *Reservoir Simulation: Mathematical Techniques in Oil Recovery*. CBMS-NSF Regional Conference Series in Applied Mathematics, Vol. 77, SIAM, Philadelphia, 2007.
- Z. Chen, G. Huan, and Y. Ma, *Computational Methods for Multiphase Flows in Porous Media*. *Computational Science and Engineering Series*, Vol. 2, SIAM, Philadelphia, 2006.
- Z. Chen, *Finite Element Methods and Their Applications*. Springer-Verlag, 2005.

### Representative Articles

1. Z. Pu, T. Liu, G. Zhang, X. Liu, M.A. Gauthier, Z. Chen and S. Sun, Nanostructured metal borides for energy-related electrocatalysis: Recent progress, challenges, perspectives, *Small Methods*, Volume 5, 2021, 1-21.
2. T. Zhang, Y. Li, Y. Chen, X. Feng, X. Zhu, Z. Chen, Y. Liu, Y. Zheng, J. Cai, H. Song and S. Sun, Review on Space Energy, *Applied Energy*, Volume 292, June 2021, Article 116896.
3. H. Zhao, P. Liu, X. Wu, A. Wang, D. Zheng, S. Wang, Z. Chen, S. Larter, Y. Li, B.-L. Su, M. G. Kibria, and J. Hu, Plasmon enhanced glucose photoreforming for arabinose and gas guel co-

- production over 3DOM TiO<sub>2</sub>-Au, *Applied Catalyst B: Environmental*, Volume 291, 2021, Article 120055.
4. Z. Pu, G. Zhang, A. Hassanpour, D. Zheng, S. Wang, Shijun Liao, Z. Chen and S. Sun, Regenerative fuel cells: Recent progress, challenges, perspectives and their applications for space energy system, *Applied Energy*, Volume 283, 2021, Article 116376.
  5. L. Zhang, X. Yu, Z. Chen, J. Li, G. Hui, M. Yang and R. Yu, Capillary dynamics of confined water in nanopores: The impact of precursor films, *Chemical Engineering Journal*, Volume 409, 2021, Article 128113.
  6. X. Yu, J. Li, Z. Chen, K. Wu, L. Zhang, S. Sheng, G. Hui and M. Yang, Determination of CH<sub>4</sub>, C<sub>2</sub>H<sub>6</sub> and CO<sub>2</sub> adsorption in shale kerogens coupling sorption-induced swelling, *Chemical Engineering Journal*, Volume 410, 2021, Article 127690.
  7. J. Bai, Y. Kang, M. Chen, Z. Chen, L. You, X. Li and G. Chen, Impact of surface chemistry and pore structure on water vapor adsorption behavior in gas shale, *Chemical Engineering Journal*, Volume 402, 2020, Article 126238.
  8. Y. Liu, J. Hou, Z. Chen, H. Su, E. Zhao, Y. Bai and N. Lu, A novel natural gas hydrate recovery approach by delivering geothermal energy through duffflooding, *Energy Conversion and Management*, Volume 209, 2020, Article 112623.
  9. M. Ahmadi, Q. Hou, Y. Wang and Z. Chen, Interfacial and molecular interactions between fractions of heavy oil and surfactants in porous media: Comprehensive review, *Advances in Colloid and Interface Science*, Volume 283, 2020, Article 102242.
  10. W. Wang, X. Pang, Z. Chen, D. Chen, X. Ma, W. Zhu, T. Zheng, K. Wu, K. Zhang and K. Ma, Methods for determination of effective sandstone reservoirs and evaluation of hydrocarbon enrichment in a petroliferous basin, *Applied Energy*, Volume 261, 2020, 114457.
  11. M. Ahmadi and Z. Chen, Challenges and future of chemical assisted heavy oil recovery processes, *Advances in Colloid and Interface Science*, Vol 275, 2020, Article 102081.
  12. L. Jiang, Z. Chen and S.M. Farouq Ali, Feasibility of carbon dioxide storage in post-burn underground coal gasification cavities, *Applied Energy*, Volume 252, 2019, Article 113479.
  13. W. Tian, K. Wu, Z. Chen, Y. Gao, Z. Chen, Y. Liu, Y. Hou, Q. Zhu and J. Li, Dynamic wetting of a solid-liquid-liquid system by molecular kinetic theory, *Journal of Colloid and Interface and Science*, 579 (2020), 470-478.
  14. J. Li, Z. Chen, K. Wu, B. Yang, W. Wang, K. Wang and J. Luo, Effects of energetic heterogeneity on supercritical methane adsorption in shale, *Applied Energy*, 251 (2019), 1-17.
  15. X. Dong, H. Liu, Z. Chen, K. Wu, N. Lu and Q. Zhang, Enhanced oil recovery techniques for heavy oil and oilsands reservoirs after steam injection, *Applied Energy*, 239 (2019), 1190-1211.
  16. K. Wu, Z. Chen, J. Li, J. Xu, K. Wang, S. Wang, X. Dong, Z. Zhu, Y. Peng, X. Jia and X. Li, Manipulating nanoconfined water fluidity by temperature stimulation, *Angewandte Chemie*, 57 (2018), 8432-8437.
  17. J. Li, Z. Chen, K. Wu, K. Wang, J. Luo, D. Feng, S. Qu and X. Li, A multi-site model to determine supercritical methane adsorption in energetically heterogeneous shales, *Chemical Engineering Journal*, 349 (2018), 438-455.
  18. M. Chen, Y. Kang, T. Zhang, L. You, X. Li, Z. Chen, K. Wu and B. Yang, Methane diffusion in shales with multiple pore sizes at supercritical conditions, *Chemical Engineering Journal*, 334 (2018), 1455-1465.
  19. H. Zeng, K. Wu, X. Cui and Z. Chen, A practical model of wettability effect on nanoconfined water flow: Insights and perspectives, *Nano Today*, 16 (2017), 7-8.
  20. K. Wu, Z. Chen, J. Li, X. Li, J. Xu and X. Dong, Wettability effect on nanoconfined water flow, *Proceedings of the National Academy of Sciences*, 114 (2017), 3358-3363.

# Adaptive Platform Trials to Transform Amyotrophic Lateral Sclerosis Therapy Development

by Merit Cudkowicz, Member EUAS

## Short Biography

### **Education**

1985	B.S. Tau Beta Pi	Chemical Engineering	Massachusetts Institute of Technology
1990	M.D.	Medicine	Harvard Medical School, Harvard-Massachusetts Institute of Technology. Division of Health, Science and Technology
1996	MSc.	Clinical Epidemiology	Harvard School of Public Health

### **Post Graduate Courses**

2010-2012	Physician Leadership Development Certificate Program	Massachusetts General Hospital
2013	Program for Chiefs of Clinical Service	Harvard School of Public Health

### **Faculty Academic Appointments**

07/95-6/97	Instructor	Neurology	Harvard Medical School
07/97-6/02	Assistant Professor	Neurology	Harvard Medical School
07/02-12/09	Associate Professor	Neurology	Harvard Medical School
01/10-	Julianne Dorn Professor	Neurology	Harvard Medical School

### **Appointments at Hospitals/Affiliated Institutions**

#### *Past*

06/96-4/03	Assistant in Neurology	Neurology	Massachusetts General Hospital
1996-1997	Research Affiliate	General Clinical Research Center	Massachusetts Institute of Technology
2004-2006	Staff Researcher	Neurology	Edith Norse Bedford Veteran's Administration Hospital
1998-04/03-4/11	Associate in Neurology	Neurology	Brigham and Women's Hospital
	Associate in Neurology	Neurology	Massachusetts General Hospital

#### *Current*

04/11-	Neurologist	Neurology	Massachusetts General Hospital
05/12-	Chief, Neurology Service	Neurology	Massachusetts General Hospital
06/20-	Clinical Consultant	Neurology	Brigham and Women's Hospital

### **Major Administrative Leadership Positions**

#### *Local*

1997-2019	Co-Director, Neurology Clinical Research Institute (NCRI)	Massachusetts General Hospital
1998-2008	Co-Director, Amyotrophic Lateral Sclerosis (ALS) Center	Massachusetts General Hospital
2001-2006	Co-Director, Harvard Center for Neurodegeneration and Repair, Core A Neurologic Clinical Trial Service	Harvard Medical School
2007-2008	Co-Director, Muscular Dystrophy Association Neuromuscular clinic	Massachusetts General Hospital
2008-2016	Director, Muscular Dystrophy Association Neuromuscular clinic	Massachusetts General Hospital

2009-2016	<i>Division Co-Chief, Neuromuscular</i>	<i>Massachusetts General Hospital</i>
2012-2013	<i>Chair, Research Strategy Team Clinical Research</i>	<i>Massachusetts General Hospital</i>
2018-2021	<i>Vice Chair, ECOR</i>	<i>Massachusetts General Hospital</i>
2018	<i>Director, Healey Center for ALS</i>	<i>Massachusetts General Hospital</i>
2019	<i>Chair, Search Committee for Psychiatry</i>	<i>Massachusetts General Hospital</i>
2021-2024	<i>Chair, ECOR</i>	<i>Massachusetts General Hospital</i>
2021	<i>Chair, Search Committee for Director Division Clinical Research</i>	<i>Massachusetts General Hospital</i>
<i>National</i>		
2007-2012	<i>Co-Director, Clinical Trial Methods Course</i>	<i>National Institute of Neurological Disorders and Stroke</i>
2007	<i>Co-Chair and Organizer, Banbury ALS Drug Discovery Workshop</i>	<i>ALS Association</i>
2007	<i>Course Director, Selecting Experimental treatments for clinical testing</i>	<i>Huntington's Disease Study Group</i>
2009	<i>Chair and Organizer, ALS Phase 2 Design Workshop</i>	<i>Muscular Dystrophy Association</i>
2014-2021	<i>Chief Medical Officer</i>	<i>ALS Finding A Cure Foundation</i>
<i>International</i>		
2008	<i>Co-Director, Biomarkers in ALS Symposium, Birmingham, UK</i>	<i>World Federation of Neurology</i>
2010	<i>Chair, International Motor Neuron Disease Symposium</i>	<i>Motor Neuron Disease Association</i>
2011	<i>Session Chair, ICSCN Workshop</i>	<i>Motor Neuron Disease Association</i>

## **Adaptive Platform Trials to Transform Amyotrophic Lateral Sclerosis Therapy Development**

Sabrina Paganoni, James D. Berry, Melanie Quintana, Eric Macklin, Benjamin R. Saville, Michelle A. Detry, Marianne Chase, Alexander V. Sherman, Hong Yu, Kristin Drake, Jinsy Andrews, Jeremy Shefner, Lori B. Chibnik, Matteo Vestrucci, **Merit E. Cudkowicz**

ANN NEUROL 2022;00:1–11

### **Abstract**

Current therapeutic development in amyotrophic lateral sclerosis (ALS) relies on individual randomized clinical trials to test a specific investigational product in a single patient population. This approach has intrinsic limitations, including cost, time, and lack of flexibility. Adaptive platform trials represent a novel approach to investigate several interventions for a single disease in a continuous manner. Already in use in oncology, this approach is now being employed more often in neurology. Here, we describe a newly launched platform trial for ALS. The Healey ALS Platform Trial is testing multiple investigational products concurrently in people with ALS, with the goal of rapidly identifying novel treatments, biomarkers, and trial endpoints.

## **A Randomized Placebo-Controlled Phase 3 Study of Mesenchymal stem cells induced to secrete high levels of neurotrophic factors in myotrophic Lateral Sclerosis**

**Merit E. Cudkowicz**, Stacy R. Lindborg, Namita A. Goyal, Robert G. Miller, Matthew J. Burford, James D. Berry, Katharine A. Nicholson, Tahseen Mozaffar, Jonathan S. Katz, Liberty J. Jenkins, Robert H. Baloh, Richard A. Lewis, Nathan P. Staff, Margaret A. Owegi, Donald A. Berry, Yael Gothelf, Yossef S. Levy, Revital Aricha, Ralph Z. Kern, Anthony J. Windebank, Robert H. Brown Jr.

### **Abstract**

#### **Introduction/Aims**

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative illness with great unmet patient need. We aimed to evaluate whether mesenchymal stem cells induced to secrete high levels of neurotrophic factors (MSC-NTF), a novel autologous cell-therapy capable of targeting multiple pathways, could safely slow ALS disease progression.

#### **Methods**

This randomized, double-blind, placebo-controlled study enrolled ALS participants meeting revised El Escorial criteria, revised ALS Functional Rating Scale (ALSFRS-R)  $\geq 25$  (screening) and  $\geq 3$  ALSFRS-R points decline prior to randomization. Participants received three treatments of MSC-NTF or placebo intrathecally. The primary endpoint evaluated efficacy of MSC-NTF through a responder analysis and safety. A change in disease progression post-treatment of  $\geq 1.25$  points/month defines a clinical response. A pre-specified analysis leveraged baseline ALSFRS-R of 35 as a subgroup threshold.

#### **Results**

Overall, MSC-NTF treatment was well tolerated; there were no safety concerns. Thirty-three percent of MSC-NTF and 28% of placebo participants met clinical response criteria at 28 weeks (OR=1.33,  $p=0.45$ ), thus the primary endpoint was not met. A pre-specified analysis of participants with baseline ALSFRS-R  $\geq 35$  ( $n=58$ ) showed a clinical response rate at 28 weeks of 35% MSC-NTF and 16% placebo (OR=2.6,  $p=0.29$ ). Significant improvements in CSF biomarkers of neuroinflammation, neurodegeneration, and neurotrophic factor support were observed with MSC-NTF, with placebo unchanged.

#### **Discussion**

The study did not reach statistical significance on the primary endpoint. However, a pre-specified subgroup suggests that MSC-NTF participants with less severe disease may have retained more function compared to Placebo. Given the unmet patient need, the results of this trial warrant further investigation.

## **Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis**

S. Paganoni, E.A. Macklin, S. Hendrix, J.D. Berry, M.A. Elliott, S. Maiser, C. Karam, J.B. Caress, M.A. Owegi, A. Quick, J. Wymer, S.A. Goutman, D. Heitzman, T. Heiman-Patterson, C.E. Jackson, C. Quinn, J.D. Rothstein, E.J. Kasarskis, J. Katz, L.

Jenkins, S. Ladha, T.M. Miller, S.N. Scelsa, T.H. Vu, C.N. Fournier, J.D. Glass, K.M. Johnson, A. Swenson, N.A. Goyal, G.L. Pattee, P.L. Andres, S. Babu, M. Chase, D. Dagostino, S.P. Dickson, N. Ellison, M. Hall, K. Hendrix, G. Kittle, M. McGovern, J. Ostrow, L. Pothier, R. Randall, J.M. Shefner, A.V. Sherman, E. Tustison, P. Vigneswaran, J. Walker, H. Yu, J. Chan, J. Wittes, J. Cohen, J. Klee, K. Leslie, R.E. Tanzi, W. Gilbert, P.D. Yeramian, D. Schoenfeld, and **M.E. Cudkowicz**

N Engl J Med 2020;383:919-30.

## **Abstract**

### **BACKGROUND**

Sodium phenylbutyrate and taurursodiol have been found to reduce neuronal death in experimental models. The efficacy and safety of a combination of the two compounds in persons with amyotrophic lateral sclerosis (ALS) are not known.

### **METHODS**

In this multicenter, randomized, double-blind trial, we enrolled participants with definite ALS who had had an onset of symptoms within the previous 18 months. Participants were randomly assigned in a 2:1 ratio to receive sodium phenylbutyrate–taurursodiol (3 g of sodium phenylbutyrate and 1 g of taurursodiol, administered once a day for 3 weeks and then twice a day) or placebo. The primary outcome was the rate of decline in the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R; range, 0 to 48, with higher scores indicating better function) through 24 weeks. Secondary outcomes were the rates of decline in isometric muscle strength, plasma phosphorylated axonal neurofilament H subunit levels, and the slow vital capacity; the time to death, tracheostomy, or permanent ventilation; and the time to death, tracheostomy, permanent ventilation, or hospitalization.

### **RESULTS**

A total of 177 persons with ALS were screened for eligibility, and 137 were randomly assigned to receive sodium phenylbutyrate–taurursodiol (89 participants) or placebo (48 participants). In a modified intention-to-treat analysis, the mean rate of change in the ALSFRS-R score was  $-1.24$  points per month with the active drug and  $-1.66$  points per month with placebo (difference,  $0.42$  points per month; 95% confidence interval,  $0.03$  to  $0.81$ ;  $P = 0.03$ ). Secondary outcomes did not differ significantly between the two groups. Adverse events with the active drug were mainly gastrointestinal.

### **CONCLUSIONS**

Sodium phenylbutyrate–taurursodiol resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks. Secondary outcomes were not significantly different between the two groups. Longer and larger trials are necessary to evaluate the efficacy and safety of sodium phenylbutyrate–taurursodiol in persons with ALS. (Funded by Amylyx Pharmaceuticals and others; CENTAUR ClinicalTrials.gov number, NCT03127514.)

# Update of Emission Factors of Greenhouse Gases and Criteria Air Pollutants, and Generation Efficiencies of the U.S. Electricity Generation Sector

by John C. Crittenden, Member EUAS



## Short Biography

*Director of the Brook Byers Institute for Sustainable Systems*

*Hightower Chair and GRA Eminent Scholar in Sustainable Technologies*

*School of Civil and Environmental Engineering – Georgia Institute of Technology*

### **EDUCATION**

*University of Michigan, Ann Arbor: B.S. Chemical Engineering 1971*

*University of Michigan, Ann Arbor: M.S. Civil and Environmental Engineering 1972*

*University of Michigan, Ann Arbor: Ph.D. Civil and Environmental Engineering 1976*

**HONORS:** *National, international, state, and regional awards for research and teaching excellence.*

*These are sample awards:*

*2020 Simon W. Freese Environmental Engineering Award and Lecture, American Society of Civil Engineers (ASCE)*

*2020 Future of Photocatalysis Paper Winning Best Feature Paper Award, American Chemical Society*

*2019 Chinese Government Friendship Award*

*2016 Elected as a Fellow of the American Society of Civil Engineers*

*2015 Chinese Academy of Sciences President's Distinguished Scientist Award*

*2015 Athalie Richardson Irvine Clarke Prize, National Water Research Institute*

*2014 Alumni Merit Award, University of Michigan, Department of Civil and Environmental Engineering*

*2013 Elected to the Chinese Academy of Engineering*

*2008 Recognized by the American Institute of Chemical Engineers as one of the "100 Chemical Engineers of Modern Era" in the category of "New Frontiers"*

*2002 Elected to the National Academy of Engineering*

*2000 AEESP Landmark Achievement Award presented annually to authors*

*1991 Recipient of the Walter L. Hubert Research Prize, awarded by ASCE for Research Contributions on Removal of Organics from Water*

*1989 Corecipient of the American Water Works Association Publication's Award for the paper which represents the most significant advancement in science and engineering as it applies to water supply practices*

*1980 Corecipient of the Rudolph Hering Medal awarded by ASCE for the most valuable contribution to the Journal of Environmental Engineering Division Proceedings of ASCE*

**RESEARCH EXPERIENCE:** *Sustainability, Pollution Prevention, Physical-Chemical Treatment Processes (Ion Exchange, Oxidation Processes, Catalytic Oxidation, Photocatalytic Oxidation, Electro-*

*catalysis, Adsorption, Electro-Adsorption, Air Stripping), Transport of Organics in Saturated and Unsaturated Groundwater, Modeling of Fixed-Bed Reactors and Adsorbers (Photocatalysis, Low Temperature Catalysis in Aqueous and Gas Phases, Transport of Organics in Saturated and Unsaturated Groundwater), Sol-Gel Chemistry for Preparation of Zeolites and Catalysts, Surface Chemistry and Thermodynamics (Prediction of Adsorption Capacities and Surface Catalyzed Rate Constants), Mass Transfer, Numerical Methods, Modeling of Wastewater and Water Treatment Processes*

**PROFESSIONAL EXPERIENCE:** Georgia Institute of Technology 2009-present. Arizona State University 2004-08. Michigan Technological University 1979-2003. University of Illinois 1978-1979. Washington State University 1977-1979. Consultant to over 45 utilities, companies and universities worldwide on adsorption technology, water quality modeling, advanced oxidation, pollution prevention since 1975.

**COURSES TAUGHT:** Sustainable Engineering, Water Chemistry, Physical and Chemical Treatment of Air and Water, Reactor Engineering, Separation Technologies and Unit Operations in Environmental Engineering, Hydromechanics, Water and Wastewater Treatment, Intro to Environmental Engineering

**RESEARCH PROJECTS:** Seventy-two research projects were successfully completed in the last 40 years. These grants and contracts accounted for \$56 million in funding in the areas of sustainable infrastructure, pollution prevention, air stripping, advanced oxidation, adsorption, and groundwater transport.

**PUBLICATIONS:** 403 publications in refereed journals, 15 books and chapters, and 161 reports or contributions to proceedings. Six copyrighted software products and seven patents in the areas of pollution prevention, stripping, advanced oxidation/catalysis, adsorption and groundwater transport. These are some sample publications:

Prof. John C. Crittenden is the director of the Brook Byers Institute for Sustainable Systems and a professor in the School of Civil and Environmental Engineering at the Georgia Institute of Technology. He holds the Hightower Chair and is a Georgia Research Alliance Eminent Scholar in Sustainable and Environmental Technologies. Prof. Crittenden received his Bachelor's degree in Chemical Engineering (1971) and his Master's degree (1972) and Ph.D. (1976) degree in Civil Engineering from the University of Michigan. Prof. Crittenden was elected to the US National Academy of Engineering in 2002, the Chinese Academy of Engineering in 2013 and the European Academy of Sciences in 2019. He is the 2015 Clarke Prize laureate, which is generally recognized as the American Nobel prize for water and received the 2020 Simon W. Freese Environmental Engineering Award and Lecture for his extraordinary accomplishments in using fundamental scientific principles and current research findings to solve the most challenging water quality problems (awarded by American Society of Civil Engineers). In 2018, Dr. Crittenden received the friendship medal from China, which considered to be the highest honor that a foreigner can receive (similar to the medal of freedom in the US). He is the co-holder of five patents and the primary author of the bestselling textbook, *Water Treatment: Principles and Design*, now in its third printing (2012, Wiley). He is the author more than 425 articles that were published in refereed journals, more than 100 book chapters, reports, and symposia and has more than 30,000 citations and a H index of 79.

Prof. Crittenden's current research focus is on sustainable urban infrastructure systems. His colleagues and he are conducting research on alternative energy technologies, sustainable materials, food energy water nexus, advanced modeling of

urban systems, sustainable engineering pedagogy, and urban form and policy. He also conducts research in various water and air treatment technologies (e.g., membrane technology, advanced oxidation processes, electrochemical advanced oxidation, photocatalytic oxidation, adsorption, selective catalytic reduction) and energy harvesting technologies (e.g., photocatalytic water splitting and aqueous phase reforming of biomass).

## **Update of Emission Factors of Greenhouse Gases and Criteria Air Pollutants, and Generation Efficiencies of the U.S. Electricity Generation Sector**

**Argonne National Laboratory  
Energy Systems Division**

### **Abstract**

The last decade has seen a steady evolution of the electricity generation sector. Fuels used for electricity generation have shifted from coal to cleaner energy sources such as natural gas and renewables including solar, wind, and other renewable sources.<sup>1</sup> The share of U.S. electricity generated from coal decreased from 45% in 2010 to 24% in 2019, and is expected to decrease further to 13% by 2050.<sup>1</sup> The conversion efficiency of electricity generation has also increased gradually for fuels such as natural gas due as less-efficient old generators are retired and more-efficient generators replace them.<sup>2</sup> These changes in the electricity generation industry are likely to cause changes in the emissions from power generation units.

Emission factors of greenhouse gases (GHG) including CO<sub>2</sub>, CH<sub>4</sub>, and N<sub>2</sub>O, and criteria air pollutants (CAPs) including CO, NO<sub>x</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and SO<sub>x</sub>, from power plants are important parameters for estimating life-cycle emissions associated with vehicle electrification, energy systems, and the production of materials and chemicals. The electricity generation technologies and associated emission factors in the Greenhouse Gases, Regulated Emissions, and Energy Use in Technologies (GREET)<sup>3</sup> model need to be updated to reflect recent developments in the electricity generation sector.

The most recent update of the electricity generation emission factors in GREET adopted a mixed method.<sup>4</sup> The emission factors of CH<sub>4</sub>, N<sub>2</sub>O, NO<sub>x</sub>, and SO<sub>x</sub> were estimated using a “topdown” approach by dividing the total emissions by the total net electricity generation, because emission data of these pollutants are readily available in the Emissions & Generation Resource Integrated Database (eGRID). For other CAPs such as CO, VOC, PM<sub>10</sub>, and PM<sub>2.5</sub>, emission data were not reported in eGRID. A “bottom-up” method was used to estimate the emission factors for these pollutants by considering generic uncontrolled emission factors and the pollutant removal efficiencies of emission control technologies adopted in the electricity generation sector. However, the uncontrolled emission factors and the emission removal efficiencies of various emission control technologies considered in the 2012 study<sup>4</sup> came from the legacy AP-42 emission factors,<sup>5</sup> and may not reflect the actual emission performances of the electricity generation sector of today.

To leverage new data that recently became available, especially emission data measured from continuous emission monitoring systems (CEMS), we developed a new “top-down” approach to estimate efficiencies and GHG and CAP emission factors for electricity generation from combustion of individual fuel types by individual combustion technologies on the basis of power-generation data from U.S. Energy Information Administration’s (EIA’s) form EIA-923,6 and plant emission data from Environmental Protection Agency’s (EPA’s) Clean Air Markets Division (CAMD) dataset and National Emissions Inventory (NEI) dataset.7-8 Detailed discussion of the method and data used in this study can be found in Section 2.1. With this topdown approach, we aim to improve the estimates of energy efficiencies and emission factors for power plants using a more consistent methodology, and to update the emission factors, generation efficiencies, and generation technologies mixes in GREET to reflect recent technology advancements in the electricity generation sector.

### **Combined Heat and Power May Conflict with Decarbonization Goals - The Air Emissions of Natural Gas Combined Cycle Power versus Combined Heat and Power Systems for Commercial Buildings**

Oswaldo Broesicke, Junchen Yan, Valerie Thomas, Emily Grubert, Sybil Derrible, **John Crittenden**

Environmental Science & Technology, 2022

#### **Abstract**

This study compares the environmental impacts of a centralized natural gas combined cycle (NGCC) versus a distributed natural gas-fired combined heat and power (CHP) energy system in the United States (U.S.). We develop an energy-balance model in which each energy system supplies the electric, heating, and cooling demands of 16 commercial building types in 16 climate zones of the U.S. We assume a best-case scenario where all the CHP’s heat and power is allocated toward building demands to ensure robust results. We quantify the greenhouse gas (GHG) emissions, conventional air pollutants (CAPs), and natural gas (NG) consumption. In most cases, the decentralized CHP system increases GHG emissions, decreases CAP emissions, and decreases NG consumption relative to the centralized NGCC system. Only fuel cell CHPs were able to simultaneously reduce GHGs, CAPs, and NG consumption relative to the NGCC-based system. The results suggest that, despite their energy efficiency benefits, standard distributed CHP-based systems typically do not have enough benefits versus an NGCC-based system to justify a reorganization of existing infrastructure systems. Since fuel cell CHPs can also use hydrogen as a fuel source, they are compatible with decarbonized energy systems and may aid in the transition towards a cleaner energy economy.

## Deep-sea Ecosystems and Functions

by Roberto Danovaro, Member EUAS



### Short Biography

*Roberto Danovaro was born in Genoa (degrees in 1988). PhD in Environmental Sciences at the University of Pisa in 1993. Full Professor in 2001 at the Polytechnic University of Marche. Director of the Department of Marine Sciences (2004 to 2010), Director of the Department of Life and Environmental Sciences (2011 to 2014) at the Polytechnic University of Marche. Pro-Rector (Delegated to the Research) at the Polytechnic University of Marche (2010-2013). President of the Scientific Council of WWF Italy, Steering Board Member of OECD (Fostering Innovation in Ocean Economy). Member of the Scientific Council of several research institutions and panels (IUCN, UNEP, EU), editor in chief of international journals and coordinator of several EU and international programs. President of the Italian Society of Ecology (2011-2013), and of the Italian Society of Limnology and Oceanography (2008-2011). President of the European Federation of Scientific Technological Societies (2008-2012). Member of the EU Academy of Sciences. RD received several Awards, including the World Prize BMC Biology (London, 2010), the Award of French Society of Oceanography (2011), and the ENI Award "Protection of the Environment" (2013). Nominated in 2013 by the Ministry of Education University and Research (MIUR), President of the Stazione Zoologica Anton Dohrn (National Institute of Marine Biology Ecology and Biotechnology). In the 2018 was renewed as President of the Stazione Zoologica (2018-2022). In December 2020 Danovaro has been recognized by ExpertScape as the top World Scientist in the Category "Ocean and Seas" for the decade 2010-2020.*

### **Education**

*1993 - PhD in Marine Environmental Sciences at the Department of Biology University of Pisa (joint PhD activity at the 2 of Ghent, Belgium)*

*1988 - Master Degree in Biology, University of Genoa*

### **Positions**

*2018-2022: Renewed President at the Stazione Zoologica Anton Dohrn, Naples, Italy*

*2013-2017: President at the Stazione Zoologica Anton Dohrn, Naples, Italy*

*2011-2014: Director Dept Life & Environmental Sciences - Polytechnic University of Marche.*

*2010-2013: Pro-rector (Delegated to Research) at the Polytechnic University of Marche.*

*2004-2010: Director of the Department of Marine Sciences - Polytechnic University of Marche.*

*2001-Present: Full Professor, Marine Biology and Ecology, Polytechnic University of Marche, Italy*

*1998-2001 Associate Professor, Department of Biology, University of Bari, Italy*

*1994-1998 Assistant Professor (Ricercatore - University of Ancona), Italy*

### **Scientific Commissions and Councils**

*2019- present Member of the Scientific Council of Slow Food International*

*2018- present Member Internat. Scientific Committee of the Holy Shroud (Sacra Sindone, Turin)*

*2018-present Member of the EU - Academy of Science*

*2017-present Member of the Steering Board OECD*

- 2016 – present member of the “Osservatorio Nazionale per la Strategia Nazionale della Biodiversità” (National observatory for the Biodiversity strategy)”
- 2016- present Member of the Scientific and Technical Commission - selection of the ENI Awards
- 2014-present Member of the Faculty of 1000 Biology
- 2014-present President of the Scientific Council of the WWF Italy
- 2013-present Member of the Scientific Committee of ENI
- 2011-2013 Member of the Scientific Council of the Stazione Zoologica “Anton Dohrn”
- 2006-2014 Member of the Scientific Council of the WWF Italy
- 2010-2012 Member of the Scientific Board of the Reef check Italy
- 2008-2010 Member of the Forum of oceans & Islands beyond national jurisdiction.
- 2005-2010 Member of the Scientific Council of the Census of Marine Life (CoML)
- 2006-2008 Member and coordinator of the “Task force Deep Sea” of the CIESM International commission for exploration of the Mediterranean.
- 2007-2009 Member of the Scientific Council of the Istituto Nazionale di Oceanografia e di Geofisica Sperimentale – IN-OGS (Trieste).
- 2005-2010 Member of the Scientific Council of the CoNISMa (Consorzio Interuniversitario Science del Mare, Roma).
- 2005-2008 Member of the SCOR WG 126 on The Role of Viruses in Marine Ecosystems

## Selected Publications 2021

### ***In situ* experimental evidences for responses of abyssal benthic biota to shifts in phytodetritus compositions linked to global climate change**

Nomaki, Rastelli, Ogawa, Matsui, Tsuchiya, Manea, Corinaldesi, Hirai, Ohkouchi, **Danovaro**, Nunoura, Amaro (2021). *Global Change Biology* 27(23), 6139-6155 (IF: 10.86)

Abyssal plains cover more than half of Earth's surface, and the main food source in these ecosystems is phytodetritus, mainly originating from primary producers in the euphotic zone of the ocean. Global climate change is influencing phytoplankton abundance, productivity, and distribution. Increasing importance of picoplankton over diatom as primary producers in surface oceans (especially projected for higher latitudes) is projected and hence altering the quantity of organic carbon supplied to the abyssal seafloor as phytodetritus, consequences of which remain largely unknown. Here, we investigated the *in situ* responses of abyssal biota from viruses to megafauna to different types of phytoplankton input (diatoms or cyanobacteria which were labeled with stable isotopes) at equatorial (oligotrophic) and temperate (eutrophic) benthic sites in the Pacific Ocean (1°N at 4277 m water depth and 39°N at 5260 m water depth, respectively). Our results show that meiofauna and macrofauna generally preferred diatoms as a food source and played a relatively larger role in the consumption of phytodetritus at higher latitudes (39°N). Contrarily, prokaryotes and viruses showed similar or even stronger responses to cyanobacterial than to diatom supply. Moreover, the response of prokaryotes and viruses was very rapid (within 1–2 days) at both 1°N and 39°N, with quickest responses reported in the case of cyanobacterial supply at higher latitudes. Overall, our results suggest that benthic deep-sea eukaryotes will be negatively affected by the predicted decrease in diatoms in surface oceans, especially at higher latitudes, where benthic prokaryotes and viruses will otherwise likely increase their quantitative role and organic carbon cycling rates. In turn, such changes can contribute to decrease carbon transfer from phytodetritus to higher trophic levels, with strong potential to affect oceanic food webs, their biodiversity

and consequently carbon sequestration capacity at the global scale.

### **Abbyssal fauna, benthic microbes, and organic matter quality across a range of trophic conditions in the western Pacific ocean**

Nomakia, Rastelli, Alves, Suga, Ramos, Kitahashi, Tsuchiya, Ogawa, Matsui, Seike, Miyamoto, Corinaldesi, Manea, Ohkouchi, **Danovaro** et al (2021)  
*Progress in Oceanography* 195, 102591 (IF: 4.080)

The abyssal plain covers more than half the Earth's surface. The main food source to abyssal ecosystems is phytodetritus, which originates from phytoplankton in the surface ocean, and thus its variability to the seafloor is a major driver of abyssal ecosystem biomass and functioning. In this study, we conducted a comparative survey on organic matter (OM) quality and quantity in abyssal plain sediments and examined the distributions of megafauna, macrofauna, meiofauna, prokaryotes, and viruses in eutrophic (39°N), oligotrophic (1°N), and ultra-oligotrophic (12°N) areas of the western Pacific. We also analyzed stable carbon and nitrogen isotopic compositions of organisms at 39°N and 1°N to assess differences in benthic abyssal food-web structures with contrasting trophic states. Sediments collected at 39°N presented highest concentrations of total organic carbon (TOC) and labile OM, and high diffusive oxygen uptake rates. By contrast, the lowest values were found at 12°N. Vertical distributions of sediment macrofauna, meiofauna, and prokaryotes matched with labile OM profiles. There were prominent differences in abundances of macro- and megafauna among stations with different OM fluxes, whereas the abundance of meiofauna and prokaryotes showed smaller differences among stations. Such differences could be explained by higher turnover rates of smaller organisms. Food-web structures of abyssal plains are likely influenced by both the type and size of primary producers in surface ocean. Our results underscore the crucial importance of OM fluxes and their compositions to the abundances and vertical profiles of labile OM and benthic biota in abyssal ecosystems.

### **A decade to study deep-sea life**

Howell, Hilario, Allcock, bailey, Baker, Clark, Colaco, Copley, Cordes, **Danovaro** et al (2021)  
*Nature Ecology & Evolution* 5, 265-267 (IF:15.46)

The health of the global ocean, on which society depends, is in decline. The importance of sustainable use to ocean health has long been recognized, yet the United Nations (UN) First World Ocean Assessment from 2017 highlighted increasing ocean pressures from accelerated expansion of human activities, including climate change. These pressures affect all ocean regions, from the coast to the deep sea. In response to this concern, and to align with several international policy commitments, the UN General Assembly proclaimed 2021–2030 the Decade of Ocean Science for Sustainable Development. The roadmap for this Ocean Decade recognizes the deep sea as a frontier of science and discovery and calls for research to advance understanding of deep-sea ecosystems, their functions, vulnerabilities and services to society. Published in March 2020, the draft implementation plan for the Ocean Decade guides the design and implementation of 'Actions' that underpin the desired move from 'the ocean we have' to 'the ocean we want'.

## **Challenges and opportunities for the eco-sustainable management of the deep sea in the UN Decade 2021-2030 “Ocean Science for Sustainable Development**

**Danovaro** (2021) *Bulletin of Geophysics and Oceanography*. 62, Supplement n. 3, 67-74

Society must address the lack of rules and appropriate tools for the sustainable use of resources, also by supporting global scientific projects, including a global deep-sea monitoring network. A new cooperation under the umbrella of the United Nations could fill the critical research gaps identified here. This cooperation should be linked to the Intergovernmental Oceanographic Commission of UNESCO and, through a scientific Advisory Board, could provide independent advice, transcending sectoral and jurisdictional limitations: i) sustain a Deep-Sea Ecosystem Monitoring Network for acquiring knowledge necessary for deep-sea management and integrate inputs from research institutions, academia, industries, and international NGOs, ii) make data available to inform policy and resolve critical needs, and iii) facilitate the conversion of scientific knowledge into “good practices” for the best, shared governance of the deep oceans. The cooperation should also contribute to the technological development and implementation of Artificial Intelligence to facilitate operational autonomy and data processing in these remote habitats. In parallel, research on mechanisms and functioning is required, made of ship-based multidisciplinary process studies, in situ and in laboratory experiments using the best biological, molecular and bioinformatic tools. The final goal is to create the knowledge able to, on one hand, make relevant scientific progresses and on the other hand identify new management tools, which can produce beneficial effects for our Society. Planning the eco-sustainable management of deep ocean requires an international initiative and the UN decade 2021-2030 Ocean Science for Sustainable Development represents a unique opportunity to launch a global effort. The expansion of biological and ecological knowledge and the integration of biotic and abiotic information at appropriate spatial-temporal scales represents the major pre-requisite for the new strategy proposed here. Deep-ocean management also requires much wider capacity building than at present and a “global vision” that spans geographic and political borders to make informed decisions on crucial topics, including deep-sea mining, protection of deep-polar regions, and exploitation of biotic resources in the areas beyond national jurisdiction.

### **Identifying priorities for the protection of deep Mediterranean Sea ecosystems through an integrated approach**

Fanelli, Bianchelli .... **Danovaro** (2021)  
*Frontiers in Marine Science* 8, 698890.

Benthic habitats of the deep Mediterranean Sea and the biodiversity they host are increasingly jeopardized by increasing human pressures, both direct and indirect, which encompass fisheries, chemical and acoustic pollution, littering, oil and gas exploration and production and marine infrastructures (i.e., cable and pipeline laying), and bioprospecting. To this, is added the pervasive and growing effects of human-induced perturbations of the climate system. International frameworks provide foundations for the protection of deep-sea ecosystems, but the lack of standardized criteria for the identification of areas deserving protection, insufficient legislative instruments and poor implementation hinder

an efficient set up in practical terms. Here, we discuss the international legal frameworks and management measures in relation to the status of habitats and key species in the deep Mediterranean Basin. By comparing the results of a multi-criteria decision analysis (MCDA) and of expert evaluation (EE), we identify priority deep-sea areas for conservation and select five criteria for the designation of future protected areas in the deep Mediterranean Sea. Our results indicate that areas (1) with high ecological relevance (e.g., hosting endemic and locally endangered species and rare habitats), (2) ensuring shelf-slope connectivity (e.g., submarine canyons), and (3) subject to current and foreseeable intense anthropogenic impacts, should be prioritized for conservation. The results presented here provide an ecosystem-based conservation strategy for designating priority areas for protection in the deep Mediterranean Sea.

# Open Dual Cycle with Composition Change and Limited Pressure for Prediction of Miller Engines Performance and its Turbine Temperature

by Antonio Lecuona-Neumann, Member EUAS

## Short Biography

*Professor*

*Dep. Ingeniería Térmica y de Fluidos*

*Universidad Carlos III de Madrid, Spain*

## **Academic record**

*Born in 1953, Ph.D. in 1980 on Aeronautical Engineering on laser driven Nuclear Fusion*

*Full Professor in 1993*

*Honored by the highest Education award in Spain “Encomienda de Alfonso X El Sabio” in 1996.*

*Been commissioned as Vice-chancellor and Head of Department.*

*Author of around 100 publications, most of them in high impact journals. H25. More than 1000 citations.*

*Participated in 40 competitive research projects, including 10 with the EU Commission.*

*Author of 13 patents and more than 100 congress talks Tutor of 13 Ph.D. thesis and more than 100 Master Thesis.*

*Member of the Editorial Board of several Journal, including “Applied Energy”.*

*Entitled and visiting Professor of master’s degrees in several Universities.*

*Visiting Professor at Stanford University, Dept. Mechanical Engineering HGTL laboratories.*

*Director of the research Institute “Pedro Juan de Lastanosa” at UC3M.*

*He acts as advisor for the Ministry of Science and Education of Spain.*

*Member of the European Advisory Board in July 2005 y of the scientific board in 2006 of the “Centro de Tecnologías Avanzadas para la Combustión Limpia del Carbón” CIEMAT, Spain.*

## **Interests**

*Professor of: Internal Combustion Engines, Turbomachines, Acoustics Engineering, Environmental Engineering, Sources of Energy, Absorption Machines.*

*Author of the following books:*

*Turbomáquinas Procesos, Análisis y Tecnología. Editorial Ariel Ciencia y Tecnología, octubre 2000 ISBN 84-344-8029-8.*

*Cocinas solares. Fundamentos y aplicaciones. Herramientas de lucha contra la pobreza energética. Editorial Marcombo, Barcelona, 2017, www.marcombo.com . ISBN 9788426724038*

*Solar convective dryers for post-collection processing. Editorial Marcombo 20/11/2019 ISBN:9788426728135 Free pdf in www.marcombo.info password SOLARI.*

*Author of teaching material for 4 Open Course Ware courses of Universidad Carlos III de Madrid*

**Lines of research**

Recently, he is interested on devices for fighting energy poverty with appropriate technologies, such as solar photovoltaic cookers with thermal energy storage, solar dryers with thermal energy storage for isolated and remote communities. More straightforward devices are the development of medium temperature air solar collector using turbocharging.

Now he is participating in a national research inter-universities consortium for the development and high-resolution measurements and simulations of green H<sub>2</sub> clean combustors for aircraft gas turbines.

Now he is working on the analytical time evolution of solar driers air heaters with integral and distributes thermal energy storage.

Recent paper

***Lecuona, A.; Nogueira, J.I.; Famiglietti, A. “Open Dual Cycle with Composition Change and Limited Pressure for Prediction of Miller Engines Performance and Its Turbine Temperature.”***

*Energies* 2021, 14, 2870. <https://doi.org/10.3390/en14102870>.

**Abstract**

An improved thermodynamic open Dual cycle is proposed to simulate the working of internal combustion engines. It covers both spark ignition and Diesel types through a sequential heat release. This study proposes a procedure that includes (i) the composition change caused by internal combustion, (ii) the temperature excursions, (iii) the combustion efficiency, (iv) heat and pressure losses, and (v) the intake valve timing, following well-established methodologies. The result leads to simple analytical expressions, valid for portable models, optimization studies, engine transformations, and teaching. The proposed simplified model also provides the working gas properties and the amount of trapped mass in the cylinder resulting from the exhaust and intake processes. This allows us to yield explicit equations for cycle work and efficiency, as well as exhaust temperature for turbocharging. The model covers Atkinson and Miller cycles as particular cases and can include irreversibilities in compression, expansion, intake, and exhaust. Results are consistent with the real influence of the fuel-air ratio, overcoming limitations of standard air cycles without the complex calculation of fuel-air cycles. It includes Exhaust Gas Recirculation, EGR, external irreversibilities, and contemporary high-efficiency and low-polluting technologies. Correlations for heat ratio  $\gamma$  are given, including renewable fuels.

## Dementia - Eliminating its Potentially Reversible Forms

by Alain L. Fymat, Member EUAS



### Short Biography

DR. ALAIN L. FYMAT is a medical-physical scientist and an educator. He is the current President/CEO and Institute Professor at the International Institute of Medicine & Science with a previous appointment as Executive Vice President/Chief Operating Officer and Professor at the Weil Institute of Critical Care Medicine, California, U.S.A. He was formerly Professor of Radiology, Radiological Sciences, Radiation Oncology, Critical Care Medicine, and Physics at several U.S. and European Universities. Earlier, he was Deputy Director (Western Region) of the U.S. Department of Veterans Affairs (Office of Research Oversight). At the Loma Linda Veterans Affairs Medical Center, he was Scientific Director of Radiology, Director of the Magnetic Resonance Imaging Center and, for a time, Acting Chair of Radiology. Previously, he was Director of the Division of Biomedical and Biobehavioral Research at the University of California at Los Angeles/Drew University of Medicine and Science. He was also Scientific Advisor to the U.S. National Academy of Sciences, National Research Council, for its postdoctoral programs tenable at the California Institute of Technology and Member of the Advisory Group for Research & Development, North Atlantic Treaty Organization (NATO). He is Health Advisor to the American Heart & Stroke Association, Coachella Valley Division, California. He is a frequent Keynote Speaker and Organizing Committee member at several international scientific/medical conferences. He has lectured extensively in the U.S.A, Canada, Europe, Asia, and Africa. He has published in excess of 525 scholarly scientific publications and books. He is also Editor-in-Chief, Honorable Editor or Editor of numerous medical/scientific Journals to which he regularly contributes. He is a member of the New York Academy of Sciences and the European Union Academy of Sciences, a Board member of several institutions, and a reviewer for the prestigious UNESCO Newton Prize, United Kingdom National Commission for UNESCO.

### **Research interests**

Dr. Fymat's current research interests are focused on neurodegenerative diseases (Alzheimer's, Parkinson's, dementias, epilepsy, and others), oncology (glioblastoma), epigenetics & ecogenetics, and nanomedicine & nanobiotechnology, and emerging infectious diseases. These are represented in part in his latest books: "**The Odyssey of Humanity's Diseases: Epigenetic and ecogenetic modulations from ancestry through inheritance, environment, culture, and behavior**" Volumes 1, 2, and 3; "**From the Heart to the Brain: My collected works in medical science research (2016-2018)**"; "**The Human Brain: Wonders and Disorders**"; "**Alzhei ...Who? Demystifying the disease and what you can do about it**"; "**Parkin...ss..oo..nn: Elucidating the disease and what you can do about it**"; "**Dementia: Fending-off the menacing disease... and what you can do about it**"; "**Cancer: The pernicious clonally evolving disease braided in our genome**"; "**Lyme disease: The great invader, evader, and imitator**"; and "**Pandemics: Prescription for prediction and prevention**".

In the absence of a cure for dementia, the following contribution is a provocative suggestion for the elimination of potentially reversible forms of dementia.

## **Dementia - Eliminating its potentially reversible forms**

We are barely emerging from the COVID-19 pandemic that we are already concerned with the coming of age of the dementia pandemic. Prompted by economic development and increasing lifespan, dementia in its several types and forms has surfaced as a major global public health concern that may devastate world's economies and health care systems. However, in the absence of a cure, certain reversible forms of dementia can apparently be potentially eliminated. This contribution is a provocative suggestion for eliminating such dementia forms. However, prerequisites are: a good understanding of what is dementia; the insufficient knowledge of its causal etiology; its characterization; the associated risk factors, signs and symptoms; the difficulties in reaching an accurate diagnosis; and the identification of those potentially reversible forms.

**What is dementia?** Dementia is an umbrella term for several brain diseases that manifest themselves by a group of symptoms affecting memory, other cognitive abilities, and behavior. Pictorially, that umbrella includes the following types of dementia: Alzheimer's (accounting for 50%-75% of cases or one in every nine people aged 65 and over), vascular (20%-30%), Lewy body (10%-25%), frontotemporal (10%-15%), and others. According to the World Health Organization's 2019 Global Health Estimates for the ten global causes of death, Alzheimer's disease and other dementias ranked seventh after ischemic heart disease; stroke; chronic obstructive pulmonary disease; lower respiratory infections; neonatal conditions; trachea, bronchus, and lung cancers; and before diarrheal diseases; diabetes mellitus; and kidney diseases.

However, dementia is not an emerging disease as it has been with us since Antiquity. It was uncommon in pre-industrial times and relatively rare before the 20<sup>th</sup> century (for a historical account, see for example my book bearing the same title). During the 19<sup>th</sup> century until the first half of the 20<sup>th</sup> century, doctors came to believe that dementia in the elderly was the result of cerebral atherosclerosis (either blockages of the major arteries supplying the brain or small strokes within the vessels of the cerebral cortex). Until the end of the 19<sup>th</sup> century, dementia was a much broader clinical concept that encompassed mental illness and any type of psychosocial incapacity. In 1907, Alzheimer's disease was described and associated with particular microscopic changes in the brain. It was seen as a rare disease of middle age because the first person diagnosed with it was a 46-year-old woman (Frau Auguste Dieter, a patient of Dr. Alois Alzheimer). By the 1960s, the link between neurodegenerative diseases and age-related cognitive decline was established. By the 1970s, the medical community maintained that Alzheimer's disease was the cause of the vast majority of mental impairments rather than vascular disease, which is rarer than previously thought. In 1976, neurologist Robert Katzmann suggested a link between senile dementia and Alzheimer's disease dementia. By the end of the 20<sup>th</sup> century, the medical community believed that dementia is a mixture of both Alzheimer's disease dementia and vascular disease dementia. In the beginning of the 21<sup>st</sup> century, on the basis of pathological examination of brain tissues, by symptomatology, and by different patterns of brain metabolic activity, a number of other types of dementia have been differentiated from Alzheimer's disease dementia and vascular disease dementia. Nonetheless, the causal

etiology of many types of dementia, including Alzheimer's disease, remains unclear and many hypotheses (theories) have been advanced, but these are largely based on risk factors.

**Has the dementia pandemic come of age?** Because of economic development and increasing lifespan, dementia in its several types and forms has surfaced as a major global public health concern that may devastate world's economies and health care systems. According to the World Health Organization, from year 2010, the increases in the number of dementia cases have been 26% (for year 2015) and 40% (for year 2017). The corresponding predicted increases are 130% (for year 2030) and 326% (for year 2050). The numbers of cases increase significantly with age and the more so for people living in low- and middle-income countries (nearly 60% of people affected), where the sharpest increases in numbers are predicted. In 2013, the number of deaths was about 1.7 million (up from 0.8 million in 1990), but they are increasing significantly with age. While smaller than the number of deaths reported for the COVID-19 pandemic, they are steadily increasing and may unfortunately approach (if not exceed) them.

**What is the causal etiology of dementia?** It still remains unclear for the many types of dementia, including Alzheimer's disease. Whereas much is known about dementia and its underlying and contributing factors, and much has been published on the subject, we still do not understand the deep biology of the disease. Lacking this understanding, we have so far failed to find a cure and continue to be limited to symptomatic treatments that have limited or no effect. To be sure, many hypotheses have been advanced but these are largely based on risk factors, correlations or associations. But, risk factors, correlations, associations, and the like ... are not causation! Likewise, risk management and symptomatic treatments... are not cure, only palliation! What is going on? Have we got the cause of dementia all wrong? I believe so far, rather than remaining focused on the primary endpoint of a cure, we have meandered around and shifted the emphasis to surrogate endpoints even though the latter had not been clinically demonstrated to correlate well with the disease. In brief, we lost the proverbial forest for the trees! Yet, hundreds of clinical trials have been undertaken and billions of dollars have been spent each year in rising healthcare costs relating to dementia, in addition to the financial and emotional burdens on families, friends, and care partners/givers. Irrespective of geographical location, racial/ethnic background, and cross-cultural and socioeconomic divides, one can die prematurely of dementia because there still are no cures or effective long-term treatments. Since 2017, I have posited that neurodegenerative diseases including dementia in many of its forms are but autoimmune diseases that have gone rogue. For example, the generally accepted amyloid-beta protein deposits (or plaques) including interactions between them and neurofibrillary tangles may only be the signs of a brain homeostasis that had broken down under an avalanche of brain insults (cytokine or/and chemokine storms).

**How are dementias categorized?** Dementias can be categorized according to (1) the affected brain area(s), (2) their progressiveness and irreversibility, (3) their derivability from another disorder (primary or secondary), and (4) their reversibility. This latter category is of particular interest here.

**What are the main contributors to dementia?** No less than 24 disorders are contributing to dementia. I shall categorize them as to whether they are main contributors, immune-mediated contributors, inherited contributors, or other associated syndromes. The main

contributors are: Alzheimer's disease dementia, vascular disease dementia, and Lewy body dementias. Other contributors are: Parkinson's disease dementia, frontotemporal disease dementia, mixed dementia, senilitic dementia, syphilitic dementia, progressive supranuclear palsy, corticobasal degeneration, encephalopathy, and Creutzfeldt-Jacob disease. Immuno-mediated contributors are: Behcet's disease, multiple sclerosis, sarcoidosis, Sjogren's disease, and celiac and non-celiac disease. Inherited contributors are: Alzheimer's disease, Krabbe's disease, Nieman-Pick disease, maple syrup urine disease, and Pelizaeus-Merzbacher disease. Associated syndromes are: fragile X-associated tremor/ataxia, San Filippo B, epilepsy, cerebrotendinous xanthomatosis, dentatorubal pallidolusian atrophy, fatal familial insomnia, glutaric aciduria type 1, neuronal ceroid lipofuscinosis, neuroacanthocytosis, organic acidemias, pino-cerebellar ataxia type 2, and urea cycle. They are confounding factors that have precluded so far the identification of the root cause of dementia and hindered its diagnosis.

**What are the risk factors, signs and symptoms, and the diagnosis for dementia?** While each form of dementia has its own risk factors, most forms have several risk factors in common. These are: age (the strongest known risk factor) although dementia is not a normal part of aging, family history, lifestyle, and pre-existing conditions (such as high blood pressure, diabetes). It is not known how treatment for these problems influences the risk of developing dementia. In addition, more than one type of dementia may exist in the same person. Further, it seems as though people who remain physically active, socially connected, and mentally engaged may be less likely to fall prey to dementia (or develop dementia later than others).

Dementia evolves in three consecutive phases (early, middle, and late phase) ending up in near total dependence and inactivity, serious memory disturbances, and more obvious physical signs and symptoms. Its signs and symptoms vary across types and stages and also with the individual. They are slow and progressive. Common symptoms are: impairment of memory, other cognitive abilities, behavioral and emotional problems, language difficulties, and decreased motivation. However, memory loss by itself does not mean having dementia; rather, it is an indication of the need for professional treatment. It should be noted that behavioral and psychological symptoms occur almost always in all types of dementia and may manifest as: agitation/aggression, anxiety, apathy, appetite changes, behavioral changes, delusions/hallucinations, depression, disinhibition, impulsivity, irritability, mood elations, motor abnormalities, psychosis, and sleep disturbances. Lastly, long-term and often gradual decrease in the ability to think and remember may be great enough to interfere significantly with a person's ability to maintain activities of daily living. Because symptoms are very similar in all types of dementia, they cannot by themselves help in reaching the correct diagnosis of dementia type(s). A diagnosis requires a change from a person's usual mental functioning and a greater decline than one would expect due to aging. Beyond the main contributors (Alzheimer's disease, vascular disease, Lewy body), the diagnosis may become more elusive when some of the many contributors to dementia enter.

**Potentially reversible conditions:** There may fortunately be potentially reversible conditions. All people with memory difficulty should at least be checked for: hypothyroidism, vitamin B<sub>12</sub> deficiency, Lyme disease, neurosyphilis, and importantly toxicants exposure and bioaccumulation. This latter factor, in particular, has been the subject of numerous studies. The several categories of elemental exposures potentially

associated with neurodegenerative diseases including dementia are:

- *Metals*: aluminum, arsenic, copper, lead, manganese, mercury, tin, and zinc that cause neurotoxic effects and contribute to cognitive decline;
- *Pesticides*: aldrin, chlordane, dichlorodiphenylchloroethylene, dichlorodiphenyltrichloroethane, dieldrin, heptachlor, maneb, methyl parathion, organophosphates, paraquat, and pyrethroids that contribute to neurotoxic effects and Alzheimer's disease;
- *Flame retardants* (brominated and chlorinated): 2,2', 4,4'-tetrachlorobiphenyl; 6-Hydroxy-2,2', 4,4'-tetrabromodiphenyl ether, decabromodiphenyl, hexabromocyclododecane, pesticides (others), perfluorinated compounds, polychlorinated biphenyls, solvents, tetrabromobisphenol, and trichloroethylene that cause neurotoxic effects and contribute to dementia;
- *Solvents*: carbon disulfide, perchloroethylene and toluene;
- *Pharmaceuticals*: anesthetic agents and benzodiazepine that contribute to Alzheimer's disease;
- *Air pollutants*: carbon monoxide, methanol, nitrogen dioxide, ozone, particulate matter, and second hand smoke (nicotine, cadmium) that cause neurodegeneration and contribute to dementia, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis;
- *Plasticizers*: bisphenol and phthalate esters;
- *Food ingredients*: artificial food constituents, dyes and lakes, food and color additives, various other ingredients (acidulants, anti-caking agents, binders, color additives, dough strengthening & conditioners, emulsifiers, fat replacers, firming agents, flavor enhancers, humectants, leavening agents, stabilizers, thickeners, texturizers, yeast nutrients, etc.); and
- *Others*: acrylamide, dioxins, formaldehyde, methanol, mycotoxins, organic compounds, petrochemicals, perfluorooctanesulfonic acid, perfluorooctanoic acid, and synthetic chemical agents that contribute to dementia.

The escalating health threats posed by exposure to the above toxicants have not been sufficiently recognized because it was believed that they are readily eliminated by the body. Yet, the continuous exposure to them, their increasing concentrations, and their long half-lives cause their bioaccumulation in various organs, resulting in various pathologies. Genius and Kelln (2015) have identified the following harm mechanisms: mitochondrial damage, oxidative stress, cell death, neurotransmitter dysregulation, endocrine disruption, and epigenetic modification. These authors have also pointed out potential treatments based on the elimination of these toxicants. They have further discussed a case report study of a single patient who presented with a significant burden of lead owing to his past occupational exposure. Tests performed to assess the levels of toxicants revealed elevated values of ferritin, immunoglobulin E, C-reactive protein, and creatinine. They also revealed positive antinuclear antibody and decreased glomerular filtration rate. Through interventions to excrete the excessive lead (skin depuration, oral DMSA, and EDTA), and nutritional supplementation (to prevent mineral deficiency), the patient reportedly recovered his good health within one year and progressively resumed a normal life with good quality after six years of therapy.

**In conclusion**, as we are entering a dementia pandemic that may devastate world's economies and health care systems, it behooves us to focus on the causal etiology of

dementia and other neurodegenerative diseases. I have posited earlier that they are the consequence of an autoimmune disease in overdrive. While that theory is under critical review with the hope that it may provide the needed ultimate treatment, we should also dedicate efforts to eliminating those potentially reversible dementia forms that are due to continual exposure to toxicants and their bioaccumulation. Detoxification therapies exist, have been proven in a variety of cases, and need to be made more widely known and available.

## References

1. Baltazar MT, Dinis-Oliveira RJ, Bastos MDL, Tsatsakis AM, Duarte JA, and Carvalho F (2014). "Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases—a mechanistic approach". *Toxicology Letters* 230:85–103, 2014.
2. Barnham KJ and Bush AI (2014). "Biological metals and metal-targeting compounds in major neurodegenerative diseases", *Chemical Society Reviews* 43(19):6727–49.
3. Billioti de Gage S, Begaud B, Bazin F *et al.* (2014). "Benzodiazepine use and risk of dementia: prospective population based study", *British Medical Journal* 349: Article ID e6231.
4. Bleecker ML, Ford DP, Lindgren KN, Hoese VM, Walsh KS, and Vaughan CG (2005). "Differential affects of lead exposure on components of verbal memory", *Occupational and Environmental Medicine* 62(3):181–7.
5. Block ML, Elder A, Auten RL *et al.* (2012). "The outdoor air pollution and brain health workshop", *NeuroToxicology* 33(5):972–84.
6. Bondy SC (2014). "Prolonged exposure to low levels of aluminum leads to changes associated with brain aging and neurodegeneration", *Toxicology* 315(1):1-7.
7. Bradberry S, Sheehan T, and A. Vale, "Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning", *QJM: An International Journal of Medicine* 102(10)721–32.
8. Bredesen DE (2014). "Reversal of cognitive decline: a novel therapeutic program", *Aging* 6(9):707–17.
9. Brewer GJ (2014). "Alzheimer's disease causation by copper toxicity and treatment with zinc", *Frontiers in Aging Neuroscience* 6:Article 92.
10. Cannon JR and Greenamyre JT (2011). "The role of environmental exposures in neurodegeneration and neurodegenerative diseases". *Toxicological Sciences* 124(2):225–50.
11. (U.S.) Centers for Disease Control and Prevention: Department of Health and Human Services (2013): "Fourth National Report on Human Exposure to Environmental Chemicals: Updated Tables", [http://www.cdc.gov/exposurereport/pdf/FourthReport\\_UpdatedTables\\_Mar2013.pdf](http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Mar2013.pdf).
12. Exley C and Vickers T (2014). "Elevated brain aluminum and early onset Alzheimer's disease in an individual occupationally exposed to aluminum: a case report", *Journal of Medical Case Reports* 8(1):Article 41.
13. Fymat AL (2017a). "Epilepsy: A Review", *Journal of Current Opinions in Neurological Science* 1(5):240-254, ISSN: 2575-5447 (21 November 2017).
14. Fymat AL (2017b). "Parkinson's Disease and Other Movement Disorders: A Review", *Journal of Current Opinions in Neurological Science* 2(1):316-343,
15. Fymat AL (2018a). "Alzheimer's Disease: A Review", *Journal of Current Opinions in Neurological Science* 2(2):415-436,
16. Fymat AL (2018b). "Alzheimer's Disease: Prevention, Delay, Minimization and Reversal", *Journal of Clinical Research in Neurology* 1(1):1-16.
17. Fymat AL (2018c). "Alzhei ... Who? Demystifying the Disease and What You Can Do About it", Tellwell Talent Publishers, pp 236, 23 December 2019. ISBN: 978-0-2288-2420-6 (Hardcover); 978-0-2288-2419-0 (Paperback).
18. Fymat AL (2018d). "Dementia Treatment: Where Do We Stand?" *Journal of Current Opinions in Neurological Science* 3(1):1-3. 599.603.
19. Fymat AL (2018e). "On Dementia and Other Cognitive Disorders", *Journal of Clinical Research in Neurology* 2(1):1-14.
20. Fymat AL (2018f). "Is Alzheimer's a Runaway Autoimmune Disease? And How to Cure It?" *Proceedings of the European Union Academy of Sciences*, 2018 Newsletter, pages 379-83.
21. Fymat AL (2019a). "Dementia: A Review", *Journal of Clinical Psychiatry and Neuroscience* 1(3):27-34.
22. Fymat AL (2019b). "The Pathogenic Brain", *Journal of Current Opinions in Neurological Science* 3(2):669-71.
23. Fymat AL (2019c). "On the Pathogenic Hypothesis of Neurodegenerative Diseases", *Journal of Clinical Research in Neurology* 2(1):1-7.
24. Fymat AL (2019d). "Dementia with Lewy Bodies: A Review", *Journal of Current Opinions in Neurological Science* 4(1):15-32.
25. Fymat AL (2019e). "What do we Know about Lewy Body Dementias?" *Journal of Psychiatry and Psychotherapy* (Editorial) 2(1)-013:1-4.
26. Fymat AL (2019f). "Viruses in the Brain...? Any Connections to Parkinson's and other Neurodegenerative Diseases?" *Proceedings of the European Union Academy of Sciences*, 2019 Newsletter, pages 249-52.

27. Fymat AL (2020a). "Recent Research Developments in Parkinson's Disease", *Current Opinions in Neurological Science* 5(1):12-30.
28. Fymat AL (2020b). "Is Alzheimer's an Autoimmune Disease Gone Rogue? The Role of Brain Immunotherapy", *Journal of Clinical Research in Neurology* 3(2):1-3.
29. Fymat AL (2020c). "Alzheimer's: What do we Know about the Disease and What Can Be Done About It?" *EC Journal of Psychology & Psychiatry* 9(11):69-74.
30. Fymat AL (2020d). "Alzheimer's: Will there ever be a Cure?" *Journal of Clinical Psychiatry and Neuroscience* 3(4): 1-5.
31. Fymat AL (2020e). "Parkinson's: What is Known about the Disease and What Can Be Done About It?", *Journal of Clinical Research in Neurology* 3(2):1-12.
32. Fymat AL (2020f). "Dementia: Should we Reorient our Approach to Treatment?" *EC Journal of Psychology & Psychiatry* 9(12):1-3.
33. Fymat AL (2020g). "Dementia – What is its Causal Etiology?", *IntJournal of Neuropsychology Behavioral Sciences* 1(1):19-22.
34. Fymat AL (2020h). "Parkin... ss..oo.nn: Elucidating the Disease... and What You Can Do About it" ,*Tellwell Talent Publishers*, pp 258, 6 April 2020. ISBN: 978-0-2288-2874-7 (Hard cover); ISBN: 10-0-2228-2874-0 (Paperback).
35. Fymat AL (2020i). "Dementia: Fending off the Menacing Disease... and What You Can Do About it", *Tellwell Talent Publishers*, 21 September 2020. ISBN: 978-0-2288-4145-3 (hardcover); 978-0-2288-4145-6 (paperback).
36. Fymat AL (2021a). "Paradigm for Pandemic Prediction and Prevention," Proc. European Union Academy of Sciences Pandemics (e2021 Symposium), *Universal Journal of Mathematics & Computation* 9:27-42.
37. Fymat AL (2021b). "The Human Brain – Wonders and Disorders", *Tellwell Talent Publishers*, 29 March 2021. ISBN: 10-0-2288-4885-7 (hardcover); 978-0-2288-4885-1 (paperback).
38. Fymat AL (2021c). "Pandemics: Prescription for Prediction and Prevention", *Tellwell Talent Publishers*, 2021. ISBN: 978-0-2288-6721-0 (hardcover); 978-0-2288-6720-3 (paperback).
39. Gatto NM, Henderson VW, Hodis HN *et al.* (2014). "Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles", *NeuroToxicology* 40:1–7.
40. Genuis SJ (2008). "Toxic causes of mental illness are overlooked", *NeuroToxicology* 29(6):1147–9.
41. Genuis SJ (2011). "Elimination of persistent toxicants from the human body", *Human and Experimental Toxicology* 30(1):3–18.
42. Genuis SJ (2012). "What's out there making us sick?" *Journal of Environmental and Public Health* 2012(Article ID 605137):10 pages.
43. Genuis SJ, Schwalfenberg G, Siy AKJ, and Rodushkin I (2012). "Toxic element contamination of natural health products and pharmaceutical preparations", *PLoS ONE* 7(11):Article ID e49676.
44. Genuis SJ, Sears ME, Schwalfenberg G, Hope J, and Bernhoft R (2013). "Clinical detoxification: elimination of persistent toxicants from the human body", *The Scientific World Journal* 2013:Article ID 238347, 3 pages.
45. Genuis SJ and Kelln KL (2015). "Toxicant exposure and bioaccumulation: a common and potentially reversible cause of cognitive dysfunction and dementia", Hindawi Publishing Corporation, *Behavioral Neurology* volume 2015, article ID 620143, <https://dx.doi.org/10.1155/2015/620143>
46. Goldman M, PJQuinlan, Ross GW *et al.* (2012). "Solvent exposures and Parkinson's disease risk in twins", *Annals of Neurology* 71(6):776–84.
47. Health Canada (2013). "Second report on human biomonitoring of environmental chemicals in Canada", <http://occupationalcancer.ca/wpcontent/uploads/2013/05/2ndHumanBiomonitoringReport.pdf>.
48. Jin CF, Haut M, and Ducatman A (2004), "Industrial solvents and psychological effects", *Clinics in Occupational and Environmental Medicine* 4(4):597–620.
49. Kanthasamy A, Jin H, Anantharam V *et al.* (2012). "Emerging neurotoxic mechanisms in environmental factors-induced neurodegeneration", *NeuroToxicology* 33(4):833–7.
50. Kilburn KH (2003). "Why is chemical brain injury ignored? Pondering causes and risks", *Archives of Environmental Health* 58(3):132–4.
51. Liu KS, Hao JH, Zeng Y, Dai FC, and Gu PQ (2013). "Neurotoxicity and biomarkers of lead exposure: a review", *Chinese Medical Sciences Journal* 28(3):178–88.
52. Lucchini R and Zimmerman N (2009). "Lifetime cumulative exposure as a threat for neurodegeneration: need for prevention strategies on a global scale", *NeuroToxicology* 30(6):1144-8.
53. Mah L, Kohli M, and Chan G (2014). "Ambient lead exposure is associated with greater risk of conversion to Alzheimer's disease and hippocampal atrophy in individuals with amnesic mild cognitive impairment", *The American Journal of Geriatric Psychiatry* 22(3):S117–S118.
54. Patterson C, Feightner JW, Garcia A, Hsiung JYR, MacKnightC , and Sadovnick AD (2008). "Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer's disease", *Canadian Medical Association Journal* 178(5):548–56.
55. Porru S and Alessio L (1996). "The use of chelating agents in occupational lead poisoning", *Occupational Medicine* 46(1):41–8.
56. Rappaport SM and Smith MT (2010), "Environment and disease risks", *Science* 330(6003):460–1.
57. Reis J and Román GC (2007). "Environmental neurology: a promising new field of practice and research", *Journal of the Neurological Sciences* 262(1-2):3–6.
58. Rhodes D, Spiro III A, Aro A, and Hu H (2003). "Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study", *Journal of Occupational and Environmental Medicine* 45(11):1144–51.

59. Richardson J, Roy A, Shalat S *et al.* (2014). "Elevated serum pesticide levels and risk for Alzheimer's disease" *Journal of American Medical Association Neurology* 71:E1–E7.
60. Rother HA (2014). "Communicating pesticide neurotoxicity research findings and risks to decision-makers and the public", *NeuroToxicology* 45:327–37.
61. Sabbath EL, Gutierrez LA, Okechukwu CA *et al.* (2014). "Time may not fully attenuate solvent-associated cognitive deficits in highly exposed workers", *Neurology* 82(19):1716–23.
62. Schofield P. (2005). "Dementia associated with toxic causes and autoimmune disease", *International Psychogeriatrics* 17(1):S129–47.
63. Sears ME (2013). "Chelation: harnessing and enhancing heavy metal detoxification—a review", *The Scientific World Journal* 2013(Article ID 219840):13 pages.
64. Squitti R (2014). "Copper subtype of Alzheimer's disease : meta-analyses, genetic studies and predictive value of non-ceruloplasmim copper in mild cognitive impairment conversion to full Alzheimer's disease", *Journal of Trace Elements in Medicine and Biology* 28(4):482–5.
65. Squitti R, Siotto M, and Polimanti R (2014). "Low-copper diet as a preventive strategy for Alzheimer's disease", *Neurobiology of Aging* 35(Supplement 2):S40–S50.
66. Stewart WF and Schwartz BS (2007). "Effects of lead on the adult brain: a 15-year exploration", *The American Journal of Industrial Medicine* 50(10):729–39.
67. Tilson HA, Rao P, and Kodavanti S (1998). "The neurotoxicity of polychlorinated biphenyls". *NeuroToxicology* 19(4-5):517–25.
68. van Wijngaarden, Campbell EJR, and Cory-Slechta DA (2009). "Bone lead levels are associated with measures of memory impairment in older adults", *NeuroToxicology* 30(4):572–80.
69. Visvanathan R (2001). "Is it truly dementia?" *The Lancet* 357(9257):684.
70. Walker B Jr. (2000). "Neurotoxicity in human beings", *Journal of Laboratory and Clinical Medicine* 136(3):168–80.
71. Yang M, Lu J, Miao J *et al.* (2014). "Alzheimer's disease and methanol toxicity (part 1): chronic methanol feeding led to memory impairments and tau hyperphosphorylation in mice", *Journal of Alzheimer's disease* 41(4):1117–29.

# Enhance the Language Ability of Humanoid Robot NAO through Deep Learning to Interact with Autistic Children

by Fuji Ren, Member EUAS



## Short Biography

*Dr. Fuji Ren is currently the Professor and Director of Affective Computing and Intelligent Robot Laboratory in Tokushima University. He is also the President of International Advanced Information Institute in Japan. He is a member of The Engineering Academy of Japan, a member of EU Academy of Sciences, a fellow of the Japan Federation of Engineering Societies, a fellow of The Institute of Electronics, Information and Communication Engineers, and a fellow of Chinese Association for Artificial Intelligence.*

*He received his B.E. degree in 1982 and M.E. degree in 1985 from the department of Computer Science, Beijing University of Posts and Telecommunications, Beijing, China. He received his Ph.D. in 1991 from Faculty of Engineering, Hokkaido University, Sapporo, Japan. From 1991 to 1994, he worked at CSK in Tokyo, Japan where he was the chief NLP researcher. He joined the Faculty of Information Sciences at Hiroshima City University as an Associate Professor in 1994. In 2001, he became a Professor in the Faculty of Engineering at Tokushima University. He has been the president of AIA International Advanced Information Institute since 2003. He serves as the Director of the Dept. of Information Science and Intelligent Systems from 2006 to 2010, the vice Dean of Information Solution Branch of Graduate School of Engineering from 2010 to 2012, and Dean of Information Solution Branch Graduate School of Engineering from 2012 to 2016 at Tokushima University.*

*He also holds professor positions at Dalian University of Technology, Harbin University of Technology and Xi'an Jiaotong University. He holds the roles of Advisory Professor at Beijing University of Posts and Telecommunications, Research Advisor at Tsinghua University, Visiting Professor at University of Science and Technology of China, Yangtze River Professor at Nanjing University, and Advisory Professor at Tongji University. He was a visiting professor at CRL (Computing Research Laboratory) at New Mexico State University, a visiting research professor in the College of Engineering, at Florida International University, and a visiting professor in Harvard University in the USA.*

His current research interests include Affective Computing and Intelligent Robot, Natural Language Processing, Artificial Intelligence, Language Understanding and Communication, Information Retrieval, Super-Function Methodology, Machine Learning, Knowledge Engineering, and Enlarged Health and Intelligence Education.

He has made fundamental contributions in the fields of human emotion recognition and robotic emotion creation, as well as natural speech understanding and emotional robotics development. He was the first in the world to propose the theory of mental state transition

network, which established a methodology for recognizing human emotions, creating machine emotions, and constructing large emotional corpuses. In addition, he researched and developed fundamental technologies for the development of robotic brains and emotions based on language, speech, and facial expressions.

He has directed and participated in over 50 research and development projects, as the PI of more than 30 grants with over 500 million Yen in total funding. He has authored or co-authored more than 20 books, 300 research journal papers and 500 conference papers. Many of his publications appeared in top conferences and journals, including IEEE, ACM, IEICE, IEEJ, CAAI and Information Sciences. He has been invited as a speaker or keynote speaker for more than 100 times in the USA, China, Japan, Singapore, France, and other countries. (Please see <http://pub2.db.tokushima-u.ac.jp/ERD/person/19966/work-en.html> for the list.) He has supervised 42 Ph.D. students (list of Ph.D. supervised by Prof. Fuji Ren) and more than 130 Masters students.

He received more than 50 Awards and Honors, such as The Chinese Government Friendship Award, PRC, 2019; Outstanding Contribution Award for the 7th Council of the Chinese Association for Artificial Intelligence, CAAI, 2019; Academician of The Engineering Academy of Japan, 2018; Academician of EU Academy of Sciences, 2018; Invention Prize, for “Multi-modal emotional computing and advanced intelligent applications”, China Association of Inventions, 2018; Science and Technology Award (Science and Technology Promotion Category), Tokushima Prefecture, Japan, 2018; Wu Wenjun Artificial Intelligence Science and Technology Progress Award, China, 2018; Fellow of The Institute of Electronics, Information and Communication Engineers, Japan, 2017; Fellow of The Chinese Association for Artificial Intelligence, China, 2017; Best Paper Award, for the paper entitled “Learning Efficient Drawing Sequence Through Training of Recurrent Neural Network Model”, CAAI and IEEE, 2017; Korakukai Foundation Award, for “To create an evolutionary advanced intelligent robot which have a brain and mind”, Japan, 2016; Industry-University-Research Cooperation Innovation Award, China Industry-University-Research Institute Collaboration Association, China, 2016; Best Paper Award, for the paper entitled “Text classification based on word co-occurrence with background knowledge”, CAAI, 2016; Outstanding Contribution Award, Scientific Chinese Person of the Year, China, 2016; Engineering Festival 2015 Excellence Award, for “Development of emotional development robot capable of rich emotional expression and recognition”, Japan, 2015; Wu Wenjun Artificial Intelligence Science and Technology Award, for “Advanced Interactive Robot based on Advanced Intelligence”, Association for Artificial Intelligence, 2014; Best Paper Award, for the paper titled “Class-indexing: The Effectiveness of Class-Space-Density in high and Low-Dimensional Vector Space for Text Classification”, IEEE, 2012; Fellow of Japan Federation of Engineering Society, Japan, 2009; Yangtze River Scholar, the highest academic award issued to an individual in higher education by the Ministry of Education of PRC, 2006; 12th Gennai Award for Natural Science Award, Japan, 2005, etc.

He served at more than 200 international conferences as chair, steering committee member, advisory committee member, executive committee member, program committee member, and organizing committee member at meetings of IEEE, CAAI, IEICE, IASTED, IJAI and other organizations. These include Founder and General Chair of the International Conference on Natural Language Processing and Knowledge Engineering, IEEE, CAAI (2003- present); Steering Committee Co-Chair, The 10th International Workshop on Assistive Engineering and Information Technology (AEIT 2020); General Co-Chair, the 4th Asian Conference on Artificial Intelligence Technology, (2019- present); Program Committee Co-Chairs, THE 3rd China Intelligence Education Conference (2019- present);

Publicity Co-Chair of 14th IEEE International Conference on Networking, Sensing and Control, (2017-2018); Program Committee Co-Chairs, IEEE International Conference on Cloud Computing and Intelligence Systems, (2011- present); Advisory Board, The 9th International Conference on Rough Sets and Knowledge Technology (RSKT 2014-2014); Steering Committee, International Workshop on Assistive Engineering (2013- present); General Co-Chair, 2011 International Conference on Information Theory and Information Security (2010-2011); General Chair, International Conference on Advanced Intelligence and Global Engineering Education (2008-2015); Program Committee Co-Chair, 2010 Multi-Conference on Advanced Intelligence (2010-2011); International Advisory Board Chair, 2009 International Conference on Information Management, Innovation Management and Industrial Engineering,(2009-2009); Organizing Committee Co-Chair, International Conference on Information,(2001-2009); International Advisory Board Chairs, International Conference on Advanced Intelligence (2008-2012); The General Chair, International Symposium on Artificial Intelligence and Affective Computing, (2006-2010); and Program Chair, Joint Workshop on Intelligent System and Information Processing (2016-2017).

He served as editor-in-chief, area editor-in-chief, and editor on more than 20 academic journals, including editor-in-chief, International Journal of Advanced Intelligence, (2009–present); editorial board, CAAI Transactions on Intelligent System, (2013–present); editorial board, Enterprise Information Systems, (2012–present); editorial board, Research Journal on Computer science and computer engineering with applications, (2010– present); editorial board, The Journal of China Universities of Posts and Telecommunications, (2006– present); editorial board, Science & Technology Review, (2006– present); editor, Journal of Chinese Information Processing, (2005-present); editor, Journal of Beijing University of Posts and Telecommunications, (2006– present); associate editor, International Journal of Innovative Computing, Information and Control, (2005– present); editor, International Journal of Information Acquisition, (2005– present); associate editor, Asian Information-Science-Life, (2002– 2004); editor, International Journal of Information Technology and Decision Making, (2004– present); area editor-in-chief, International Journal of Information, (1998– present); editor, International Journal COLIPS, (1996-2005); editor-in- chief, Journal of Science and Technology, (1995-1998); editorial board member, Electronics, and others.

He was invited to be a senior overseas consultant for the BUPT (Beijing University of Posts and Telecommunications) Academic Committee, a consultant for the Beijing Lab. of Multi-Media, a senior consultant for Japan PtoPA Inc. and AGI Inc., an academic committee member of the Chinese national laboratory of pattern recognition, an overseas assessor of the Chinese Academy of Sciences, and a senior overseas consultant of China Council for the Promotion of Applied Technology Exchanges with Foreign Countries. He is Honorary Vice President of Chinese Association for Artificial Intelligence, (2019-present); Vice President of Chinese Association for Artificial Intelligence, (2010-2019); Member of Human Resources Development Committee of EAJ, Japan, (2018-present); President of The Association for Chinese Scientists in Japan, (1993-1995); President of Chinese Academy of Science and Engineering in Japan, (2001-2005); Honorary President of Chinese Academy of Science and Engineering in Japan, (2006-present), and others.

## Enhance the Language Ability of Humanoid Robot NAO through Deep Learning to Interact with Autistic Children

Tianhao She and Fuji Ren

*Electronics* **2021**, *10*

### Abstract

Autism spectrum disorder (ASD) is a life-long neurological disability, and a cure has not yet been found. ASD begins early in childhood and lasts throughout a person's life. Through early intervention, many actions can be taken to improve the quality of life of children. Robots are one of the best choices for accompanying children with autism. However, for most robots, the dialogue system uses traditional techniques to produce responses. Robots cannot produce meaningful answers when the conversations have not been recorded in a database. The main contribution of our work is the incorporation of a conversation model into an actual robot system for supporting children with autism. We present the use of a neural network model as the generative conversational agent, which aimed at generating meaningful and coherent dialogue responses given the dialogue history. The proposed model shares an embedding layer between the encoding and decoding processes through adoption. The model is different from the canonical Seq2Seq model in which the encoder output is used only to set-up the initial state of the decoder to avoid favoring short and unconditional responses with high prior probability. In order to improve the sensitivity to context, we changed the input method of the model to better adapt to the utterances of children with autism. We adopted transfer learning to make the proposed model learn the characteristics of dialogue with autistic children and to solve the problem of the insufficient corpus of dialogue. Experiments showed that the proposed method was superior to the canonical Seq2Seq model and the GAN-based dialogue model in both automatic evaluation indicators and human evaluation, including pushing the BLEU precision to 0.23, the greedy matching score to 0.69, the embedding average score to 0.82, the vector extrema score to 0.55, the skip-thought score to 0.65, the KL divergence score to 5.73, and the EMD score to 12.21.

# Retaining Structures and Bridges in Unstable Rock or Soil Slopes

by Heinz Brandl, Member EUAS

## Short Biography

*Prof. H. Brandl has been Full Professor for Soil and Rock Mechanics and Foundation Engineering (including Tunnelling) since 1977, chairing until 2009 the prestigious Institute for Soil Mechanics and Geotechnical Engineering, which was founded by Prof. Karl Terzaghi in 1928 at the Vienna University of Technology. Since 2008 he is Prof. Emeritus.*

*Professor Brandl authored about 580 scientific publications (including 21 books), partly published in 18 languages. The subjects cover laboratory and field testing, soil and rock mechanics, foundation engineering, slope engineering, earthworks, tunnelling, urban undergrounds, restoration of historical buildings, road and railway engineering, hydro/hydraulic engineering and environmental engineering, geosynthetics, geothermal engineering (“energy foundations”, “energy tunnels” etc.), natural disaster mitigation and rehabilitation, etc. He also published on philosophical aspects and on ethics in the profession. From the very outset of his professional work H. Brandl has been bridging the gap between theory and practice. He has been fully responsible for nearly 4000 projects of civil engineering, geotechnical and environmental engineering in Austria and elsewhere.*

*Prof. Brandl has been active world-wide since 1968 as chairman, general reporter, state-of-the-art reporter, special-, keynote- and opening lecturer, discussion leader and panellist at numerous international conferences on geotechnical engineering, environmental engineering, geosynthetics, etc. He was Rankine Lecturer (2001), Giroud Lecturer (2010), and he created the prestigious “Vienna Terzaghi Lecture”.*

*He was Vice-President ISSMGE (1997 - 2001), and from 1973 to 2015 President of the Austrian Geotechnical Society. Moreover, he is a member of the Royal Academy of Sciences of Belgium, of the International Academy of Engineers (Moscow) and other Scientific Academies. Since June 2003 he has been President of the Austrian Society for Engineers and Architects (founded in 1848). He received numerous national and international awards (e.g. Kevin Nash Gold Medal), honorary doctorates and other honours.*

## **Retaining structures and bridges in unstable rock or soil slopes**

5th Symposium of the Macedonian Association for Geotechnics - an ISRM Specialized Conference  
23.-25.06.2022

Heinz Brandl

## **Abstract**

Rockfall and landslide prevention and stabilisation as well as risk assessment are essential for the design, construction and maintenance of structures in unstable slopes. Roads, highways and railways are frequently running in landslide-prone areas which often are seismic zones as well. The paper underlines the influence of water and shear parameters on slope stability, and the importance of determining the

residual shear strength. Creeping causes excessive lateral pressures on structures; details for calculation are presented in this paper. Building in unstable slopes requires engineering flexibility and structures which can be strengthened step by step if necessary. This involves semi-empirical design (“active design”) based on calculated risk and the observational method including contingency plans and long-term monitoring. Several case histories demonstrate this engineering philosophy which has proved suitable for nearly 50 years.

### **Long-term settlement (creeping) of soft soils, and ground improvement**

GeoMEast 2019, Egypt, Cairo: International Congress and Exhibition "Sustainable Civil Infrastructures"

10.-14.11.2019

Heinz Brandl

#### **Abstract**

The keynote paper focuses on the long-term settlement (creeping) of highly compressible soils, considering also soft sludge. Long-term oedometer tests lasted up to 42 years and were performed on silty sand, (organic) clayey silt, peat and (pre-treated) sewage sludge. Secondary consolidation (creep) could be observed in all cases, lasting over many years and occurring widely linear with the logarithm of time. However, temporary acceleration may also be observed, indicating a discontinuous nature of internal deformations due to accelerated rearrangement in the fabric – mainly in very soft soils with peaty components. This long-term phase is followed by tertiary creeping with a long lasting fading out period. In both phases microcrystalline sliding occurs.

In addition to the laboratory tests results of comprehensive field measurements are summarized, showing the influence of different ground improvement methods on the creeping behaviour of highly compressible fine-grained soils (partly organic). Most data were collected from a highway junction with embankments on very soft, heterogeneous ground (locally 15 m deep and with a natural water content up to 1000%), constructed between 1972 and 1974, and monitored since. Different ground improvement methods were compared, disclosing details of primary, secondary and tertiary settlement: Deep dynamic compaction/consolidation (heavy tamping), vibro-flotation (piled embankments), temporary surcharge loading, and local combinations of the previous methods, including also vertical drains.

### **Stability and barrier systems of municipal waste deposits**

XVII European Conference on Soil Mechanics and Geotechnical Engineering, Reykjavik Iceland

01.- 06.11.2019

Heinz Brandl

**Abstract**

The paper underlines that an appropriate pre-treatment of waste is crucial to avoid the passing-on of environmental impacts of today's landfills to future generations. Moreover, multi-barrier systems are recommended, especially in case of hazardous waste. For geotechnical stability analyses of waste deposits a compatibility investigation of the sometimes fundamentally different shear stress-strain behavior of waste and subsoil is recommended. Horizontal barriers commonly require composite liner systems, unless pre-treated or mono-waste of low risk potential is deposited. Assumptions for risk analyses are presented in this paper.

## Fluid - Mosaic Membrane Structure

by Garth L. Nicolson, Member EUAS

### Short Biography

#### **Professor Emeritus Garth L. Nicolson, PhD, MD (H)**

Professor Emeritus Garth L. Nicolson is the Founder, President, Chief Scientific Officer and Emeritus Research Professor of Molecular Pathology at the Institute for Molecular Medicine in Huntington Beach, California. He is also a Conjoint Emeritus Professor at the University of Newcastle (Australia). He was previously the David Bruton Jr. Chair in Cancer Research and Professor and Chairman at the University of Texas M.D. Anderson Cancer Center in Houston, and he was Professor of Internal Medicine and Professor of Pathology and Laboratory Medicine at the University of Texas Medical School, Houston. Professor Nicolson has published over 700 medical and scientific papers, including editing 20 books, and he has served on the Editorial Boards of 30 medical and scientific journals and was Senior Editor of four of these. Professor Nicolson has won many awards, such as the Burroughs Wellcome Medal of the Royal Society of Medicine (United Kingdom), Stephen Paget Award of the Metastasis Research Society, U.S. National Cancer Institute Outstanding Investigator Award, the Innovative Medicine Award of Canada and the EU Academy of Sciences. He is also a Colonel (O6, Honorary) of the U. S. Army Special Forces and a U.S. Navy SEAL (Honorary) for his work on Armed Forces and veterans' illnesses.

#### **Professional Experience:**

##### **Primary Appointment:**

1996-Present, President and Founder, Chief Scientific Officer and Emeritus Professor of Molecular Pathology, The Institute for Molecular Medicine, PO Box 9355, S. Laguna Beach, CA 92652

##### **Secondary Appointments:**

2003-Present, Conjoint Emeritus Professor, Faculty of Science and Technology, University of Newcastle, Newcastle, Australia

##### **Previous Appointments:**

1989-00, Professor, Department of Internal Medicine, The University of Texas Medical School, Houston, TX

1981-99, Adjunct Professor, Department of Pathology, School of Veterinary Medicine, Texas A & M University, College Station, TX

1982-99, Professor, Department of Pathology and Laboratory Medicine, The University of Texas Medical School, Houston, TX

1980-96, David Bruton Jr. Chair in Cancer Research, Professor and Chairman, Tumor Biology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

1980-96, Professor, The Graduate School of Biomedical Sciences, The University of Texas Health Science Center, Houston, TX

1980-87, Florence M. Thomas Professor of Cancer Research, The University of Texas M. D. Anderson Cancer Center, Houston, TX

1978-80, Professor, Department of Physiology and Biophysics, College of Medicine, University of California, Irvine, CA

1977-80, Associate Director, Oncology Program, University of California, Irvine, CA

1975-80, Professor, Department of Developmental and Cell Biology, University of California, Irvine

1974-76, Chairman, Department of Cancer Biology, The Salk Institute, La Jolla, CA

1972-74, Head, Cancer Council Laboratory, Director, Electron Microscopy Laboratory, The Salk Institute, La Jolla, CA

1970-71, Senior Research Associate, Cancer Council Laboratory, The Salk Institute, La Jolla, CA

1967-70, USPHS Predoctoral Fellow University of California, San Diego, CA

#### **Honors and Awards:**

European Union Academy of Sciences, 2019-

Doctor of Medicine, M.D. (H), University of the Republic of Uruguay, 2015

Yanagimachi Distinguished Lectureship, University of Hawaii School of Medicine, 2012

John Drulle Memorial Lectureship, International Lyme and Associated Diseases Society (ILADS), 2008

Annual Award of the Common Cause Medical Research Foundation (Canada), 2006

Innovative Medicine Award (Canada), 2002

Stephen Paget Award, Metastasis Research Society, 1998

Albert Schweitzer Award (Portugal), 1998

*First Norman N. Durham Lectureship, Environmental Institute, OSU, 1996*  
*Indo-American Society for Health & Laboratory Professionals Award, 1996*  
*Distinguished Presentation Award, Third International Cancer Molecular Biology Symposium, 1996*  
*COLONEL (Honorary), U. S. Army Special Forces, 1995*  
*SEAL (Honorary), U.S. Navy Special Forces, 1995*  
*Haskel Visiting Professorship, University of Pennsylvania, 1995*  
*Burroughs Wellcome Medal, Royal Society of Medicine Foundation, London, 1991*  
*Outstanding Faculty Award, The University of Texas Health Science Center at Houston, 1991*  
*U.S. National Cancer Institute U.S.S.R. Scientist Exchange Award for Collaborative Research on*  
*Molecular and Genetic Aspects of Tumor Metastasis, 1991*  
*Evan and Marion Helfaer Distinguished Lectureship, The Cancer Center of the Medical College of*  
*Wisconsin, 1990*  
*Dean's Teaching Excellence List, The University of Texas Health Science Center at Houston Graduate*  
*School of Biomedical Sciences, 1985-1994*  
*Teaching Excellence Award for Best Course, The University of Texas Medical School at Houston, 1990*  
*NCI/NIH Outstanding Investigator Award, 1987*  
*Annual Award of the Japan Histochemical Society, 1976*  
*Eli Nadel Memorial Lecture in Biochemistry, 1983*  
*Rita Ferdinand Memorial Lectureship, 1982*  
*Guy Lipscomb Memorial Lecture in Chemistry, 1980*  
*Upjohn Biology Education Award, 1976*  
*Presidential Award, Electron Microscopy Society of America, 1971*

## Fluid-Mosaic Membrane Structure

Early cell membrane models placed most proteins external to lipid bilayers in trimolecular structures or as modular lipoprotein units. These thermodynamically untenable structures did not allow lipid lateral movements independent of membrane proteins. The Fluid–Mosaic Membrane model accounted for these and other properties, such as membrane asymmetry, variable lateral mobilities of membrane components and their associations into dynamic complexes. Integral membrane proteins can form into globular structures that are intercalated to various degrees into a heterogeneous lipid bilayer matrix. This simplified version of cell membrane structure was never proposed as the ultimate biomembrane description, but it provided a basic nanometer scale framework for membrane organization. Subsequently, structures associated with membranes were considered, including peripheral membrane proteins, and cytoskeletal and extracellular matrix components that restricted lateral mobility. In addition, lipid-lipid and lipid-protein membrane domains, essential for cellular signaling, were proposed and eventually discovered. The presence of specialized membrane domains reduced significantly the extent of the fluid lipid matrix so that membranes have become more mosaic with some fluid areas over time. However, the fluid regions of membranes are very important in lipid transport and exchange. Various lipid globules, droplets, vesicles and other membranes can fuse to incorporate new lipids or expel damaged lipids from membranes, or they can be internalized in endosomes that eventually fuse with other internal vesicles and membranes.

### Publications in this area:

Nicolson, G.L. The Singer-Nicolson Fluid—Mosaic Membrane Model and Membrane Lipid Replacement. *Univ. J. Fluid Mech.* 9: 35-50 (2021).

Nicolson, G.L. and Ferreira de Mattos, G. A brief introduction to some aspects of the Fluid—Mosaic Model of membrane structure and its importance to Membrane Lipid Replacement. *Membranes* 11(12): article 947 (2021).

## Membrane Lipid Replacement

Membrane Lipid Replacement (MLR) uses natural membrane lipid supplements to safely replace damaged, oxidized lipids in membranes in order to restore membrane function, decrease symptoms and improve health. Oral MLR supplements contain mixtures of cell membrane glycerolphospholipids, fatty acids and other lipids and can be used to replace and remove damaged cellular and intracellular membrane lipids. Membrane injury, caused mainly by oxidative damage, occurs in essentially all chronic and acute medical conditions, including cancer and degenerative diseases, and in normal processes, such as aging and development. After ingestion the protected MLR glycerolphospholipids and other lipids are dispersed, absorbed and internalized in the small intestines, where they can be partitioned into circulating lipoproteins, globules, liposomes, micelles, membranes and other carriers and transported in the lymphatics and blood circulation to tissues and cellular sites where they are taken in by cells and partitioned into various cellular membranes. Once inside cells the glycerolphospholipids and other lipids are transferred to various intracellular membranes by lipid carriers, globules, liposomes, chylomicrons, or by direct membrane-membrane interactions. The entire process appears to be driven by 'bulk flow' or mass action principles, where surplus concentrations of replacement lipids can stimulate the natural exchange and removal of damaged membrane lipids while the replacement lipids undergo further enzymatic alterations. Clinical studies have demonstrated the advantages of MLR in restoring membrane and organelle function and reducing fatigue, pain and other symptoms in chronic illness and aging patients.

### Publications in this area:

Nicolson, G.L., Ferreira de Mattos, G., Ash, M., Settineri, R. And Escribá, P.V. Fundamentals of Membrane Lipid Replacement, a natural medicine approach to reducing fatigue, pain, and other symptoms while restoring function in chronic illnesses and aging. *Membranes* 11(12): article 944 (2021).

Nicolson, G.L. and Settineri, R. No evidence of allergic reactions to soy lecithin phospholipids used in Membrane Lipid Replacement studies. *Bioactive Comp. Health Dis.* 4(1): 9-13 (2021).

Medica, A.J., Aitkin, R.J., Nicolson, G.L., Sheridan, A.R., Swegan, A., De Luliis, Gib, Z. Glycerophospholipids protect stallion spermatozoa from oxidative damage in vitro. *Reproduction & Fertility* 2: 199-209 (2021).

## Chronic Infections in Disease and Treatments

The effects of certain systemic viral and bacterial infections on morbidity and mortality are considered as examples of recent emerging infections. We have focused on three examples of infections that are important in pregnancy and early childhood: SARS-CoV-2 virus, Zika virus, and *Mycoplasma* species. The basic structural characteristics of these infectious agents will be examined, along with their general pathogenic mechanisms. Coronavirus infections, such as caused by the SARS- CoV-2 virus, likely evolved from zoonotic bat viruses to infect humans and cause a pandemic that has been the biggest challenge for humanity since the Spanish Flu pandemic of the early 20th century. In contrast, Zika Virus infections represent an expanding infectious threat in the context of global climate change. The relationship of these infections to pregnancy, the vertical transmission and neurological sequels make these viruses highly relevant to the topics of this special issue. Finally, mycoplasma infections have been present before mankind

evolved, but they were rarely identified as human pathogens until recently, and they are now recognized as important coinfections that are able to modify the course and prognosis of various infectious diseases and other chronic illnesses. The infectious processes caused by these intracellular microorganisms are examined as well as some general aspects of their pathogenesis, clinical presentations, and diagnoses. We finally considered examples of treatments that have been used to reduce morbidity and mortality of these infections and discuss briefly the current status of vaccines, in particular, against the SARS-CoV-2 virus.

#### **Publications in this area:**

Ferreira, G., Santander, A., Guirado, M., Sobrevia, L. and Nicolson, G.L. SARS-CoV-2, Zika viruses and Mycoplasma: structure, pathogenesis and some treatment options in emerging viral and bacterial infectious diseases. *Biochim. Biophys. Acta Mol. Basis Dis.* 1867: 166264 (2021).

Ferreira, G., Blassina, F., Rey, M., Anesetti, G., Sapiro, R. Chavarría, L., Cardozo, R., Rey, G., Sobrevia, L. and Nicolson, G.L. Pathophysiological and molecular considerations of viral and bacterial infections during maternal-fetal and –neonatal interactions of SARS-CoV-2, Zika and Mycoplasma infectious diseases. *Biochim. Biophys. Acta Mol. Basis Dis.* 1868: 166285 (2022).

#### **Effects of Heavy Metals on Membranes and Health**

Lead and mercury are heavy metals that are highly toxic to life forms. There are no known physiological processes that require them, and they do not have a particular threshold concentration to produce biologic damage. They are non-biodegradable, and they slowly accumulate in the environment in a dynamic equilibrium between air, water, soil, food, and living organisms. Their accumulation in the environment has been increasing over time, because they were not banned from use in anthropogenic industrial production. In their +2 cationic state they are powerful oxidizing agents with the ability to interfere significantly with processes that require specific divalent cations. Acute or chronic exposure to lead and mercury can produce multisystemic damage, especially in the developing nervous systems of children and fetuses, resulting in variety of neurological consequences. They can also affect the cardiovascular system and especially the heart, either directly through their action on cardiomyocytes or indirectly through their effects on innervation, humoral responses or blood vessel alterations. For example, heart function modified by these heavy metals are heart rate, contraction, excitability, and rhythm. Some cardiac molecular targets have been identified and characterized. The direct mechanisms of damage of these heavy metals on heart function are discussed. We conclude that exposure to these heavy metals, should be considered as a major relevant risk factor for cardiac diseases.

#### **Publications in this area:**

Ferreira, G., Santander, A., Costa, C., Sobrevia, L. and Nicolson, G.L. Functional consequences of lead and mercury exposomes in the heart. *Molec. Aspects Med.* 81: 101048 (2021).