EU ACADEMY OF SCIENCES
EUAS

EU ACADEMY
2015 ANNUAL REPORT

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Professor E.G. Ladopoulos (2000 Outstanding Scientists 20th-21st Centuries)

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Professor S. Nakamura (Nobel Physics 2014)

Professor P. Higgs (Nobel Physics 2013)

Professor W. Ketterle (Nobel Physics 2001)

Professor A. Geim (Nobel Physics 2010)

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Professor Y.T. Lee (Nobel Chemistry 1986)

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Professor M.Levitt (Nobel Chemistry 2013).

Board of Governors in the Division of Medicine:

Professor C. Greider (Nobel Medicine 2009)

Professor R. Schekman (Nobel Medicine 2013)

Professor S. Yamanaka (Nobel Medicine 2012).

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Professor D. Kahneman (Nobel Economics 2002)

Professor P. Krugman (Nobel Economics 2008)

Professor J. Stiglitz (Nobel Economics 2001)

Professor E. S. Phelps (Nobel Economics 2006).

Contents

Universal Mechanics, Universal Equation of Elasticity & Universal Equation of Thermo-Elasticity for Future Aircraft & Spacecraft - Relativistic Elasticity & Thermo-Elasticity

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 20th Century by Cambridge Bio Centre.
Included in the list of 2000 Outstanding Scientists of 21st Century by Cambridge Bio Centre.
Included in the list of 100 Top Scientists of 2007 by Cambridge Bio Centre.
Over 300 publications in high quality scientific journals.
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.
President & CEO of the EU Academy of Sciences.
Member of several Academies in USA.

In the near future we expect the International Aeronautical Industries to effect a competitive technological advantage in several strategic areas of new and rapidly developing advanced technologies. Hence, this considerably big market share includes the design of a next generation aircraft with speeds even in the range of 50,000 km/h. Consequently, as the design of new generation turbojet engines makes possible the design of such type of large aircraft, then there is a need of elastic stress design and analysis for the construction of the total parts of such type of next generation aircraft.

Besides, the scope by the International Space Agencies is to achieve in the future, a next generation spacecraft moving with very high speeds, even approaching the speed of light. How far could be this future ? According to the present article such future could be much closer than everybody believes. For the next generation 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.

On the other hand, the suitable choice of the solid which should be used for the construction of the future spacecraft is under investigation, but such solid will be very much different than the usual composite materials.

There is a significant 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 the difference of the two stress tensors will be very much increased. Hence, for bigger velocities like c/3, c/2 or 3c/4 (c=speed of light) the relative stress tensor is very much different than the absolute one and for velocities near the speed of light the values of the relative stress tensor are much bigger than the corresponding values of the absolute stress tensor.

The study of the connection between the stress tensors of the absolute frame and the airframe is included in the theory proposed by E.G.Ladopoulos under the term ***"Relativistic Elasticity"*** and ***"Relativistic Thermo-Elasticity"*** and the final formula which results from the above theories is called the ***"Universal Equation of Elasticity"*** and the ***"Universal Equation of Thermo-Elasticity"***, correspondingly.

So, *"Relativistic Elasticity"* results as a combination of the theories of Elasticity and General Relativity. On the other hand, *"Relativistic Thermo-Elasticity"* results as combination between the theories of Thermo-Elasticity and General Relativity. Furthermore, both theories of *"Relativistic Elasticity"* and *"Relativistic Thermo-Elasticity"* are included in a more general theory under the term ***"Universal Mechanics"***.

Consequently, *"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 E.G. Ladopoulos. Hence, by E.G.Ladopoulos is completed the theory of Albert Einstein for the whole universe regarding mechanics behavior. ***Thus, this theory could be nominee for a Nobel prize in physics***.

Also, E.G.Ladopoulos proposed singular integral equation methods applied to elasticity, plasticity and fracture mechanics theories. In the above methods the ***Singular Integral Operators Method (S.I.O.M.)*** was used for the numerical evaluation of the multidimensional singular integral equations in which the stress tensor analysis of the linear elastic theory is reduced. In addition, the theory of linear singular integral equations was extended to non-linear singular integral equations, too. Hence, the theory of *"Universal Mechanics"* and correspondingly the theories of *"Relativistic Elasticity"* and *"Relativistic Thermo-Elasticity"* will be applied for the design of the elastic stress analysis of the airframes.

Besides, as was proved by E.G. Ladopoulos the **"*relative stress tensor is not symmetrical*"**, while, as it is well known, the **"*absolute stress tensor is symmetrical*"**. Such a difference is very important for the design of the next

generation aircraft and spacecraft of very high speeds. Finally, the "structural design" of super speed vehicles requires the consideration of mass pulsation and energy-mass interaction at high velocity space-time scale.

Table 1 shows the values of γ 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	∞

From Table 1 follows that for small velocities 50,000 *km/h* to 200,000 *km/h*, the absolute and the relative stress tensor are nearly the same. On the other hand, for bigger velocities like $c/3$, $c/2$ or $3c/4$ (c = speed of light), the variable γ 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 γ takes bigger values, while when the velocity is equal to the speed of light, then γ tends to the infinity.

For the design of the future aircraft and spacecraft are further used the *"Universal Stress Intensity Factors"*. So, as was shown by E.G.Ladopoulos 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 next generation aircraft and spacecraft, as for their fracture mechanics analysis a combination of all the three intensity factors should be used. Thus, because of the above difference of the stress intensity factors, follows that the fracture behavior of the next generation aircraft and spacecraft would be much different and thus special materials should be used for their construction.

Groundbreaking Experiments Regarding the Two-dimensional Material Graphene

by Sir Andre Geim, Governor EUAS

<u>Short Biography</u>
Regius Professor of Physics; Royal Society Research Professor
University of Manchester
Published over 250 peer-refereed research papers, including approx. 30 in Science and Nature.
More than 80 of the papers are cited >100 times, with 20 cited >1,000 times each, and three cited >10,000 times.
According to ISI's Essential Science Indicators, responsible for initiating three new research fronts (graphene, van-der-Waals adhesives and diamagnetic levitation).

Awards
*2010 - **Nobel Prize** for "groundbreaking experiments regarding the two-dimensional material graphene" (shared with Kostya Novoselov)*
*2015 - **Lifetime Governor** of the EU Academy of Sciences*
*2013 - **Copley Medal** for "numerous scientific contributions and, in particular, for initiating research on two dimensional atomic crystals and their artificial heterostructures"*
*2011 - **Niels Bohr Medal** for "outstanding contributions to the development of physics"*
*2010 - **Hughes Medal** for "discovery of graphene and elucidation of its remarkable properties"*
*2010 - **John Carty Award** from the US National Academy for "realization and investigation of graphene, the two-dimensional form of carbon"*
*2009 - **Körber Prize** for having "developed the first two-dimensional crystals made of carbon atoms"*
*2008 - **EuroPhysics Prize** "for discovering and isolating a single free-standing atomic layer of carbon (graphene) and elucidating its remarkable electronic properties" (shared with Kostya Novoselov)*
*2007 - **Mott Prize** "for the discovery of a new class of materials – free-standing two-dimensional crystals – particularly graphene"*
*2000 - **IgNobel Prize** for "levitating frogs" (shared with Michael Berry)*
***Knighthoods** from Netherlands (C.N.L. 2010) and the UK (Kt 2012)*
More than 20 prize lectures

Extras
Fellow of the Royal Society; Foreign Associate of the US National Academy of Sciences.
Honorary Doctorates from Delft University, ETH Zurich & Universities of Antwerp, Manchester &Gothenburg.
Hon Professor at Moscow Phys-Tech & University of Nijmegen; Hon Fellow of the Institute of Physics; Hon Fellow of the Royal Society of Chemistry; "Einstein Professor" of the Chinese Academy of Sciences; Hon Fellow of Singapore Institute of Physics; Corresponding Member of the Dutch Academy; Foreign Member of the Bulgarian Academy.
2009, 2010 & 2011 - Repeatedly named by Thomson-Reuters among top 10 most active, "hottest" researchers.

Πλανήτη GRAPHENE

The reader may find some of the cited ideas and historical papers irrelevant, but I tried my best to avoid any pre-2004 result, especially experimental, being overlooked. All the mentioned studies poked in the right direction, but there were no big surprises to spark a graphene gold rush. This is probably because the earlier experiments had one thing in common. They were observational. They observed ultra-thin graphitic films, and occasionaly even monolayers without reporting any of graphene's distinguishing properties. The very few electrical and optical measurements cited above were done using thin films of graphite and could not assess the physics that graphene has brought to the fore since 2004.

Our *Science* paper provided a clear watershed. Of course, the article reported the isolation of graphene crystals large enough to do all sorts of measurements, beyond the observation in an electron or scanning probe microscope. The method of graphene isolation and identification it described was so straightforward and accessible that even schoolchildren could probably do it. This was important but, if we were to stop there, just with the observations, our work would only add to the previous literature and, I believe, disappear into oblivion. It is not the observation and isolation of graphene but its electronic properties that took researchers by surprise.

Our measurements delivered news well beyond the Scotch tape technique, which persuaded many researchers to join in the graphene rush. First, the 2004 paper reported an ambipolar electric field effect, in which resistivity changed by a factor of ~100. This is thousands of times more than the few per cent changes observed previously for any metallic system and amounted to a qualitative difference. To appreciate the exquisiteness of this observation, imagine a nanometre thick Au film. No matter what you do with such a film by physical means, it will remain a normal metal with the same properties. In contrast, properties of graphene can be altered by simply varying the gate voltage. We can tune graphene from a state close to a normal metal with electrons in concentration $\sim 10^{21}$ cm^{-3} to a metal with a similar concentration of holes, all the way through a 'semiconducting' state with few charge carriers.

Even more remarkably, our devices exhibited an astonishing electronic quality. Graphene was completely unprotected from the environment, as it was placed on a microscopically rough substrate and covered from both sides with adsorbates and a polymer residue. Still, electrons could travel submicron distances without scattering, flouting all the elements outside. This level of electronic quality is completely counterintuitive. It contradicts the common wisdom that surface science requires ultra-high vacuum and, even then, thin films become progressively poorer in quality as their thickness decreases. Even with hindsight, such electronic quality is mystifying and, in fact, not fully understood so far.

In semiconductor physics, electronic quality is described in terms of charge carrier mobility μ. Our *Science* paper reported graphene with room-T μ ≈10,000 cm2/Vs (as of 2010, μ can be 10 and 100 times higher at room and low T, respectively). For a general reader, 10,000 may sound like just another number. To

explain its significance, let us imagine that in 2004 we made devices from, for example, reduced graphene oxide, which exhibits μ ~1cm2/Vs due to its irreversibly damaged crystal lattice.

In our second paper on graphene, we reported 2D dichalcogenides with equally low μ. Since then, there has been little interest in them. The reported ballistic transport over submicron distances was essential to spark interest in graphene and to allow the observation of many quantum effects reported both in 2004 and later. This would have been impossible if graphene exhibited μ below several 1,000 cm2/Vs. If not for graphene's high quality and tunability, there would be no new physics and, therefore, no graphene boom. In this respect, graphene history has something in common with that of solar planets. Ancient Greeks observed them and called them wandering stars, πλανήτες. After the physics behind this wandering was discovered, people started perceiving planets quite differently from πλανήτες. Similarly, during the last six years people discovered what graphene really is, which completely changed the earlier perception. Our *Science* paper offered the first glimpse of graphene in its new avatar as a high quality 2D electronic system and beyond.

MAGIC OF FLAT CARBON

What is this new incarnation? For me, 2004 was only the starting point for the unveiling of many unique properties of graphene. Since then, we have demonstrated that charge carriers in graphene are massless fermions described by a Dirac-like equation rather than by the standard Schrφdinger equation. In bilayer graphene, electrons receive yet another makeup as massive Dirac fermions. These properties were unveiled by the observation of two new types of the integer quantum Hall effect, which corresponded to the two types of Dirac fermions. We also found that graphene remained metallic in the limit of no charge carriers, even when just a few electrons remained present in a micron-sized device.

Our experiments have revealed that graphene exhibits a universal optical conductivity of $\pi e2/2h$, such that its visible opacity is just $\pi\alpha$, where α is the fine structure constant. We suggested that the phenomenon of Klein tunnelling, which was known in relativistic quantum physics for many decades but assumed non-observable, could be probed using graphene devices. Several groups later demonstrated this experimentally. We were lucky to be slightly quicker than others in showing that bilayer graphene was a tuneable-gap semiconductor and that graphene could be carved into devices on a true nm scale. We demonstrated sensors capable of detecting individual molecules, more sensitive than any sensor before.

We suggested that strain in graphene creates pseudo-magnetic fields that alter its electronic properties and later discussed the possibility of creating uniform pseudo-fields and observation of the quantum Hall effect without an external magnetic field. Pseudo-magnetic fields in excess of 400 T were reported experimentally half a year later. We made the first step into graphene chemistry by experimentally introducing its derivatives, graphane and stoichiometric fluorographene. This is not even an exhaustive list of the nice phenomena that we and our collaborators found

in graphene and, of course, many other researchers reported many other beautiful discoveries that propelled graphene into its new status of a system that can nearly deliver magic.

ODE TO ONE

After reading about the beautiful properties of graphene, the reader may wonder why many atomic layers stacked on top of each other, as in graphite, do not exhibit similar properties. Of course, any graphitic derivative has something in common with its parent, but in the case of graphene, differences between the parent and descendants are fundamental. To appreciate this, let us simplify the task and compare graphene with its bilayer. The crucial distinctions are already there. First, graphene exhibits record stiffness and mechanical strength. As for its bilayer, this strength is jeopardised by the possibility that the two layers will slide relative to each other. This leads to a principal difference if, for example, graphene or any thicker platelets are used in composite materials.

Second, graphene chemistry is different depending on whether one or both surfaces of a monolayer are exposed. For example, atomic hydrogen cannot bind to graphene from one side but makes a stoichiometric compound (graphane) if both surfaces are exposed. This makes graphene much more reactive than its bilayer. Third, an electric field is screened in graphite at distances of about the interlayer separation, and the electric screening becomes important even for a bilayer. For multilayer graphene, the electric field can dope no more than a couple of near-surface atomic planes, leaving the bulk unaffected. This makes it naive to speculate about the use of graphitic multilayers in active electronics. Fourth, charge carriers in a monolayer are massless Dirac fermions whereas they are massive in a graphene bilayer. This leads to essential differences in many electronic properties including Shubnikov-de Haas oscillations, quantum Hall effect, Klein tunnelling and so on. The Sorites paradox refers to a moment when a heap is no longer a heap if the grains are removed one by one. For graphene, even its bilayer is so different that two already make a heap.

New Aspects for Epidemiology & Cancer Therapy

by Hans-Olov Adami, Member EUAS

<u>Short Biography</u>
Education

1969	*M.D., Medicine, Uppsala Univesity, Sweden*
1978	*Ph.D., Surgery, Uppsala University, Sweden*
1979	*Associate Professor (Docent) of Surgery, Uppsala University, Sweden*

Certification

1974	*Board Certified General Surgeon*

Positions and Employment

1969-71	*Resident in anesthesiology, University Hospital, Uppsala, Sweden*
1971-75	*Intern and resident in Surgery, County Hospital, Karlstad, Sweden*
1975-90	*Senior Registrar, Assistant Professor, Associate professor of Surgery, University of Uppsala, Sweden*
1986-90	*Appointed for a full-time position in cancer epidemiology by the Swedish Cancer Society*
1990-97	*Professor of Cancer Epidemiology, Uppsala University, Sweden*
1992-2007	*Adjunct Full professor of Epidemiology at Harvard University School of Public Healt Boston*
1997-2005	*Professor of Cancer Epidemiology and Chair Department of Medical Epidemiology ar Biostatistics, Karolinska Institutet, Stockholm*
2005-08	*Professor of Cancer Epidemiology, Dept of Med Epidemiology and Biostatistics, Karolinska Institutet, Stockholm*
2006-08	*Visiting Professor, National University of Singapore*
2007-09	*Visiting Professor, Department of Epidemiology, Harvard School of PublicHealth*
2008-10	*Director of Population Sciences, Dana Farber/Harvard Cancer Center, Boston*
2007-11	*Chair, Department of Epidemiology, Harvard School of Public Health, Boston*
2008-	*Emeritus Professor of Cancer Epidemiology, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm*
2010-12	*Professor of Epidemiology (with tenure), Department of Epidemiology, Harvard School of Public Health, Boston*
2012-	*Adjunct Professor of Epidemiology, Department of Epidemiology, Harvard School of Public Health, Boston*

Honors

1991	*Cutter Lecturer of Preventive Medicine at Harvard School of Public Health, Boston*
1998	*The Jubilee Prize, Swedish Society of Medicine*
1998	*Honorary Doctor of Medicine, University of Athens, Greece*
2000	*Medal Academia Medica Wratislaviensis Polonia, Medical University of Wrocław, Poland*
2001	*Distinguished Visiting Lecturer, Harvard Center for Cancer Prevention*
2006	*The Tore Andersson's Prize for Epidemiologic Research*
2010	*Honorary Doctor of Medicine, University of Iceland*
2011	*Distinguished Professor Award, Karolinska Institutet, Stockholm*
2011	*Big Silver Medal from Karolinska Institutet, Stockholm*

Other experience and professional memberships *(selected)*

1984-1987	*Member, working party for developing guidelines for controlled (selected) clinical trials, Dept. of Drugs, National Board of Health and Welfare (NBHW)*

1986-1989	*Member of Medical Advisory Committee, Swedish Cancer Registry, NBHW*
1987-1995	*Vice chairman, Committee on Epidemiology and Clinical Oncology, and Deputy member, Scientific Board, Swedish Cancer Society*
1988-1994	*Member of the Board, WHO Collaborating Center for International Drug Monitoring, Medical Products Agency*
1988-2000	*Member of the Urological Board, NBHW*
1992-1996	*Member of the Awards Assembly of General Motors Cancer Research Foundation*
1996-2001	*Chairman, Expert Committee for Quality Assessment in Health Care, National Board of Health and Welfare*
1996-2000	*Scientific Adviser, Swedish Food Administration*
1996-	*International member of the American Association for the Advancement of Science*
1998-2008	*Member of the Nobel Assembly*
1998-2000	*Member of the Nobel Committee*
1999-2002	*Scientific Adviser, Swedish Medical Products Agency*
2000-2006	*Member, Scientific Board, Swedish Council on Technology Assessment in Health Care*
2004-2009	*Member of the External Scientific Advisory Board for the Nurses' Health Study, Boston*
2005-2009	*Member, Board, Epidemiologic Center (EpC) National Board of Health and Welfare*
2007-	*Member of the Royal Academy of Sciences*
2010-	*Member Governing Board, European Academy of Cancer Sciences*
2011-	*Member Governing Board, The International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH)*
2013-	*Member of the International Advisory Board, Advances in Clinical and Experimental Medicine, Wroclaw, Poland*
2014-	*Member of the Scientific Strategic Committee, ARC Foundation, Paris, France*
2015-	*Member of the EU Academy of Sciences*

Doctoral thesis advisor/tutor

Tutor for more than 25 completed doctoral theses. Thirteen of these graduate students have been promoted to full professors.

Publications

As of January 2016, I have published about 845 scientific papers that have been cited over 47,000 times and generated an h-index of 111. In 2002, I published – together with two co-editors – Text Book of Cancer Epidemiology (Oxford University Press). A second edition was published in 2008.

1. A large case-control study of nasopharyngeal carcinoma in southern China with Adami as Principal Investigator.

2. Pilot studies in four African countries in preparation for a large-scale prospective epidemiologic study of non-communicable diseases in Sub-Saharan Africa led by Professors Michelle Holmes and Hans-Olov Adami at Harvard.

3. Clinical prostate cancer trials based on: SPCG-4, a randomized comparison between radical prostatectomy and watchful waiting in early prostate cancer, ongoing since 1989, published four times in the New England Journal of Medicine and still undergoing follow-up; a randomized trial of active surveillance for low and intermedium risk of prostate cancer initiated by Professors Anna Bill-Axelson, Lars Holmberg, and Hans-Olov Adami, funded by the Swedish Research Council and currently being rolled out in Sweden and most likely other European countries.

4. Extensive analyses of immediate consequences of a cancer diagnosis in collaboration with researchers in Iceland, studying primarily depression, heart attacks and accidents as well as their impact on long-term prognosis.

5. A study of the heritability of cancer based on merging of all four Nordic Twin Cancer Registries in close collaboration with Harvard University generating several recent publications whereof one in JAMA (January 5, 2016).

6. Prospective cohort studies in Sweden including the Women's Lifestyle and Health study initiated in 1991 and the National March Cohort Study initiated in 1997, both undergoing continued follow-up.

7. A series of studies on colorectal cancer, including one nation-wide study in Sweden on the risk of colorectal cancer following adenoma removal; a large-scale European randomized trial comparing different surveillance strategies following adenoma survival; and planning of a Scandinavian large study of cancer risk among patients with inflammatory bowel disease.

Latest Contributions in Theoretical Physics

by Dick Bedeaux, Member EUAS

Short Biography
Education and degrees
Master degree in Theoretical Physics, Utrecht University,
The Netherlands, November 1964.
PhD degree for a thesis on "The relation between the virial coefficients
and the scattering operator." Advisor Prof. Dr. N.G. van Kampen, Institute
for Theoretical Physics, Utrecht University, The Netherlands, May 1969

Positions
Research associate, Instituut Lorentz, University of Leiden, The Netherlands, 1972-1981.
Professor of Theoretical Physics, Norges Tekniske Hogskole, Trondheim, Norway, 1981-1983.
Professor of Physical Chemistry, University of Leiden, The Netherlands, 1984-2006, emeritus from 2006.
Professor II of Physical Chemistry, Norwegian University of Science and Technology, Trondheim, Norway, 2003-2011, emeritus from 2011.

Publications and citation statistics, Aug. 2015
Google Scholar: Hirsch factor 47 (Citations since start: 7297 since 2010: 2498)
ISI Web of science: (without books): Hirsch factor 38 (Citations 5114)
Erdös number: 3
Total Publications: 279

Granted patent
S. Kjelstrup, T.V. Island, E. Sauar, and D. Bedeaux, Fremgangsmåte for optimalisering av entropiproduksjon i en eller flere kjemiske reaktorer, Norsk patent nr. 311286, filed June 17 1998, Accepted Nov.12, 2001

Prizes/Awards/Academy memberships
1996-: Foreign member of the Norwegian Academy of Technology
1997:   Onsager medal
1997-: Fellow of the American Physical Society
1997-1998: Onsager professor, NTNU, Trondheim, Norway
1997-2005: Guest professor, University of Strathclyde, Glasgow, UK.
2007-2008: Extraordinary sabbatical at Centre of Advanced Studies, Oslo.
2011-: Member of the Royal Norwegian Society of Science and Letters
2015-: Member of the EU Academy of Sciences

Research Grants
- Co-recipient, with J.V. Sengers, US, and P. Mazur, NL, of a NATO travel grant, 1976-1979
- Co-recipient, with R. Greef, UK, and J. Vlieger, NL, of a NATO travel grant, 1983-1985
- Co-recipient, with J.M. Rubi, Spain, of a EC contract for Guest Scientists, 1985-1990
- Co-recipient, with T. Ytrehus, Norway, of a NATO travel grant, 1989-1992
- Co-recipient, with P. Schaaf, France, and J.M. Rubi, Spain, of an EU Laboratory Twinning

Contract, 1991-1994
- Participant in the EU Network on Thermodynamics of Complex Systems,
- Coordinator B. Lavenda, University of Camerino, Italy, 1993-1998
- Co-recipient, with A.I. Murdoch, Glasgow, UK, of a SERC research grant, 1994-1995
- Co-recipient, with K. Kitahara, of a research grant from the Japanese government, 1998 -2002
- Recipient of a research grant from the Research Council of Norway, 2003-2005
- Participant in a Storfork grant to Signe Kjelstrup, Research Council of Norway, 2005-2010
Management experience
- *Chairman of the Department of Physical and Macromolecular Chemistry, University of Leiden, The Netherlands, 1986-2002*
- *Member, secretary and chairman of the Working Group on "Liquids and Interfaces" of the Dutch Research Organization S.O.N. in Chemistry, 1990-1997*
- *Chairman of the Department of Chemistry, University of Leiden, The Netherlands,1993-1995*
- *Member of the Board of the Leiden Institute of Chemistry, University of Leiden, The Netherlands, 1995 -1998*

My 2002 monograph, 'Optical Properties of Surfaces', with Jan Vlieger, Imperial College Press, London, UK, 2nd revised edition, 2004, (cited 159 times) developed a completely new way to describe the optical properties of surfaces. The crucial element was the introduction of excess polarizations parallel and normal to the surface. The Maxwell equations were extended to describe such contributions. Exact solutions could for instance be given for distributions of spheroidal islands on a substrate.

The 2008 monograph on 'Non-Equilibrium Thermodynamics of Surfaces', with Signe Kjelstrup, extends the work of Gibbs to non-equilibrium systems using excess densities, Series on Advances in Statistical Mechanics, Vol.16, World Scientific, (cited by 237), is a bestseller.

The 2010 monograph 'Non-Equilibrium Thermodynamics for Engineers', with Signe Kjelstrup, Eivind Johannessen, Joachim Gross, World Scientific, 2nd revised edition expected in 2016, is also a bestseller. (present edition cited by 57 and an older one by 49).

Together with Signe Kjelstrup and Jan V. Sengers I edited 'Experimental Thermodynamics X; Non-Equilibrium Thermodynamics with Applications'; International Union of Pure and Applied Chemistry; 2015, Royal Society of Chemistry, Cambridge, UK. In it I coauthored chapters: 1, Basis and Scope; 4, Local Equilibrium in Non-Equilibrium Thermodynamics; 8, Non-Equilibrium Thermodynamics for Evaporation and Condensation; 10, Electrochemical Energy Conversion. The book reviews the present status of the field. As it appeared very recently, it has not yet been cited.

Gastritis Improvements Over the Last Years

by Toshio Fujioka, Member EUAS

Short Biography
Professor Emeritus
Department of Gastroenterology and General Medicine, Faculty of Medicine, Oita University.
Education-Occupational Career
1971 Bachelor degree in Faculty of Medicine, Nagasaki University. (Medical Doctor)
1978 Doctoral degree in Medicine (PhD, Nagasaki University).
1981 Assistant Professor of Internal Medicine, Medical College of Oita
1985 Associate Professor of Internal Medicine, Medical College of Oita
1988 Visiting Professor (University of California Los Angeles : UCLA)
2000 Professor of Gastroenterology and General Medicine, Faculty of Medicine, Oita University.
2003 Councilor of Oita University
2007 Vice President, Oita University
2013 Prof. Emeritus, Oita University
Affiliated Association
The Japanese Society of Gastroenterology (a board of directors)
The Japan Gastroenterological Endoscopy Society
Japanese Society for Helicobacter Research (President : 2003~2008)
American Gastroenterological Association-International Member
Corresponding fellow of European Helicobacter Study Group
Member of the EU Academy of Sciences
Awards
- Award of the Uehara Memorial Foundation (1996 : From Uehara Memorial Foundation)
- Kiyoshi Shiga and Sahachiro Hata Memorial Award (2003 : From Kitasato Institute)

MicroRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14-3-3zeta.

We investigated expression profiles of microRNA (miRNA) in gastric carcinomas by use of a miRNA microarray platform covering a total of 470 human miRNAs. We identified 39 differentially expressed miRNAs in gastric carcinoma, of which six were significantly downregulated and the other 33 were upregulated. We found that miRNA-375 (miR-375) was the most downregulated and that its ectopic expression in gastric carcinoma cells markedly reduced cell viability via the caspase-mediated apoptosis pathway. Interestingly, we found that expression of miR-375 inhibited expression of PDK1, which is a direct target of miR-375, followed by suppression of Akt phosphorylation. Further analysis by gene expression microarray revealed that 14-3-3zeta, a potent antiapoptotic gene, was significantly downregulated at both the mRNA and protein levels in cells transfected with miR-375. The activity of a luciferase reporter containing the

miR-375 binding sequence at the 3' untranslated region (UTR) of 14-3-3zeta mRNA was repressed by the ectopic expression of miR-375, suggesting that miR-375 targets the 3' UTR of 14-3-3zeta. In addition, knockdown of either PDK1 or 14-3-3zeta in gastric carcinoma cells induced caspase activation, which was also observed in miR-375-transfected cells, suggesting that miR-375 may exert its proapoptotic function, at least in part, through the downregulation of PDK1 and 14-3-3zeta. Taken together, we propose that miR-375 is a candidate tumor suppressor miRNA in gastric carcinoma.

Genomic profiling of gastric carcinoma in situ and adenomas by array-based comparative genomic hybridization.

Although genomic copy number aberrations (CNAs) of gastric carcinoma at the advanced stage have already been extensively characterized by array comparative genomic hybridization (array CGH) analysis, those of gastric carcinoma in situ (CIS) are still poorly understood. Furthermore, no reports have demonstrated correlations between CNAs and histopathological features of gastric adenoma. In this study, we investigated CNAs of 20 gastric CISs (Vienna category 4.2) and 20 adenomas including seven low-grade adenomas (LGA; Vienna category 3) and 13 high-grade adenomas (HGA; Vienna category 4.1), using oligonucleotide-based array CGH. The most frequent aberrations in CIS were gains at 8q (85%) and 20q (50%), and losses at 5q (50%) and 17p (50%), suggesting that these CNAs are involved in the development of CIS. We found that the pattern of CNAs in HGA was quite different from that in LGA. The most frequent CNAs in HGA were gains at 8q (62%) and 7pq (54%), whereas those in LGA were gain at 7q21.3-q22.1 (57%) and loss at 5q (43%). Interestingly, gains at 8q and 7pq, both of which occurred most frequently in HGA, were not detected in any cases of LGA. Of note, 8q gain was detected most frequently in both HGA and CIS but was undetected in LGA. Since HGA is believed to have a higher risk of progression to invasive carcinoma than LGA, these data suggest that 8q gain is important for the malignant transformation of gastric adenoma.

Clinical relevance of cagPAI intactness in Helicobacter pylori isolates from Vietnam.

The purpose of this research is to investigate the relationship between clinical outcome and the intactness of cagPAI in Helicobacter pylori strains from Vietnam. The presence or absence of 30 cagPAI genes was investigated by polymerase chain reaction (PCR) and dot-blotting. H. pylori-induced interleukin-8 secretion and hummingbird phenotype, and H. pylori adhesion to gastric epithelial cells were examined. The serum concentration of pepsinogen 1, pepsinogen 2, and gastrin was also measured in all patients. cagPAI was present in all 103 Vietnamese H. pylori isolates, of which 91 had intact cagPAI and 12 contained only a part of cagPAI. Infection with the partial cagPAI strains was less likely to be associated with peptic ulcer and chronic gastric mucosal inflammation than infection with strains possessing intact cagPAI. The partial cagPAI strains lacked almost all ability to induce interleukin-8 secretion and the hummingbird phenotype in gastric cells. Their adhesion to epithelial cells was significantly decreased in comparison with intact cagPAI strains. Moreover, for the first time, we found an association between cagPAI status and the serum concentration of pepsinogens 1 and 2 in infected patients. H. pylori strains with internal deletion within cagPAI are less virulent and, thus, less likely to be associated with severe clinical outcomes.

Helicobacter pylori infection and gastroduodenal diseases in Vietnam: a cross-sectional, hospital-based study.

The rate of H. pylori infection in Vietnam is reportedly high, but the spectrum of H. pylori-associated gastroduodenal diseases has not been systematically investigated. Moreover, despite the similarities of ethnicity and diet, the age-standardized incidence rate of gastric cancer in the

northern city of Hanoi is higher than that in the southern city of Ho Chi Minh, but the reason for this phenomenon is unknown. The virulence of Vietnamese H. pylori has also not been investigated in detail.

Individuals undergoing esophagogastroduodenoscopy were randomly recruited. H. pylori infection status was determined based on the combined results of culture, histology, immunohistochemistry, rapid urine test and serum ELISA. Peptic ulcer (PU) and gastroesophageal reflux disease was diagnosed by endoscopy, and chronic gastritis was determined histologically. H. pylori virulence factors were investigated by PCR and sequencing.

Among the examined patients, 65.6% were infected with H. pylori. The prevalence of infection was significantly higher in those over 40 years of age than in those aged ≤40. Chronic gastritis was present in all H. pylori-infected individuals, 83.1% of whom had active gastritis, and 85.3% and 14.7% had atrophy and intestinal metaplasia, respectively. PU was present in 21% of infected patients, whereas its incidence was very low in non-infected individuals. The prevalence of PU was significantly higher in Hanoi than in Ho Chi Minh. The prevalence of vacA m1, which has been identified as an independent risk factor for PU in Vietnam, was significantly higher among H. pylori isolates from Hanoi than among those from Ho Chi Minh.

H. pylori infection is common in Vietnam and is strongly associated with PU, active gastritis, atrophy and intestinal metaplasia. vacA m1 is associated with an increased risk for PU and might contribute to the difference in the prevalence of PU and gastric cancer between Hanoi and Ho Chi Minh.

Impact of Helicobacter pylori CagA diversity on gastric mucosal damage: an immunohistochemical study of East-Asian-type CagA.

Recently, we successfully produced an anti-East-Asian-type CagA-specific antibody called α-EAS Ab, which is specifically immunoreactive only with East-Asian-type CagA but not Western-type CagA. In this study, the correlations between Helicobacter pylori CagA protein diversity and gastric mucosal condition was investigated using immunohistochemical staining with α-EAS Ab in Japan.

There were 254 H. pylori-positive patients enrolled in this study. α-EAS Ab was used to determine the CagA phenotype instead of cagA sequencing, and, moreover, the histological findings and endoscopic gastric mucosal condition were evaluated according to the updated Sydney System and the Kimura-Takemoto classification system, respectively.

A total of 224 (88.2%) of the patients were immunoreactive for α-EAS Ab. The remaining 30 (11.8%) were negative for α-EAS Ab, suggesting that they were infected with either Western-type CagA or CagA-negative strains (i.e. non-East-Asian-type CagA strains). The grades of activity of gastritis, mucosal atrophy and intestinal metaplasia according to the updated Sydney System were significantly higher in patients infected with East-Asian-type CagA strains than those infected with non-East-Asian-type CagA strains. The grade of endoscopic gastric mucosal atrophy evaluated using the Kimura-Takemoto classification system was similar. All 28 strains isolated from patients with gastric cancer possessed the East-Asian-type CagA.

Infection with East-Asian-type CagA H. pylori was more closely associated with gastric mucosal atrophy and gastric cancer than infection with non-East-Asian-type CagA H. pylori. The efficiency of immunohistochemical analysis for CagA should be equivalent to that of cagA sequencing.

Prevalence of two homologous genes encoding glycosyltransferases of Helicobacter pylori in the United States and Japan.

jhp0562 and β-(1,3)galT (jhp0563) of Helicobacter pylori have been suggested as novel virulent factors; however, the clinical associations and functions of these genes remain unclear. We examined the prevalence of jhp0562, β-(1,3)galT, and cagA in the United States (US) and Japanese populations.

A total of 308 strains (171 from the US and 137 from Japan) were examined for the status of jhp0562, β-(1,3)galT, and cagA by polymerase chain reaction.

There were significant differences in the status of jhp0562, β-(1,3)galT and cagA between the US and Japanese populations ($P < 0.001$). In the US, the prevalence of β-(1,3)galT was significantly lower in strains isolated from patients with duodenal ulcer (DU) or gastric ulcer (GU) than those with gastritis (47.8% and 32.1% vs 72.0%, $P < 0.01$), and the absence of β-(1,3)galT was an independent factor discriminating DU and GU from gastritis (adjusted odds ratios, 4.21 and 8.52; 95% confidence intervals, 1.75 to 10.12 and 2.76 to 26.33, respectively). In the US, the prevalence of the jhp0562-positive/β-(1,3)galT-negative genotype was significantly higher in strains from DU and GU patients than in those from gastritis patients (50.0%, 67.9%, and 24.4%, $P < 0.01$) and the cagA status was significantly correlated with that of jhp0562 and inversely correlated with that of β-(1,3)galT. In contrast, the prevalence of these three genes was not significantly different in Japan.

jhp0562 or β-(1,3)galT can be used to discriminate peptic ulcers from gastritis in the US, but not in Japan.

Genomic profiling of submucosal-invasive gastric cancer by array-based comparative genomic hybridization.

Genomic copy number aberrations (CNAs) in gastric cancer have already been extensively characterized by array comparative genomic hybridization (array CGH) analysis. However, involvement of genomic CNAs in the process of submucosal invasion and lymph node metastasis in early gastric cancer is still poorly understood. In this study, to address this issue, we collected a total of 59 tumor samples from 27 patients with submucosal-invasive gastric cancers (SMGC), analyzed their genomic profiles by array CGH, and compared them between paired samples of mucosal (MU) and submucosal (SM) invasion (23 pairs), and SM invasion and lymph node (LN) metastasis (9 pairs). Initially, we hypothesized that acquisition of specific CNA(s) is important for these processes. However, we observed no significant difference in the number of genomic CNAs between paired MU and SM, and between paired SM and LN. Furthermore, we were unable to find any CNAs specifically associated with SM invasion or LN metastasis. Among the 23 cases analyzed, 15 had some similar pattern of genomic profiling between SM and MU. Interestingly, 13 of the 15 cases also showed some differences in genomic profiles. These results suggest that the majority of SMGCs are composed of heterogeneous subpopulations derived from the same clonal origin. Comparison of genomic CNAs between SMGCs with and without LN metastasis revealed that gain of 11q13, 11q14, 11q22, 14q32 and amplification of 17q21 were more frequent in metastatic SMGCs, suggesting that these CNAs are related to LN metastasis of early gastric cancer. In conclusion, our data suggest that generation of genetically distinct subclones, rather than acquisition of specific CNA at MU, is integral to the process of submucosal invasion, and that subclones that acquire gain of 11q13, 11q14, 11q22, 14q32 or amplification of 17q21 are likely to become metastatic.

A large-scale nationwide multicenter prospective observational study of triple therapy using rabeprazole, amoxicillin, and clarithromycin for Helicobacter pylori eradication in Japan.

In recent years in Japan, the rate of clarithromycin (CAM) resistance in Helicobacter pylori has risen to around 30%, and the eradication rate with triple therapy [proton pump inhibitor + amoxicillin (AMPC) + CAM] has been trending downward to around 70%. In 2007, rabeprazole (RPZ)-based triple therapy (RPZ + AMPC + CAM: RAC therapy) was approved in Japan, and a large-scale nationwide study was therefore initiated to evaluate the efficacy and safety of RAC therapy in clinical practice.

Patients with H. pylori-positive gastric/duodenal ulcer (including ulcer scars) were administered triple therapy comprising RPZ 10 mg, AMPC 750 mg, and CAM 200 mg (or 400 mg), twice daily for 7 days.

The eradication rate was 80.7% (2,551/3,162). The results of multivariate analysis indicated the following as factors affecting the eradication rate: sex, treatment compliance, history of H. pylori treatment, presence of urologic disease, presence of respiratory disease, and year of starting treatment. The incidence of adverse drug reactions (such as diarrhea and dysgeusia) was 4.4% (166/3,789). The results of multivariate analysis indicated the following as factors affecting the incidence of adverse drug reactions: sex, daily CAM dose, and history of allergies.

In a large-scale nationwide study of use in clinical practice, RAC therapy was confirmed to be effective and safe.

Ten-year prospective follow-up of histological changes at five points on the gastric mucosa as recommended by the updated Sydney system after Helicobacter pylori eradication.

Atrophic gastritis and intestinal metaplasia (IM) are well known as precancerous lesions of gastric cancer. The present study evaluated the gastric mucosa for 10 years after H. pylori eradication at five points of the stomach as recommended by the updated Sydney system to clarify the relationship between H. pylori eradication and gastric cancer prevention.

Among the comprised 373 patients, 323 were H. pylori-positive while 50 patients were H. pylori-negative. Patients with successful eradication underwent follow-up endoscopic examination every year. Biopsy specimens were taken from five points of the stomach, as recommended by the updated Sydney system, and were evaluated for the degree of gastritis prospectively.

Two hundred ninety-four out of the 323 H. pylori-positive patients successfully achieved eradication. Of the 197 patients on whom five-point biopsy was performed, the courses of 30 patients were able to be observed every year for 10 years after successful eradication. Inflammation, activity, and atrophy score at all five points were significantly reduced half a year to 6 years after eradication. IM scores fluctuated intensely up and down during all observation periods; however, IM score of the lesser curvature of the corpus continued decreasing gradually and showed a significant decrease 6 years after (0.97 ± 0.09 to 0.42 ± 0.17, $P < 0.05$).

In 10 years after H. pylori eradication, atrophy at all sites and IM in the lesser curvature of the corpus gradually and significantly decreased. These results suggest that the improvement of gastric atrophy and IM might have association with the reduction of gastric cancer occurrence.

Recent Developments in Nanotechnology

by Herbert Gleiter, Member EUAS

Short Biography
Institute of Nanotechnology, Research Center Karlsruhe, Germany

Herbert Gleiter received his Ph.D. in Physics from the University of Stuttgart, Germany. In 1973, Gleiter became Chair Professor of Materials Science at the University of the Saarland in Germany In 1994, he was appointed Member of the Executive Board 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 of Science and Technology founded the "Herbert Gleiter Institute of Nanoscience" and appointed him as the Institute's Founding Director as well as Zijin Professor of this University.

Among Gleiter's more than 40 awards and honors are the Masing Prize of the German Society for Metals (1972);; the Leibniz Prize of the German National Science Foundation (1988); Max-Plack Research Prize (1993); Gold Medal of the Federation of European Material Societies (1995); Heyn Medal of the German Society for Materials Science (1998); Heisenberg Medal (1998) and Humboldt Medal (2006); Gold Medal of Acta Materialia (2007); the Von Hippel Award of MRS (2008); the Mehl Award of the TMS Society (2009), the 2009 Blaise Pascal Medal of the European Academy of Sciences and the Cothenius Medal, the highest award of the German National Academy. His publications have been cited more than 22 000 times. Six universities in Europe and abroad awarded him honorary doctorates.

He is a Member of 10 Academies of Science and/or Engineering: e.g. of the German National Academy of Sciences Leopoldina (1999), US National Academy of Engineering (2004), Indian National Academy of Engineering (2006), the American Academy of Arts and Sciences (2004), the Indian National Academy of Sciences (2009), the European Academy of Sciences (2009), the European Academy of Sciences and Arts (2014) as well as the Academia Europaea and the EU Academy of Sciences (2015).

Herbert Gleiter and his group invented and developed two new concepts in Materials Science and Solid State Physics.

The first concept is to synthesize solids with new atomic and/or chemical structures by introducing a large volume fraction (>50vol. %) of inter-crystalline interfaces. These solids/materials were called ***nano-crystalline or nano-structured matrials/solids*** because the large volume fraction of inter-crystalline interfaces was achieved by reducing the crystal size of a polycrystalline solid to a few nanometers. As the atomic arrangements in inter-crystalline interfaces differ from the ones of crystalline and/or glassy materials with the same chemical compositions, the resulting nano-crystalline materials new atomic structures and, moreover, new properties that turned out to be technologically attractive. For example, nano-crystalline materials were found to exhibit improved strength, diffusivity, magnetic

properties etc. As a consequence, nano-crystalline materials became in recent years one of the most rapidly growing areas of Materials Science with annually about 800 publications and about 10 international conferences. In addition, most conferences in the area of Materials Science have one or several sessions on nano-materials, e.g. the 2011 MST Conference of ASM and TMS (18 sessions on nano-structured materials, ~ 350 papers). This field is expanding at a remarkable rate: In 2011 more than 60 000 publications in this field (Web of Science) appeared,According to a recent study of the German Government, the annual value of the products based on nano-structured materials is already now beyond 2 billion US$ with a growth rate of about 15 to 20% per year. The same applies to the number of annual publications.

The <u>second concept</u> invented by Herbert Gleiter and his group pioneers *a new kind of non-crystalline materials, so called nano-glasses*. Different from today's glasses (produced by freezing a melt) nano-glasses consist of nanometer-sized glassy regions connected by glass/glass interfaces with new non-crystalline structures (deviating from the structure of the glassy regions). By varying the sizes and/or the chemical compositions of the glassy regions, the volume fraction of these interfaces and hence the atomic structures as well as the chemical composition and therefore also the properties of nano-glasses were varied in partially spectacular ways.

For example, FeSc nano-glasses were revealed to be strong ferro-magnets although melt-quenched glasses (with the same chemical compositions) were paramagnetic. Similar variations were noted for other properties as well, e.g. the ductility, the biocompatibility, the catalytic properties of nano-glasses were improved by one or several orders of magnitude in comparison to the corresponding properties of today's glasses. Just like in crystalline materials (metals, semi-conductors, ceramics etc.) the properties of which may be changed by varying the sizes and/or chemical compositions of the crystallites, the properties of nano-glasses may be changed by varying the sizes and/or chemical compositions of the glassy clusters.

This analogy opens the following remarkable historical perspective. By utilizing the new properties of nano-glasses, in the foreseeable future a new age of technologies - a "glass age"- may be ushered in, similar to the bronze age, the iron age etc. that developed in the past when the new properties of these materials were recognized. By using today's glasses, a glass age could not been developed so because today's glasses do not permit to vary their properties in a similar way as we do it in the crystalline materials that provide the basis for today's technology. Nano-glasses have now removed this limitation. An international advisory board of the Chinese Academy of Sciences (CAS) selected nano-crystalline materials and nano-glasses to be the most promising development in modern materials opening the way to a new period of technologies. Based on this evaluation it was recommended to start up a new research institute (similar to a Max Planck Institute in Germany) working on nanoscience at Nanjing University with the name of "Herbert Gleiter

Institute of Nanoscience".

The <u>third field</u> of Herbert Gleiter's present activities is the **application of methods** that were initially developed in **nanotechnology** (such as the design of new cluster beam sources, cluster detectors etc.) to ***probe the applicability limits of Quantum Physics to objects of macroscopic size*** i.e.. to objects with a size of a few nanometers such as viruses, clusters comprising many thousands of atoms etc by means of Poisson's Spot experiments.

These experiments are expected to be of fundamental scientific significance, because they are likely to permit to answer the following fundamental question: Does Quantum Physics apply to systems of all sizes ranging from elementary particles all the way to systems of macroscopic dimensions or is there a limiting size beyond which Classical Physics is the appropriate way to represent the reality. If the Quantum Physics would be found to apply to systems of all sizes, it would mean that the macroscopic world does not exist objectively but is the result of the entanglement of the wave functions of the objects considered with the wave functions of their environment. In other words, it would be of fundamental importance for our understanding of what we mean by reality.

The new long range perspective of these experiments is to utilize methods developed in nanoscience and nanotechnology as a tool for performing new kinds of studies in other areas of science. Developments of that kind appear to be similar to – for example – the application of NMR (developed in nuclear physics) in medicine or of the decay of radioactive isotopes to measure the age of archaeological objects.

Latest Contributions in Theoretical Chemical Physics

by Antonio Varandas, Member EUAS

<u>Short Biography</u>

A.J.C. Varandas received a diploma in Chemical Engineering from the University of Oporto (Portugal), and a Ph.D. in Theoretical Chemistry from the University of Sussex (U.K.) under the direction of Professor John N. Murrell.

After graduation in Oporto, he joined the staff at the Department of Chemistry of the University of Coimbra as Assistant Professor, where he occupies since 1988 a position of Full Professor and directs the group of Theoretical & Computational Chemistry. In 1988, he was Invited Professor and Visiting Research Scholar of Minneapolis Supercomputer Institute at the University of Minneapolis (USA) and, from June-July 1995, Cherry L. Emerson Fellow at the Department of Chemistry of Emory University in Atlanta (USA).

In 2009, he was awarded a Visiting Professorship for Senior International Scientists from the Chinese Academy of Sciences. His research interests cover a wide range of topics in theoretical chemistry from potential energy surfaces to non-adiabatic effects in ro-vibrational spectroscopy and reaction dynamics. Some of his studies have implications on theoretical environmental chemistry, particularly in combustion chemistry and issues related to the ozone chemistry at the middle atmosphere.

He has 400 research papers in those areas, and co-authored a monograph entitled Molecular Potential Energy Functions (Wiley, 1984). Edited special issues of Physica Scripta (IOP, 2011), and Advances in Physical Chemistry (Hindawi, 2012), and co-edited a book in memorial of Ruy Couceiro da Costa (Universidade de Coimbra, 2011). Wrote 2 books and 2 books of lectures notes, all in portuguese, devoted to Computational Methods, Quantum Chem-istry, and Statistical Mechanics.

Oriented 30 PhD students from various nationalities, including Brazil, China, Cuba, India, Italy, Moldavia, Portugal, and Spain. Received the following awards: ”Artur Malheiros” Prize for Physics and Chemistry of the Lisbon Academy of Sciences (1985); ”Ferreira da Silva” Prize of the Portuguese Chemical Society (1991); Prize Stimulus to Excellence of the Portuguese Ministry of Science, Innovation and High Studies (2004).

Received honorific titles from Insituto Superior de Tecnologias y Ciencias Aplicadas (La Habana, Cuba, 1998), Dalian Institute of Chemical Physics (Dalian, China, 2005), and Henan Normal University (Henan, China, 2006). In 2006, he was elected corresponding member of the Lisbon Academy of Sciences. Also, in 2015 he was elected member of the EU Academy of Sciences.

My research interests have focused on theoretical studies of molecular systems, covering both energetic and dynamics aspects. In addition to fundamental research, I have been involved in the application of theoretical methods to specific systems of practical interest. Some examples of the progress that I and my collaborators have made on specific problems are highlighted in the following paragraphs.

Early studies focused on perturbation theory. We developed a variation-perturbation method for dynamic polarizabilities, and a new perturbative approach

to the potential energy curves of rare gas dimers in the region of the van der Waals minimum. The method, which combines first-order exchange perturbation calculations with a realistic second-order dispersion interaction, has been a precursor of successful semiempirical approaches in use today.

The calculation and modeling of potential energy surfaces using the methods of quantum mechanics are topics of extreme importance in theoretical chemical physics. Since my Ph.D. studies, I have employed both ab initio and semiempirical methods to calculate such surfaces. Amongst the early ab initio studies, I emphasize the identification of a conical intersection in the potential surfaces of LiNaK using the theorems due to Longuet-Higgins. The approach is frequently used today to identify such intersections. In the field of potential energy surfaces for reaction dynamics, I developed with J.N. Murrell and other Colleagues a general strategy known as the many-body expansion (MBE), a method which has since afforded great popularity amongst dynamicists.

In 1984, I proposed a double many-body expansion (DMBE) theory. While keeping much of the simplicity of MBE, the DMBE theory has a stronger physical basis, and covers in a formally correct way the complete configuration space of the molecule. The DMBE theory has been shown to handle both chemically stable molecules and less stable complexes of the van der Waals type. Indeed, some of the most accurate potential energy surfaces currently in use for well known benchmark systems such as H_3 and HO_2 are of the DMBE type. In 1995, the DMBE method was extended to multisheet potential energy surfaces for molecules with atoms of any spin multiplicity and angular momentum.

An important requirement of DMBE is to know the dependence of dispersion coefficients on the intramolecular coordinates of the participating subsystems, a requisite in turn essential if the potential is to be used to interpret experimental data where the vibrational coordinates of the interacting subsystems are involved. Focusing on this, we have proposed and tested new semiempirical techniques for the evaluation of such coefficients. We have also developed virial theorem constraints for the n-body energy terms of potential energy surfaces, and used the virial theorem to decompose such surfaces and assess their reliability.

In reaction dynamics and kinetics, we have used both classical and quantum mechanical methods. While such studies served as tests on the adequacy of our own surfaces, some focused in reactions with relevance in areas of practical interest such as atmospheric chemistry and combustion processes. We have also developed and tested classical capture theories, and accounted for recrossing in exothermic reactions proceeding over barrier-free potential energy surfaces with deep wells. Moreover, we suggested a new method for quasiclassical trajectories on local potential energy surfaces defined from gradients and Hessians, thus avoiding a global potential energy surface.

We have also investigated the so-called zero-point energy problem of classical dynamics, and proposed and tested both 'active' and 'nonactive' schemes as fixes to the leakage of zero-point vibrational energy in trajectory calculations. In 1995, I have proposed a method to extract the cross section from quantum mechanical reactivities calculated for zero total angular momentum. This is important to extrapolate the results of accurate quantum calculations, which are seldom viable for situations involving non-zero total angular momentum. Starting in 1996, we developed a general theory to include tunnelling effects into quasiclassical trajectory calculations.

The major areas of my research in the past few years reflect a consistent continuation of previous work, focusing on four major topics: (a) ab initio calculation and modelling of potential energy surfaces; (b) generalization of the Born-Oppenheimer approximation to molecular systems with electronic degeneracies; (c) dynamics (classical and quantum) of reactions with relevance in atmospheric chemistry and combustion processes; (d) direct methods for the calculation of partition functions. The following surveys some of the major developments achieved thus far. In (a), besides ab initio calculations for specific systems, I developed a semi-theoretical approach to extrapolate the correlation energy to the complete basis set limit. I have also proposed an 'energy-switching' method to construct global potential energy surfaces of spectroscopic accuracy at regions where such an accuracy is known from experimental work.

Alternatively, we have shown how to refine a DMBE surface to attain spectroscopic accuracy via a multiproperty fit which includes such a data. In (b), we reported detailed quantum studies of vibrational spectroscopy for the 'trough' and 'cone' states of H_3 (and its isotopomers) and Li_3 both with consideration and without consideration of the so-called geometric phase effect. Most recently, we have extended such calculations to study the ro-vibrational spectroscopy of the interstellar H_3^+ ion in its triplet state. A proper assignment of all calculated ro-vibrational levels for values of the total angular momentum up to J = 10 (i.e., the lowest 19 bands) has been presented. Their estimated accuracy of 0.1-0.3 cm^{-1} may therefore stimulate experiments aiming at their observation in astrochemistry and hydrogen plasmas. Although the geometric phase effect turned out to have little effect for the trough states in the lowest triplet sheet, it plays a crucial role for those in the upper sheet.

However, the novelty has perhaps been the development of new single-surface equations to carry out GP calculations by using the 'mixing angle' to represent the geometric phase. Also noteworthy is our most recent work on cyclic phases at N - fold Jahn-Teller degeneracies, where it has been shown for the first time that the GP effect is a property inherent to inversion of the adiabatic electronic wave vectors in the N-dimensional wave-vector space. The salient features in (c) are perhaps the detailed study of the reactions $H + O_3 \rightarrow OH + O_2$ (and its reverse), $OH + O_3 \rightarrow O_2 + HO_2$ (and its reverse), $HO_2 + O_3 \rightarrow OH + 2\,O_2$, and the suggestion that the reverse

OH(v′) + O$_2$(v″) and O$_2$ (v′) + HO$_2$ (v) reactions may offer clues for ozone related problems in the middle atmosphere under plausible conditions of local thermodynamic disequilibrium (commonly referred to as non-local thermodynamic equilibrium). Exact quantum wave-packet reactive scattering calculations on a highly reliable potential energy surface for the N(^{2}D) + H$_2$ reaction using a highly accurate DMBE potential energy surface should also be highlighted.

In relation with topic (b), we are performing quantum wave-packet calculations of reaction probabilities and cross sections for the prototypical H + H$_2^+$ reaction in its lowest triplet state potential energy surface including the GP effect, aiming to test whether a recently suggested cancellation of such effects holds irrespective of the system. In (d), we have developed a Monte Carlo simulation method to calculate the classical partition function, and applied the technique to several prototypical systems. Semiempirical schemes to calculate quantum corrections to the classical partition function were also exploited with the results suggesting the method to be quite promising.

Further Aspects
in Applied Mechanics Theory

by Nicolaie Cristescu, Member EUAS

<u>Short Biography</u>

Corresponding member (9 March 1991) and member (11 December 1992) of the Romanian Academy. Member of the EU Academy of Sciences (2015).

He attended the Faculty of Mathematics and Physics of the University of Bucharest; he obtained his PhD in mathematics and physics in 1955; he obtained his PhD docentin 1967. He was anassistant at the Institute of Geology and Mining Technique (1950-1951), then assistant (1951-1955), lecturer (1955-1957), professor associate (1957-1966) and professor (1966); Head of Department (1982-1990) at the University of Bucharest, whose rector was (1990-1992); "Visiting professor" at The Johns Hopkins University, Baltimore (1968-1969), consulting professor at Drexel Institute of Technology in Philadelphia (1969), Professor (1970) and "The Graduate Research Professor" (1971-1976, 1992-2009) at the University of Florida, Gainesville. His research addresses various fields: the theory of plasticity and viscoplasticity, wave propagation, rock mechanics, mechanics of composite materials, theory of metalworking processes, mechanics of granular materials.From 1953 he worked in the theory of plasticity, hitherto unexplored in Romania and which proved of great importance in many areas of technology (metalworking, earth and rock mechanics, plastics, powders etc.). He was concerned about the mechanics of "composite" bodies and at the request of metallurgical enterprises and the Metallurgical Research Institute, developed mathematical models to describe various metalworking processes. His research of elastic-plastic materials processes and for the establishing of the constitutive equations for these materials have diversified over time by a mechanical approach to composite materials and suggesting a mechanism of sequential delamination; he gave a new theory of slow deterioration of rocks by dilatant and a correlation between mechanical effects and acoustic emission. Following a contract with a group of geomechanicsresearchers, he made a number of applications in mining: the calculation of vertical and horizontal holes in mining, taking into account the deterioration in time. The results of his research were published in more than 200 papers, published in our country and abroad, under own signature or in collaboration with other specialists. Among the books published we mention: Dynamic Problems in Plasticity Theory (1958); Mechanical of Fibers Elongation(1964, published in Chinese); Dynamic Plasticity (1970, published also in Japanese); Introduction to Rate-dependent Plasticity (a Dynamic Aproach) (1971); Viscoplasticity (1982 et al.); Mechanics of Composite Materials (1983); Rock Mechanics (1984); The Theory of Plasticity in Metalworking Applications (1985 et al.); Rock and Soil Rheology(1988, et al.); Rock Rheology (1989); Rock Mechanics-Rheological Aspects

(1989); Visco-Plastic Behavior of Geomaterials (1994 et al.); Time Effects in Rock Mechanics (1997 et al.); Basic and Applied Salt Mechanics (2002, et al.); Mechanics of Elastic Composites (2003 et al.); Dynamic Plasticity (2007). Editor-founder of the journal "International Journal of Plasticity", a member of the editorial committee of the magazines "International Journal of Mechanical Sciences", "International Journal of Impact Engineering", "Mechanics Research Communications", "Mechanics of Cohesive-Frictional Materials", "RevistaItaliana di Geotehnica". Member of the European Mechanical Committee, founding member of the International Society for Interaction of Mechanics and Mathematics, member of the American Society of Mechanical Engineers, member of the Society Sigma XI, of the French Group of Rheology, member of the Academy Europaea (1997).

Cable dynamics. The first research interest has been in the domain of extensible strings and cables: elastic, visco-elastic, viscoplastic. Mainly non-linear stress-strain relations of rate type have been considered as well as finite deformations. Three dimensional equations of motions, properties and interaction between longitudinal and transverse waves, order of propagation, reflection from fixed or moving points and shock waves in extensible cables have been studied. As applications have been considered: the motion of two bodies connected by an extensible cable, the braking of a fast moving body by a stretched cable, etc.

Dynamic Plasticity. Research has been carried out in the domain of dynamic deformation of elastic/plastic materials (metals, soils and rocks, plastics). Both elastic-plastic and elastic-viscoplastic waves have been considered. The nature of plastic waves, why the plastic waves are coupled, i.e. why they are simultaneously dilatational and shearing waves, the combined dilatational-shearing loading in plates and membranes, etc. were the investigated problems. The fundamental problem of plasticity has been addressed: finding the mathematical models able to describe the rapid plastic deformation of metals. New elastic/viscoplastic constitutive equations were proposed which would be able to describe dynamic relaxation, overstress, propagation of waves in plastic bodies with elastic velocities. Several papers were devoted to the longitudinal impact of aluminum bars, interaction between elastic (loading and unloading) waves and plastic waves and how the experimental data can be used to formulate an appropriate constitutive equation. Numerical procedures have been developed for time-dependent and time-independent constitutive equations in order to describe the dynamic loading and unloading of metallic bars. Comparison of theoretical prediction with the data are excellent. The characteristics of the plastic waves, as described by various constitutive equations, was investigated. It has been shown that according to the classical theories of plasticity the plastic waves are always coupled, and that the coupling is due to the way in which the yield condition or work-hardening condition are involved in these theories. The coupling problem was studied for rate type constitutive equations as well, and it was shown how various plastic waves interact. This problem is instrumental in in the selection of the appropriate constitutive equation for a certain material. From the other plasticity problems considered let us mention: the dynamic deformation of elastic/plastic membranes, the Bauschinger effect, the Corona effect, the torsion of metallic bars at elevated temperatures, etc.

Theories of Metal Working. At the request of several metallurgical companies mathematical models for metal working were developed. Departing from existing approaches viscoplastic constitutive equations were used, since these are able to describe

the "speed influence" on plastic deformation during fast metal working. Theories for fast drawing of wires, drawing of tubes with fixed plugs, drawing of tubes with floating plugs or without plugs, hot extrusion using glass as lubricant, use of ultrasonic fields in metal working, heating due to fast deformation or friction, etc. were some of the problems solved and industrially applied. These theories allow the optimization of the metal working process i.e. the reduction of working forces, correct design of tools, significant increase of working speed, reduction of the wearing of tools, etc.

Mechanics of Composite Materials. The problem of dynamic delamination and perforation of laminates was studied. The mechanism of sequential delamination of composites subjected to a transverse impact was analyzed. The problem is related to the design of composite plates with distinct perforation strengths when impacted from one side or another one.

Rock and Soil Mechanics. The main problem considered is the formulation of mathematical models able to describe the slow deformation of rocks around various underground openings. The kind of tests necessary to formulate such rheological models were analyzed and the procedure was described in detail. These new rheological models are able to describe the creep of rocks, both transient and stationary, dilatancy and/or irreversible compressibility during creep, slow damage taking place during creep, failure and creep failure, work-hardening, etc. Examples for a variety of rocks , based on own experimental data or experimental data obtained by other authors, were given. A theory of long-term damage produced by dilatancy was developed for rocks, where dilatancy is related to the microcracking energy. A correlation between acoustic emission and the irreversible volumetric behavior was established. A general procedure to determine the a *nonassociated elastic/viscoplastic constitutive equation* for geomaterials was formulated, and examples for a variety of geomaterials was given (granite, andesite, rock salt, various kind of coal, dry and wet sand, etc.). Temperature influence on the elastic/viscoplastic behavior of bituminous concrete was also studied. Many mining and petroleum engineering problems were solved as: creep, dilatancy and/or compressibility of rocks around vertical mining shafts or petroleum wells (taking into account an internal pressure as well), or around deep caverns, or around horizontal tunnels, etc. The long-term damage around these openings was also analyzed, as well as instantaneous or long-time failure. A theory was formulated for the interaction between a creeping rock (viscoelastic or viscoplastic) and an yielding self-adjusting lining, for several kinds of yielding linings, including elastic and non-elastic self-adjusting linings. A mathematical theory for several self-adjusting linings was developed. The compressibility of a stratum of broken rock was also described by mathematical models of the elastic/viscoplastic type and used to show its influence, when such a stratum is placed between an yielding lining and a creeping rock. Creep of coal in long-wall working is another problem which was addressed. Several papers concerning creep, stability, failure, and closure of rectangular caverns and galleries have been published; the evolution in time of dilatancy and thus of damage in the surrounding rocks was also analyzed for the cases when the caverns are subjected to an internal pressure or not. The interaction between rock creep and internal pressure was also considered.

Recently a theory to describe **landslides** was formulated taking into account that under its own weight the soil is compacting and thus the mechanical properties wary with depth. It is shown that density is varying linearly with depth, but the yield stress cannot wary linearly. A procedure to determine a viscoplastic constitutive equation (non homogeneous Bingham) solely from in situ inclinometer readings was given (no laboratory tests are

necessary). Examples of applications of the theory to several landslides show very good results.

Particulate Mechanics. The problem addressed is to find out mathematical models able to describe the mechanical behavior of particulate materials (compaction, dilation, flow) subjected to a certain stress field. Triaxial testing devices are used for this purpose for both dry and saturated powders. It is shown when the powders are compacting and when they dilate. The incipient powder flow was also studied. A new triaxial aparatus for testing dry powders at law confining pressures was invented. The influence of particle size, initial density, air flow, etc. are considered

Present Projects

Modeling of Damage in Concrete and Geomaterials (*Air Force*). The research is aiming at formulation of constitutive equations to describe the elastic/viscoplastic behavior of concrete and some geomaterials, subjected to high strain rate deformation. A theory of damage which would take into account the energy of microcracking as well, is also to be formulated.

New Constitutive Equation for Rock Salt (*BGR -Germany and SANDIA)* . The research continue previous efforts to formulate a constitutive equation for rock salt, able to describe instantaneous response, creep and relaxation as well as irreversible volumetric changes (dilatancy and compressibility) during creep. This model will be applied to design underground radioactive repositories in salt. Evolution in time of damage is of major concern for such problems and should ge described by the constitutive equation.

New Numerical Algorithm in Elastoviscoplasticity with Application to Geomechanics (*National Research Council/Twining Program*). This is a cooperative effort with the Mathematical Institute of the Romanian Academy to develop numerical algorithms needed for the solving of geomechanical problems when the constitutive equation is of elastic/viscoplastic type.

Particulate Mechanics (*NSF, and several Chemical Companies*). The projects deals with compaction, dilation and flowing of particulate materials (ceramics, various chemical products in the form of powder, or geomaterials containing useful minerals). The effort is to find out experimentally their dominant mechanical properties, and to formulate mathematical models (constitutive equations) able to describe these properties. These models can afterwards be used to design products with controlled density or porosity, or to find out in what condition they can flow, or how can they be cutten faster, etc.

Transition from Genetics to Clinical Trials: Successes and Failures of Mendelian Randomization Identified LDL Cholesterol Lowering Pathways

by Robert Rosenson, Member EUAS

<u>Short Biography</u>

Robert S. Rosenson, MD, is Professor of Medicine at the Icahn School of Medicine at Mount where he serves as Director of Cardiometabolic Disorders. He is a Fellow of the American Heart Association Council on Epidemiology and Prevention, Fellow of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology, Fellow of the National Lipid Association and a past Fellow of the American College of Chest Physicians (inactive). He has been the recipient of a number of awards and honors, including the Ground-Breaking Doctors Award from Chicago magazine, and in 2015 New York Top Doc. In 2015 and 2016, he received the Simon Dack award for his contributions to the Journal of the American College of Cardiology.

Dr. Rosenson earned his medical degree from Tulane University in New Orleans, Louisiana where he conducted research on prostaglandin metabolism in coronary arteries. This work was recognized when he was awarded the Querens-Rives-Shore Award for best thesis in Cardiology. He then served his residency in medicine at Brigham and Women's Hospital in Boston, Massachusetts. He later completed a fellowship in cardiovascular medicine at the University of Chicago that was followed by an additional year of training as a Research Associate in lipoprotein metabolism.

Dr. Rosenson is a Diplomate of the American Board of Internal Medicine, with a subspecialty in cardiovascular disease, the National Board of Medical Examiners, and National Lipid Association. He currently serves on a number of committees for professional societies. He has served on nine committees for the American College of Cardiology, and he served as a member of the Expert Document Committee for the American College of Cardiology and ACCF Representative to the ADA Aspirin Therapy in Diabetes Position Statement. He has been extensively involved with the National Lipid Association where he serves a National Board Member and Northeast Lipid Association Board Member. Dr. Rosenson served as Co-Chair for the task force on HDL biology, and he is the current Chair of the Statin Safety Expert Muscle Document Committee. Dr. Rosenson led three international working groups on HDL that resulted in seminal articles on HDL nomenclature, HDL and macrophage cholesterol, and HDL functionality.

Dr. Rosenson has been involved in numerous grant-supported research investigations studying the effects of lipid-lowering therapy, hypoglycemic therapy, and antihypertensive agents in inflammation, thrombogenesis, and rheology. His laboratory was the first to demonstrate that statins reduce pro-inflammatory cytokine production. He has continued this work through mechanistic studies on inflammatory markers with studies on fenofibrate. Most recently, he has conducted research with selective inhibitors of inflammatory pathways such as lipoprotein-associated phospholipase A2, and secretory phospholipase A2. He has made important contributions concerning the prognostic significance of lipoprotein subclasses in coronary atherosclerosis, cardiovascular events

and prediction of type 2 diabetes. He has served as Principal Investigator on a number of NIH-funded research studies, pharmaceutical-sponsored drug trials, and multicenter studies. He served as Global Principal Investigator of the PLASMA I, PLASMA II and FRANCIS trials. He has authored more than 260 peer-review journal articles, and 700 book chapters, abstracts, and electronic publications for Up To Date Medicine.

Genetic factors have been used to understand causative variants for complex diseases. Differences in genetic traits are quantified by the presence of specific single nucleotide polymorphisms (SNP). Studies conducted on large populations of individuals have provided insights into genetic pathways associated with atherosclerotic cardiovascular disease (CVD). These genome-wide association studies (GWAS) have identified traits involved in multiple atherosclerotic processes.

Mendelian randomization is the application of an instrumental variable that is strongly associated with the outcome of interest, and results only from the exposure to the biomarker of interest. According to the Mendelian randomization paradigm, the naturally randomized distribution of genotype occurs at conception and exerts itself throughout the lifetime of the individual. Causality for the trait is implied when its absence is associated with a disease state or clinical event. Most often, the SNP is related to a gene encoding a known intermediary biomarker of interest. This approach has been used in pharmacological development to enhance confidence regarding the validity of a specific biological pathway. However, atherosclerotic vascular disease is a complex process in which the cellular microenvironment may potentially activate silent inflammatory genes or co-transcription factors that are relevant at different stages of the atherosclerosis process. This overview discusses genetic traits involved in low density lipoprotein (LDL) metabolism, and the success of pharmacological therapies that modulate this pathway in clinical trials.

HMG-CoA Reductase Inhibition and Statin Therapy

Statins lower LDL cholesterol (LDL-C) levels through a dual mechanism that involves inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR), the rate limiting step in cholesterol biosynthesis, and secondarily by increasing LDL receptor (LDLR) synthesis. The magnitude of HMG-CoA reduction corresponds with reduction in cardiovascular events; however the therapeutic response is variable. A genetic risk score selected from traits identified at a gnome-wide level was developed to evaluate the heterogeneity of risk reduction in two trials of primary prevention and two trials of secondary prevention. The benefit of statin therapy on incident and recurrent coronary events increased across the low (13%), intermediate (29%) and high (48%) genetic risk categories. High genetic risk participants enrolled in primary prevention trials had larger absolute risk reduction in CHD events resulting in a threefold decrease in the number needed to treat to prevent one CHD event. This approach demonstrates the expanding role of genetics in the assessment of risk even among the most studied cholesterol-lowering therapies.

NPC1L1 and Ezetimibe Therapy

Niemann-Pick C1-like1 (NPCL1) is expressed in the small intestine where it serves as a transporter of dietary cholesterol from the intestinal lumen to the enterocytes. Ezetimibe, a

pharmacological agent that inhibits the function of *NPC1L1*, lowers LDL-C by 15 to 20%; however some patients have unexpectedly larger reductions in LDL-C of 60%. Ezetimibe hyperesponders had unique variants in *NPC1L1*. Naturally occurring inactivating mutations in *NPC1L1* are associated with a lower LDL-C level of 0.31 mmol/L. Carriers' status for an inactivating mutation was associated with a 53% relative reduction in the risk of coronary heart disease (CHD). Mendelian randomization examined the effects of inhibiting *NPC1L1*, *HMGCR* or both on CHD events from prospective and case-control studies. *NPC1L1* polymorphisms were associated with a 2.4 mg/dL lower LDL-C and 4.8% lower risk of CHD, while the group with *HMRCR* polymorphisms had a 0.075 mmol/L lower LDL-C and 5.3% lower risk of CHD. Among individuals with both *NPC1L1* and *HMGCR*, polymorphisms, LDL-C was lower by 0.15 mmmol/L, and there was a larger 10.8% lower risk of CHD. This 2 x 2 genetic analysis provides support for NPC1LI as a valid target for pharmacological intervention in combination with statin therapy. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial confirmed the Mendelian randomization studies concerning incremental cardiovascular protection with combined ezetimibe and statin therapy. IMPROVE-IT randomized post acute coronary syndrome patients to simvastatin 40 mg daily or simvastatin 40 mg daily and ezetimibe 10 mg daily. Treatment with simvastatin and ezetimibe reduced cardiovascular events by 6.4%.

PCSK9 and Cardiovascular Events

Genetic studies have identified missense and nonsense loss of function variants in proprotein convertase subtilisin kinexin 9 (*PCSK9*). Nonsense mutations in African Americans were associated with lower LDL-C and fewer myocardial infarctions than missense mutations in Caucasians. These support the concept that lifelong lower levels of LDL-C are accompanied by lower risk of CHD. Successful pharmacological approaches to PCSK9 inhibition include the use of monoclonal antibodies directed at circulating levels of PCSK9. In pooled analyses, the completely human monoclonal anti-PCSK9 antibodies (alirocumab, evolocumab) reduces LDL-C levels by 55 to 72 percent; and in post hoc analysis of phase II trials, cardiovascular events were reduced by 53 percent and 54 percent respectively. Meta-analyses of PCSK9 trials have reported 55 cent lower all-cause mortality. However, formal clinical event trials with completely human monoclonal antibodies and humanized monoclonal antibodies against PCSK9 have not been completed.

CETP and Pharmacological Inhibition

Cholesteryl ester transfer protein (CETP) promotes mass transfer of cholesteryl esters from high density lipoprotein cholesterol (HDL-C) to other lipoproteins, and results in an increase in HDL-C and decrease in LDL-C for all agents except dalcetrapib. LDL-C reductions for various CETP inhibitors are 24.9% with torcetrapib, 26% with evacetrapib, 38% with anacetrapib, and 45.3% with TA-8995. CETP variants located near or in the *CETP* gene at 16q13 are associated with lower LDL-C, higher HDL-C and lower risk of cardiovascular events. In the Copenhagen City Heart Study, individuals carrying 4 versus 0 CETP polymorphisms had 0.1 mmol/L lower LDL-C and 24% lower risk for ischemic vascular events. The Women's Health Study reported that 9 CETP polymorphisms that are associated with HDL-C, a 24% lower risk of myocardial infarction. Unfortunately, LDL-C values were not reported. In a larger meta-analysis that re, Voight et al reported that the CETP variant rs3764261 was associated with 0.03 mmol/L lower LDL-C and 4% lower

risk of myocardial infarction. However, the use of small molecules directed at CETP inhibition has not yet established this target as a viable candidate for CVD prevention. Despite the failure of clinical trials with certain CETP inhibitors (torcetrapib, dalcetrapib, evacetrapib), it remains to be determined whether other CETP inhibitors do not have hazardous off-target toxicity of torcetrapib or may be more effective than dalcetrapib and evacetrapib agents for lowering LDL-C (anacetrapib, TA-8995) reduce cardiovascular events. However, CETP inhibition with three agents has not been accompanied by a reduction in cardiovascular events suggesting other pathways may interfere with CETP-mediated lipid changes in statin-treated patients.

Conclusions

Mendelian randomization is a powerful tool that has confirmed findings from clinical trials, and provided insight into variable biomarker and cardiovascular protection with pharmacological therapies. This genetic approach to drug selection provided confidence in the rapid approval of PCSK9 inhibitors. In contrast, CETP variants have been associated with cardiovascular events in multiple meta-analyses. Thus far, CETP inhibition is a failed strategy for the prevention of cardiovascular events. A clinical trial with the more potent CETP inhibitor anacetrapib is ongoing, and the status of TA-8995 remains uncertain.

While the evidence supporting combination therapy in statin treated patients has been demonstrated for ezetimibe, and post-hoc analyses with PCSK9 inhibitors are suggestive, statins may interfere with CETP-mediated cholesterol efflux via ABCA1. Thus, the context of new lipid modifying therapies must account for background evidence-based treatments. Further developments in the translation of genetic traits to clinical practice require improved understanding of the proteome, lipidome and metabolome.

Recent Developments in Catalyst Discovery

by Graham Hutchings, Member EUAS

Short Biography

1972 BSc in Chemistry with First Class Honours, University College London; 1975 PhD in Biological Chemistry, University College London. Supervisor: Prof C Vernon; 2002 DSc (University of London).

Professional Appointments:

1975– 1984	*ICI Petrochemicals Division, Technical Officer*
1984– 1987	*University of Witwatersrand, S Africa; promoted Professor 1987*
1987– 1997	*University of Liverpool; promoted Professor 1994*
1997 – present	*Cardiff University; Professor of Physical Chemistry, HoS 1997-2006; PVCR 2010-2012; Director Cardiff Catalysis Institute 2008- date*

Prizes/ Distinctions

Langmuir Distinguished Lecturer Award, Division of Colloid and Surface,Science, ACS, August 1996; DGMK 2001 – Kolleg Lectureship, Germany, 2001; IChemE Entech Medal 2004; RSC 2004 Award for Heterogeneous Catalysis; 2005 François Gault Lecturer of the European Federation of Catalysis Societies; I Chem E Impact Award for Applied Catalysis 2005; RSC Green Chemistry Lecturer 2007; IChemE Environwise Award for Green Chemistry 2007; Winner Dow Methane Challenge 24th January 2008; Elected Fellow of the Royal Society 2009; RSC Award for Surfaces and Interfaces 2009; I Chem E Sustainability Award 2009; Elected member Academia Europaea September 2010; Elected Founding Fellow Learned Society of Wales; IPMI Henry J. Albert Award 2011; France Great Britain Chemistry Prize 2011; Dechema Alvin Mittasch Award 2012; International Association of Catalysis Societies Heinz Heinemann Award 2012; Thompson Reuters Citation Laureate September 2012; Distinguished Visiting Lecturer, Catalysis Society of South Africa, 2013; Royal Society Davy Medal 2013; Dewar Lectureship, Queen Mary College, London; Thompson Reuters Most Cited Scientist Award 2014 and 2015; Xingda Lecturer University of Peking 2015; IChemE Global Innovative Product Award 2015.

External positions of note

Editor J. Catal. 1999-date; Member of 15 Journal Editorial Boards; Member of the Fachbeirat of the Fritz-Haber-Institut, Berlin 1999-2015; and MPI Coal Conversion Mulheim 2012-14; Member of Sasol (South Africa) Heterogeneous Catalysis Advisory Board 2000-2009; Member of NIOK International Review Group 2000, 2006, 2010 (Chair), member of review team for Chem Eng in the Netherlands 2015; Invited Professor in Residence at the Université Pierre et Marie Curie, Paris, 2003-4; RAE panel member for Chemistry (Panel 18) 2005-2008; Chair of SCORE 2010-2013; REF Panel member and Deputy Chair for Chemistry (Panel B8) 2011-2014; President Faraday Division RSC 2012-2015; Inaugural Director UK Catalysis Hub 2013-2015.

Publications

703 publications (587 refereed journal research articles; 42 Patents; 57 Review articles; 17 Edited works, over 23500 citations (Web of Science 21.12.15) 7711 citations since 1.1.13, h-index 71, over 220 Research lecture presentations. Over 300 PhD students supervised and over 150 pdras supervised to date over my 30 year academic career.

Graham Hutchings is distinguished for his work on heterogeneous catalysis and in particular in respect of catalyst discovery. He is currently Director of the Cardiff Catalysis Institute in the School of Chemistry at Cardiff University. He has not had standard career path for an academic. He was initially trained as a biological

chemist, completing his PhD on ATP in 1975; but on joining ICI in 1975 as a scientist he transferred to research on heterogeneous catalysis; a field that at that time was exceptionally challenging as fundamental understanding was limited. After 9 years in industry, with 3 years in production management, he became an academic and in his 31 years in academia he has pioneered catalyst discovery and design for a number of challenging reactions publishing over 700 papers to date. Together with other researchers in the UK he played a leading role in establishing the UK Catalysis Hub which is a research collaboration involving over 40 UK universities and he was the first Director from 2012-2015.

Hutchings is probably best known for his work in the field of catalysis by gold in which he has been active for over 30 years, being one of the first researchers to recognise the significance of the catalytic potential of gold. In 1985 he was the first to predict that gold would be the most active heterogeneous catalyst for reactions of acetylenes. His subsequent studies confirmed this prediction. He was, therefore, amongst the first to recognise the potential of gold, particularly in cationic form, as an active catalyst at low temperatures. Hitherto it was almost universally regarded that gold was an inactive catalyst. This is because gold has to be highly dispersed as nanoparticles for any significant catalysis to be observed. Since this initial work there has been an enormous explosion of interest in gold as a catalyst, with over 3000 publications and several international conferences devoted solely to this topic. He is undoubtedly one of the leading pioneers in this new field. He has continued to play a leading role in gold catalysis and was the first to show that small gold particles could be effective catalysts for the formation of hydrogen peroxide from dilute H_2/O_2 mixtures. This is a key discovery since the high activity selective catalysts designed on the basis of this work will permit the direct synthesis of H_2O_2, under intrinsically non-explosive conditions paving the way for this process to have commercial potential. His most significant paper on this topic appeared in *Science* in 2009 and showed for the first time that a catalyst that could synthesise hydrogen peroxide and did not simultaneously destroy it through decomposition/hydrogenation. This catalysis is now being pioneered for water purification and this is being taken to a demonstration level. As a winner of the Dow methane challenge he has recently pioneered gold catalysts for hydrocarbon oxidation. Published in 2011 in *Science* this concerns the selective oxidation of toluene to benzyl benzoate with yields of over 95%.

Most significantly, his initial discovery that gold would be the best catalyst for the manufacture of vinyl chloride has now been taken up by Johnson Matthey and the highly efficient gold catalyst is now commercialised in China with the company building a new facility in China in 2015 to manufacture the catalyst. This is the first time in over 50 years that there has been a complete change in a catalyst formulation for the manufacture of a commodity chemical. The gold catalyst will replace a highly polluting mercury mercury catalyst and so this will have enormous environmental benefits.

In recent years he has maintained his interest in the discovery of new catalysts for challenging reactions. He discovered that CuFeZSM5 could catalyse the selective oxidation of methane to methanol at 50 ^{o}C giving 10% conversion and 95% selectivity. This is a grand challenge reaction and his work has opened up new research in the area. As part of his research with his ERC Advanced Grant "AftertheGoldrush" he has shown a new reaction is possible whereby glycerol reacts with water as hydrogen donor with MgO as catalyst giving a new low pressure route to methanol. Glycerol is a byproduct from biodiesel manufacture and this now route to *green* methanol, published in *Nature Chemistry* is being taken up commercially. Most recently, he has found that georgeite a rare copper mineral can be prepared by a simple antisolvent method and is the most effective catalyst for the low temperature water gas shift reaction. This work has been recently published in *Nature*. At present he is continuing to study the challenging reactions of methane activation, the direct synthesis of hydrogen peroxide and the utilization of carbon dioxide.

Finite and Generalized Finite Element Method

by Ivo Babuska, Member EUAS

<u>Short Biography</u>
University of Texas at Austin

Education

Technical University Prague	*Civil Engineering*	*Dipl Ing*	*1949*
Technical University Prague	*Technical Sciences*	*Dr.*	*1951*
Czechoslovak Academy of Sciences		*Dr. Sc*	*1960*

Honorary doctorates

University of Westminster	*Gr. Britain*	*1994*
Brunel University	*Gr. Britain*	*1996*
Charles University	*Czech Republic*	*1997*
Helsinky University of Technology Finland		*2000*
Czech Tecnical University	*Czech Republic*	*2007*

Academies

Learned Society Czech Republic	*1994*
EU Academy of Sciences	*2015*
US National Academy of Engineering	*2005*
Engineering Academy of Czech Republic	*2007*

Fellowships

Internat.Assoc. Comp. Mech	*2002*
SIAM	*2009*

Awards Some

Birkhoff Prize (Am. Math Soc., SIAM)	*1994*
J. v Neumann Medal US Assoc Comp. Mech	*1995*
Bolzano Medal Czech Academy of Sciences	*1996*
Congress Medal of Internat Assoc Mech	*2006*
Leroy P Steele Prize for Lifetime Achievements	
American Mathematical Society	*2012*
Asteroid 36060 was named Babuska	*2003*

Field of interest
Numerical Mathematics, Partial differnrtial equations, Probability theory, Computational Science

Finite element method (FEM) is a computational method for solving partial differential equations. It is widely used in the engineering and physics. The basic idea of the method is not new. Although under the name Finite Element Method it was used already in 1960-ties [1], the theory was developed only in the 1970-ties. See [2] for the history until 1970 and [3]. In the seventies the basic theory of FEM was developed. I Babuska significantly contributed to it. Few of his papers [2]-[7] with the citations illustrate the impact. FEM method approximates the solution by piecewise linear or biquadratic functions, called the shape functions. The accuracy resp. the convergence to the exact solution u by the FEM solution u_h is achieved by the mesh refinements with the size of elements $h \to 0$. Hence the name *h−version* of FEM. In [8], [9] I Babuska introduced the *p−version* and the *h−p−version* of the FEM. The convergence is then achieved by using fixed mesh and

polynomials with increasing degree $p \to \infty$ as the shape functions respectively simultaneously size of the elements $h \to 0$ and the degrees of the shape functions $p \to \infty$.

The solution u is not smooth for example when it has singularities in the corners of the domain or the material constant are rough i.e when the material has microscale. Then the mesh is refined. The proper mesh construction is not simple. Hence, I Babuska suggested to use special local elemental shape functions called enrichment functions which are analytic or are numerically constructed. The partition of unity method is used to construct the enrichment space S_R by these local functions. The approximation space is then $S_R \oplus S_{FE}$ where S_{FE} is the basic FE space of piecewise linear or polynomial shape functions. Hence this method is called partition of unit method (PUM). The methods and its theory is in [10]. When the partition of unity function is the classical FEM "hat" function, the method is called the generalized Finite Element Method (GFEM). It was further elaborated in [11],[12]. These three papers [10],[11],[12] are cited more than 5000 times. This shows well the impact and broad use of this method. The survey of this method with the applications is in [13]. The GFEM method could lead to the system of linear equations with large condition number which will slow down the iterati0nsd. This is important when the method is used for solving large problems of system of tens or hundreds millions of equations. Hence in [14] I Babuska suggested a version of GFEM called stable GFEM (SGFEM). It is a version of the GFEM which condition number is the same as of the FEM.

The major problem of the GFEM and SGFEM is to create the proper enrichment shape functions. This could be done by different approaches. One possibility is to solve the problem on overlapping "patches" for some boundary conditions using fine mesh. Other possibility is to construct the shape functions as special eigenfunctions of the problem on the superpatches which are the domains which boundary has positive distance to the boundary of the patches This construction leads to the exponential rate of convergence of the GFEM and SGFEM when the problem is of elliptic partial differential equations. This was proven in [15].

Let us now explain the major idea of the FEM and GFEM. In the FEM firstly the mesh is defined. It divides the domain into triangles in 2 dimensions and tetrahedrons (simplexes) in the three dimensions. Denote by τ_i, $i = 1,2,......n(\tau)$ these (closed) triangles called elements and $x_j, j = 1,2,......n(x)$ theirs vertices called nodal points. Further denote by ω_l, $l=1,2,..n(\omega)$ the " patches" which are (open) unions of the the elements with joint node ξ_l The most simple basic finite element method approximates the solution u by the linear combination of the "hat" functions φ_i which are linear on every element belonging to ω_i, $\varphi(x_i) = 1$ and have support on ω_i. Hence $u(x) = \sum_{j=1}^{n(\xi)} u(x_j)\varphi_j(x)$ with $u(x_j) \in R^1$ to be determined by solving a system of linear or nonlinear equations. In the GFEM in some nodal points $x_j, j \in I_R$ the enrichment points, the approximation of $u(x)$ is enriched by the functions $\sum_{j \in I_R} \int \mathbf{w}(x_j)\psi_j(x,\mathbf{w}_j)\varphi_j(x)$. Function $\psi_i(x,\mathbf{w}_j)$ is a function defined on ω_i possibly depending on k_j parameters $\mathbf{w}(x_j) = (w^{(1)}(x_j),.........,w^{(k_j)}(x_j))$ functions $\psi_j(x,\mathbf{w}_j)$ are called the enrichment functions. These functions approximate well local the

solution u. The parameters $w^{(k)}(x_j)$ together with $u(x_j)$ are determined using some functionals for example the energy functional. The system for these unknowns is linear or nonlinear. The bad condition number of the system depends how well the functions ψ_j could be approximated by linear functions. If this is the case the enrichment functions ψ are properly modified. If the modification is such that the stability of the enriched formulation The condition number) is the same as of the FEM only, the method is called the Stable FEM= SGFEM. Of course the accuracy of the SGFEM has to be optimal.

GFEM and SFEM is used for many different problems. For example the crack propagation problem when the basic FEM mesh is independent of the crack length, various multiscale problems etc. Although lot of results of these methods were achieved during last 10 years still many problems are open.

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Further Developments in Environmental Management

by Matthias Ruth, Member EUAS

Short Biography
Dr. Matthias Ruth is Professor at the School of Public Policy and Urban Affairs and at the Department of Civil and Environmental Engineering at Northeastern University. He serves as Director of the Policy School and the founding director of Northeastern's Resilient Cities Laboratory and the Urban Informatics program.
Professor Ruth holds a Masters degree in Economics from the University of Heidelberg, Germany, and a PhD in Geography from the University of Illinois, USA, where he also received training in engineering and biology. After almost a decade at Boston University and more than a decade at the University of Maryland where he was the Roy F. Weston Chair in Natural Economics and Policy Advisor on Sustainability to the Chancellor, he joined Northeastern University in 2012.
Prof. Ruth's research focuses on dynamic modeling of natural resource use, industrial and infrastructure systems analysis, and environmental economics and policy. His theoretical work heavily draws on concepts from engineering, economics and ecology, while his applied research utilizes methods of non-linear dynamic modeling as well as adaptive and anticipatory management. Applications of his work cover the full spectrum from local to regional, to national and global environmental challenges, as well as the investment and policy opportunities these challenges present. Professor Ruth has published 15 books and over 120 papers and book chapters in the scientific literature. He is a founder of Ecological Economics, serves on the boards of numerous journals and scientific organizations, is a founding Editor-in-Chief of the journal Urban Climate, and collaborates extensively with scientists and policy makers worldwide.

1. Motivation

Much of my research focuses on the interplay of innovation, technological change and economic growth in the context of the biophysical constraints that have, and always will, set the boundaries within which human society flourishes. As the foundation was laid during the industrial revolution for fundamental changes to the interactions among sectors of the economy and society, new opportunities arose to explore and harness new resources. At the same time, new models for industry-government relations emerged, and incentive structures were put in place that fostered rent seeking through further development and deployment of technologies. Many of these incentive structures – and the social and political processes that maintained or improved upon them – continue today to stimulate subsequent technological and economic changes.

Because of fundamental physical principles, most notably the second law of thermodynamics, extraction, conversion and use of resources – be those materials or energy – unavoidably result in irreversible changes in the environment. And because of the path-dependency of biological and socioeconomic processes, past actions can rarely be undone at the scales that are relevant for development. In this context, my research addresses the following questions: What are the prospects for technology and innovation

to help bring about interactions between humans and their biophysical environment that actually can be sustained in the long run? What opportunities and challenges lie ahead for investment and policy making to promote technology and innovation that foster sustainability? How will global environmental change affect prosperity in the long run, and how can humanity prepare itself today for the dynamics it has set in motion already? The remainder of this article provides brief perspectives on each of these topics.

2. Complexity and the Futility of Management

Herman Daly (2005, 2009) speaks of an empty world in which human use of resources and the release of waste products were small enough to be accommodated by the local ecosystems in which production and consumption took place. With increases in population, production, consumption and pollution, the abilities of ecosystems to provide environmental goods and services became increasingly compromised. Yet, the behaviors and incentives to further grow the human enterprise in this full world are hardly changed as the world became fuller, and are in principle no different from those during early exploration and expansion – economic growth is widely regarded as the primary mechanism to increase standards of living and to solve the social and environmental problems created by growth.

Another perspective on the world as being "empty" or "full" is conceptual in nature. In a full world ever more processes are linked with each other, and there is no reason to believe that any and all of these linkages are well behaved. Instead, the feedback processes that connect human actions and environmental performance will change in strength and direction, resulting in oscillations, meeting thresholds and bifurcation points, or expressing themselves in myriad other ways. Well-intended actions to control socioeconomic or environmental changes may have unintended consequences that will likely give rise to further interventions, with their own side effects.

To the extent that institutions are a product of collective experiences and rules that accumulated over time they may transcend the interests of any given individual and help identify solutions that are more in tune with collective and long-term interests. Yet, to the extent that these institutions also lock in rules and procedures that benefit their own purposes and have their origins within the growth paradigm, they may perpetuate the challenges they are designed to address, even while pressures are mounting to divert from past behaviors. For example, a transportation agency charged with providing adequate and reliable movement of people and goods may perpetuate the growth of roads and road networks, as well as the rule for operating and expanding them. Economic growth my result, which further stimulates shipments of goods and services, and possibly leads to the fragmentation of the economic landscape as has been the case in the US and many other industrialized nations. Along the way, the powers of the agency are bolstered and the expansion of roads is perceived as a seemingly logical solution to the problems generated by the expansion of roads.

Given the complexity of human-environment interactions, it should not come as a surprise that there are clear limits to the ability to "engineer ourselves" out of many of the problems that were generated by shortsighted deployment of technology. For instance, where floods persist, levies and dikes are put in place, and insurance schemes are devised to compensate for residual risk. The consequence of such actions often is a continued accumulation of people and assets in flood-prone areas. As extreme weather events

become increasingly frequent and severe, and as sea levels rise as a result of climatic change, expected future damages increase, rather than decline, with the traditional engineering and institutional approaches of coastal protection doomed to ultimately fail.

3. Global Environmental Change and Human Prosperity

One traditional approach to addressing emerging environmental challenges is to harness the powers of markets, which assumes that proper design of incentive systems can guide behaviors towards desirable outcomes. Rising prices would suggest that scarcity of a resource is increasing and thus stimulate a decline in demand and a search for alternatives. Where unintended consequences of production and consumption are encountered, externalities may be internalized to adjust prices and the signals they give to change behaviors and technologies. But what if the world is more complex than presumed here? What if prices are not only the product of rational economic decision-making and instead reflect deep-seated social tensions and long-overlooked environmental constraints? For example, in societies in which women and children hold limited rights for self-expression and self-determination, the wages paid to them for their labor will be depressed. In places where environmental standards are low, resource extraction and environmental pollution may cause harms that remain unaccounted for in economic decision-making. The prices of goods and services in conditions of social and environmental exploitation are then not worth much with respect to their ability to guide economic decisions towards optimal outcomes (Røpke 1999). More likely, they will entrench unsustainable practices.

The concept of optimality, as normally conceived in economic analysis, makes little sense from a complex systems perspective (van den Bergh and Stagl 2003). But if optimality is passé as a guiding principle in such settings, then what may take its place? At a minimum, decision-making will need to recognize that there are always multiple criteria by which performance must be assessed, and multiple objectives must be pursued at any given point in time to meet the different objectives of members in the community. Multi-criteria, multi-objective decision making is far from new, and has gradually made inroads into debates about, for example, choices of technologies, developments of infrastructures, and social and environmental policies (see, for example, Eiselt and Laporte 1992). Science may place bounds on some of the uncertainties, and thereby provide stakeholders with information with which to estimate benefits and costs (Ruth and Bullard 1993).

4. Taking the Long View

Deep-seated belief in economic growth and the power of technology as the means to overcome environmental constraints and geographic distance for faster delivery of goods and services in order to satisfy human needs and wants will be hard to overcome after centuries of rising life expectancies and quality of life in the "developed world" – despite the fact that empirical evidence keeps mounting that high rates of development are possible at low rates of energy use (Steinberger and Roberts 2010). But even if the beliefs, motivations and structures by which society operates could be readily changed, it remains unclear, *a priori*, what form such change should assume because the future is fundamentally open and potentially rich in uncertainties and surprises. Identifying those actions that undermine sustainability remains much easier than describing behaviors to take their place. At a minimum, however, the challenge is for innovation to occur faster than biophysical constraints on human welfare are approached. Since fundamental physical laws prevent technological innovation from overcoming those limits, the only long-term

viable strategy is for sufficiently rapid social innovation. Given the complexity of human-environment interactions, this will mean a need for considerable openness towards trial and error even though – or because – the stakes are high. A wide range of experiments need to be carried out at local and regional scales, and the lessons from these experiments need to be continuously assessed and shared, then aggregated to establish and revise the rules by which society engages in changes of its environment. Such a perspective on the role of technology and innovation for sustainable development markedly contrasts with the nature of existing laws, market incentives and social reward systems that are less open to community engagement, experimentation, and adaptation.

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Targeting Endothelial Metabolism in Angiogenesis

by Peter Carmeliet, Member EUAS

Short Biography

Laboratory of Angiogenesis and Vascular Metabolism, Vesalius Research Center - VIB, Department of Oncology – KU Leuven, 3000 Leuven, Belgium.

Peter Carmeliet graduated as Doctor in Medicine in 1984, and completed his PhD in Medicine in 1989. In 1992, Carmeliet started his own research group with a focus on how blood vessels grow (angiogenesis) in health and disease.

The Carmeliet lab is currently studying how endothelial cells change their metabolism during vascular branching and is exploring the therapeutic potential of targeting endothelial metabolism for anti-angiogenic strategies. The role of several key metabolic enzymes in endothelial cell biology and angiogenesis in vivo are under investigation.

AWARDS & HONORS (SELECTED LIST)

Interbrew Baillet Latour Prize (2005); Feodor Lynen Lecture, Nature Biotechnology (2006); Lucian Award for Circulatory Disease, McGill University (2007); Francqui Leerstoel, UCL (2008); Prijs Baron van Gysel de Meise, GSKE (2009); Paulo Gontijo Prize, Brasil (2009); Ernst Jung Medical Award, Hamburg (2009); J. Maisin Prize for Excellence, Brussels (2010); Doctor Honoris Causa, Goethe University, Frankfurt (2010); Member German Academy of Science, Leopoldina (2010); Blaise Pascal Medal in Medicine, EU Academy of Science (2011); Award of the Hubertus Wald Foundation, Hamburg, Germany (2013); Münster Heart Center Award – University Hospital Münster, Germany (2015); noble appointment to Baron by King Filip of Belgium (2015), European Atherosclerosis Society - Anitschkow Prize, Gothenborg, Sweden (2016)

MAIN RESEARCH FIELDS : Angiogenesis, endothelial cell metabolism, cancer

PUBLICATION SUMMARY

584 Pubmed-listed publications - cited 60.438 times*. h-index is 115. The best-cited (first or last author) publication is Carmeliet P & Jain RK Angiogenesis in cancer and other diseases, Nature 407: 435-439 (n=4,567).

INTERNATIONAL LECTURES AND SEMINARS AS INDEPENDENT RESEARCHER:

In total, P. Carmeliet gave 359 invited lectures in the past 10 years, of which many as Keynote or Plenary lectures at high-impact international meetings: Keystone Meetings on Angiogenesis, Hypoxia, Metabolism (yearly since 2000), Gordon Research Conferences (yearly since 1994), Nobel Forum Lecture at Karolinska Institute Sweden (2008, 2013, 2014), Nature Meetings (2006, 2010), American Association for Cancer Research (2005, 2007, 2009, 2010, 2015), Dahlem College Max Planck Institute (2009), Kloster Seeon Meeting Germany (2008, 2010, 2012, 2014), Japanese Society for Thrombosis and Haemostasis (2005, 2008), Japanese Pharmacological Society (2010-2015), NAVBO (2006, 2008, 2015), Annual Meetings of the European Society for Hematology (2005, 2006, 2007, 2008, 2009, 2015), International Conference on Tumor Angiogenesis Monte Verita (2005, 2007, 2010, 2013, 2015), etc.

MEMBERSHIP IN SCIENTIFIC SOCIETIES (SELECTED LIST)

1999-Elected Member of the European Molecular Biology Organization (EMBO), 2002-Elected Member of the American Society of Clinical Investigation, 2006-Elected Member of the American Association for Cancer Research, 2010-Member of the German Academy of Sciences Leopoldina

PARTICIPATION IN ORGANIZATION OF INTERNATIONAL MEETINGS

Member of the Scientific Program Committee / Scientific Advisory board of over 40 international meetings, such as Intl. Congr. Fibrinolysis (1993-1995-2000), Eur. Soc. Cardiology (1997), Eur. Vascular Biology Assoc. (1998), Eur. Atherosclerosis Assoc. (1998), Eur. Soc. Hematology (1999-2000-2001), FASEB Conf. (1999), Intl. Soc. Heart Research (1999), Intl. Soc. Thrombosis & Haemostasis (1999-2000-2001), Keystone Symposium Angiogenesis (2002-2006), Intl. Vascular Biology Meeting (2002), Mtg Models of Thrombosis (1998-1999-2000-2001), Intl. Symp. Atherosclerosis (2003), etc.

Vessel sprouting by migrating tip and proliferating stalk endothelial cells (ECs) is controlled by genetic signals (such as Notch), but it is unknown whether metabolism also regulates this process. Here, we show that ECs relied on glycolysis rather than on oxidative phosphorylation for ATP production and that loss of the glycolytic activator PFKFB3 in ECs impaired vessel formation. Mechanistically, PFKFB3 not only Regulated EC proliferation but also controlled the formation of filopodia/lamellipodia and directional migration, in part by compartmentalizing with F-actin in motile protrusions. Mosaic in vitro and in vivo sprouting assays further revealed that PFKFB3 overexpression overruled the pro-stalk activity of Notch, whereas PFKFB3 deficiency impaired tip cell formation upon Notch blockade, implying that glycolysis regulates vessel branching.

During vessel sprouting, a migratory endothelial tip cell guides the sprout, while proliferating stalk cells elongate the branch. Tip and stalk cell phenotypes are not genetically predetermined fates, but are dynamically interchangeable to ensure that the fittest endothelial cell (EC) leads the vessel sprout. ECs increase glycolysis when forming new blood vessels. Genetic deficiency of the glycolytic activator PFKFB3 in ECs reduces vascular sprouting by impairing migration of tip cells and proliferation of stalk cells. PFKFB3-driven glycolysis promotes the tip cell phenotype during vessel sprouting, since PFKFB3 overexpression overrules the pro-stalk activity of Notch signaling. Furthermore, PFKFB3-deficient ECs cannot compete with wild-type neighbors to form new blood vessels in chimeric mosaic mice. In addition, pharmacological PFKFB3 blockade reduces pathological angiogenesis with modest systemic effects, likely because it decreases glycolysis only partially and transiently.

Strategies targeting pathological angiogenesis have focused primarily on blocking vascular endothelial growth factor (VEGF), but resistance and insufficient efficacy limit their success, mandating alternative antiangiogenic strategies. We recently provided

genetic evidence that the glycolytic activator phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) promotes vessel formation but did not explore the antiangiogenic therapeutic potential of PFKFB3 blockade. Here, we show that blockade of PFKFB3 by the small molecule 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) reduced vessel sprouting in endothelial cell (EC) spheroids, zebrafish embryos, and the postnatal mouse retina by inhibiting EC proliferation and migration. 3PO also suppressed vascular hyperbranching induced by inhibition of Notch or VEGF receptor 1 (VEGFR1) and amplified the antiangiogenic effect of VEGF blockade. Although 3PO reduced glycolysis only partially and transiently in vivo, this sufficed to decrease pathological neovascularization in ocular and inflammatory models. These insights may offer therapeutic antiangiogenic opportunities.

The metabolism of endothelial cells during vessel sprouting remains poorly studied. Here we report that endothelial loss of CPT1A, a rate-limiting enzyme of fatty acid oxidation (FAO), causes vascular sprouting defects due to impaired proliferation, not migration, of human andmurine endothelial cells. Reduction of FAO in endothelial cells did not cause energy depletion or disturb redox homeostasis, but impaired de novo nucleotide synthesis for DNA replication. Isotope labelling studies in control endothelial cells showed that fatty acid carbons substantially replenished the Krebs cycle, and were incorporated into aspartate (a nucleotide precursor), uridine monophosphate (a precursor of pyrimidine nucleoside triphosphates) and DNA. CPT1A silencing reduced these processes and depleted endothelial cell stores of aspartate and deoxyribonucleoside triphosphates. Acetate (metabolized to acetyl-CoA, thereby substituting for the depleted FAOderived acetyl-CoA) or a nucleoside mix rescued the phenotype of CPT1A-silenced endothelial cells. Finally, CPT1 blockade inhibited pathological ocular angiogenesis in mice, suggesting a novel strategy for blocking angiogenesis.

Endothelial cells (ECs) are plastic cells that can switch between growth states with different bioenergetic and biosynthetic requirements. Although quiescent in most healthy tissues, ECs divide and migrate rapidly upon proangiogenic stimulation. Adjusting endothelial metabolism to the growth state is central to normal vessel growth and function, yet it is poorly understood at the molecular level. Here we report that the forkhead box O (FOXO) transcription factor FOXO1 is an essential regulator of vascular growth that couples metabolic and proliferative activities in ECs. Endothelial-restricted deletion of FOXO1 in mice induces a profound increase in EC proliferation that interferes with coordinated sprouting, thereby causing hyperplasia and vessel enlargement. Conversely, forced expression of FOXO1 restricts vascular expansion and leads to vessel thinning and hypobranching. We find that FOXO1 acts as a gatekeeper of endothelial quiescence, which decelerates metabolic activity by reducing glycolysis and mitochondrial respiration. Mechanistically, FOXO1 suppresses signalling by MYC (also known as c-MYC), a powerful driver of anabolic metabolism and growth. MYC ablation impairs glycolysis, mitochondrial function and proliferation of ECs while its EC-specific overexpression fuels these processes. Moreover, restoration of MYC signalling in FOXO1-overexpressing endothelium normalizes metabolic activity and branching behaviour. Our findings identify FOXO1 as a critical rheostat of vascular expansion and define the FOXO1–MYC transcriptional network as a novel metabolic checkpoint during endothelial growth and proliferation.

In healthy individuals, the endothelium plays a fundamental role in normal health in the

maintenance of vascular homeostasis. Endothelial cell (EC) dysfunction results in the development of several pathologies. In diabetes, in particular, sustained hyperglycemia, a characteristic of diabetes, contributes to EC dysfunction and consequently mediates the pathogenesis of diabetes-associated micro- and macrovasculopathies. Hyperglycemia-induced EC dysfunction is triggered by elevated levels of oxidative stress derived from several mechanisms, with the mitochondria as a key source, and is exacerbated by a subsequent hyperglycemia-induced self-perpetuating cycle of oxidative stress and aberrant metabolic memory. Recent reports have highlighted the importance of metabolic pathways in EC and suggested the therapeutic potential of targeting EC metabolism. This review focuses on the current knowledge regarding differences in the metabolism of healthy ECs vs. diabetes-associated dysfunctional ECs, and outlines how EC metabolism may be targeted for therapeutic benefit.

Higher organisms rely on a closed cardiovascular circulatory system with blood vessels supplying vital nutrients and oxygen to distant tissues. Not surprisingly, vascular pathologies rank among the most life-threatening diseases. At the crux of most of these vascular pathologies are (dysfunctional) endothelial cells (ECs), the cells lining the blood vessel lumen. ECs display the remarkable capability to switch rapidly from a quiescent state to a highly migratory and proliferative state during vessel sprouting. This angiogenic switch has long been considered to be dictated by angiogenic growth factors (eg, vascular endothelial growth factor) and other signals (eg, Notch) alone, but recent findings show that it is also driven by a metabolic switch in ECs. Furthermore, these changes in metabolism may even override signals inducing vessel sprouting. Here, we review how EC metabolism differs between the normal and dysfunctional/diseased vasculature and how it relates to or affects the metabolism of other cell types contributing to the pathology. We focus on the biology of ECs in tumor blood vessel and diabetic ECs in atherosclerosis as examples of the role of endothelial metabolism in key pathological processes. Finally, current as well as unexplored EC metabolism-centric therapeutic avenues are discussed.

The endothelium is the orchestral conductor of blood vessel function. Pathological blood vessel formation (a process termed pathological angiogenesis) or the inability of endothelial cells (ECs) to perform their physiological function (a condition known as EC dysfunction) are defining features of various diseases. Therapeutic intervention to inhibit aberrant angiogenesis or ameliorate EC dysfunction could be beneficial in diseases such as cancer and cardiovascular disease, respectively, but current strategies have limited efficacy. Based on recent findings that pathological angiogenesis and EC dysfunction are accompanied by EC-specific metabolic alterations, targeting EC metabolism is emerging as a novel therapeutic strategy. Here, we review recent progress in our understanding of how EC metabolism is altered in disease and discuss potential metabolic targets and strategies to reverse EC dysfunction and inhibit pathological angiogenesis.

Vessel sprouting relies on the differentiation of endothelial cells (ECs) into a migratory tip cell leading at the forefront, proliferating stalk cells elongating the vessel stalk, and quiescent phalanx cells lining the perfused vessel.1 The tip versus stalk cell balance is under the control of vascular endothelial growth factor (VEGF) and Notch signaling, respectively. During recent years, the transcription factor SRY-related HMG box 17 (SOX17) has emerged as a regulator of arterial (at the expense of venous) EC specification, but its role in inducing the tip versus stalk EC behavior remained incompletely defined. In this issue of Circulation Research, Lee et al identified SOX17 as

an inducer of the tip cell phenotype and showed that Notch signaling suppresses SOX17 levels to promote a stalk cell phenotype. However, using similar genetic mouse models, another recent study reported noncongruent findings. Can we explain these divergent interpretations and what are the possible implications of these results?

Clinically approved therapies that target angiogenesis in tumors and ocular diseases focus on controlling pro-angiogenic growth factors in order to reduce aberrant microvascular growth. Although research on angiogenesis has revealed key mechanisms that regulate tissue vascularization, therapeutic success has been limited owing to insufficient efficacy, refractoriness and tumor resistance. Emerging concepts suggest that, in addition to growth factors, vascular metabolism also regulates angiogenesis and is a viable target for manipulating the microvasculature. Recent studies show that endothelial cells rely on glycolysis for ATP production, and that the key glycolytic regulator 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) regulates angiogenesis by controlling the balance of tip versus stalk cells. As endothelial cells acquire a tip cell phenotype, they increase glycolytic production of ATP for sprouting. Furthermore, pharmacological blockade of PFKFB3 causes a transient, partial reduction in glycolysis, and reduces pathological angiogenesis with minimal systemic harm. Although further assessment of endothelial cell metabolism is necessary, these results represent a paradigm shift in anti-angiogenic therapy from targeting angiogenic factors to focusing on vascular metabolism, warranting research on the metabolic pathways that govern angiogenesis.

Endothelial cells line the blood vessel lumen and are critical for blood flow homeostasis. Excessive and deregulated vessel overgrowth is a hallmark of pathological (tumor) angiogenesis. The purpose of this review is to describe the metabolic features of endothelial cells, in comparison with those of the cancer cells, and to discuss novel antiangiogenesis approaches based on targeting endothelial cell metabolism. Recent findings: To form new blood vessels, endothelial cells switch from quiescence to a highly active state, characterized by migration and proliferation of endothelial cells. To date, growth factors, cytokines, and other molecules have been demonstrated to regulate vessel sprouting. However, recent evidence indicates that endothelial cell metabolism also importantly regulates angiogenesis. Whereas cancer cell metabolism has been studied extensively, endothelial cell metabolism is still in its infancy. Summary: We will discuss metabolic pathways that regulate vessel sprouting, and highlight the commonalities with cancer cells for as much as studied. We will also consider new opportunities for the development of alternative antiangiogenic therapies by targeting endothelial cell metabolism.

For eukaryotic cells to function properly, they divide their intracellular space in subcellular compartments, each harboring specific metabolic activities. In recent years, it has become increasingly clear that compartmentalization of metabolic pathways is a prerequisite for certain cellular functions. This has for instance been documented for cellular migration, which relies on subcellular localization of glycolysis or mitochondrial respiration in a cell type-dependent manner. Although exciting, this field is still in its infancy, partly due to the limited availability of methods to study the directionality of metabolic pathways and to visualize metabolic processes in distinct cellular compartments. Nonetheless, advances in this field may offer opportunities for innovative strategies to target deregulated compartmentalized metabolism in disease.

Coupled Validation with Verification of Deterministic Modeling and Analysis of Engineering Structures.

by Erwin Stein, Member EUAS

Short Biography
Univ.-Prof. em. Dr.-Ing. habil. Dr.-Ing. E.h. Dr. h.c. mult.
Institute of Mechanics and Computational Mechanics
Leibniz Universität Hannover, Germany
Studies of Civil Engineering and Mathematics at Polytechnical University of Darmstadt, Germany, Construction and Analysis of wide-spanned Bridges in industry, Promotion and venia legend at the University of Stuttgart, Ordinarius of the Chair of Mechanics and Computational Mechanics of the University of Hannover, Official Inspection Engineer for Structual Engineering in the Land of Lower Saxony
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Honorable-Member of IACM and GAMM
Member of several Academies of Sciences in Germany and Europe
Editorial board-member of 8 international scientific journals
Lead editor of the Encyclopedia of Computational Mechanics (ECM), forthcoming 2ndelectronic edition
425 scientific publications (including 16 books as author, co-author, editor, and/or co-editor) on kinematic, material, and mathematical modeling of technical objects together with computational mechanics, i.e. computer-oriented numerical methods (esp. finite element methods), error analysis and adaptivity, algorithms, and software engineering in continuum and structural mechanics, and application to complex engineering problems. Principal editor of the "Encyclopedia of Computational Mechanics" with 3 volumes consisting of 75 articles on approx. 3.000 pages, published by John Wiley & Sons, Chichester, UK, and also available on the Internet since October 2004. First electronic revision in 2007. Forthcoming second electronic edition in 2016.
Co-editor and member of the Editing Boards of 8 national and international scientific journals 51 DFG research projects, including "Special Research Areas", chairman of "Priority Projects" within Germany, chairman of "Priority Projects" at the University of Hannover and individual research projects.
4 joined research projects, supported by the Volkswagen Foundation, Hannover
Several industrial research projects, mostly concerning the evaluation of damage and failure
Initiation and supervision of 54 doctor theses of students at our Institute and reviews of 30 further doctor theses
Initiation and reviews of 9 habilitation theses of institute members and 4 further habilitation theses at

other universities
As a result of nearly 30 years of establishing a school of Computational Mechanics as a new important subject at the Leibniz Universität Hannover, 10 former members of the institute became full professors (with chairs) at German universities, and 13 former members became professors at universities of applied sciences (Fachhochschulen)

Two main lines of research were followed by me in the last five decade: *Coupled validation with verification* of deterministic modeling and analysis of engineering structures, mainly directed to the behavior of systems, and multiscale material mechanics for detecting the sources and onsets of damage and fracture for dimensioning real structures and guaranteeing safety and reliability.The methodologies require integrated physical and engineering modeling combined with sound mathematical analysis and computer science. The subjects of research are reliable and efficient mathematical models, including parameter identification. The related FE-type adaptive direct variational methods are based on a priori and a posteriori error estimates and object-oriented computer programs for various types of complex and large structures under regular and exceptional loading scenarios in civil and mechanical engineering. Of course, the main goal behind all these efforts is the design, construction and building of advanced engineering structures, guaranteeing safety, functionality and the planned life span as well as efficiency of costs and time of engineering design, construction and maintenance.

So far, my research was primarily directed to deterministic modeling with separate consideration of probabilistic and stochastic influences on load and material parameters. One has to realize that so far, generally acknowledged material parameters as mean values and standard deviations for standard materials are still not available. The same holds for many types of natural loadings which are usually officially stated in technical codes and norms.

(i) *Verification*: Numerical FEM-based solutions of complex structural systems with advanced materials, including damage, shake down, crack initiation and propagation of elastic and inelastic material deformations in connection with buckling and failure of structural systems.

Verification means error-controlled numerical solutions – here for several variants of the Finite-Element-Method (FEM) –, based on a priori and a posteriori error estimates with at least upper bound property. Verification is reached when the sequence of numerical solutions for a boundary value problem (BVP) with optimal adaptively refined FE-meshes and Ansatz-spaces converges to the analytical solution of the used BVP – which only has to exist – in a mathematically admissible norm.

(ii) **Integrated Validation and Verification:** Obviously, it is the most important task of an engineer to find the appropriate mathematical modeling for the mechanical behavior of a structural system under the demand of the engineering requirement: *as accurate as necessary and as simple as possible*, combining the crucial combination of safety and reliability on one hand and economic efficiency on the other.

Engineers are mainly thinking bottom-up, mathematicians top-down. The engineering mentality has to be "Safety first". This includes not to rely only on numerical solutions of large-dimensional systems of algebraic equations but also to get an "engineering feeling" of safety by modeling with rather simple systems and looking for global equilibrium and continuity of deformations of parts and the total structure in an expansive modeling process.

Thus, expansive modeling is an adequate strategy for validation – including verification

in each expanded step of modeling –, which was used in my group since the 1990s for essentially static loadings, accompanied with many publications, Figure 1. Different from this, reductive modeling was also extensively investigated, esp. by Prof. J.T. Oden and his group in Austin, TX, USA. Within this strategy the most complicated physical and mathematical model, which is expected to be necessary for a distinct mechanical problem, is analyzed, and from there approximated simpler models are investigated according to the real behavior of systems and materials. This procedure is obviously much less appropriate and efficient for static problems in structural mechanics. However, model reductions play an important role for the numerical reductions of large dimensional dynamic problems, e.g. for the engineering analysis of the vibrations of an airplane.
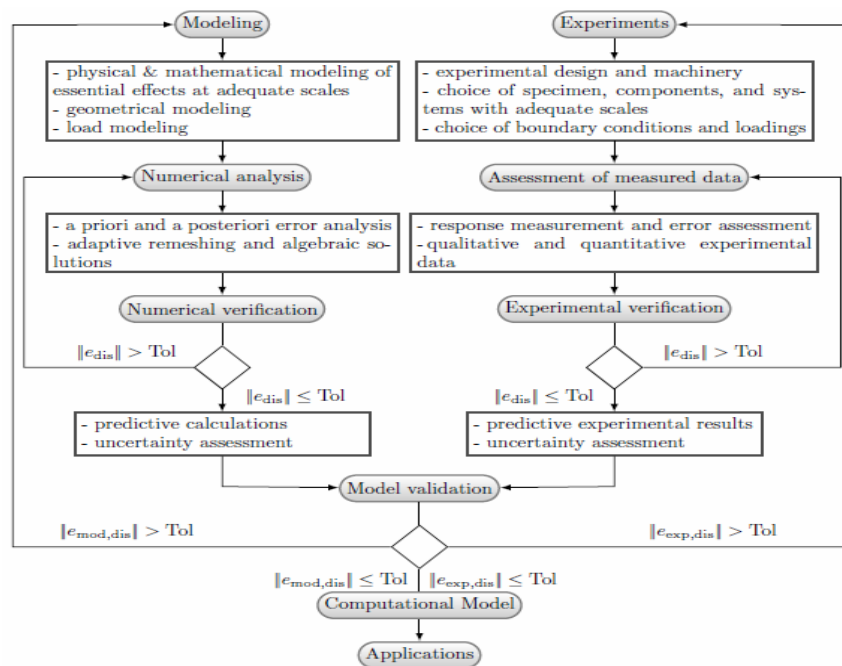
Figure 1: Coupled validation and verification - flow Chart for adaptive error-controlled expansive model and numerical solution adaptivity

Efficient variants of direct variational calculus and their bounded error estimates, esp. for quantities of interest, as the basis for adaptive remeshing and test spaces

Coupled validation and verification requires a superordinate concept for efficient combined model error and numerical solution error analysis and calculation mainly for quantities of interest for which dual variational problems have to be solved additionally to the primal variational problems, usually in terms of displacements. Explicitly computable residual error estimators have an unknown constant C due to the pollution error in the strategy of local-to-global error estimation, and therefore they are not suitable as estimates for mesh adaptivity. Implicitly computable error estimates require the solution of algebraic equation systems on element level or on element patches. In recent years a variety of those estimators were developed partly from mathematical and partly from engineering point of view. Especially some engineering contributions require extended calculations and sometimes do not have at least save upper bounds, and also their efficiency for adaptive meshes may be questionable. The extension of error estimates for quantities of interest should always be based on sound mathematical convergence and stability theories. Moreover, error analysis is required not only for primal variational problems, but also for

different types of mixed variational formulations as well as for GFEM (generalized FEM), XFEM, Meshless Methods, RKPM (Reproducing Kernel Particle Method), Isogeometric Analysis and further variants.

These advanced variational methods with adequate error estimators are not yet available in commercial FE-program systems. Mostly, only the Zienkiewicz-Zhu gradient-smoothing error estimators are implemented. This is partly caused by the fact that the data bases in most commercial FE-programs are still located at the FE-level, not at the geometric or desirable at the parametric level of the complete object, especially when optimization is to be included. Therefore, the access to data at element interfaces of neighbored elements for remeshing with Neumann-type implicit error estimators is hardly possible in these programs. We have studied all these estimators with applications to crack initiation and propagation for brittle elastic materials including volumetric damage as well as for ductile elastic-inelastic materials. Furthermore, the necessity for molecular-kinetic modeling for realistic detection of crack initiation in brittle elastic materials like zirkonium-based ceramics as thermal shields is emphasized. For crack propagation the transition from the molecular model to the classical C^1-continuous kinematic model of continuum mechanics has to be realized within the variational formulations and mesh adaptivity, according to verification and validation.

Many theoretical, algorithmic and software problems have to be solved in the future. This requires a balanced university education of fundamental and applied subjects, new integrated software developments with advanced error analysis and efficient equation solvers on distributed computer systems. Sometimes, a distinction is made between so-called *Numerical Simulation* – which is the strategy outlined above – and so-called *Finite Element Modeling*, addressing calculations using an element library without providing evidence of the underlying engineering and mathematical problems, i.e. not guaranteeing physical, mathematical and numerical accuracy; this last line is not in the focus of my research.

I would like to extend this overview to my enduring research on G. W. Leibniz's technical inventions in the frame of his *Scientia generalis* and *Calculus logicus*. His main principles – also for the new *Berlin-Brandenburgische Sozietät der Wissenschaft* – are: *Theoria cum praxi* and *Bonum commune*, and these are still valid today. Leibniz's design and construction of the first decimal *Four-species-calculating machine* and his description of the first *Cypher machine* show the success of this new type of thinking and acting in science and technology at the beginning of the age of enlightenment. His holistic methodology follows the conviction that *all is connected with everything*. And of equal importance is his challenge for social balance and empathy to all human beings. With a complete mathematical model and the Pareto-optimization of Leibniz's decimal calculating machine we could build a slightly optimized machine based on eight design variables which is fully functional. But it has to be stated that the reproach of non-completed decimal carries in the original Leibniz machine could be rejected by Leibniz himself, because we found in his documents that in this case, e.g. for a multiplication, one only has to set the multiplicand to zero and to rotate the magna-rota crank so often – so to say idling – until all pentagon disks, indicating non-completed carries, are turned back to the initial positions.

Density Functional and Density Matrix Theory - Applications in Chemistry and Physics

by Evert Jan Baerends, Member EUAS

<u>Short Biography</u>
Education: Vrije Universiteit, Amsterdam, The Netherlands
Thesis: "Self-consistent molecular Hartree-Fock-Slater calculations", Amsterdam, 1975.
Professor of Theoretical Chemistry, Vrije Universiteit, Amsterdam, 1981 - 2010
World Class University Professor, Pohang University of Science and Technology, Pohang, South-Korea, 2009 - 2013.
Schrödinger Medal of the World Association of Theoretical and Computational Chemists (WATOC), 2010.
Member International Academy of Quantum Molecular Science, 1999.
Member Royal Netherlands Academy of Science, 2004.
Ca, 450 publications, 45 000 citations, H-index 90.

The application of quantum mechanics to the elucidation and prediction of molecular properties has started almost immediately after the development of quantum mechanics in the 1920s. After the advent of computers, the field started to grow rapidly in the late sixties and the seventies and eighties. However, only after the density functional theory (Nobel prize Walter Kohn, 1998) proved its great practical value for molecular property calculations, the theoretical and computational approach to chemical problems became a main-stream tool in chemistry. Density functional theory formulates the complicated N-body problem of N electrons moving in the field of nuclear charges in terms of one-particle equations (the Kohn-Sham (KS) equations). The effective field in these one-particle equations is not known and has to be approximated. My research has concentrated on:

1) Development of new computational and mathematical techniques for the efficient solution of the one-particle KS equations for large chemical systems (molecules, clusters) and physical systems (solids, surfaces, molecule-surface interactions). This has resulted in the Amsterdam Density Functional (ADF) suite of computer programs, commercially available form SCM NV (www.scm.com).

2) Study of relativistic effects in chemical bonding.

3) Development of methods for spectroscopic properties, mostly based on time-dependent density functional theory.

3) Theoretical and computational approaches to heterogeneous catalysis (reactivity of molecules at surfaces) and homogeneous catalysis (reactivity at transition metal centers in solution).

4) Theoretical aspects of density functionals, KS potentials, and extension to density matrix functionals.

Improvements in Computer & System Sciences

by Michael Elkin, Member EUAS

<u>Short Biography</u>
Full professor in the Ben-Gurion University of Negev, Department of Computer Science
A member of associate editors board of Journal of Computer and System Sciences, since 2014.
Academic Awards
- *Toronto Prize for excellence in research (May 2013).*
- *The paper "Deterministic Distributed Vertex Coloring in Polylogarithmic Time", joint with my student Leonid Barenboim, won the best paper award in PODC 2010 conference.*
- *Feinberg School prize for Ph.D. students, 2002.*
- *Excellence fellowship for Ph.D. students by Israeli ministry of education, 2000, 2001, 2002.*
- *Feinberg School fellowship of distinction, 2000.*
According to google-scholar the total number of citations to my publications is 1570 and my h-index is 24. My ISI H-index is 7.
Research Grants
- *Israeli Science Foundation.*
The grant title is "Spanning Trees and Subgraphs". The grant was approved in July 2006. Period of grant is Oct. 2007 - Sep. 2010.
- *Binational Science Foundation.*
The grant title is "Metric Data Structures". It was approved in July 2009. Period of grant Oct. 2009 - Sep. 2013. The grant was joint with Seth Pettie from Ann Arbor Michigan University. I was a PI of this grant.
- *Israeli Science Foundation.*
The grant title is "Distributed Coloring, MIS, and Related Problems". The grant was approved in July 2011. Period of grant is Oct. 2011 - Sep. 2015. I am the only PI in this grant.

My research so far can be roughly divided into four directions. The first direction is the area of *low-distortion embeddings.* The objective of the research in this area is to understand to what extent an arbitrary metric space may be approximated by a "simpler" target metric. The *spanners approach* to this problem suggests to consider original metrics as induced by graphs, and to study embeddings of these graphs into their sparse *subgraphs,* called *spanners.* The interest in the mathematically deep and challenging problem of constructing sparse spanners with low distortion can also be motivated by the central role that spanners play in distributed computing, and by other algorithmic applications. Despite the fact that the last two decades witnessed a very intensive research of low-distortion embeddings, and that this research was very diverse in the choice of the target metrics for the studied embeddings, nevertheless the concept of *multiplicative distortion* appears to be common to all the publications on this subject. A new *relaxed* notion of distortion was introduced in my publication. The relaxation suggests to study how large is the distortion of the *large* distances under different embeddings, and it turns out that there are embeddings that introduce *almost no distortion* at all to distances that are *greater than a certain constant,* while distorting the small distances to the same extent as the best possible embeddings distort all the distances.

It is known that for any unweighted undirected n-vertex graph G and any $\kappa = 1, 2,...$, there exists a κ-spanner (that is, a subgraph that distorts all the distances of G by at most a multiplicative factor of κ) with $\eta^{1+o(1/\kappa)}$ edges. This result indicates a *tradeoff* between the *sparsity* of the spanner and its *distortion,* and this tradeoff is known to be essentially the best

possible. In my publication Peleg and I showed that all the distances greater than a certain constant threshold can be approximated with *arbitrarily small distortion* by *arbitrarily sparse spanners.* Note that this result eliminates the aforementioned tradeoff between the sparsity and distortion, and, instead, shows a tradeoff of completely different nature between the sparsity and the distortion on the one hand, and the value of the constant threshold on the other. In another publication I devised an algorithmic proof of this result, which is conceptually different from the original proof. I used this algorithmic proof to devise an efficient algorithm for computing almost shortest paths in a graph. The latter algorithm provides more accurate approximation of distances than all the other known algorithms that have similar running time. A yet another proof of this result was published by Thorup and Zwick. Other closely related results were published in the followup papers of Pettie.

In another publication, Bollobas, Coppersmith and I continued this line of research, and studied the problem of *preserving* (instead of approximating) large distances by sparse spanners. We showed tight upper and lower bounds on the size of these *preserving subgraphs.* Besides, in another publication, Coppersmith and I studied the problem of preserving distances between given pairs of vertices, and showed that for an η-vertex graph and a set of $p = O(\sqrt{n})$ pairs of vertices, there exists a subgraph of *linear size* that *preserves* the distances between these pairs of vertices, and that this is not the case when $p = \omega(\sqrt{n})$. In another publication I studied the problem of constructing sparse spanners in the *streaming* model of computation. In this model the algorithm reads the edges of the input graph one after another. Upon reading an edge e the algorithm has to decide whether it inserts the edge into the spanner, and this decision cannot be changed later. I devised an algorithm that constructs a (2k - 1)-spanner of near-optimal size (O(k · $n^{1+1/k}$) edges), that spends only O(1) time per edge and uses space proportional to the size of the spanner. This algorithm can also be seen as a nearly optimal dynamic incremental algorithm for maintaining spanners.

In a new publication, Emek, Spielman, Teng and I studied a related problem of constructing a *spanning tree* of an undirected possibly weighted graph G that provides a fairly good approximation of all the distances of G *on average.* This problem was introduced in a seminal paper by Alon, Karp, Peleg and West, that showed that for every graph there is a spanning tree with an average stretch of $\exp\{O(\sqrt{\log n \log\log n})\}$. They also showed a lower bound of Ω(log n) for this problem. Closing this gap was considered a major open problem in the area of low-distortion embeddings for more than a decade. In another publication we narrowed this gap significantly, and showed an upper bound of O(log² *n* log log *n*). (The paper was accepted to the special issue of the the SIAM J. on Computing devoted to the selected papers of the STOC'05 conference.) As part of our proof of this result we introduced a novel graph-decomposition technique, which we called the *star-decomposition.* This technique was also exploited in the papers by Abraham, Bartal and Neiman and Abraham and Neiman, that improved our upper bound further to O(log *n* log log *n*).

In another work in this area Dinitz, Solomon and I showed that for every metric space there exists a spanning tree that has small weight, hop-diameter, and weighted diameter *simultaneously.* We called these trees *shallow-low-light trees,* and provided nearly tight upper and lower bounds on their parameters. Along the way we resolved a long-standing open problem in Computational Geometry, and showed that there exist sets M of n points in the plane for which any Euclidean spanner has either weight at least Ω(log *n*) times the weight of the minimum spanning tree of M or it has hop-diameter at least Ω(log *n*). This lower bound is tight up to constant factors. (The matching upper bound is due to Arya et al.) The three Editors-in-Chief of the prestigious Discrete and Computational Geometry (DCG) journal, Prof.

Goodman, Pach and Pollack invited this paper to publication in this journal. By now the paper appeared in FOCS'08 and in DCG. In a continuation work [51] my Ph. D. student Shay Solomon studied tradeoffs between diameter and sparseness of Euclidean spanners. His single-authored paper won *the best student paper award* in SODA'11 conference.

In future I plan to pursue the study of low-distortion embeddings, with the emphasis on spanners and spanning trees. I plan also to study other types of low-distortion embeddings, hoping to resolve major open problems in this area.

The second direction of my research is the area of *Distributed Algorithms*. In particular, in some publications I studied the *distributed minimum spanning tree (MST)* problem. Besides, I devised a distributed algorithm with improved running time for this fundamental problem. Also, I explored the *hardness of approximation* of this problem, and showed that for any $0 < \varepsilon < 1$, approximating the *MST* in distributed setting within a factor $H = n^{1-\varepsilon}$ requires $T = \Omega(n^{\varepsilon/2})$ rounds of distributed computation. An *unconditional* (i.e., relying on no complexity-theoretic or other assumptions) *lower bound* on *time-approximation tradeoff* of $T^2 \cdot H = \Omega(n)$ follows. This was one of the first results concerning hardness of approximation of a distributed problem. Soon after the publication of this result, a number of important results that prove lower bounds on the approximability of several central distributed problems were published by Kuhn, Moscibroda and Wattenhofer. Among these problems are the maximum matching, the minimum dominating set, and the minimum vertex cover. Upon a request of the editor of the Distributed Column of ACM SIGACT News Bulletin, Prof. Sergio Rajsbaum, I wrote a survey on the subject of hardness of distributed approximation. During the research of the distributed *MST* problem, and my work on this survey, I became increasingly interested in the area of the distributed hardness of approximation, and I intend to explore this direction further.

More recently I studied (jointly with Leonid Barenboim who was my student at that time) the distributed maximal independent set (MIS) and coloring problems. These problems are among most fundamental, central and well-studied problems in Distributed Computing. In our PODC'08 paper Barenboim and I devised the *first sublogarithmic* algorithm for the MIS problem on planar graphs, improving the twenty-year-old result of Goldberg, Plotkin and Shannon (STOC'87). Furthermore, our algorithm applies to graphs of bounded genus, to graphs with bounded tree-width, and to graphs that exclude a fixed minor. Our paper was invited and accepted to the Special Issue of the Distributed Computing Journal devoted to selected papers of PODC'08.

In another closely related STOC'09 paper of ours, Barenboim and I devised a distributed algorithm that constructs a $(\Delta + 1)$-coloring of a graph with maximum degree at most Δ. Our algorithm runs in $O(\Delta + \log^* n)$ time, significantly out-performing all previous algorithms for this problem. In another publication Barenboim and I devised a *deterministic* algorithm with poly- logarithmic running time ($O(\log \Delta \log n)$) that produces a $\Delta^{1+\zeta}$-coloring of the input graph, for any arbitrarily small constant $\zeta > 0$. This result of ours answers affirmatively a long-standing open question of Linial. In his seminal FOCS'87 paper Linial devised a deterministic $O(\Delta^2)$-coloring algorithm that runs in $O(\log^* n)$ time. In the end of his paper Linial asked whether one can achieve significantly less colors by a deterministic algorithm that runs in polylogarithmic time. Another paper won the *best paper award* in the PODC 2010 conference. Finally, our most recent paper with Barenboim studies distributed edge-coloring problem, and achieves significantly improved bounds for it. This paper won *the best student paper award* in the PODC 2011 conference. I intend to continue exploring this direction of study, and devise yet more efficient distributed algorithms for the MIS and coloring problems. I also plan to work on lower bounds for these problems.

The third direction of my research is the study of the *broadcast* and *multicast* problems in *telephone* networks. Several approximation algorithms with a polylogarithmic ratio, including one with logarithmic ratio, were known for *undirected* variants of these problems prior to my publications. All these algorithms involve solving huge linear programs. In my new publication Kortsarz and I devised an *efficient combinatorial logarithmic approximation* algorithm for the *directed and undirected broadcast* problems, and for the *undirected multicast* problem. Furthermore, in another publication we devised an *efficient combinatorial sublogarithmic approximation* algorithm for the *undirected multicast* problem. The approximation ratio of the algorithm is $O(\dfrac{\log n}{\log\log n})$, and it is the first polynomial-time (combinatorial or not combinatorial) algorithm for this problem that provides a *sublogarithmic approximation* guarantee. Also, we improved the previously best known lower bounds on the approximability of these problems (from 3/2 to 3 - ε) for undirected broadcast problem, and from 3/2 to $\Omega(\sqrt{\log n})$ for the directed one). In addition, we studied the *radio* broadcast problem, and have shown that it is *additively* $\Omega(\log^2 n)$-*inapproximable*, i.e., that it is (quasi-)NP-hard to distinguish between instances that admit a solution of length at most *OPT* and instances that admit only solutions of length $OPT + \Omega(\log^2 n)$, for all values of *OPT* in the range $\Omega(\log n) < OPT < n$ — o(n). On the positive side we showed that the problem can be approximated within an *additive approximation* of $O(\sqrt{R}\log^2 n)$, where the *radius R* is a parameter of the input graph. For small values of *R* both upper and lower bounds are polylogarithmic, and thus these results exhibit one of the first examples of a problem with a polylogarithmic approximation threshold. Later, Gasiniec, Peleg and Xin further improved our upper bound and provided an additive $O(\log^2 n)$-approximation for the problem. Their result implies that our lower bound is tight. I intend to continue exploring the phenomenon of *polylogarithmic inapproximability*.

Finally, the fourth direction of my research involves the problem of constructing dense progression- free subsets of $\{1, 2, \ldots, n\}$. This is a classical problem that was introduced by Erdos and Turan in 1936. Salem and Spencer (1942) [50] improved the bound of Erdos and Turan, and their bound was further improved by Behrend in 1946. The result of Behrend remained the state-of-the-art till the beginning of 2008, and improving it was a central open problem in Number Theory. Upper bounds on | S| were shown by a number of most prominent mathematicians of the second half of 20th century, including Roth, Szemeredi and Bourgain.

In my recent paper I improved the bound of Behrend, and constructed progression-free sets S of different size $\Omega(\ )$, that is, by a factor $\Theta(\sqrt{\log n})$ greater than sets constructed by Behrend. The technique I have developed for proving this result is from the area of Discrete Geometry, and it has some important applications to a number of problems in Algorithmics and in Computational Geometry. Recently a prominent mathematician and one of the leading scholars in the area of Discrete Geometry Prof. Gil Kalai published a post that describes this work of mine in his web-log. This line of study was continued by Green and Wolf and O'Bryant. Specifically, Green and Wolf devised an alternative simpler proof of my result. They point out, however, that "the only advantage of our approach is brevity: it is based on ideas morally close to those of Elkin, and moreover, his argument is more constructive than ours. In an even more recent development O'Bryant has combined my techniques with those of Rankin and Green and Wolf, and improved Rankin's lower bound by a factor $\log^\varepsilon n$, for some small positive ε = ε(k). I intend to continue working on this problem, with the objective to narrow the gap between upper and lower bounds further.

Modelling Intrinsic Chemical Properties Through Non-covalent Interactions

by Manuel Yáñez, Member EUAS

<u>Short Biography</u>
Full Prof. of Physical Chemistry at the Universidad Autónoma de Madrid. He got his bachelor in Chemistry at the Universidad de Santiago de Compostela in 1970 and his PhD at the Universidad Autónoma de Madrid in 1973. He was postdoc with John Pople from 1974 to 1976 in Carnegie-Mellon University. He received several research awards, among them, the Award of the UAM Foundation in 1993, the Research award in Physical Chemistry of the Royal Spanish Society of Chemistry in 2001, and the Bettancourt-Perronet Award from France in 2003. He is Academic of the Royal Academy of Science of Spain. He coordinates an Erasmus+ Master on Theoretical Chemsitry and Computational Modelling (TCCM) and an ITN-EJD of the MSCA Programme. His current research interests lie in the field of gas-phase chemistry, in particular gas-phase ion chemistry and non-covalent interactions. Visiting Professor at Universities in Europe, Canada and Australia. Editor of Computational and Theoretical Chemistry. Member of the Steering Committee of the European Division of Computational and Theoretical Chemistry and of the World Association of Theoretical and Computational Chemists (WATOC). He is author of more than 400 papers and several book chapters.

Chemical bonding is at the very heart of chemistry and is probably one of its most fundamental concepts. However, there is not a clear cut definition of what a chemical bond is, and in general the most commonly used criterion to define a chemical bond is the stabilization of the system when two units interact. In fact according to the IUPAC "when forces acting between two atoms or groups of atoms lead to the formation of a stable independent molecular entity, a chemical bond is considered to exist between these atoms or groups",[1] so in general the denomination of *chemical bond* is reserved for strong interactions either covalent or ionic. Also, in general, "non-covalent interactions" are used to design weak interactions, typically between close-shell systems with no electron sharing between the interacting subunits.[2] There is a great variety of non-covalent interactions attending both to their energy ad to their nature, and some of them are almost as strong as conventional covalent linkages.[2] More importantly, non-covalent interactions play a crucial role in nature, because they are responsible for the organization of practically all molecular assemblies, either of natural origin like DNA, or of artificial origin as the so-called metal-organic-frameworks (MOFs),[3,4] or "soft matter", term usually employed to describe materials that are held together by non-covalent interactions involving energies of the order of the thermal energy, kT.[5]

However, one of the most important signatures of non-covalent interactions is the deformation they entail. These effects were known for long time, but it was not until very recently that the effects of these deformations on the characteristics and the strengths of non-covalent interactions were shown to be relevant not only to understand the nature and the strength of many covalent interactions but to be able to modulate at will the intrinsic reactivity of many compounds.[6-8] Indeed, a great majority of the non-covalent interactions known nowadays such as hydrogen bonds,[9,10] dihydrogen bonds,[11] halogen bonds,[12] pnicogen bonds,[13] beryllium bonds[14] chalcogen-chalcogen[15] or tetrel interactions[16] involve closed-shell systems, one of which behaves as a Lewis base, i.e., as an electron donor and the other as a Lewis acid, i.e., as an electron acceptor. The obvious consequence is that the electron density distributions of both interacting systems change with respect to the isolated species. More importantly, these

perturbations of the electron densities usually result in changes in the structure of the systems and on their intrinsic reactivity. The well known hydrogen bonds (HBs) A-H····B, between a AH proton donor and a B proton acceptor are a good example of the geometry changes triggered by this non-covalent interaction. As a matter of fact one of the signatures of the HBs is the lengthening of the A-H distance and the red-shifting undergone by the A-H vibrational stretching frequency.[9,10] In the limit of extra-strong HBs, an spontaneous proton transfer from the proton donor to the proton acceptor may take place with the formation of a A^-BH^+ ion-pair.[17] The geometrical distortions are even more apparent when beryllium bonds are formed.[14] A beryllium bond is a closed-shell molecular linker in which a BeX_2 or $BeXY$ derivative acts as a Lewis acid. These interactions have been proved to be stronger than conventional HBs, due to the fact that beryllium is an electron-deficient system and accordingly an excellent electron acceptor. The formation of the beryllium bond, as it is illustrated in Figure 1 for the particular case of the $Cl_2Be:NH_3$ complex, involves a significant charge transfer from the lone-pair of the base, in this example ammonia, into the $\sigma_{BeCl}*$ antibonding orbitals and into the empty p orbitals of Be. The first of these charge transfers results in a significant lengthening of the Be–Cl bonds, whereas the second entails a hybridization change of the Be atom, with a significant bending of the $BeCl_2$ moiety in the complex.[14]
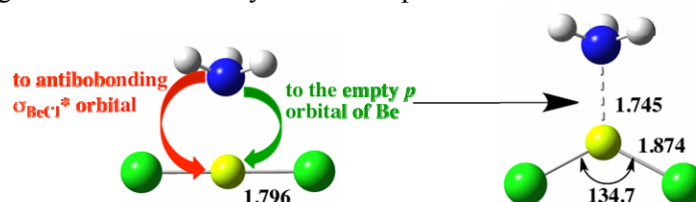
Figure 1. Charge donations responsible of the formation of a beryllium bond between ammonia and beryllium dichloride. The red and green arrows indicate the donation from the lone-pair of ammonia into the antibonding $\sigma_{BeCl}*$ orbital of the $BeCl_2$ moiety and into the empty p orbital of Be, respectively. The figure on the right shows the equilibrium structure of the complex formed. Bond lengths are in Å and bond angles in degrees.

These large structural distortions render the interaction energies, E_{int}, defined as the energy of the complex minus the energy of the two interacting subunits with the geometry they have in the complex, substantially larger than the dissociation energy, D_0, defined as the energy of the complex minus the energy of the two interacting subunits in their equilibrium conformation (see Table 1).[14]

Table 1. Dissociation energy, D_0, and interaction energy, E_{int} for complexes stabilized through beryllium bonds between $BeCl_2$ and different Lewis bases. E_{def} is the deformation energy defined as the difference between the interaction energy and the dissociation energy. all values are in $kJ\ mol^{-1}$.

Base	D_0	E_{int}	E_{def}
NH_3	125	179	54
H_2O	96	143	47
FH	39	71	32
PH_3	44	92	48
SH_2	43	81	38
ClH	17	41	24
HCN	71	119	48
OCH_2	82	135	53
$NHCH_2$	136	194	58

However one of the most important consequences of the geometry distortion produced by non-covalent interactions is the, sometimes dramatic, change they induce on the reactivity patterns of the system. A very good illustration of this signature is the Lewis acidity trends of borane, BH_3, derivatives as a function of the successive substitution of the H atoms of the parent compound by electronegative susbtituents.[6] According to common ideas contained in most of the text books in chemistry one should expect the Lewis acidity, i.e., the electron acceptor capacity of the fluorine derivatives of borane to follow the trend $BH_3 < BH_2F < BHF_2 < BF_3$, because the F substituent being a strong electron withdrawing system, the substitution of H atom by a fluorine atom should increase the electron acceptor capacity of the systems and accordingly one should expect the interaction energies of this series of compounds with a Lewis base to follow the trend indicated above. Quite surprisingly, however, the calculated interaction energies for the complexes formed with three different Lewis bases, namely ammonia, methaneimine and lithium cyanide show a totally different behavior. As illustrated in Figure 2 the interaction energy goes through a minimum for BHF_2, which according to the previous arguments should be a stronger Lewis acid than BH_2F and much stronger than BH_3.[6]

The explanation of this unexpected behavior is again closely related to the deformation, in this case of the Lewis acid. As shown in the right part of Figure 3, although the isolated BH_3 molecule is strictly planar in its equilibrium conformation, it becomes significantly pyrimidalized in the $H_3N:BH_3$ complex as shown by the value of the HBH bond angle, which differs significantly form 120º which would correspond to a planar structure.
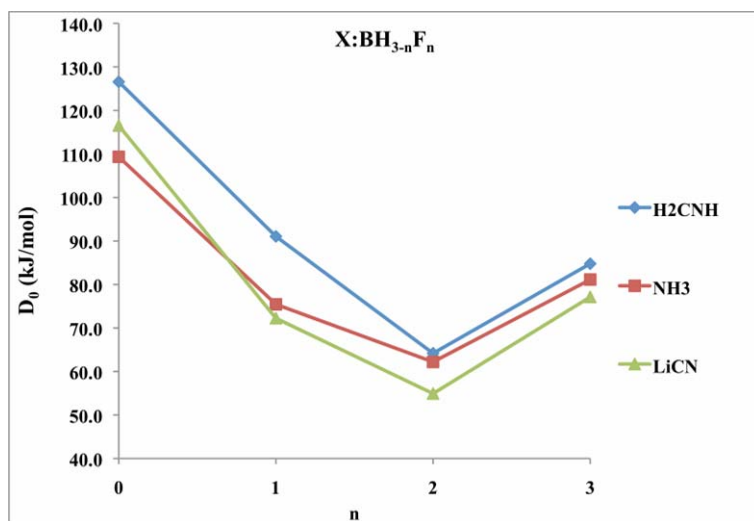
Figure 2. Variation of the dissociation energy of $X:BH_{3-n}F_n$ (n = 0, 1, 2, 3; X= H_2CNH, NH_3, LiCN) as a function of the number, **n**, of fluorine substituents.

The important fact is that this distortion triggers a significant change in the electron density distribution of the system and in the relative energies of its molecular orbitals.[6] Indeed, as shown in left part of Figure 3, whereas the energy of the LUMO (Lowest Unoccupied Molecular Orbital), which according to the Frontier Orbital Theory, is a good measure of the electron acceptor capacity of the system, increases almost linearly with the fluorine substitution for the isolated molecules, it goes through a maximum for the distorted molecules within the complex for n = 2, indicating that BHF_2 should give the weakest bound complex of the series, in agreement with the values of their dissociation energies.
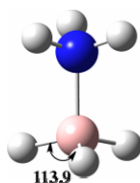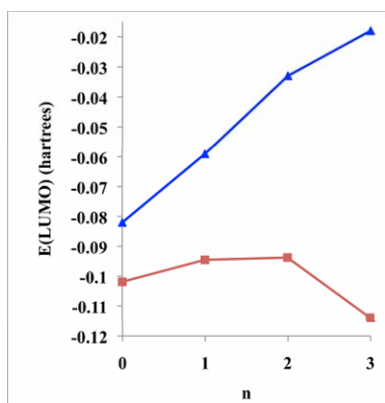
Figure 3. Variation of the energy of the LUMO of $BH_{3-n}F_n$ derivatives as a function of the number, **n**, of fluorine substituents. The blue curve corresponds to the isolated molecules and the red one to the molecules within the complexes with ammonia. On the right part the optimized structure of the $H_3N:BH_3$ complex is shown.

These electron density redistributions also induce, as mentioned above, dramatic changes in the intrinsic reactivity of the interacting systems. Let us take aniline as a suitable example.[18] This organic compound is a well-known base, and leads to strong beryllium bonds when interacting with BeH_2. However, the charge transfer from aniline to BeH_2 is so large that aniline becomes electron deficient, and its amino hydrogens very acidic. The ultimate consequence is that the intrinsic acidity of the aniline:BeH_2 complex (see Figure 4) increases by more than 150 kJ mol^{-1} with respect to the isolated base. The surprising results is that this complex becomes a Bronsted acid *stronger* than phosphoric acid.[18]
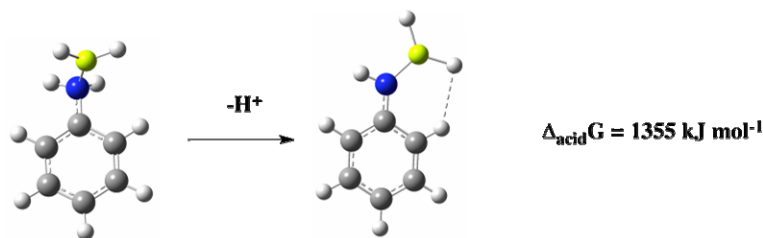
Figure 4. The deprotonation process of the complex aniline:BeH_2 in terms of Gibbs free energies is 150 kJ mol^{-1} more favorable than the deprotonation of isolated aniline ($\Delta_{acid}G$ = 1507 kJ mol^{-1}). This acidity enhancement implies an increase of 16 orders of magnitude in the corresponding ionization equilibrium constant.

In summary, covalent interactions induce electron density redistributions of the interacting molecules, which are mirrored in significant structural distortions and changes in the reactivity patterns.

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17   I. Alkorta; I. Rozas; O. Mó; M. Yáñez; J. Elguero *J. Phys. Chem. A* 2001, **105**, 7481.
18   M. Yáñez; O. Mó; I. Alkorta; J. Elguero *Chem. Eur. J* 2013, **35**, 11637.

Computational Quantum Chemistry, Organosilicon Chemistry & Mechanistic Organic Chemistry

by Yitzhak Apeloig, Member EUAS

Short Biography

Professor and incumbent of the Nahum Guzik Distinguished Academic Chair, Technion - Israel Institute of Technology, Haifa, Israel.

Co-Director, Lise Meitner – Minerva Center for Computational Quantum Chemistry.

At the Technion since 1976, Professor of Chemistry since 1988, Chair in Chemistry since 1993, Distinguished Professor since 2011.

Chairman of the Faculty of Chemistry 1995 – 1999.

President of the Technion – Israel Institute of Technology, 2001-2009

 Visiting Academic Appointments

Research Fellow, Princeton University, Princeton, NJ, USA 1974-1976

Visiting DAAD Fellow,Universität Erlangen-Nürnberg,

Erlangen, W. Germany Summers 1979, 1985, 1992

Visiting Lecturer, Tel Aviv University, Israel 1983, 1986

Visiting Professor, Cornell University, Ithaca, NY, USA 1983-1984

Visiting DAAD Professor, Technische Universität Berlin Summers 1985, 1991

Visiting JSPS Professor, Kyushu University, Japan Summer 1991

Visiting Alexander von Humboldt Professor, Technische Universität Berlin 3-9/1994, Summer 1997

Visiting Alexander von Humboldt Professor, Universität Ulm, Germany Summer 1997

Visiting JSPS Professor, Tohoku University, Sendai, Japan Spring 1999

Visiting Professor, University of Utah, Salt Lake City, USA Summer 2000

Visiting JSPS Professor, Tsukuba University, Tsukuba, Japan Spring 2010

Visiting Alexander von Humboldt Professor, Technische Universität Berlin Summer 2010

Visiting Professor, University of Utah, Salt Lake City, USA Spring 2011

Prizes, Awards, Honors and Research Fellowships

Annual Prize for Distinction in Chemistry Studies, Hebrew University, Jerusalem, Israel 1965-1967

The Prize for Distinguished Student of the Dean of the Faculty of Sciences, Hebrew University, Jerusalem, Israel 1971

The Yashinski Prize for Distinguished Ph.D. Thesis 1974

Bat-Sheba de Rothschild Fellow 1977-1978

DAAD (Deutscher Akademischer Austauschdienst) Fellowship 1979

DAAD (Deutscher Akademischer Austauschdienst) Visiting Professor 1985, 1991

The Louis Klein Visiting Professorship in Australian Universities 1986

Distinguished Teacher Award by the Technion Student Association 1986, 1993, 1997

Technion Award for Academic Excellence, Technion (The New England-Taub Prize) 1988

The Henri Gutwirth Prize for Excellence in Research,Technion 1991, 1993

Included in "Who's Who in Science and Engineering", Beginning Second Edition 1993

Included in the "International Who's Who of Contemporary Achievement", Beginning Third Edition 1993

Incumbent of a Chair in Chemistry 1993

Israel-Italy National Council for Research and Development, Senior Scientist Exchange Fellow 1993

Alexander von Humboldt - Lise Meitner Senior Research Award 1994-1999, 2010

Granted a Minerva Center in Computational Quantum Chemistry 1996

Japan Society for the Promotion of Science (JSPS), Senior Visiting Professor Award 1991, 1999,2010
C. A Coulson Lecturer, University of Georgia, Athens, USA 2002
The Israel Chemical Society Prize 2002
Honorary Doctorate of Science (Dr. Honoris Causa) Technische Universität Berlin, Germany 2006
Wacker Silicone Award, Germany 2007
Honorary Member, Academia de Ciencias, Mexico 2008
A Special Issue of Chemistry - A European Journal in honor of Yitzhak Apeloig 2009
Fellow, American Association for the Advancement of Sciences 2009
American Chemical Society Frederic Stanely Kipping Award in Silicon Chemistry 2010
American Academy of Arts and Sciences, Foreign Honorary Member 2010
Order of Merit (First Degree) of the President of the Federal Republic of Germany 2011
Member of the Intenational Advisory Board of the Alexander von Humboldt Foundation 2014
Editorial Advisory Boards
Journal of Computational Chemistry 1998 – present
Theoretical Chemical Accounts 2001 – present
Israel Journal of Chemistry 1986 – 1990; 2010- present
Journal of the American Chemical Society 2010- present

Professor Apeloig was one of the first experimentalists in the world, and the first in Israel, who recognized the vast potential of *ab initio* quantum mechanical calculations and who already 40 years ago applied these calculations to a broad spectrum of "real" chemical problems. He soon became one of the world's leading "prophets" of the computational idea among organic and silicon chemists, despite the general reluctance of these communities to accept the computational methods as a legitimate and reliable tool to study chemical questions. In 1996, he established (together with S. Shaik at the Hebrew University) the Lise Meitner Minerva Center for Computational Quantum Chemistry, which played (and continues to play) a major role in bringing the message of computational chemistry to the Israeli chemical community, especially to M.Sc. and Ph.D. students. The ideas, which he has pioneered throughout his research, are now widely accepted and computational chemistry plays an important role in many fields of chemistry and in some fields of biology and has many practical applications, such as in the rational design of new materials with predesigned properties and of new drugs.

A unique characteristic of Apeloig's research is the synergistic use by his group of both experimental techniques and theoretical methods to solve important chemical questions. In contrast to most other promoters of computational chemistry who practiced only theory, Apeloig's group routinely backed their theoretical predictions by creative experimental work, carried out either by Apeloig's group or in collaboration with others. His research has convincingly exemplified the synergistic use of theory and experiment as an effective way to discover and to explore new chemistry, inspiring and setting an example for other chemists worldwide. His research, which is characterized by creativity and the ability to use calculations to predict new types of compounds, including compounds which were believed not to exist, inspired many experimentalists to test his predictions. Many of his theoretical predictions were indeed later verified experimentally either by his own group or by others. This was a crucial step in convincing the chemical community that quantum mechanical calculations are an extremely valuable research tool in chemistry.

Below, I highlight several examples, which demonstrate the creativity and impact of Apeloig's work, as well as the theoretical-experimental synergism that is typical to his research.

Organosilicon Chemistry

Organosilicon chemistry has been one of the fastest developing fields of chemistry in the last three decades due to its many useful applications as well as to fundamental breakthrough in the understanding of this field. Apeloig's theoretical and experimental work has played a pivotal role in the fast development of this field as evidenced by the fact that he was awarded the two most prestigious prizes in silicon chemistry; the Wacker Silicone Award (2007) and the F.S. Kipping Award in Silicon Chemistry of the American Chemical Society (2010). In particular Apeloig has made seminal contributions to the fundamental understanding of the structures and chemical reactivity of many organosilicon compounds, in particular to the study of compounds with multiple bonds to silicon and of silicon-centered reactive intermediates, compounds which only 30 years ago were widely believed not to exist.

Apeloig's theoretical predictions in this dynamic fast-developing field have inspired and guided experimental chemists for the last three decades. Many of his theoretical predictions in this field have been verified experimentally, some by his own research group. One example is his 1997 theoretical prediction of how to stabilize compounds with (then unknown) triple bonds to silicon, one of the "Holy Grails" of silicon chemistry. He then followed the theoretical predictions in a joint theoretical-experimental study (with H. Schwarz) and in a well-planned experiment demonstrated the existence of the first known compound of this type. This inspired the synthesis of the first stable compound with a Si-Si triple bond, for which he measured the NMR spectrum, confirming his earlier theoretical predictions about the electric structure of this interesting group of compounds. Another example, is the prediction that some compounds with Si=Si bonds would have unprecedented bridged structures rather than the expected classical doubly-bonded structures. These predictions were later verified experimentally, leading to the synthesis of novel intriguing compounds and enlightening the unique bonding characteristics of silicon.

Apeloig's group has also made seminal synthetic contributions to silicon chemistry, some following their own theoretical predictions. His group developed a new general method for the synthesis of silenes ($R_2C=SiR_2$) as transients and as stable isolable compounds and have explored their chemistry. They have also developed general strategies for the synthesis of the synthetically important silyl anions, including the longest known polysilyl anion ; unique dilithiosilanes ; the first silene-organometalic complex ; the first silylenoid ; unique stable silyl radicals ; the first di-Grignard silanes (and geminal dizinciosilanes); and recently synthesized the first silenyl lithiums ($R_2C=SiRLi$) which open new horizons for synthesizing novel silicon compounds.

Apeloig's group has also made seminal synthetic contributions to silicon chemistry, some following their own theoretical predictions. His group developed a new general method for the synthesis of silenes ($R_2C=SiR_2$) as transients and as stable isolable compounds and have explored their chemistry. They have also developed general strategies for the synthesis of the synthetically important silyl anions, including the longest known polysilyl anion ; unique dilithiosilanes ; the first silene-organometalic complex ; the first silylenoid ; unique stable silyl radicals ; the first di-Grignard silanes (and geminal dizinciosilanes); and recently synthesized the first silenyl lithiums ($R_2C=SiRLi$) which open new horizons for synthesizing novel silicon compounds.

Reactive intermediates and mechanistic studies

The study of reactive intermediates is crucial to the understanding and control of chemical reactivity and selectivity. Apeloig's combined experimental-theoretical work has made important fundamental contributions to the study of a variety of reactive intermediates, both in organosilicon chemistry as well as in more traditional areas of organic chemistry. The wide spectrum of problems that he studied include: silylenes and silylenoids ; α - and β -silyl substituted carbocations ; silyl cations ; silyl radicals ; vinyl and phenyl cations; hyperconjugation; nucleophilic vinylic substitution; strained molecules, and other reactive intermediates. Apeloig's theoretical predictions have also provided the clues, which lead, after decades of frustrations, to the first syntheses of the elusive silyl cations and phenyl cations.

Apeloig's work, published in more than 200 original papers and reviews in leading international journals, has received worldwide recognition. His papers are frequently quoted in advanced textbooks of physical and mechanistic organic chemistry and in monograms of silicon chemistry and many of his publications were selected as "scientific highlights" by *Chemical and Engineering News*, etc. The 3-volume book on "The Chemistry of Organic Silicon Compounds" which he edited (with Z. Rappoport) is the most important and influential book written in this field.

Apeloig is frequently invited to present plenary lectures in major international conferences and has won wide international recognition and received many awards, such as: the Israel Chemical Society Prize (2002), the Wacker Silicone Award (2007), the F.S. Kipping Award in Silicon Chemistry of the American Chemical Society (2010), the Alexander von Humboldt Research Award (twice), the Senior Visiting Professorship Award from the Japan Society for the Promotion of Science (3 times). In 2006, he received an Honorary Doctorate (*Dr. Honoris Causa*) from the Technical University of Berlin. In 2009, he was elected Fellow for the Association for the Advancement of Science (AAAS) and he is a Foreign Honorary Member of the American Academy of Arts and Science since 2010. In 2011 he received the Order of Merit (first degree) of the President of Germany.

Yitzhak Apeloig has made important contributions to chemistry by his imaginative implementation of quantum mechanical calculations, providing elegant examples of the germination of ideas for experiments that have led to the discovery of new chemistry and in particular for his pioneering ground-breaking discoveries in silicon chemistry. His research has convincingly exemplified the synergistic use of theory and experiment as an effective way to discover and explore chemistry, inspiring many others. In particular, his research has played a pivotal role in developing a fundamental understanding in organosilicon chemistry, especially regarding multiply-bonded silicon compounds and silicon reactive intermediates, and in pushing forward the frontiers of this fast developing field of chemistry.

Finally, it is worthwhile mentioning that during his 8 years as President of the Technion (2001-2009), Apeloig continued to supervise an active research group, which included masters and doctorate students. During his Presidency years, he continued to publish extensively in leading chemical journals and was frequently invited to lecture in scientific conferences. Remarkably, after his two terms as President of Technion were completed he returned to teach and to lead a very active research group -a unique example among university presidents.

# Computational Methods for Moving Boundary Problems

by Timon Rabczuk

Short Biography
Prof. Dr.-Ing. at Bauhaus University Weimar, Chair of Computational Mechanics
Former Director of the Institute of Structural Mechanics, Bauhaus University Weimar
National High End Foreign Expert at Tongji University, Shanghai, China
More than 200 SCI publications
Listed in ISI Highly Cited 2014 and 2015 in 'Computer Science' and 'Engineering'
ERC-CoG COMBAT
Coordinator of ITN-INSIST and IRSES-MULTIFRAC

Problems involving moving boundaries play a significant role in Engineering applications. Propagating cracks up to material and structural failure, two-or multiple-phase flow, fluid-structure interaction, grain growth, biofilm or tumor growth are classical examples. However, moving boundaries occur also in inverse analysis and topology optimization. Computational methods are often used to support, complement and sometimes even substitute experimental testing. However, modeling problems involving moving boundaries are challenging. The most common computational method for large scale Engineering application of such problems is probably the finite element method though for certain applications alternatives including meshfree methods, boundary element methods or finite difference schemes can be strong competitors. One key difficulty in such computational methods is the requirement to adjust the discretization when the boundaries propagate. The extended finite element method (XFEM) developed in 1999 by Belytschko, Moes and Dolbow belongs to the most elegant and efficient methods for moving boundary problems. XFEM is based on a so-called local partition of unity enrichment and was originally developed for propagating cracks, i.e. fracture. XFEM allows for moving boundaries without adjusting the boundary to the finite element mesh. Physical criteria for propagating the boundary strongly depends on the problem. For instance, while in two-phase flow, the boundary encompasses a closed surface and propagates orthogonal to it, a crack is an open boundary and its propagation direction is arbitrary. In brief: Moving boundary problems require two important ingredients: 1. An efficient computational method and 2. (physical) criteria governing the propagation.

Timon Rabczuk's key contribution for moving boundary problems concern applications to nonlinear fracture, particularly for complex fracture patterns as they occur in dynamic fracture or in three-dimensions. The prediction of non-linear material and structural failure poses numerous challenges on computational methods and models. Material failure can be modelled as continuous or discrete fracture. The first approaches are commonly easier to implement but computational

more costly. In many problems, they are generally capable of capturing the global response of a structure but are less suitable when more detailed local phenomena are of interest. The discrete approach captures the nucleation and propagation of cracks and shear bands explicitly. There are two major challenges in discrete fracture models: One challenge is the representation of the propagating fracture surface, i.e. the moving boundary, while the other difficulty is to find efficient failure criteria to determine whether new cracks or shear bands nucleate or existing ones propagate or interact (propagation of the moving boundary). The failure criterion, which is in turn closely related to the underlying physical problem and constitutive model, also needs to determine their orientation and 'length'. The choice of a model or computational method also severely depends on the application. While in some applications only a few cracks occur, other applications such as fracture in composites or dynamic fracture and fragmentation involve very complex fracture patterns.
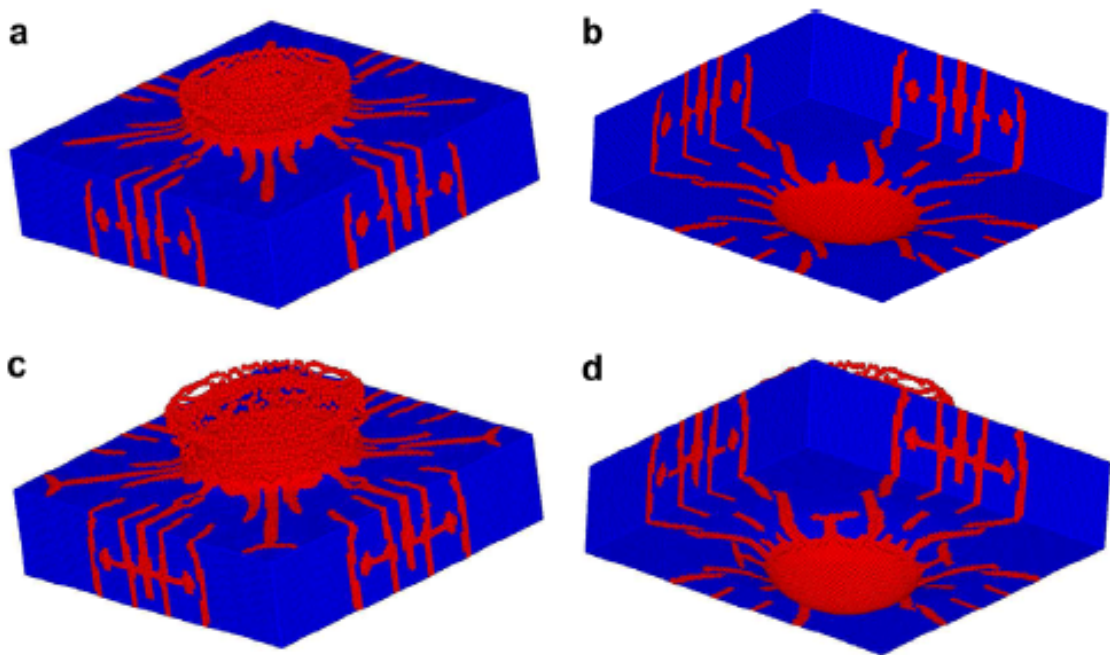
Figure 1: Fragmentation of a reinforced concrete slab, from 'Rabczuk T., Belytschko T.: A three dimensional large deformation meshfree method for arbitrary evolving cracks, Computer Methods in Applied Mechanics and Engineering, 2007, 196(29-30), 2777-2799'

Timon Rabczuk has contributions to efficient models and methods on both classes of methods, continuous and discrete, but his most seminal methods fall in the area of discrete approaches. He has developed innovative, efficient and robust partition of unity enriched computational methods for complex fracture patterns with applications involving a moderate number of propagating, nucleating and joining cracks in three dimensions. In those methods, the crack topology is assumed

to be continuous and represented by a topological mesh which is uncoupled to the underlying mechanical discretization. He extended these approaches to three-dimensional problems in heterogeneous materials, especially composites, making his methods not only applicable to predict the behaviour of engineering structures but also for the design of new materials. His methods account for arbitrary crack propagation in the bulk material and also along and around interfaces including the interaction of interface/interphase fracture and fracture in the bulk material.

Computational methods for dynamic fracture and fragmentation is another key strength of Timon Rabczuk. He is the inventor of so-called 'cracking particle methods'. Those methods belong to the class of discrete crack methods though they are not based on a continuous representation of the fracture surface but describe fracture as a set of crack segments combining the strength of continuous and discrete fracture methods. Most importantly, they do not require any criteria for crack branching and coalescence or crack interactions. They are quite simple to implement and were applied to study numerous challenging Engineering problems. They were for instance used to explain the micro-branch instability problem which explains why the experimentally measured crack speed is below the maximum theoretical crack speed for quasi-brittle materials.

Timon Rabczuk also developed efficient computational methods for fracture in thin structures. He is one of the first exploiting the higher order continuity of meshfree methods in the context of Kirchhoff Love shell formulations which are based on fourth order partial differential equations and require therefore C1 continuity in computational methods based on the weak form. These formulations developed in 2006 and 2007 do not require any rotational degrees of freedom or the discretization of the director field and fulfill the Kirchhoff-Love constraint due to the higher continuity of the meshfree approximation; this idea was adopted in IGA (Isogeometric Analysis) shell formulations around 4 years later. The meshfree thin shell formulation was also extended to model fracture by exploiting a partition of unity enrichment. The absence of the discretization of the direction field and rotational degrees of freedom drastically facilitate the implementation of fracture by partition of unity enrichment.

Timon Rabczuk also proposed efficient computational methods for moving boundary problems involving fluid-structure interaction with fracture, i.e. so called immersed particle methods. Those methods do not need to treat the FSI interaction for intact *and* fracturing solids differently. Hence, they allow the fluid flow through opening cracks in a very efficient way. Figure 1 shows an application of the method, i.e. a fracture structure due to an implosion in a pipeline. Those methods have meanwhile be used successfully for some industrial projects in Asia.
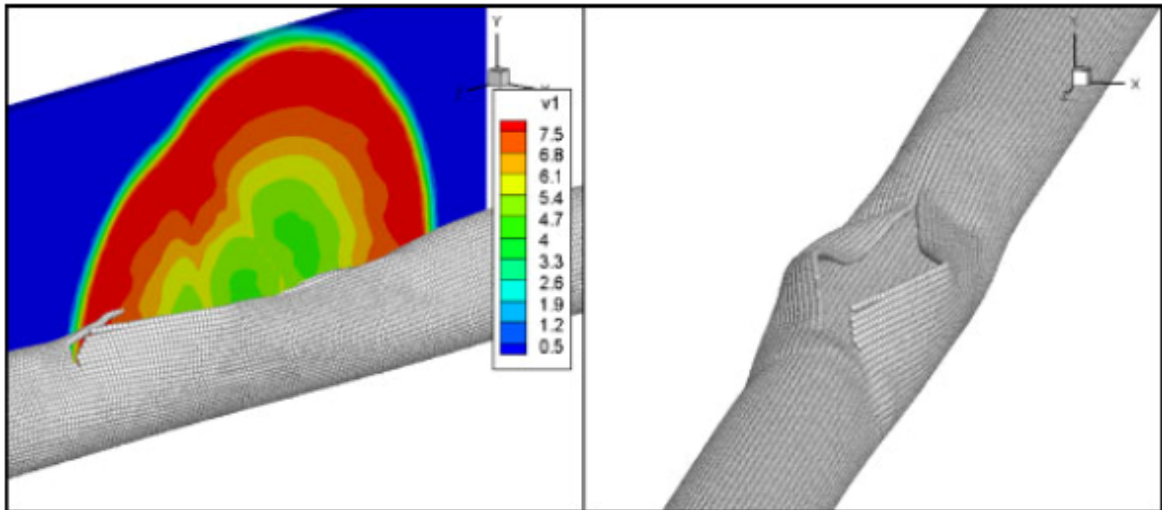
Figure 2: Fracture of thin shells due to fluid-structure interaction, from 'Rabczuk T., Gracie R., Song J.H., Belytschko T.: Immersed particle method for fluid-structure interaction, International Journal for Numerical Methods in Engineering, 2010, 81(1), 48-71'

Other contributions of Timon Rabczuk on moving boundary problems include inverse analysis and topology optimization of nanostructures. Those methods basically exploit the extended finite element method and level set methods to describe the interface of the moving boundary. One very interesting application is on piezoelectric and flexoelectric nanostructures with view on energy harvesters. In the proposed topology optimization, surface effects have been accounted for and it was shown that they have a significant impact on the energy conversion factor when the structure is small enough (in the order of nanometers).

Frontiers of Computational Chemistry: Understanding Molecular Reaction Dynamics and Spectroscopy by Atomistic Simulations

by Robert Benny Gerber

<u>Short Biography</u>
Professor Emeritus of Chemistry, Hebrew University of Jerusalem; Professor Emeritus of Chemistry, University of California at Irvine.
Education: B.Sc. (Chemistry), Hebrew University of Jerusalem (1965); D.Phil., University of Oxford (1968), Advisor: Prof. C.A. Coulson; Postdoctoral Research Associate, Harvard University (1968-69), Advisor: Prof. M. Karplus.
Academic positions:
Senior Researcher, Weizmann Institute of Science (1969-75); Associate Professor (1976); Professor (1980); Saerree K. and Louis P. Fiedler Professor Chemistry (from 1989); Emeritus from 2012), Hebrew University of Jerusalem; Professor of Chemistry (from 1990), University of California at Irvine (Emeritus from 2014); Finland Distinguished Professor, University of Helsinki (2011-2015).

Computational Chemistry has grown in recent years to become a highly successful, influential and exciting discipline of science. One impressive direction of progress has been the interpretation of molecular properties and processes by first-principles atomistic simulations. The research goals of the Gerber group aim at extending this capability for systems of increased complexity and extended sizes, e.g. for reactions of solid particles, liquid droplets and macromolecules. Furthermore, the research focuses on close cooperation with experimental groups, with the view that a joint theoretical-experimental attack on a problem of interest offers unique advantages, both for providing in-depth interpretations and for guiding experiments by theoretical predictions. Activities in the Gerber group involve: (1) Development of approximation methods, to render the problems computationally feasible; (2) Development of algorithms for efficient computational implementation; (3) Applications to chemical problems, often carried out in cooperation with experimental groups.

The main topics of recent and current research include: (1) <u>Discovering and explaining the mechanisms of important atmospheric reactions</u>: The chemistry of the atmosphere is governed by a vast number of processes. Very little is presently known on the microscopic mechanisms of these reactions, especially of reactions that take place at surfaces or in the bulk of liquids and of solid particles. For example, a paper co-authored by Gerber and several other theorists and experimentalists demonstrated that the high reactivity of salt aerosols with ozone and with OH radicals is due to the relative presence of the anions for locations at the surface of the salt aerosol. This paper, published in *Science* in 2000 has proved very

influential in atmospheric chemistry, leading to understanding of reactivity of salt aerosols in important processes. This was followed by more recent results, mostly in cooperation with the experimental group of Prof. B.J. Finlayson-Pitts on mechanisms whereby the pollutant Cl (atomic chlorine) is produced in the atmosphere, and the mechanism whereby the molecule HONO, a key player in many atmospheric processes is formed in the atmosphere. Our current research is focused in particular on molecular reactions at surfaces of liquid water and of ice. Using powerful methods that combine Molecular Dynamics with quantum chemical methods for the interaction potentials, Gerber and coworkers were able to throw light on reactions whereby the surfaces of liquid water and of ice, and provide an explanation how this works from an atomistic point of view. A major research direction that the Gerber group is developing now are studies of particles present in the atmosphere: How are the particles formed and grow, which conditions are decisive in determining which types of particles grow in the atmosphere and which do not, what is the composition of different particles and what are their thermodynamic, chemical, structural and other properties. Also these issues are investigated by atomistic simulation, and pursued in cooperation with leading experimental groups. It seems that these studies are already having a major impact on atmospheric chemistry, a field that not many years ago was essentially purely experimental. The unraveling of the molecular mechanisms of atmospheric processes at surfaces and particles is still a young, fast growing field. There are prospects of future discoveries, that seem exciting.

(2) <u>Computational spectroscopy and determination of the structures of isolated biological macromolecules</u>: Structural molecular biology ranks arguably with the most successful sciences since the middle of the previous century. The prime tools for determining the structures of peptides, proteins and most other families of biomolecules have been X-ray crystallography and NMR. However, not for all systems and conditions are these methods applicable. There is a great need for tools of structure determination of macromolecules for systems where X-ray or NMR are inapplicable. Structure of biological molecules in mass spectrometric experiments is one such field. Vibrational spectroscopy is an obvious approach to consider for this purpose. However, calculations of the spectroscopy of such large systems and at a sufficient level of accuracy is a major outstanding challenge. Work by Gerber and coworkers led to major progress on this problem. The Gerber group developed the Vibrational Self-Consistent Field (VSCF) method and its extension. This is a quantum-mechanical method that proved successful in computing the spectra of systems of up to about 50 atoms or so, and was extensively applied by the Gerber group as well as by other groups, in cooperation with experimental spectroscopists also in the context of structure determination. VSCF is an approximation, but it is far more accurate than the standard harmonic approximation, and its accuracy seems adequate for comparison with spectroscopy experiments in the context of structure determination. Hitherto, applications of the method have been to systems such as selected conformers of amino acids and their complexes with water, monosaccherides and their complexes with water, some nucleic acid bases and their

complexes, and several dipeptides. Gerber's current research on this topic is to introduce methodological and algorithmic developments that will enable spectroscopic calculations of adequate accuracy for systems as large and challenging as polypeptides and proteins. This implies a huge leap of capabilities, and it will also open a vast field of important applications, since structures of many polypeptides and proteins remain to be unraveled. The consequence of this research will hopefully be to greatly enhance the role and power of vibrational spectroscopy as a tool of structure determination in molecular biology.

(3) <u>Discovering new types of molecules and solid materials, their bonding motives and properties: Novel compounds of the noble gases, molecular solids of polynitrogen molecules, and other exotic species</u>: The prediction of new molecules and materials is an exciting goal for theorists and computational chemists, and the development of state of the art methods especially in quantum chemistry make this pursuit increasingly practical and rewarding. Current research by the Gerber group in this direction builds on accomplishments in recent years. The search for several compounds and solids by Gerber's group is guided by the pursuit of novel types of bonding motives that can lead to a new class of molecules. This already led to the prediction, followed by experimental discovery, of several types of exotic molecules. A very interesting case of a successful prediction has led to the discovery of <u>acetylenic</u> compounds of the noble gases. The prediction was made within the family of compounds known as noble-gas hydrides. These are of the form HNgY where Ng is a noble-gas atom and Y an electronegative group. The bonding motif in this experimentally established family of compounds is that it can be thought of as involving a covalent bond within $H\text{-}Xe^+$, with an ionic bond within $H\text{-}Xe^+$, with an ionic bond between $(H\text{-}Xe^+)$ and Y^-. Based on the properties of the acetylenic group, Gerber and coworkers predicted the class of noble-gas acetylenic compounds, such as HXeCCH, HXeCCXeH, HKrCCH, and several others. These and other compounds of the same type were prepared shortly after the prediction by M. Räsänen and his team in Helsinki. By now the acetylenic noble-gas hydrides rank with the largest classes of noble gas compounds. Current research by the Gerber group in this field focuses on the possible existence of new solids made of noble-gas molecules. This includes molecular crystals made of molecules such as HNgY, the existence of liquid states of these materials, the possible existence of the energetic HNgY molecules in molecular hosts, e.g. CO_2, and a host of related materials, some of which may hopefully prove to have practical applications. The group is also studying other types of new materials, some of which can be described as exotic. A recent success in this new direction of research for the Gerber group is the prediction of the existence of a molecular solid made of the polynitrogen species N_8. This is predicted to be stable at atmospheric pressure at low temperatures. Investigations of other types of new materials, their microscopic structure, their stability and chemical reactivities are under way. Hopefully, this may lead also to materials of technological applications.

Solid-State Chemistry: Design, Synthesis and Application of Heterogeneous Catalysts for Environmentally Benign Processes; Electron Microscopy and its Application in Chemistry and Materials Science; Popularisation of Science Among Schoolchildren and Adults

by Sir John Meurig Thomas

Short Biography

Former Director of the Royal Institution (RI) of Great Britain and of the Davy-Faraday Research Laboratories. Former Head of the Department of Physical Chemistry, University of Cambridge. Former Master of Peterhouse (the oldest college in Cambridge). Taught and researched in the University of Wales for twenty years until 1978 at Bangor and Aberystwyth.

Published over 1000 research articles and over a 100 review ones. Author of three university texts on heterogeneous catalysis, and of a biography of Michael Faraday, translated into Chinese, Japanese and Italian. H-index 89.

Served as Member of the UK Cabinet Advisory Committee (1982-86); as Chairman of Chemrawn (Chemical Research Applied to World Needs); as 1851 Exhibition Research Committee Member. Former Trustee of the Science Museum, London. Former Trustee of the Natural History Museum, London.

A new mineral, meurigite, named in his honour in recognition of his contributions to geochemistry.

Recipient of the Blaise Pascal Medal for Materials Science of the Academy.

Holder of the Linus Pauling Gold Medal; Kapitza Gold Medal; Stokes Gold Medal; Natta Gold Medal; Willard Gibbs and Zewail Gold Medals, along with several others.

A Fellow of the Royal Society (1977) and of the American Philosophical Society (1992), and several other national academies.

The following titles (with Abstracts) convey the essence of my recent research interests:

1.   On the dynamical nature of the active center in a single-site photocatalyst visualized by 4D ultrafast electron microscopy.
Proc. Nat. Acad. Sci., (USA) 2016, **113**, 503-508

The nature of the active site in (photo) catalysis is fundamental to our understanding of the processes involved, and to their control. Four-dimensional ultrafast electron microscopy (UEM) provides a dynamic probe for catalytic active site in photocatalytic materials thanks to its unprecedented resolution both in time (femtosecond) and space (angstrom). In this contribution, we visualize the femtosecond atomic movement at the titanium active center in a single-site photocatalyst. UEM allows us to investigate the structural dynamics of the radiation sensitive specimen by measuring time-resolved diffraction intensities from different

lattice planes. These findings contribute fundamental insights for developing advanced photocatalysts and suggest broad ranges of applications.

2.   The rapidly changing face of electron microscopy.
Chemical Physics Letters, 2015, **631-2**, p113
This short but wide-ranging review is intended to convey to chemical physicists and others engaged in the interfaces between solid-state chemistry and solid-state physics the growing power and extensive applicability of multiple facets of the technique of electron microscopy.

3.   Some of tomorrow's catalysts for processing renewable and non-renewable feedstocks, diminishing anthropogenic carbon dioxide and increasing the production of energy.
Energy and Environmental Sci., 2016, **9**, 687
This review provides a wide-ranging summary of several aspects of heterogeneous catalysis and its impact on the increasing need to generate more energy, less CO_2 and the production of more commodities required by an expanding world population. Particular attention is paid to the options (some of which are already a practical reality) now available for the use of anthropogenic CO_2 as a source for the production of platform chemicals required to sustain civilized life. In this connection, Rubisco-inspired methods of utilizing CO_2 are discussed, as is the utilization of algae to yield ethanol and O_2 from water, CO_2 and sunlight. In addition, the increasing use of methanol (derived from CO_2) as an energy vector, as well as a source of ethene and propene (which are in growing worldwide demand), is adumbrated. As far as strategies for the design of new solid catalysts are concerned, summarizing accounts are given of the emerging popularity and recent successes of supported "single-atom", chemo-selective catalysts (of Pt, Pd, Ir and Au), of so-called "single-atom alloy" catalysts for selective hydrogenations, and of monophasic single-site heterogeneous catalysts (SSHCs) for a range of chemical processes, some of which have already been commercialized. SSHCs can, in general, be assembled from earth-abundant elements (C, N, O, Mg, Al, P, Fe), and are effective for shape-selective, regio-selective and enantio-selective catalytic conversions. We also briefly discuss the prospect of converting anthropogenic CO_2 into CH_4, and touch upon the action needed to reduce atmospheric CO_2 so as to fulfil the aims of the recent (December 2015) UN Climate Change Conference in Paris (COP-21).
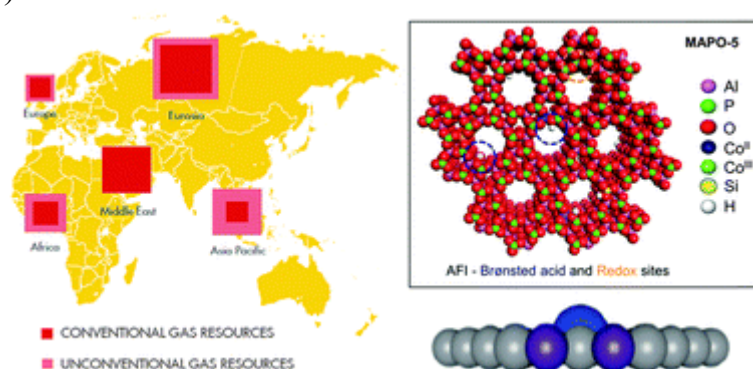
4.   Tens of thousands of atoms replaced by one.
Nature, 2015, **525**, 325
Many catalysts comprise metal nanoparticles on solid supports. The discovery that single atoms of palladium anchored to a solid support also exhibit high catalytic activity might help to conserve the supply of this and related rare metals.

5.   (A Monograph) Design and Applications of Single-Site Heterogeneous Catalysts: Contributions to Green Chemistry, Clean Technology and Sustainability.
(World Scientific and Imperial College Press, 2012, ISBN 978-1-84816-909-8)
For far too long chemists ad industrialists have relied on the use of aggressive reagents such as nitric and sulphuric acids, permanganates and dichromates to prepare the massive quantities of both bulk and fine chemicals that are needed for the maintenance of civilised life – materials such as fuels, fabrics, foodstuffs, fertilisers and pharmaceuticals. Such aggressive reagents generate vast quantities of environmentally harmful and often toxic by-products, including the oxides of nitrogen, of metal oxides and carbon dioxide.
Now, owing to recent advances made in the synthesis of nanoporous solids, it is feasible to design new solid catalysts that enable benign, mild oxidants to be used, frequently without utilising solvents, to manufacture the products that the chemical, pharmaceutical, agro- and bio-chemical industries require. These new solid agents are designated single-site heterogeneous catalysts (SSHCs). Their principal characteristics and that all the active sites present in the high-area solids are identical in their atomic environment and hence in their energy of interaction with reactants, just as in enzymes.
Single-site heterogeneous catalysts now occupy a position of growing importance both academically and in their potential for commercial exploitation. This text, the only one devoted to such catalysts, dwells both on principles of design and on applications, such as the benign synthesis of nylon 6 and B3. It equips the reader with unifying insights required for future catalytic adventures in the quest for sustainability in the materials used by humankind.

New Aspects in Wind Engineering
by Yukio Tamura

<u>Short Biography</u>

Current Occupation

- Professor Emeritus, Program Coordinator, Wind Engineering Joint Usage / Research Center,
 Tokyo Polytechnic University, Japan (since 2015)
- 1000 Foreign Talents Professor, Beijing's Key Laboratory of Structural Wind Engineering and Urban Wind
 Environment, School of Civil Engineering, Beijing Jiaotong University, China (since 2014)

Current Appointments at Universities

- Honorary Professor, Shantou University, Shantou, China, (since 2015)
- Guest Professor, University of Malaysia Pahang, Malaysia, (since 2014)
- Honorary Professor, Nanjing University of Aeronautics and Astronautics, Nanjing, Jiangsu, China, (since 2013)
- Honorary Professor, Shanghai Normal University, Shanghai, China, (since 2013)
- Honorary Professor, Southwest Jiaotong University, Chengdu, China, (since 2011)
- Guest Professor, Huangshi Institute of Technology, Huangshi, China, (since 2011)
- Honorary Professor, Beijing Jiaotong University, Beijing, China, (since 2011)
- Guest Professor, Chan'An University, Xi'an, China, (since 2010)
- Adjunct Professor, University of Notre Dame, Notre Dame, Indiana, USA, (since 2010)
- Guest Professor, Shijiazhuang Railway University, Shijiazhuang, China, (since 2009)
- Guest Professor, Zhejiang University, Hangzhou, Zhejiang, China, (since 2008)
- Guest Professor, Shenzhen University, Shenzhen, Guangdong, China, (since 2006)
- Guest Professor and Part Time Professor for PhD Students, Harbin Institute of Technology, Harbin,
 Heilongjiang, China, (since 2004)
- Advisory Professor, State Key Laboratories for Disaster Resistance in Civil Engineering, Shanghai, Tongji
 University, Sipping Rd, Shanghai, China, (since 2004)
- Guest Professor, Opole University of Technology, Poland, (since 1998)

Academic and Professional Qualifications

- Officially Qualified Building Standards Examiner, Ministry of Land, Infrastructure, Transport and Tourism,
 Japanese Government, 2006
- Doctor of Engineering: Waseda University, 1980
- Registered First-class Architect: Ministry of Construction. Japanese Government, 1973
- Master of Engineering: Waseda University, 1971
- Bachelor of Engineering: Waseda University, 1969

Prizes and Awards

- Alan G. Davenport Medal, International Association for Wind Engineering, 2016
- Japan Association for Wind Engineering Award (Outstanding Individual Contribution), Japan, 2016
- Robert H. Scanlan Medal, American Society of Civil Engineering, USA, 2016
- Japan Association for Wind Engineering Award (Design Category: Tokyo Sky Tree), Japan, 2015

- State Specially Recruited Experts, 1000 Talent Plan for High-Level Foreign Experts, China, 2014
- Japan Association for Wind Engineering Award (Publication Category), Japan, 2014
- Honorary Fellow, Indian Society of Wind Engineering, India, since 2013
- Foreign Fellow, Indian National Academy of Engineering, India, since 2013
- Member, Engineering Academy of Japan, since 2011
- Member, Science Council of Japan, since 2006
- Jack E. Cermak Medal, American Society of Civil Engineers, USA, 2004
- Japan Association for Wind Engineering Award (Paper Award Category), Japan, 1994
- The Prize of Architectural Institute of Japan, 1993
- Tachu-Naito Prize, Waseda University, Japan, 1969
Partial List of Social and Academic Activities
- Chairman, International Thematic Group for Wind-Related Disaster Risk Reduction (IG-WRDRR),
United Nations International Strategy for Disaster Reduction (UN/ISDR) (2009 - present)
- President, International Association for Wind Engineering (2007 - 2015)
- Member, Executive Board, World Wind Energy Association (2007 - 2015)
- President, Japan Association for Wind Engineering (2004 - 2008)

Professor Tamura is an Emeritus Professor of Tokyo Polytechnic University, Japan, serving as Program Coordinator of the Wind Engineering Joint Usage/Research Center. He is con-currently working for the School of Civil Engineering, Beijing Jiaotong University, China, as a Professor. He is also serving as Honorary/Advisory/Adjunct Professor at 15 universities including the University of Notre Dame (US), Zhejiang University, Harbin Institute of Technology, Southwest Jiaotong University, Tongji University, Nanjing University of Aeronautics and Astronautics, and so on.

Professor Tamura has had significant research achievements over a wide range of wind engineering problems. Especially noteworthy are his innovative works on the following:
- A mathematical model of vortex-induced vibration and combined effects of vortex-induced vibration
and galloping;
- Universal equivalent static wind load distributions especially for long-span structures;
- Comprehensive studies on aerodynamic characteristics of super-tall buildings and tower-like
structures with various configurations;
- Wind pressure distributions imposing maximum wind force components;
- Combination and correlation of wind-force components;
- Wind speed standardization considering long-term variation of ground roughness and estimation of
design wind speed;
- Innovation of simultaneous multi-channel pressure measuring system and application of POD
technique to pressure fields consisting of large numbers of pressure points;
- Proposal of damping predictors and discovery of "critical tip drift ratio" showing the maximum
damping ratio;
- Human perception thresholds by body sensation alone and those by visual sensation alone; and
- Wind-induced response monitoring of buildings and structures using RTK-GPS.

Besides those research achievements, Professor Tamura has established two important databases. One is the Japanese Damping Database. He organized a research committee on

damping in buildings, and established a reliable database of dynamic properties based on 285 buildings and structures in Japan (2000). This damping database is utilized in the Engineering Virtual Organization "VORTEX-Winds" created in the University of Notre Dame. The other is the TPU Aerodynamic Database, which is disclosed to the public through the internet. There are some difficulties in traditional paper-based codes/standards for design, such as complicated coupled multi-mode behaviors of buildings and structures, unconventionally-shaped buildings, interference effects of adjacent buildings and structures, nonlinear elasto-plastic behaviors, non-linear effects of damping devices, non-linear effects of base-isolation systems, and so on. These situations often require time-domain response analyses. Professor Tamura and his group established the TPU Aerodynamic Database providing fluctuating pressure fields acting on buildings and structures through the internet (http://www.wind.arch.t-kougei.ac.jp/system/eng/contents/code/tpu). Pressure fields obtained by SMPMS for 239 isolated low-rise building models, 22 isolated medium-rise and high-rise building models, and 112 non-isolated low-rise building models and 120 non-isolated high-rise building models have been disclosed. Anybody can download fluctuating wind pressure fields of 13,599 cases including different wind directions. These data have been widely used as benchmark data for CFD simulations, time-domain response analyses for research and practical design. The data were qualified by the NIST group and it has been decided to officially approve it as an available database in the next ASCE-7 (2016).

Prof. Tamura has published many books including Advanced Environmental Wind Engineering (2016), Advanced Structural Wind Engineering (2013), Wind Resistant Design of Buildings (1996), and so on. Some of these text books and their translated versions have been widely used in teaching graduate students, and have made contributions in giving high level education to provide well trained engineers and researchers. He has made significant contributions worldwide in the wind engineering field. Professor Tamura has served as a supervisor of many important projects including the 634m-high Tokyo Sky Tree in Tokyo, Japan (2012). His contributions have also been significant in practical application and implementation of wind engineering knowledge and technologies.

Professor Tamura has received awards/prizes of different types including the ASCE Jack E. Cermak Medal in 2004, the ASCE Robert H. Scanlan Medal in 2016 and the IAWE Alan G. Davenport Medal in 2016 for his research activities, the JAWE Publishing Award in 2014 for his book entitled Advanced Structural Wind Engineering, and the JAWE Design Award for his contribution to wind resistant design of the 634m-high Tokyo Sky Tree. He is currently a member of the Engineering Academy of Japan (EAJ) and is a member of the Science Council of Japan (SCJ). He is also a Foreign Fellow of the Indian National Academy of Engineering. He was elected President of the International Association for Wind Engineering (IAWE) in 2007, and after completion of his four-year tenure, he was re-elected in 2011 for another four-year term until June 2015. Professor Tamura has contributed to society by way of various social activities. One of these is the establishment of the International Thematic Group for Wind-related Disaster Risk Reduction (IG-WRDRR) under the auspices of the United Nations International Strategy for Disaster Reduction (UN/ISDR) Secretariat, and he has been serving as Chairman of the IG-WRDRR since 2009.

Professor Tamura founded the International Symposium on Wind Effects on Buildings and Urban Environment (ISWE) in 2004, which has provided a stimulating and

constructive forum for exchanging the latest scientific and technical information in the wind engineering field, and totally 6 ISWEs have been held in Tokyo so far. He also founded the Workshop on "Regional Harmonization of Wind Loading and Wind Environmental Specifications in Asia-Pacific Economies" (APEC-WW) in 2004, which has provided a forum for researchers and engineers specializing in problems of wind loading and wind environment. The purposes of APEC-WW are to harmonize structural loading standards/codes in the APEC area, and to harmonize bylaws/specifications on wind environmental problems in the APEC area. APEC-WWs have been held 7 times in 6 countries (Japan, China, India, Taiwan, Korea and Vietnam) so far, and have helped to reach a common understanding of wind loading, to exchange information on the current status of wind loading standards/codes, to improve individual standards, to discuss bylaws/specifications for wind environmental assessment related to pedestrian level winds in an urban environment, and to discuss bylaws/specifications for air quality outside and inside buildings. Professor Tamura co-founded the Korea-Japan Joint Meeting on Wind Engineering (JaWEiK) in 2005. This was achieved with the cooperation of the Japan Association for Wind Engineering (JAWE) and the Wind Engineering Institute of Korea (WEIK). Its purpose is to share information on wind engineering among wind engineers of Japan and Korea. The Chinese Wind Engineering Group has participated in this joint workshop since 2012, and the name of the workshop was then changed to CJK Wind Workshop, and organized annually by the three countries. Including those symposiums and workshops, he has organized and chaired almost 40 international conferences, symposiums, and workshops on wind engineering, and has made significant contributions to international cooperation in research and education in wind engineering. He was also heavily involved in codification activities including publication of the ISO4354 "Wind actions on structures" (2009).

Professor Tamura also has a strong commitment to raising the level of wind engineering worldwide, and has devoted himself to education in wind engineering. He founded the International Advanced School (IAS) on Wind Engineering in 2006, and has since organized 3- or 5-day IASs 12 times in 9 countries (Japan, China including Hong Kong, Korea, Poland, India, Philippines, Malaysia, Taiwan, and Brazil) in collaboration with local wind engineering communities. Each IAS gathered 50 - 100 students, young researchers and engineers, and totally more than 700 people have been able to take state-of-the-art and advanced lectures in the wind engineering field given by more than 40 world eminent professors and researchers. The next IAS13 will be held in Beijing, China, in October, 2016.   Professor Tamura founded Wind Engineering Open Seminars in 1985 as one of his laboratory's activities. He also served as the Director of The 21st Century COE Program and the Global COE Program for 10 years from 2003 - 2013, and as one of their important activities, organized Wind Engineering Open Seminars. These seminars functioned as a very constructive platform for frank exchange of new knowledge. It also provided good opportunities to young researchers, especially students, to obtain the latest knowledge and to keep abreast of current developments in wind engineering research. So far, totally more than 120 Open Seminars have been held and more than 3,000 people have attended them. Professor Tamura has supervised 28 post-doctoral/research fellows from 11 countries, 19 PhD students from 8 countries, 40 short-term fellows from 16 countries, and 31 PhD internship fellows from 10 countries, and has served as an external examiner for 18 PhD candidates in 7 countries. Thus, he has supervised 135 researchers and PhD students in total.

Develpments in Materials Science Engineering

by S. C. Tjong

<u>Short Biography</u>

Professor, Department of Physics and Materials Science
City University of Hong Kong
Prof. S C. Tjong graduated B.Sc. in Physics from National Taiwan University in 1973, followed by postgraduate studies in materials science at The University of Manchester (United Kingdom). He received M.Sc. and Ph. D. degrees in 1974 and 1976, respectively. After graduating from the University of Manchester, he worked as a materials engineer in China Steel Corporation (Taiwan) for nearly two years. He then went to the U.S.A as a Visiting Scientist at the Materials Science and Engineering Program, University of Texas at Austin, and Case Center for Electrochemical Sciences, Case Western Reserve University with famous electrochemist Professor E. B. Yeager. The research topics were related to the corrosion behavior of stainless steels welded by homopolar techniques (at Texas), and the fundamental mechanisms responsible for the passivation of Fe-based alloys using electrochemical, Raman and surface analytical techniques (at Case Western). Thereafter, he joined National Su Yat-Sen University (Taiwan) as an Associate professor and professor in materials engineering.

He supervised research students on the development of Fe-Mn-Al alloys for substituting chromium-based stainless steels. This was due to chromium element being considered as a strategic and scarce material at that period. He made contribution to the understanding of the structure, monotonic and cyclic (fatigue) mechanical properties as well as the corrosion properties of such alloys. He also conducted several consultancy projects with governmental agencies and the industrial sectors. Prior to joining the Department of Physics and Materials Science, City University of Hong Kong in 1990, he was employed as a Principal Scientist, Council for Mineral Technology, South Africa. The area of research was focused on the use of platinum group metals (Pt, Pd and Ru) for enhancing corrosion resistance of the Fe-Cr alloys. Currently, he is a professor at the City University of Hong Kong. Prof. Tjong has published over 370 SCI papers with 10,093 citations and an h-index of 52 (SCI), and 14,044 citations in Goggle with an h-index of 61, as well as six books. These books are:

(1) S. C. Tjong, "Nanocrystalline Materials: Their Synthesis-Structure-Property Relationships and Applications", Elsevier, 2006, ISBN 0-080-44697-3.
(2) S. C. Tjong, "Carbon Nanotube Reinforced Composites: Metal and Ceramic Matrices", Wiley VCH, 2009, ISBN 978-3-527-40892-4.
(3) S. C. Tjong, "Advances in Biomedical Science and Engineering", Bentham, 2009, ISBN978-1-60805-040-6.
(4) S. C. Tjong, Y.W. Mai, "Physical Properties and Applications of Polymer Nanocomposites", Woodhead Publishing (Elsevier), 2010, ISBN 978-1-84569-672-6.
(5) S. C. Tjong, "Polymer Composites with Carbonaceous Nanofillers: Properties and Applications", Wiley-VCH, 2012, ISBN 978-3-527-41080-4.
(6) S. C. Tjong, "Nanocrystalline Materials", 2nd Ed., Elsevier, 2014, ISBN 9780-1240-77966.

Professor S.C. Tjong serves as an editor of Open Physics (De Gruyter), and a member of editorial boards of Materials Science & Engineering A: Structural Materials (Elsevier), Materials Chemistry and Physics (Elsevier), Journal of Applied Polymer Science (Wiley) and Express Polymer Letters. He is a Chartered Engineer (C.Eng.) of the Engineering Council of U. K., and Chartered Scientist (C. Sci.) of the Science Council of U.K. He is a Fellow member of the Institute of Materials, Minerals and Mining of U.K. (FIMMM) and Fellow of the Institution of Engineers, Hong Kong (FHKIE).

His previous research topics at CityU (Hong Kong) were focused on:
(a) Structure–property relationship of *in situ* and *ex situ* metal-matrix composites (MMCs). This covered the development, characterization, corrosion and mechanical (creep, tensile, fatigue and wear) behaviors of microcomposites and nanocomposites reinforced with ceramic micro-particles and nanoparticles. Particular attention was paid to the development of *in-situ* TiB_2 particles in the aluminum-based MMCs and *in-situ* TiB whiskers in the titanium-based MMCs.

One of the results entitled "Microstructural and mechanical characteristics of *in-situ* metal matrix composites" was published in Materials Science and Engineering R: Reports with a citation of more than 748 (SCI). His group also first introduced 1Vol.% Si_3N_4 nanoparticles to aluminum, and found that the reinforcing effect of low loading level of Si_3N_4 nanoparticles was better than 20 vol.% SiC microparticles.

(b) Fabrication and fracture behavior of polymer micro- and nanocomposites. This involved the preparation, structural, physical, mechanical and thermal characterizations of polymer microcomposites reinforced with short glass fibers and natural sisal fibers, and polymer nanocomposites filled with nanoclays, carbon nanotubes and ZnO. Especially, the essential work of fracture (EWF) was introduced to characterize the fracture toughness of polymer micro- and nanocompoosites.

(c) Electric and dielectric behaviors of polymer nanocomposites filled with carbon nanotubes and nanofibers. His research accomplishments in these three areas have been presented in over 270 papers and 6 books as well as international conferences, seminars, etc.

His present research interests lie in the development of load-bearing polymer nanocomposites for biomedical engineering applications and the development of antibacterial polymer nanocomposite scaffolds filled with silver nanoparticles and hydroxyapatite nanorods (nHA) for soft tissue engineering applications in orthopedics. Furthermore, some progress has been made in the development of flexible transparent conductive films (TCFs) based on silver nanowires and reduced graphene oxide. The Ti-6Al-4V and other metallic alloys currently used in orthopedics for load-bearing applications have many drawbacks including stress

shielding effect, cytotoxicity of metallic ions and wear/corrosion problems. Polyetheretherketone (PEEK) shows promise for biomedical applications since its mechanical stiffness and biocompatibility can be tailored and improved by adding nHA, graphene sheet or carbon nanotubes. Accordingly, nHA, graphene or carbon nanotubes have been incorporated into PEEK for improving its performances. Similarly, nHA and silver nanostructures can improve mechanical strength and antibacterial activity of polymer scaffolds.

At present, flexible TCFs have received great attention for use in the touch screen, solar cells, smart window, etc. Silver nanowire (AgNWs) networks exhibit excellent electrical conductivity and optical transparency but suffer from the haze. Hybridizing AgNWs with reduced graphene oxide can minimize haze issues. Such hybrid dispersions or inks can be used to produce flexible TCFs in a large scale and low cost using inkjet printing or Mayer rod coating process.

Major Academic Achievements and the Contribution to the Chinese Natural Gas Industry

by Jinxing Dai

Short Biography

Prof. Jinxing Dai is a famous specialist on natural gas geology and geochemistry. He was born in Rui'an, Zhejiang Province on 19th, March, 1935. Now he is a professor and Ph.D. supervisor in the Institute of Petroleum Exploration and Development, PetroChina. Prof. Dai was elected as a member of the Chinese Academy of Sciences in October, 1995 and a member of International Academy of Sciences for Europe and Asia on December, 2012.

Prof. Jinxing Dai graduated from the Geology Department of Nanjing University in August, 1961. From September, 1961 to May, 1962, he worked in the Research Institute of Ministry of Petroleum Industry. From June, 1962 to May, 1972, he took up research work on petroleum exploration in the Jianghan Oilfield, Hubei Province. Since June, 1972, he has carried out the geological and geochemical research on natural gas in the Research Institute of Petroleum Exploration and Development, PetroChina. During 1983-1998, Prof. Dai served as a chief scientist of the National Key Science and Technology for natural gas four times. He has been appointed as an adjunct professor of more than ten universities, including Nanjing University, Zhejiang University, University of Science and Technology of China, Jilin University, Northwest University, China University of Petroleum (Beijing and Eastern China). Prof. Dai has worked as a member of the editorial board of more than 10 journals such as Science in China (Earth Science), Chinese Journal of Geology, Acta Petrolei Sinica, Oil and Gas Geology and Earth Science Frontiers. At present, Prof. Dai holds the position of Chief Editor of Petroleum Exploration and Development (SCI, EI) and Natural Gas Geoscience (EI).

Major Academic Achievements

Prof. Dai has been engaged in the geological and geochemical research work of natural gas in the past 40 years. He has established the coal-derived gas theory in China which shed light on a new exploration field for natural gas in the country and made great contributions to establish the first batch of abiogenic alkane gas fields and abiogenic CO_2 gas fields and their geochemical characteristics. He has made a distinguished contribution to the identification of natural gases with different genetic types; made significant contribution to the formation condition, quantitative and semi-quantitative controlling factors, and the prediction of favorable areas of giant gas fields in China. Professor Dai has made contributions to the geochemical research on unconventional natural gas (coalbed methane, tight sand gas and shale gas) in China. In a word, systematic and creative contributions have been made by Prof. Dai that fostered the rapid development of the Chinese natural gas industry.

Coal-derived gas theory in China

Based on the petroleum and coal field exploration data, Prof. Dai found hydrocarbon shows generally exist in Chinese coal measures, and at the end of 1970s, he proposed that coal and coal series can be good source rocks as well as the target zone for gas exploration for the first time (Dai, 1979, 1980). He systematically studied the geochemical characteristics of coal, coaly mudstone and related hydrocarbon, revealed the geochemical characteristics and change law of the hydrocarbon derived during coalification, and established the relationship of $\delta^{13}C_1$—Ro for both Chinese oil-type gas and coal-derived gas. The famous geochemist Galimov (2006) pointed out that the Stahl's $\delta^{13}C_1$—Ro curve (Stahl, 1977) is fairly well approximated by the "instantaneous" curve, whereas the curve established by Dai is closer to the "cumulative" line. Prof. Dai guided and promoted the development of Chinese organic geochemistry of coal-derived hydrocarbons (Dai, 1979, 1986; Dai and Qi, 1989). The coal derived gas theory promoted the development of the Chinese natural gas industry.

The first to propose that gas is dominant over oil in hydrocarbon generation from coal measures

Since the 1960s, coal-related oil fields have been successfully found around the world, and there was an upsurge for coal-derived hydrocarbon study and exploration in China during 1980-1990. However, Prof. Dai studied the hydrocarbon generation characteristics of coal measures and in 1979 published a paper titled "Petroleum and natural gas generation during coalification" to definitely pointed out that "Gas is dominant over oil in hydrocarbon generation from coal measures". reconfirmed Dai et al (2005) and more recent Chinese petroleum exploration results have confirmed this point.

Establish systemic identification theory and methods on genetic types of natural gas

Through long term, painstaking research and based on extensive domestic and foreign literature, Prof. Dai proposed 21 comprehensive indices of 4 types to classify the genetic origin of alkane gas and carbon dioxide (e.g. biotic, abiogenic, biogenic, oil-type and coal-derived gas), and with deepening research, he has proposed 29 indices and several identification charts to provide a sound basis on the research of natural gas source and genesis (Dai, 1992; Dai et al., 1992). The charts and relative parameters in Jinxing Dai's paper of "Identification of various alkane gases" (Dai, 1992), were cited 7 times by Norway scholars Odden et al. (1998) for oil-source rock correlation in the central area of Norway. Academician of Chinese Academy of Engineering Guangming Zhai and Academician of Chinese Academy of Sciences Jun Chen cited comprehensive identification table in their monographs of "Petroleum Geology of China" (1997) and "Geochemistry" (2004), respectively, and these tables have been cited by many monographs and papers, and the relative indices are widely used for gas-source rock correlation in the gas fields of China.

Demonstrate the world's first abiogenic alkane gas fields and mantle-derived carbon dioxide gas fields

Based on the analyses of abiogenic gas and gas reservoirs in the main petroliferous basins in China, Jinxing Dai pointed out that petroliferous basins in China Eastern rift have advantages for the formation of abiogenic gas and gas fields, and demonstrated that Xingcheng and Changde alkane gas fields in Xujiaweizi fault depression of Songliao Basin were of abiogenic origin (Dai et al., 2005a, 2008, 2009a), which are the world's first geochemically documented abiogenic alkane gas fields. According to the carbon isotope characteristics of CO_2 and helium isotopes, he pointed out that carbon dioxide gas reservoirs in eastern China were mantle-derived, rather than the contact reaction formation of igneous rock and carbonate rock proposed previously (Dai et al., 1996, 2000). In addition, he suggested that there was abiogenic gas in the depths of the earth, based on the discussion of the death point of alkane gas and carbon dioxide, and proposed indices to identify alkane gas and carbon dioxide between biogenic and abiogenic origins. This has filled the void of natural gas geology and geochemistry, and been unique on the theory of abiogenic natural gas.

Geochemical research of unconventional gas in China

Dai Jinxing is one of the earliest scholars to research geochemical characteristics of unconventional gas (coalbed methane, shale gas and tight gas) in China. In 1987, his paper "A research on chemistry composition, stable carbon isotope, origin of coalbed methane and its significance in China" was published in "Science China". This paper is the first systematic research on the geochemical features of coalbed methane in China, and it was cited by the world famous geochemist D.D. Rice 9 times (Rice, 1993). In addition, Prof. Dai studied the geochemical characteristics of tight gas in the Ordos and Sichuan basins in China as early as 1980s and 1990s (Dai et al., 2005c, 2009b, 2012a, b, 2014). Moreover, he also did work on the geochemical characteristics of shale gas. His paper "Geochemistry of the extremely high thermal maturity Longmaxi shale gas, southern Sichuan Basin" has been accepted by the journal "Organic Geochemistry".

Quantitative and semi-quantitative studies on the formation of large gas fields

Dai Jinxing started his systematic research on the control factors, distribution and the lowest intensity of gas generation for the formation of medium to large gas fields from 1986–1990. The quantitative and semi-quantitative studies of the control factors have guided and promoted natural gas exploration and exploitation, and also accelerated the discoveries of large gas fields in China. For example, the factor "gas generation center and its surrounding (intensity of gas generation > $2\times10^9\,m^3/km^2$)" controlling the distribution of medium to large gas fields (Dai et al., 1997, 2008b) still guides natural gas exploration in China. The large gas fields in the Ordos Basin and the Kuqa depression of Tarim Basin were discovered based on this theory.

Contribution to the Chinese natural gas industry

The coal-derived gas theory established mainly by Jinxing Dai not only developed the natural gas origin theory, but also opened up a new exploration fields for coal-derived gas and extended the guiding theory of natural gas exploration from a single source type (oil-type gas) to include a second source type (coal-derived gas) in China. Since the emergence of the coal-derived gas theory, the large gas fields and gas reserves in coal measures and related strata increased rapidly and made China into a gas power from a poor gas producing country, as demonstrated by the following data. In 1978, before the establishment of the coal-derived gas theory, the total proved gas reserves and production of China were $226\times10^9\,m^3$ and $13.7\times10^9\,m^3$, respectively, while after the emergence of the coal-derived gas theory, at the end of year 2011, the proved reserves and the production of China were 36.8 and 7.5 times of the ones in 1978, and in 2011 China was the sixth largest gas producing country in the world. The coal-derived gas accounted for 69.7% and 63.2% of the total proved gas reserves and production of China in 2011 (Dai, 2014).

Prof. Dai has published 281 scientific papers in domestic and foreign scientific journals, and 25 scientific books including 4 written in English and 2 translations, such as Natural Gas Geology in China (Vol. I and II), Accumulation Zones of Natural Gas in China, Formation Conditions and Distribution Patterns of Medium-Large Gas Fields in China, Selected Works of Natural Gas Geology and Geochemistry of Jinxing Dai (Vols. I, II, III, IV, V, the Vol. V is written in English), Conditions Governing the Formation of Abiogenic Gas and Gas Pools in the Eastern China (English edition). Professor Jinxing Dai's works are widely cited and the works are cited as many as 1804 times by articles published in SCI indexed journals, including 1287 citations by others. Professor Dai's works are cited 4112 times by articles published in CSCD (Chinese Science Citation Database) indexed journals, 3505 times by other researchers.

Professor Jinxing Dai won the Advanced Individual Award of National Scientific and Technological Project three times in 1986, 1991 and 1996, the First Prize of the State Science and Technology Progress in 1987 and 1997 for the projects of "Development of Chinese Coal-derived Gas", and "Formation Conditions and Distribution of Middle to Large Gas Fields in China",

respectively. Professor Dai won the Science and Technology Progress Prize of Ho Leung Ho Lee Foundation in 2001. In 2010, he won the Second Prize of the National Natural Science Awards for the excellent work of "Natural Gas Genesis and Identification in China". Among all the winning projects above, Pofessor Dai was the primary contributor.

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A New Subject Area: Fire Engineering

by W. K. Chow

Short Biography

Appointed as an Assistant Lecturer by the Hong Kong Polytechnic in 1981, promoted to Lecturer in 1982, Senior Lecturer in 1988, Principal Lecturer in 1989, Senior Lecturer at College of Degree Studies in 1993 and Reader in 1994.

Named as Professor in 1995, promoted to Chair in Building Services Engineering in 1998, and retitled as Chair Professor of Architectural Science and Fire Engineering since 1998 at the Department of Building Services Engineering of The Hong Kong Polytechnic University.

Director of Research Centre for Fire Engineering since 2000.

Acting Head, and then Head of Department, Department of Building Services Engineering of The Hong Kong Polytechnic University since 2008.

Research on Architectural Science, Fire Science and Engineering, and Building Services Engineering for over 35 years and being Principal Investigator for many funded research projects.

Over 1000 papers published in journals and conference proceedings with about half cited by SCI/EI, and successfully supervised over 50 PhD candidates as Chief Supervisor.

Founding President of Society of Fire Protection Engineers - Hong Kong Chapter since 2002.

President of the Asia-Oceania Association for Fire Science and Technology since 2007.

Appointed as a Justice of the Peace by the Chief Executive of the Hong Kong Special Administrative Region in 2013.

Elected as the Chair of SFPE Asia-Oceania Chapters Coordinating Group, Society of Fire Protection Engineers, USA in 2015.

Member of Board of Directors, Society of Fire Protection Engineers, USA in 2016.

Fellow of professional bodies including Hong Kong Institution of Engineers, CIBSE, SFPE, ASHRAE and ASME.

Served on many government committees on establishing new generation of building fire codes and reviewing new project submissions in Hong Kong and Mainland China since 1998.

Technical Advisor to the IFireE – Hong Kong Branch since 1999.

Editorial Board Member of many SCI engineering journals.

Visiting Professor at universities in UK, China and Australia.

Guest Professor and Supervisor of doctoral degree candidates at universities in China.

Elected to be a Fellow of the Hong Kong Academy of Engineering Sciences in 2012.

Performance-Based Approach

There are many large-scale construction projects with new architectural designs all over the world, particularly in the Asia-Oceania regions with rapid economic growth in the past three decades. Large and tall halls without compartmentation, multi-purpose complexes in Central Business Districts, supertall landmark buildings, deep subway stations in old towns, long tunnels of high speed railway systems and green constructions such as timber apartments in many of these projects failed to comply [1,2] with the current prescriptive fire safety codes. Engineering Performance-Based Fire Codes (EPBFC) [3] as in other subjects such as structural engineering and wind engineering are desired.

Before EPBFC is established through systematic long-term research, performance-based approach is allowed for determining fire safety provisions. Performance-based approach is commonly referred to as performance-based design (PBD) [4-7] in many countries. This is called fire engineering approach (FEA) in some areas in the Asia-Oceania regions such as Hong Kong [8,9]. Both PBD and FEA are not yet EPBFC. Therefore, four levels in the current fire code systems [1,2] can be identified. These are Prescriptive Code PC [8,9] or deemed-to-satisfy (DTS) approach [6] having now, FEA specified in the PC [8,9], PBD [4,5,7] allowed in some countries, and EPBFC desired [3]. Consequently, a new area on fire engineering integrating fire safety and built environment appears to handle PBD-FEA projects. PBD-FEA supports innovative architectural design in demonstrating equivalence to current prescriptive fire codes. However, applying PBD-FEA to reduce [10] the construction cost would give many problems as reviewed [1]. Many projects were identified in those places where the fire officers, not consulting engineers, have to be responsible for the hazardous consequences. More in-depth fire safety research related to the fire safety of big constructions, particularly in the Asia-Oceania regions should be carried out to meet the new challenges.

Current Problems Identified

Numerous fire safety problems in existing buildings adopting PBD-FEA approach were identified [1,2]. Shortcomings in the interpretation, application and implementation of PBD process in USA, Canada, Australia, Japan, UK and other European countries were pointed out. A common problem on estimating egress time in the timeline analysis by comparing the Available Safe Egress Time (ASET) with the Required Safe Egress Time (RSET) was pointed out by Babrauskas et al. [11]. Similar concerns on not applying the timeline analysis properly in fire safety assessment in PBD-FEA projects in the Asia-Oceania regions were also raised [12]. Another example in applying PBD-FEA was on adopting low design fires. In many vehicular tunnels allowing heavy goods vehicles to use, small fire less than 5 MW was allowed in PBD-FEA report submitted decades ago. There were even arguments saying that fire resisting structural walls specified in PC are unnecessary if the fire is small. However, keeping a small accidental fire to match with the design hazard scenarios would require even more resources in fire safety management than providing fire resisting walls. Data on heat release rate for local combustible products in many places are not available. Estimations were based on very crude assumptions under low radiative heat fluxes without projects [e.g. 13] supported by systematic full-scale burning tests. Such methods of estimating probable heat release rates to give low values were reviewed in the literature. These calculations applied to PBD-FEA projects should be further justified. Although the development of Computational Fluid Dynamics (CFD) fire models [14] is slow, the models were widely applied for fire hazard assessment in PBD-FEA projects. CFD models based on Reynolds Averaged Navier-Stokes equation (RANS) models were used three decades ago. Large eddy simulation [15] is now widely used to study the fire-driven fluid flow. Very few works were reported on the three key elements on simulating turbulent mixing between air and unburnt fuel, combustion process and thermal radiation. The shortcomings of CFD results are [1] mainly because fire phenomena are substantially three-dimensional. Three-dimensionality and instability of the fire-induced flow fields are difficult to fully address. The ability of CFD to resolve the turbulent exchange flow through the opening is in doubt. Further, air pressure and turbulence parameters are not presented in many fire hazard assessment reports for PBD-FEA projects [1]. Results are seldom justified by full-scale burning tests or scale modelling experiments on typical scenarios. All these problems start to appear [16]. Hidden fire

problems in these PBD-FEA projects have to be carefully considered, although no big fire disasters have occurred yet. For example, the owners concerned were asked to implement very complicated fire safety management or upgrade the fire safety provisions. Additional firefighting training and equipment has to be provided in some fire departments. Officers approving PBD-FEA projects are now watching the problems carefully and requesting appropriate justifications for all new and existing projects involving timeline analysis, particularly in crowded underground subway stations [17].

Supporting Sustainable Development

There are many conflicts [18-20] between green constructions and fire safety regulations as experienced in the past two decades. The hidden adverse effects on fire hazard for some architectural features have been discussed with examples in Hong Kong identified [18]. Several architectural design features, such as some double-skin building façade designs [21], do not comply with the PC in many countries. People even forgot the frequent big wood house fires experienced before [22] while constructing tall timber buildings. There was even an incident of collapse of a big green roof on steel and glass structure recently at a university. Therefore, hazards of some green features for sustainable buildings have to be assessed more seriously, particularly those designed for high occupant loading. Another green issue to watch is the use of clean fuel liquefied petroleum gas (LPG) vehicles. A gas explosion [23] occurred in a garage for repairing LPG taxis in Hong Kong in April 2015. This gas explosion not only damaged the building structure, but also killed the owners staying inside. Causes of the incidents are mainly attributed to the lack of awareness of the LPG leakage by the occupants, carelessness of workers when carrying works and possible suicide attempts by occupants. Vehicles using other clean fuels including hydrogen [24] make the situation more complicated, although very little damage to the hydrogen vehicle was observed in full-scale experiments [25]. However, as alerted by the above explosion of LPG taxi in a garage [23], hydrogen cars can be more hazardous when safety schemes during repair and maintenance are not properly followed. Therefore, it is necessary to study fire and explosion of LPG, hydrogen and other clean fuel cars in a garage. Further, many clean refrigerants used [23] in environmental friendly air-conditioning and refrigeration (ACR) equipment are flammable hydrofluorocarbons, hydrofluoroolefins and hydrocarbons. Explosion of clean refrigerant occurred before in a small restaurant [23] in 2013, alerting the general public. There is a need to study the fire hazards arising from using clean refrigerants in ACR systems.

Appropriate fire safety management has to be adopted for addressing the issue of fire and explosion hazards. Note that firefighters are always exposed to the risk of big fires and explosion when carrying out rescue operation in the gas-filled environment. The explosion pressure has to be better understood for protecting firefighters during their operation. Useful information on pressure and temperature rise due to explosion of LPG, used in vehicles and as clean refrigerant, should be worked out for firefighters for taking appropriate fire action plans.

Research Needs

Systematic research on the fire safety objectives, acceptance criteria, engineering tools for hazard assessment, statistical fire records and verification methods should be carried out. The relevant fire data for supertall buildings, long tunnels, deep underground stations, large halls and buildings with green architectural features are not yet compiled systematically. Research funding is not adequate [26] to support the huge amount of fire

research activities required. Furthermore, it would take a long time for officials to shift from implementing PC to EPBFC. Training and education should be provided to engineering professionals on implementing EPBFC, PBD and FEA. At the moment, the total fire safety concept integrating software fire safety management with hardware fire safety provisions, both active and passive, has to be applied to handle those problems identified in PBD-FEA projects. More resources should be allocated to upgrade fire safety provisions and implement tighter fire safety management in places with inadequate fire safety provisions which can only handle small fire scenarios. Note that very few accidental fires occurred in large timber palaces in Ancient China Empires because many imperial guards were assigned under fire safety management. The officers had to be responsible for having a small fire.

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Building Objects & Structures in Outer Space

by Behrokh Khoshnevis

Short Biography

Adademic Experience

2005-present Director, Center for Rapid Automated Fabrication Technologies (CRAFT)

1997-present Professor of Industrial & Systems Engineering, and Director of Manufacturing Engineering Graduate Program (since 1992) University of Southern California.

1987-1997　　Associate Professor of Industrial and Systems Engineering, and Associate Director of Manufacturing Engineering Program (1984-1992), University of Southern California.

1983-1987　　Assistant Professor of Industrial and Systems Engineering, University of Southern California.

1980-1983　　Assistant Professor of Industrial and Systems Engineering, Ohio University.

1979-1980　　Visiting Assistant Professor of Industrial Engineering and Management, Oklahoma State University.

Professional Affiliations

National Academy of Inventors, Fellow

European Union Academy of Sciences, Member

Institute of Industrial Engineers, Fellow
- *Chairman, Academic and Research Committee on IE in Construction. 2003-present*
- *USC IIE Student Chapter Faculty Advisor, 1984-1990*
- *Chairman of IIE Manufacturing Division for Region XII, 1985-86*
- *Chairman of IIE Production and Inventory Control Division for Region XII, 1984-85*
- *Conference Chairman, IIE Los Angeles Chapter Conference, March 1984*

Society for Computer Simulation, Fellow
- *Member of Board of Directors, 1994-5*
- *Member and past Chairman of Steering Committee, Western Simulation Council, 1991-2002*

Society of Manufacturing Engineers, Senior Member

American Association for Advancement of Science (AAAS), Member

Standing Member of the Emerging Technology Committee, Infrastructure Resilience Division, American Society of Civil Engineering (ASCE)

Learning International Network Consortium (LINC), Member of Advisory Board

Sharif University of Technology Association (SUTA), Member of Scientific Advisory Board

Association of Professors and Scholars of Iranian Heritage, Member of Advisory Board

Editorial Boards

Member of Editorial Board of: Journal of 3D Printing and Additive Manufacturing, Int. journal of Rapid Manufacturing, Journal of Intelligent Manufacturing, Int. Journal of Industrial & Systems Engineering, Journal of Computers & Industrial Engineering, and Journal of Industrial & Systems Engineering. Guest Editor of Journal of Automation in Construction on Large Scale 3D Printing.

Awards & Recognitions

1. *Khwarizmi International Award recipient (KIA Laureate), 2016*
2. *Elected as Member, European Union Academy of Sciences, 2015*
3. *Hall of Fame Inductee, Oklahoma State University College of Engineering and Architecture, 2015*
4. *3D Printing World Award, Mumabi, 2015*
5. *Best Paper Award, 2015 Solid Free Form Fabrication Symposium*
6. *Received the Orange County Engineering Council Distinguished Engineering Merit Award, February 2015.*
7. *Appointed as Dean's Professor at USC in December 2014.*
8. *Inducted as Fellow of the National Academy of Inventors in 2014.*
9. *Recipient of the Grand Prize (as the top among 1000+ globally competing technologies) of the NASA Creating the Future design contest for invention of the Contour Crafting robotic construction technology. The program is sponsored by Intel, HP and several other major industries.*
10. *Best Paper Award, 2014 Solid Free Form Symposium.*
11. *Best of 2014 Papers, special issue of 3D Printing and Additive Manufacturing*
12. *Selected as one of only two US university faculty to present research project at Capitol Hill on NASA Technology Day 2013*
13. *Best Paper Award by ISA PMCD - 58th International Instrumentation Symposium, 2013*

14. *TEDx presentation on automated construction has been ranked by the TED organization as one of top five among more than 30,000 TEDx talks and has been viewed over a million times (as of Dec 2013) and counting (see the TEDx talk at www.ContourCrafting.org)*
15. *Creative-Iran Society Gold Trophy Award 2012*
16. *Sharif University Alumni Achievement Award, 2012*
17. *Awarded Fellow status, NASA Innovative Advanced Concept (NIAC), 2011*
18. *Winner of Innovation in Curriculum Completion Runner-up, Institute of Industrial Engineering, 2008*
19. *Automated construction invention selected as one of top 25 inventions among 4300 contestants by The National Inventor's Hall of Fame, History Channel Modern Marvels program, and Time Magazine, 2006*
20. *USC School of Engineering Senior Research Award, 2005*
21. *2005 Pete Lohmann Medal (Best OSU Engineering Alumni)*
22. *Awarded Fellow of the Society for Computer Simulation, 2004*
23. *Technical Innovation in Industrial Engineering Award, Institute of Industrial Engineering, 2004*
24. *Highest Honor Award for Innovation in Construction, Construction Specification Institute, Gulf State Region, 2004*
25. *Best Paper Award, selected by Emerald Publisher's Rapid Prototyping Journal Editorial Board ,2004*
26. *Outstanding Scholar Award, Association of Professors and Scholars of Iranian Heritage, 2004*
27. *Best Paper Award, 19th International Symposium on Automation and Robotics in Construction, 2002*
28. *Best Paper Award, Solid Free Form Symposium, 2002*
29. *Awarded Fellow of the Institute of Industrial Engineers, 1999*
30. *Member of Alpha Pi Mu, Omega Rho, and Tau Beta Pi Honorary Societies*
31. *Contour Crafting has been exhibited at numerous science as well as art museums worldwide*

Abstract

Two NASA international award winning technologies conceived and developed by the author are presented for construction of infrastructure elements on the Moon and Mars and for building of a variety of objects using in-situ material on these celestial bodies, and in zero-gravity condition for fabrication in space and inside the International Space Station.

Introduction

Early exploration of arctic regions on Earth utilized single engine small airplanes that could land on snow. Later exploitation of those regions required heavier vessels that could carry large crew and heavy equipment for activities such as oil well drilling. Several exploratory missions have been conducted to investigate Moon and Mars but not much change has been made to the landscape of these celestial bodies that promise numerous possibilities for humans. The vessels that have so far landed on Moon and Mars have been analogous to those small airplanes that landed on arctic snow. Lunar and Martian infrastructures suitable for much larger landers and more extensive operations are needed in order to conduct future missions that benefit from the opportunities that may be offered by Moon and Mars.

There is currently an international race for targeted expeditions to our closest celestial body, the Moon, which offers the possibility for installation of high power communication relay stations, telescopes that will have a clear view of heavens without atmospheric interference, abundant rocket fuel and much less energy demanded for rocket launch due to much lower gravity, availability of precious materials (including rare-earth materials), and abundance of helium 3, which is believed to make the fusion energy economically possible on Earth.

Current extraterrestrial settlement buildup philosophy holds that in order to minimize the materials needed to be flown in, at great transportation costs, strategies that maximize the use of locally available resources must be adopted but feasible construction approaches using in-situ material have been hard to conceive. This article reports some of the activities in our NASA Innovative Advanced Concept (NIAC) projects, which focus on a unique architecture weaving the robotic building construction technology with designs for assisting rapid buildup of initial operational capability Lunar and Martian bases. Material processing tools and construction equipment flown as cargo from Earth are proposed to build required infrastructure to support future missions and settlements on Moon and Mars.

Economically viable and reliable building systems and tool sets centered around the Contour Crafting (CC) robotic construction technology and Selective Separation Sintering (SSS), invented by the author, are being sought, examined and tested for extraterrestrial infrastructure buildup.

Tools and heavy equipment flown as cargo from Earth are proposed to build required infrastructure to support future missions and settlements on the Moon and Mars. The growing list of commercial space companies whose business plan is to do this profitably is a good indicator that the time is now! Construction of infrastructure elements such as landing pads, blast protection walls, roads, hangars, shade walls, radiation shields, etc. which this project addresses is the precursor to all other major planetary expeditions.

Several unique systems including the Lunar Electric Rover, the unpressurized Chariot rover, the versatile light-weight crane and Tri-Athlete cargo transporter as well as the habitat module mockups and a new generation of spacesuits are undergoing coordinated tests at NASA. This project intends to draw up a detailed synergetic plan to utilize these maturing systems coupled with modern robotic fabrication technologies based primarily on 3D Printing, tailored for swift and reliable Lunar and Martian infrastructure development.

Progress

Our research activities have been advancing on many fronts. So far we have engaged in systems architecting of planetary outpost and its elements, as well as launch plan and control elements. Due to near-absolute vacuum making water based concrete in the Lunar environment is very difficult. Also water is hard to get on both Moon and Mars. Accordingly, we have devised new ways of making construction materials using in-situ resources, performed materials and process studies, built experimental machines and conducted laboratory experiments, and conducted structural design and analysis studies.

Conceptual Infrastructure Designs:

We first concentrated on the landing pad and road requirements and are now concentrating on blast walls, hangars, and shade walls for the remaining part of the project. Lunar vacuum and low gravity will make it very difficult to contain or curtail high energy debris that results from direct lander exhaust plume impingement on the exposed, free and loose surface regolith. The extreme natural environment of the Moon coupled with the reference Altair-class (45-50 metric tons) lunar lander touchdown profile will create a very challenging dust and debris environment for safe sortie operations. Due to the comparatively much larger landers, ground effects will be far more severe than experienced during Apollo missions. Review of recent literature clearly points to the need to provide stabilized surfaces for landing heavy payloads.

One way to accommodate this extreme transient temperature and dynamic pressure pattern is to reinforce the core of the landing pad with appropriate materials and design features to mitigate the exhaust effects. The technologies that we have newly explored may offer a way to create inter-locking refractory tiles in such a manner as to be able to resist and dissipate the heat and energy of the lander engines effectively.

The landing pad apron has much less stringent requirements than the landing pad center segment and as such materials with lower melting point (e.g., sulfur concrete for Mars and shady areas on Moon) may be reasonably good candidates for its construction. We are considering several different methods or a combination of these methods for road construction as well.

Our concept designs of landing pad, apron, blast walls, and road and hangar robotic construction scenarios are depicted in visualization shown in Figures 1, 2 and 3.
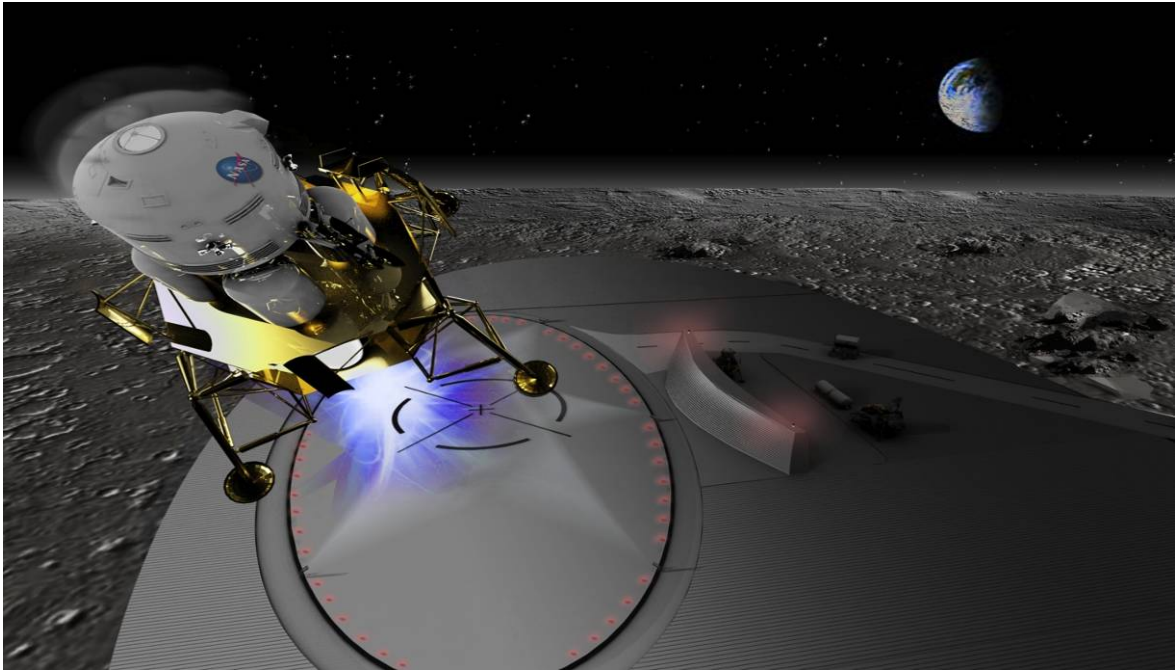
Figure 1. *A lander is shown coming in to land on a lunar landing pad. The landing pad has been designed as an ellipse with its length in line with the direction of landing and takeoff with a central landing area lit up by lights, surrounded by a broader dust-free apron. A blast wall is also visible, protecting the entire settlement and items of equipment stored behind it.*
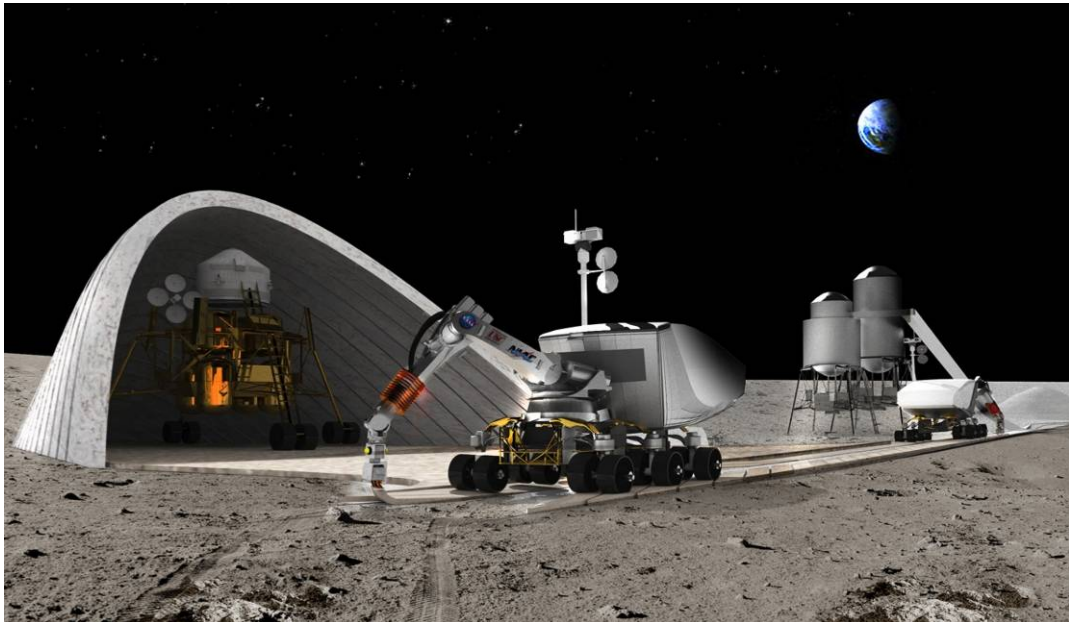
Figure 2. *A Contour Crafting robot is shown here mounted on NASA's Chariot Rover printing a road in front of a parabolic hangar structure housing a lunar lander. In the background can be seen a plant intended for processing regolith that will be used in the construction process.*
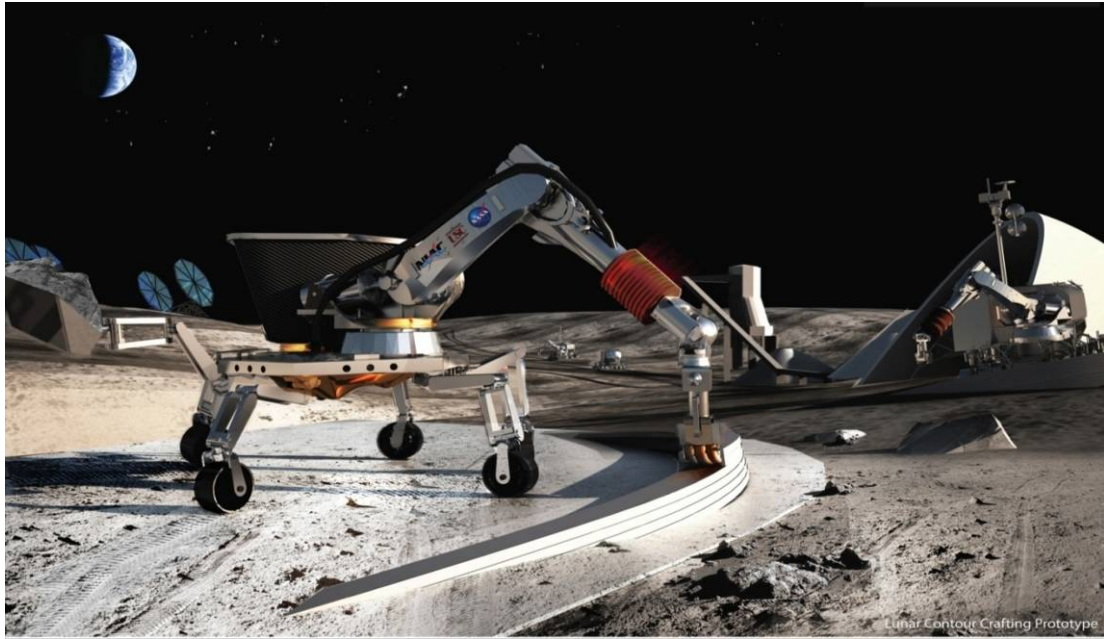
Figure 3. A Contour Crafting robot, housed on the NASA JPL's ATHLETE rover, is shown here printing a parabolic vault structure out of processed regolith. The structure is intended to house a lunar lander or other equipment, and is unpressurized. The parabolic form has been adopted, because it is structurally efficient and lends itself to the Contour Crafting mode of construction. In the background can be seen an array of solar panels intended to supply power to the robot.

Construction Materials and Fabrication Technologies:

We have considered a variety of practical construction material for different planetary structural applications. Water is present on Moon and Mars and other researchers have demonstrated the possibility of creating hydraulic (water based) concrete on these planets. Accordingly, our years of research on hydraulic concrete construction for terrestrial applications using Contour Crafting and the resulting technological solutions are applicable to extraterrestrial condition with relatively minor alterations but we have decided to stay away from the difficult task of handling water in a high or low temperature and near-vacuum environment. We have hence decided to focus our attention on other construction materials including sulfur based concrete, molten regolith concrete, and sintered regolith tiles. We have performed some preliminary successful studies with sulfur based concrete by mixing and hot-extruding sulfur and JSC1-A regolith stimulant (the Lunar dust look-alike initially made at Johnson Space Center). We have also melted regolith stimulant by means of concentrated sunlight using large Fresnel lenses, by resistive heating and by microwave. The silica component in the regolith melts at about 1100 C and acts as the cement in binding other regolith constituents (primarily metal oxides) that serve as concrete aggregates. We then tested the compressive and tensile strengths of the resulting solid. To improve tensile strength we have performed a number of experiments, the most successful of which was mixing regolith with 5% metal powder and melting the mix. Finally, using our small sintering furnaces we have examined the sintering process of regolith in making ceramic tiles.

Contour Crafting Technology using Sulfur Concrete:

Much like on earth, water is not available in many regions on Moon and Mars and concrete production may involve some complex stages and require complex facilities especially under vacuum. Creation of sulfur based concrete is fairly straightforward and

simple, on the other hand, once sulfur is extracted from regolith. As shown in the left portion of Figure 4, sulfur concrete is made of about 80% regolith and 20% sulfur. Contour Crafting structures using sulfur concrete requires mixing the two components and then extruding the dry mix through a CC nozzle barrel that is heated to 130 C, the melting temperature of sulfur. Sulfur concrete structures can have a compressive strength of 3000 psi which is higher than the strength of most ordinary hydraulic concrete structures, such as those built with concrete blocks.

Extrusion of granular abrasive material is never straightforward. Lacking water which serves as lubricant to ease the concrete flow, the extrusion of the highly viscous and abrasive sulfur and regolith mix to be challenging. In our experimental device a gear motor turns an auger that forces the dry mixture of sand and sulfur out of a vibrating hopper and into a hot barrel and nozzle. The auger is also equipped with a high frequency vibrator to prevent possible clogging. As the mixture is pushed inside the hot barrel of the extrusion nozzle, the sulfur portion heats up in the upper portion of the barrel and melts in the lower portion, but with aggressive aggregates in the mix the possibility of arch phenomenon that leads to clogging is very high. To effectively deal with the clogging issue we have devised a hard-wired controller that activates a piezo electric auger vibrator only at clogging times (as vibration uses energy and negatively impacts the useful life of the system). This is done by sensing the gear motor current which increases as beginning of clogging increases the motor load. The more serious the clogging the higher the motor current becomes. A circuit activates the auger vibrator with a vigor that is proportional to the gear motor current. As it is not possible to change the frequency of piezo vibrators (as they are tuned to the natural frequency of their transducer horn) we are using a variable duty cycle regimen. At normal motor load levels the vibration motor remains inactive. A second piezo electric vibrator always operates at the orifice of the nozzle to assure smooth departure and good surface quality for the extrudate.

Building landing pads and fabricating other objects by Selective Separation Sintering (SSS):

Selective Separation Sintering (SSS) is a novel powder based additive manufacturing method that can build parts of various scale out of metals, ceramics and composites. This can be done at relatively high speed and with minimal machine complexity. In the SSS process, a thin wall of high temperature separator powder material (S-powder) is deposited within the base material powder (B-powder) to form a barrier on the boundary of each layer. This barrier creates a separation between the part and surrounding material, which allows for the separation of the part from the surrounding powder after sintering is complete.

The nozzle opening in SSS may be tall and thin vertical slot along the length of the nozzle which would allow the deposition of a tall wall of separator powder. Accordingly, large-scale parts may be built with layers that could be as thick as bricks thereby allowing rapid construction of large structures with cementitious or other materials. This property makes SSS an ideal process for planetary construction of free standing or interlocking ceramic tiles, bricks, etc. Figure 6 shows the progression of fabrication of interlocking ceramic tiles out of lunar regolith simulant, and Figure 7 shows the autonomous process of tiling using a rover on which the SSS nozzle and a microwave generator for sintering are installed. The last reference link shows a video of the operation for construction of lading pad.
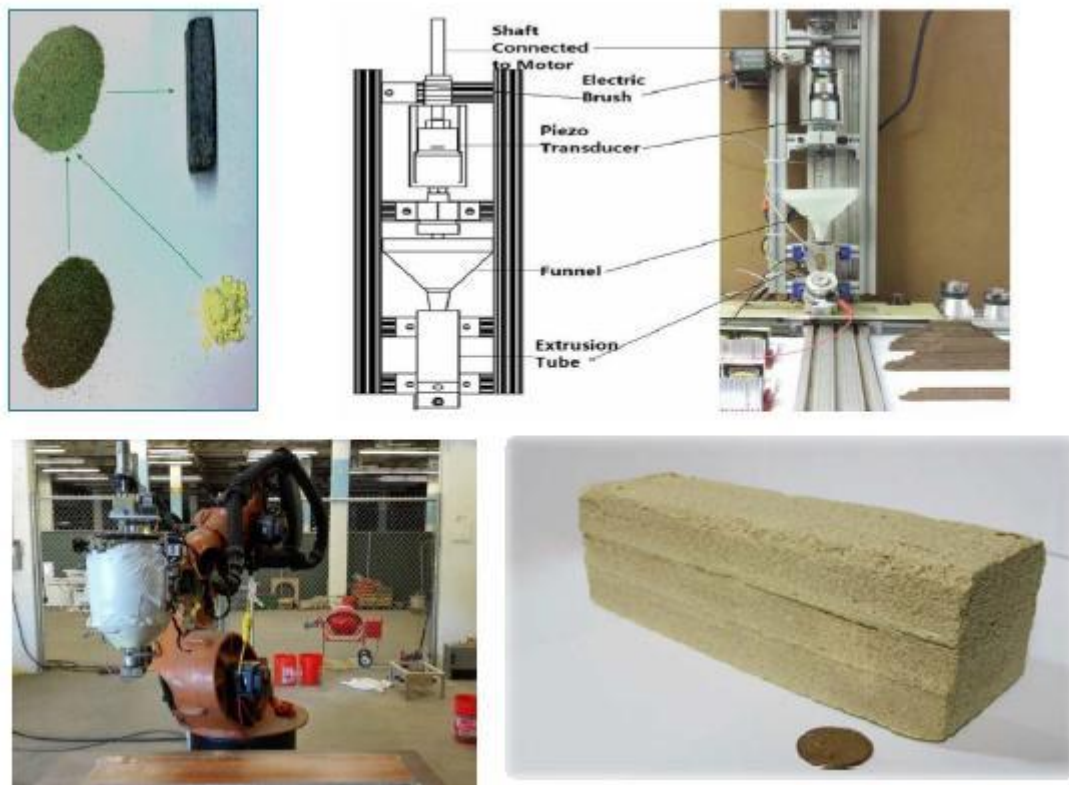
Figure 4. Top left: Sulfur, sand, sulfur/sand mix yielding sulfur concrete; Right top: Simplified mechanism for extrusion of sulfur concrete; Bottom: The CC sulfur concrete machine and specimen
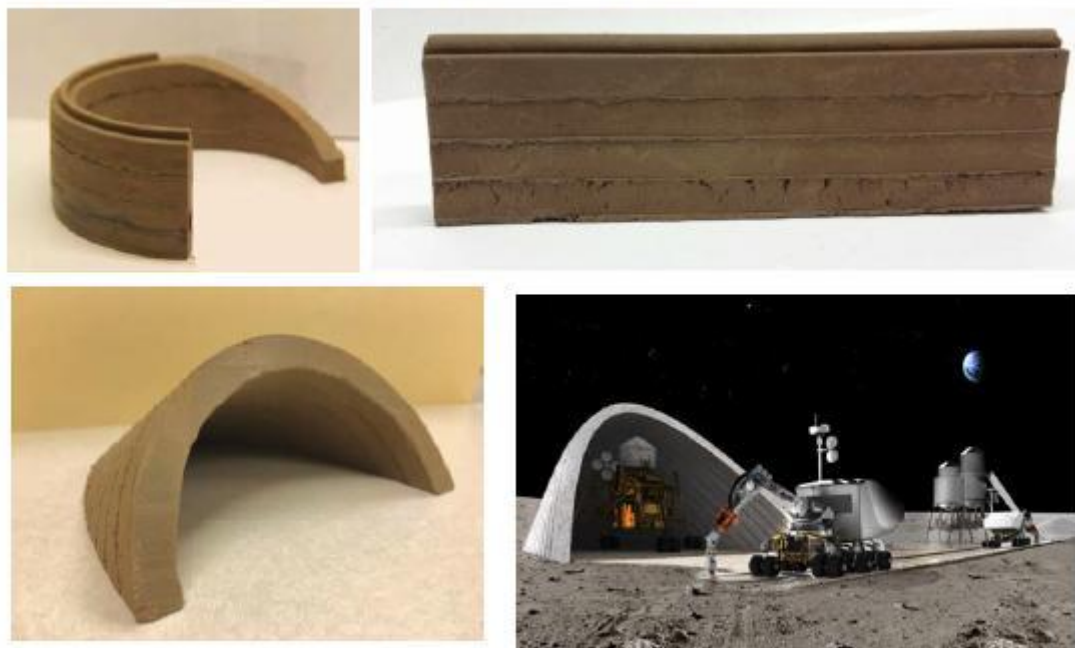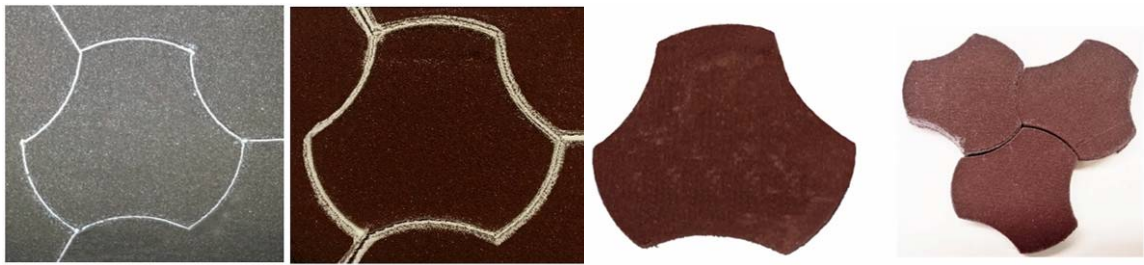

Figure 5. Specimens built with sulfur concrete made with Martian regolith simulant and an application scenario for construction of a hangar for protection of landers

SSS can process any material with high melting point as long as there is another material with a higher melting point that can be used as separator agent, and it can build very fast because it only treats part surfaces, not its volume. SSS can also be more accurate than spot-heating processes that use laser and electron beam because in spot-heating processes heat expands through conduction hence the process resolution is not as good as the beam diameter. Finally, SSS is the only powder-based AM process that can operate without powder layering by inserting its nozzle deep into the base powder and depositing the separation powder to define the part surfaces inside the powder vat. Among other advantages, this property of SSS makes it the only powder-based Additive Manufacturing approach that can work in zero gravity.

Preliminary experiments with metallic and ceramic base materials have demonstrated the feasibility of the approach. The method has been used successfully with various metals, ceramics and composites. Metallic parts have been built out of a variety of metals including bronze and stainless steel. Figure 7 shows some metallic objects built with SSS.

Environmental Factors:

Dust is a primary concern and architectural designs must address this concern directly. Meteorites, radiation and light intensity can also be a problem. The regolith concrete must form the desired inhabited and uninhabited spaces as well as resist and provide durability against meteorites, radiation, thermal loading and direct sunlight. An optimal solution will be sought that takes advantage of increased buckling strength to minimize the material but still resist meteorites and provide a barrier for radiation.

Severe temperature differences exist between stark daylight and shadow, and even more severe surface temperature differences can be found in the diurnal thermal cycling. Fixed structures induce internal stresses based on thermal gradients and temperature differences from initial construction temperatures. A Lunar structure that is partially shaded can develop large unbalanced thermal stresses (-250 F in shade and +250 F under sunlight). Uniformly heated or cooled structures can be designed more readily to accommodate thermal expansion and contraction and minimize the unbalanced stresses that may introduce tension and cracking. Severe temperature differences may also arise based on sun angle. Sunlight can be harvested and if consideration is being made for developments near the South Pole, this will be necessary to reduce heating demands for habitation and for fluidity of the concrete regolith during construction.

Plan Summary

Our planetary infrastructure construction strategy is based on robotic system deployment, digital fabrication using 3D Printing, and ISRU (NASA term for in-situ resource utilization) for feedstock. As with all space missions, cost of transport of equipment to site is the dominant part of extraterrestrial technology deployment and operations. Current values are around $10,000 /kg to low Earth orbit, $100,000/kg for lunar orbit and another order of magnitude for landing payloads on Mars. These are exorbitant transportation costs, and once again, robotic construction technology-derived solutions offer great promise. A lunar setup based on existing CC machine components, for example, could weigh as low as 500 kg on the launch pad, not including the rover platform system. We expect such a CC system to be compactly packed into a payload volume of 5 m x 2 m x 2 m and could be adapted as auxiliary payload on a variety of launchers. We also expect the cost of transportation to drop significantly as private launchers like SpaceX Falcon 9 become serviceable for lunar and Martian missions.

An extraterrestrial robotic construction system offers tremendous advantages over crew doing complex building tasks manually. First of all, it eliminates the risk associated with using astronauts on dangerous tasks. By relegating crew to supervisory tasks and anomaly resolution alone, robotic fabricators allow the builder to hold to schedule with minimal slippage. The ability of such systems to work continuously allows for rapid infrastructure buildup.

Our current estimate suggests that a rover fabricator setup, once deployed on the lunar terrain, could fully make use of one lunar day (14 Earth days), to build using solar panel power a 30 meter diameter, stabilized landing pad for an Altair-class lander in sortie operations using the SSS process. Robotic fabricator effectiveness is enhanced when multiple copies of a structure need to be commissioned. When coupled with ISRU materials and technologies like real time tele-robotics, such fabricators offer a versatile building system, which over a period of time could construct numerous structures and vast settlements.

What is anticipated after this Research

We anticipate NASA and/or other sources to fund further development of these promising technologies and the structures they can produce. As an initial next step, samples of infrastructure elements subject to Lunar and Martian environmental loadings would be made using robotic construction technology (TRL 2-4). This will help validate our simulations and the feedback may influence refinements to the infrastructure designs. After that, samples of infrastructure elements would be made with robotic construction methods in an environment similar to the Moon or Mars and subject to Lunar and Martian environmental loadings (TRL-5). This will also help validate our simulations and the feedback may influence refinements to the infrastructure designs. Further maturity of the robotic construction technology and structures it can make would lead to full scale prototypes of infrastructure components built in vacuum or Martian-like atmosphere and be subjected to thermal and blast loading (TRL-6). This test performance will be used to demonstrate agreement with finite element analysis (FEA) simulation predictions.

In addition to research that will advance the maturity of this architecture, we anticipate other divisions of NASA to be interested in expanding the robotic construction methods to build other types of ISRU based components beyond basic infrastructure. Robotic construction technologies and specialized Additive Manufacturing equipment could build tools, other robots, scientific equipment and many other objects that can be formed from excavated and processed extraterrestrial materials. We also anticipate major contributions

by robotics researchers at NASA divisions to integrate our proven fabrication technologies with space-worthy advanced class of NASA robotics hardware and intelligent software. Once such integration materializes exciting demonstrations at a simulation site such as the Arizona desert site, D-RATS, can be performed and following successful demonstration and refinement the ultimate dream of actual Lunar and Martian settlement construction can be materialized.

Automated building construction technologies will revolutionize the way structures are built on Earth, in dense urban environments, in difficult-to-build and difficult-to-service sites, or in remote and hostile regions of the globe. The technologies under development by our group have the potential to simplify construction logistics, reduce the need for hard physical labor by assigning humans to a strictly supervisory role, eliminate issues relating to human safety, and produce intricate and aesthetically refined designs and structures at significantly reduced construction cost. Space architecture in general and Lunar and Martian structures in particular will also provide a rich new aesthetic vocabulary for architects to employ in the design and creation of buildings that employ high technology and building information modeling that is vital for optimizing use of materials and energy that is critical to building economics. As a dual use case, we are initiating work with the State of Hawaii, which has exorbitant amounts of volcanic sand as well as sulfur, to evaluate the use of our technologies for creation of a large variety of structures using these abundant materials. We anticipate our research endeavor to ultimately lead to revolutionizing construction on our planet and significantly impacting the future of planetary exploration and colonization.
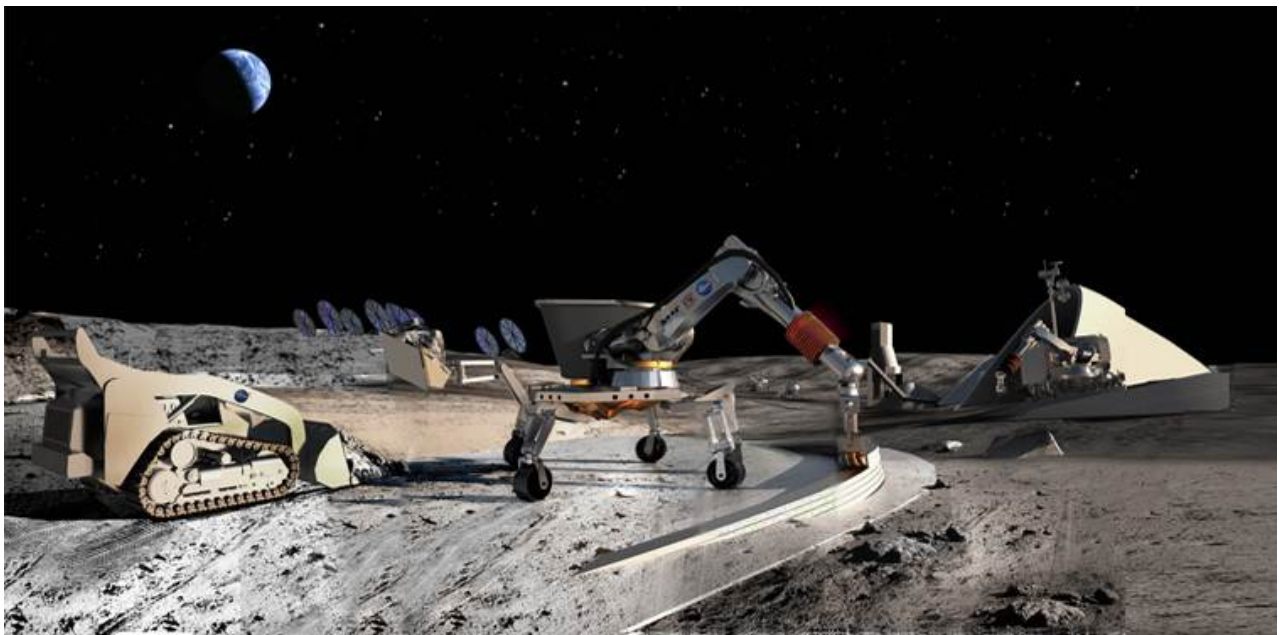
Figure 7. Planetary infrastructure construction scenario using autonomous heterogeneous equipment and tele-robotic ground-based high-level planning system

Related Links:

- www.ContourCrafting.org
- http://www.nasa.gov/offices/oct/stp/niac/2012_phaseII_fellows_khoshnevis.html
- http://www.nasa.gov/offices/oct/home/niac_countour_crafting.html
- http://www.washingtonpost.com/blogs/innovations/post/is-a-moon-colony-on-the-horizon/2012/08/15/e1af23be-e717-11e1-936a-b801f1abab19_blog.html
- https://news.usc.edu/97707/new-3-d-printing-process-could-lead-to-construction-on-mars-and-the-moon/

Screening for Heart Disease:
A Mandate for better Survival

by Matthew Budoff

Short Biography
Professor of Medicine, David Geffen School of Medicine, Harbor-UCLA Medical Center
Program Director and Director of Cardiac CT, Division of Cardiology, Harbor-UCLA Medical Center
Endowed Chair of Preventive Cardiology, Los Angeles Biomedical Research Institute, Torrance, CA USA 1124 West Carson Street, Torrance, CA, 90502, USA
Dr. Budoff has been listed among America's Top Doctors every year since 2005. In the past two years alone, Dr. Budoff has been honored with multiple awards recognizing his professional skills and accomplishments. Of particular note is his receipt of the Einstein Award for Scientific Achievement from the International Biographical Centre, Cambridge, U.K.; being named to the US News list of Top Doctors; and named to "Worlds Most Influential Scientific Minds" in 2014. In 2015, he was named the Endowed Chair of Preventive Cardiology at his institution and was awarded the Arthur S. Agatston Cardiovascular Disease Prevention Award. In 2016, he was awarded the prestigious Gold Medal Award from the Society of Cardiovascular Computed Tomography.
Dr. Budoff works on at least 20 active medical research trials at any given time, and is a frequent lecturer on topics of cardiology at symposia, congresses and annual conferences on every continent. He has authored or co-authored over 800 research papers, seven books, and 45 book chapters.

Cardiovascular disease remains the leading cause of mortality worldwide, and no widespread screening for this number one killer has been implemented. Early breast cancer detection with mammography is a standard and widely implemented in clinical practice. Despite the fact that heart disease will claim more than 10 times the number of women as compared to breast cancer, there is little focus on early detection of cardiovascular disease. Traditional risk factor assessment (ie risk calculators) does not fully account for the coronary risk and dramatically overestimates the prediction of risk even in patients with established risk factors for atherosclerosis. Coronary artery calcium (CAC) represents calcified atherosclerosis in the coronary arteries, and been shown to be the strongest predictor of adverse future cardiovascular events. CAC consistently outperforms traditional risk factors, inflammatory biomarkers, and other tests of atherosclerosis such as carotid intimal media thickness (CIMT), endothelial function and ankle-brachial index to predict future CV events. It has been incorporated into both the European and American guidelines for risk assessment. CAC is the most robust test today to reclassify individuals based on traditional risk factor assessment and provides the opportunity to better strategize the treatments for these subjects (converting 77% of patients from intermediate risk to either high or low risk).

The risk for future adverse cardiovascular events increases with increasing CAC scores; however the absence of CAC presents a very unique situation which is

associated with very low risk status for the individual (10 year event rate of ~1%). It has been proposed that those without calcification may be at such a low risk status, that further intervention with pharmacology may be unnecessary. The absence of CAC is associated with a very low risk of future cardiovascular events, presence of severe CAD, myocardial perfusion abnormalities as well as likelihood of ACS.

The cumulative data provides strong confirmatory evidence that CAC is a strong predictor of events and that as radiation doses are being reduced to a minimum, may be a useful tool in the prevention armamentarium to assess atherosclerosis progression non-invasively. Dr Budoff has done extensive validation of this test (publishing over 500 papers on this topic), evaluating in whom and when it should be used, and participated in multiple writing groups incorporating this into standard cardiac care. Based on available published evidence, CAC has been incorporated into the ACC/AHA guidelines for screening of asymptomatic individuals for CVD. Dr Budoff, using a large prospective population (the Multi-Ethnic Study of Atherosclerosis), demonstrated a 10 fold increased risk for calcium scores >100 and a 14 fold increase for scores >300. All other prospective studies (St Francis, Heinz-Nixdorff Recall Study, Dallas Heart, Rotterdam and others) demonstrate that CAC is the most robust method to identify patients at increased CV risk.

Dr. Matthew Budoff is at the forefront of the medical community's efforts to develop early detection methods for cardiac disease, the number one cause of death in the U.S. Given that approximately 50 percent of U.S. heart disease victims learn of their illness by experiencing a sometimes fatal heart attack, Dr. Budoff has devoted much of his time over the past 20 years to advancing procedures that can help doctors identify cardiac patients early, and place them on a therapeutic path to prevent a heart attack.

Advancing Acute Management of Stroke

by Geoffrey Donnan

Short Biography
Professor Geoffrey Donnan is Director of The Florey Institute of Neuroscience and Mental Health and Professor of Neurology, The University of Melbourne. His major interests are in neuroimaging and clinical trials.
He was co-founder of the Australian Stroke Trials Network (ASTN) and Neuroscience Trials Australia (NTA). His major contributions have been in the introduction of new stroke interventions such as thrombolysis and thrombectomy as well as developing a better understanding of the evolution of viable cerebral ischaemic tissue, the ischaemic penumbra. He has also had a major interest in the interface between the basic and clinical sciences in stroke medicine and establishing new standards for the conduct of preclinical research.
Professor Donnan has published over 400 papers in peer reviewed journals, over 60 book chapters, edited four books and has been Lecturer or Visiting Professor in numerous countries.
He is Editor-in-Chief of the International Journal of Stroke, Past President of the Stroke Society of Australasia, the Australian Association of Neurologists and the World Stroke Organization. He has received numerous awards including the American Stroke Association William Feinberg Award for excellence in clinical stroke research, the World Stroke Organization's leadership award and the Karolinska Stroke Award for excellence in stroke research. He was appointed as an Officer within the Order of Australia (AO) for his distinguished service to neurology and research contributions and is a founding Fellow of the Australian Academy of Health and Medical Sciences.

Stroke is the second most cause of death worldwide and the primary cause in many parts of Asia. It is the single major cause of disability and hence represents one of the great public health challenges globally. Fortunately, mortality has been reducing over the last 50 years although has levelled off somewhat over the last decade. The reasons for the improvement in mortality most likely relate to better management of risk factors including blood pressure control, cessation of smoking, new agents to reduce cholesterol levels and an array of blood thinning agents to prevent stroke recurrence. Better risk factor control has also led to reductions in stroke incidences in some Western countries although in many less developed regions of the world incidence continues to rise.

Over the last 30 years there have been quite remarkable advances in stroke prevention and treatment. From a baseline of no proven interventions to improve stroke outcome in the hours and days after stroke onset, we now have a number which are being translated into everyday clinical management around the world. These include the following:

Proven treatments for acute stroke 2015

INTERVENTION	INITIAL OR IMPORTANT STUDIES, YEAR	NNT_1
Stroke unit	Langhorne et al, 1993	26
Thrombolysis (tPA)	NINDS, 1995	18
Aspirin	IST, 1997	83
Hemicaniectomy	Vahedi et al, 2007	4
BP reduction	Anderson et al 2013	8
Clot retrieval	Berkefeld 2015, Campbell 2015	3

From GA Donnan et al., Lancet, 2008.

THE FLOREY

The most recent intervention, clot removal with a catheter retrieval device (thrombectomy), has proven to be the most effective. As seen from the table, the statistical expression of number of patients treated needed to benefit one person is about five. This represents one of the most powerful interventions in clinical medicine. A number of clinical trials including our own have demonstrated this effectiveness if the procedure is carried out within about six hours. One of the critical factors which we believe is largely responsible for the effectiveness of the procedure is selecting patients who still have a large component of viable brain tissue. This viable tissue is termed the "ischaemic penumbra".

The ischaemic penumbra was first demonstrated in the 1970s but it is only more recently that it has been able to be imaged in vivo in humans in a simple and practical fashion. The technique used is either computerised axial tomography (CAT scanning) or magnetic resonance imaging (MRI). With both of these techniques the underlying principle is the use of an injected perfusion agent which may demonstrate the presence of viable brain tissue and possible blood vessel occlusion. We have demonstrated that viable brain tissue may persist for as long as 48 hours after stroke onset although this prolonged period of tissue survival is in a diminishing number of patients.

By selecting patients using these imaging techniques we have been able to show that thrombectomy is superior to standard therapy with clot dissolving agents such

as tPA. The success of this management approach is in the process of revolutionising stroke management worldwide so that centres of excellence where these procedures can be efficiently and safely carried out are being established so that the maximum number of people may benefit.

We are also in the process of determining whether the time window for administration of standard tPA therapy can be extended beyond the currently restricted 4.5 hours. This also involves selecting patients using the imaging techniques described earlier. In particular, patients who unfortunately develop their stroke while asleep are included where the time of onset may often be uncertain. The outer limit of our studies will take the therapeutic window to as long as nine hours.

New therapeutic agents, new thrombectomy devices and other advances will likely improve the outlook of patients experiencing stroke in subsequent years.

Smart Energy Systems

by Henrik Lund

Short Biography
*Dr.Techn, Ph.D., M.Sc.Eng and Prof. in Energy Planning at Aalborg University, Denmark Holds a **Ph.D.** in Implementaion of Sustainable Energy Systems (1990), and a **Dr.Techn**. in Choice Awareness and Renewable Energy Systems (2009).*
*Listed among ISI Highly Cited researchers ranking among the **top 1% researchers in the world** within engineering in **both 2014 and 2015**.*
Author of more than 300 publications listed in GoogleScholar with 8000+ citations Link to GoogleScholar.
Author of the Book: Renewable Energy Systems - A Smart Energy Systems Approach to the Choice and Modeling of 100% Renewable Solutions, Academic Press, 2nd 2014.
Member of The Danish Academy of Technical Sciences (ATV) http://www.atv.dk/en/
Head of 4DH (Strategic Research Centre for 4th Generation District Heating Technologies and Systems. www.4dh.dk
*Architect and maker of the **Advanced Energy Systems Analysis Tool EnergyPLAN** - Today, the model has more than 3000 registered users in more than 100 countries*
***Editor-in-Chief** of **Energy** with annual 5000+ submissions.*

In recent years, a number of new terms and definitions of sub-energy systems and infrastructures have been promoted to define and describe new paradigms in the design of future energy systems such as *smart grid*, *4th generation district heating*, *Vehicle-2-Grid* and *power to gas*. All these infrastructures are essential new contributions and represent an important shift in paradigm in the design of future renewable energy strategies. However, they are also all sub-systems and sub-infrastructures which cannot be fully understood or analysed if not properly placed in the context of the overall energy system. Moreover, they are not always well defined and/or are defined differently by different institutions.

The idea of the concept *smart energy systems* is to take a holistic view. As opposed to, for instance, the *smart grid* concept, which takes a sole focus on the electricity sector, *smart energy systems* include the entire energy system in its approach to identifying suitable energy infrastructure designs and operation strategies. One main point is that in order to do a proper analysis of any smart grid infrastructure, one has to define the overall energy system in which the infrastructure should operate. Another main point is that different sub-sectors influence one another and one has to take such an influence into consideration if the best solutions are to be identified.

Today, the design of the energy system is based on fossil fuels. The future energy system will rely on renewable energy resources such as wind and solar power. These resources do not contain large amounts of stored energy, but instead the energy from the wind, sun, waves and tides must be captured and used immediately. This is one of the key technological challenge facing energy systems in the future.

The question is: How can the future energy system, which will be based on renewable energy, operate without the flexibility currently being provided by large amounts of stored energy in fossil fuels, while simultaneously providing affordable energy and utilising a sustainable level of the resources available? The solution will be to find new forms of flexibility within the energy system, which are affordable and utilise renewable energy resources in an efficient manner. This is called a smart energy system.
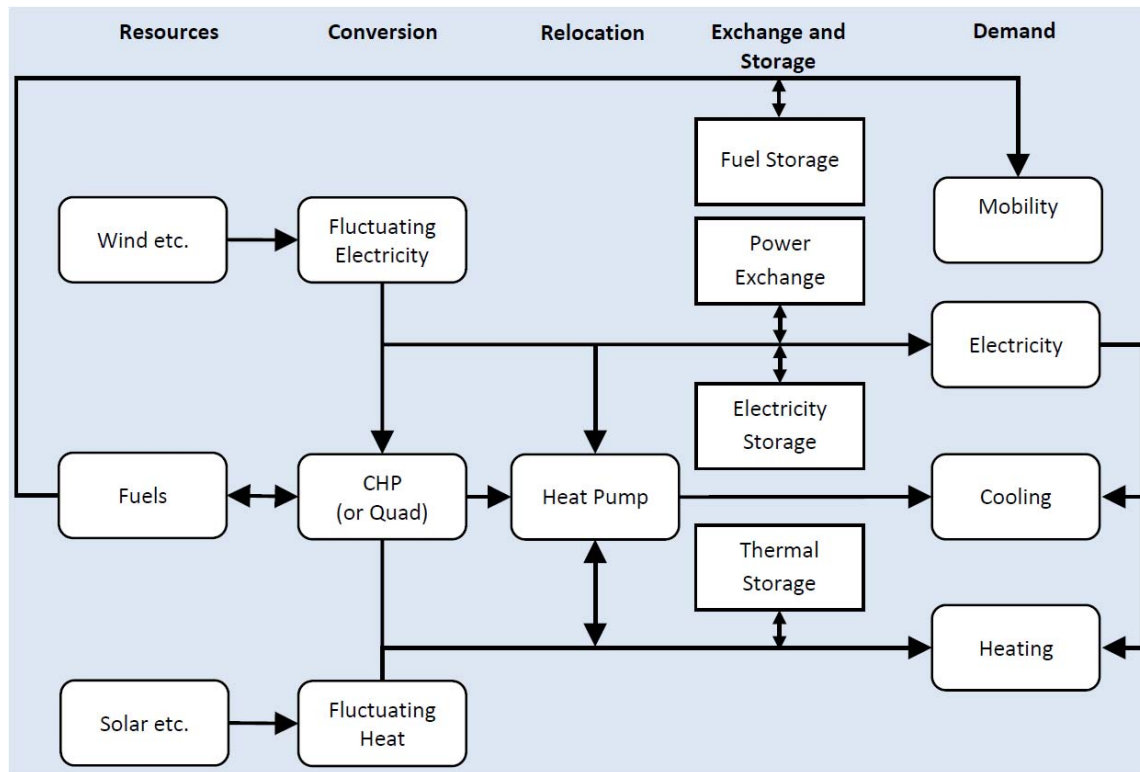
Fig. 1: *Illustration of a Smart Energy System based on the integration of the power, heating, cooling, gas and transportation sectors and infrastructures.*

A smart energy system consists of new technologies and infrastructures which create new forms of flexibility, primarily in the 'conversion' stage of the energy system. This is achieved by transforming from a simple linear approach in today's energy systems (i.e. fuel to conversion to end-use), to a more interconnected approach. In simple terms, this means combining the electricity, thermal, and transport sectors so that the flexibility across these different areas can compensate for the lack of flexibility from renewable resources such as wind and solar. The smart energy system is illustrated in Fig. 1 and uses technologies such as:

- **Smart Electricity Grids** to connect flexible electricity demands such as heat pumps and electric vehicles to the intermittent renewable resources such as wind and solar power.

- **Smart Thermal Grids** (District Heating and Cooling) to connect the electricity and heating sectors. This enables thermal storage to be utilised for creating additional flexibility and heat losses in the energy system to be recycled.
- **Smart Gas Grids** to connect the electricity, heating, and transport sectors. This enables gas storage to be utilised for creating additional flexibility. If the gas is refined to a liquid fuel, then liquid fuel storages can also be utilised.

Additional to the storage issue future energy systems also has to face the challenge of meeting transport demands without exceeding the sustainable biomass potential. The biomass resources available for energy purposes are limited due to demands for food and materials as well as biodiversity. Furthermore, they are limited to such a degree that it is hard to see how biomass alone could cover current energy demands in the transportation sector. Moreover, a transportation system based solely on renewable energy requires some sort of biomass-based gas and/or liquid fuel to supplement the direct use of electricity. The point is that, for the sake of transportation, some biomass needs to be turned into either gas or liquid fuel. Moreover, biomass in the form of gas helps in achieving better flexibility and efficiencies in future CHP and power plants.

However, not only biomass is relevant to gas production; but electricity in "power to gas" systems may also be highly relevant to boost and supplement the limited biomass resources. Such "power to gas" technologies may have substantial synergies if they are combined with the production of gas from biomass in technologies such as fermentation, gasification and hydrogenation.

To ease the pressure on the biomass resources and the investments in renewable energy, feasible solutions to future renewable energy systems involve substantial elements of energy conservation and energy efficiency measures. District heating has an important role to play in the task of making these scarce resources meet the demands. The inclusion of district heating in future renewable energy systems allows the use of CHP together with the utilization of heat from waste-to-energy and various industrial surplus heat sources as well as the inclusion of geothermal and large-scale solar thermal heat. In the future, the industrial processes may involve various procedures of converting solid biomass fractions into bio(syn)gas and/or different types of liquid biofuels for transportation fuel purposes among other things.

To be able to fulfil its role in future renewable energy systems, the present district heating system must undergo a radical change into low-temperature district heating networks interacting with low-energy buildings as well as smart electricity grids. These future district heating technologies have been defined as 4th Generation District Heating Technologies and Systems (4GDH). For obvious reasons, district heating has higher potential in countries with cold climates than countries with warm climates. However, in warm climates, district cooling may be an option and, in some countries, both types of networks and/or a combination would be desirable.

In principle, district cooling can be applied in two different ways. One solution is to use a district heating network to distribute heat which then by individual absorption units is turned into cooling in the individual building. This option is well suited for locations at which both heating and cooling of buildings is required during different seasons of the year. Moreover, the network can be used to supply both cooling and hot water to the building at the same time. The other solution is to produce central cooling and distribute the cold water. This option has the advantage of being able to include "natural" cooling, such as cold water from rivers or harbours.

As illustrated above, all smart grids are important contributors to future renewable energy systems. However, each individual smart grid should not be seen as separate from the others or separate from the other parts of the overall energy system. Firstly, it does not make much sense to convert, e.g., the electricity supply to renewable energy if this is not coordinated with a similar conversion of the other parts of the energy system. Secondly, better solutions arise for the implementation of the smart energy system and the individual sectors if their implementation is coordinated.

In other words, there are several synergies connected to taking a coherent approach to the complete *smart energy system* compared to looking at only one sector. This does not only apply to finding the best solution for the total system, but also to finding the best solutions for each individual sub-sector. Such synergies include the following:

- Electricity for heating purposes makes it possible to use heat storage instead of electricity storage, which is both cheaper and more efficient. Moreover, it provides a more flexible CHP production.
- Electricity for heating may be used for balancing in regulating power markets, etc.
- Biomass conversion to gas and liquid fuel needs steam, which may be produced on CHP plants, and produces low-temperature heat, which may be utilized by district heating and cooling grids.
- Biogas production needs low-temperature heat which may be supplied more efficiently by district heating compared to being produced at the plant.
- Electricity for gas such as hydrogenation makes it possible to use gas storage instead of electricity storage which is cheaper and more efficient.
- Energy savings in the space heating of buildings make it possible to use low-temperature district heating which, in addition, makes it possible to utilize better low-temperature sources from industrial surplus heat and CHP.
- Electricity for vehicles can be used to replace fuel and provide for electricity balancing.

Cardiovascular Disease Risk Prediction: Aims, Development, Use and Future: Insights from Framingham

by Ralph B. D'Agostino

<u>Short Biography</u>
Professor, Mathematics/Statistics, Epidemiology and Biostatistics, Boston University
Among 400 Most Influential Biomedical Scientists in Biomedical Literature, listed by European Journal of Clinical Investigation, 2013
In Top 1 % of the Most Cited Authors in Clinical Medicine, by Thompson Reuters, 2014
In World's Most Influential Minds in Clinical Medicine, by Reuters, 2015
Fellow American Heart Association
Fellow American Statistical Association
Senior Investigator, Co-Principal Investigator 30 years, Framingham Study
Principal Investigator in Development of Major Framingham Risk Functions
Who's Who in the World, Who's Who in America
Over 700 publications in high quality journals
Coauthor/editor of 10 books
Special Government Employee, Food and Drug Association (FDA). Twice recipient of FDA's Commissioner's Special Citation (1981 and 1995), Voting participant in numerous Advisory Committee meetings
Editor, Statistics in Medicine
Editorial Board (Statistical Consultant), New England Journal of Medicine
Editor, Wiley Encyclopedia of Clinical Trials

Background

Cardiovascular Disease (CVD) has been and remains a major cause of death and disability in the world. In the 1930s to 1950s the major competitors, which were infectious diseases including diarrheal disease, tuberculosis and pneumonia, came under control due greatly to improvements in sanitation and the introduction of penicillin. The problem of infectious diseases was replaced by the serious increasing epidemic of CVD. In the 1950s one out of every three men in the United States developed CVD before reaching the age of 60 years. While CVD was less prevalent in women, it still had debilitating and fatal consequences. It became the leading cause of death and the main reason why life expectancy beyond 45 years did not increase.

The problem of CVD had to be addressed. Two approaches arose. First, there was the set of activities of developing methods to treat and reverse the process of CVD. A second approach under consideration which ultimately led to the Framingham Study was the preventive approach which hypothesized that while complete avoidance may not be possible, the onset possibly could be delayed by appropriate preventive actions. If onset could be delayed, possibly life expectancy

could be significantly increased. Further, it was recognized that CVD is a multifactorial disease and develops over time, so a longitudinal study is needed. It is necessary to identify people without CVD, note their lifestyle and other factors such as age, sex and blood pressure, and then follow them over time, and relate the collected factors to the development of CVD. There was need for a study that could follow the natural history of development of CVD and identify those factors that related to its development. A longitudinal cohort was deemed necessary to achieve this.

The Framingham Heart Study (or because of its increasing breath over time, the Framingham Study) was initiated to addressed this preventive approach. A systematic sample of 2 out of 3 every families in the town of Framingham, Massachusetts was selected. People aged 30 to 60 in the families were invited to join. Ultimately, 5209 individuals (2,336 men and 2,873 women) joined the study. The major objective was to obtain epidemiologic data. The participants came in every two years for a physical examination. Factors (later called risk factors) such as blood pressure, total cholesterol, smoking and drinking behavior, physical activity, smoking behavior and diabetes were collected. Other variables were added over time as were a second and third generation.

Development of Framingham Risk Functions

Within ten years of it initiation the Framingham study became a leader in identifying CVD risk factors such as sex and age. More exciting it identified modifiable risk factors such systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking behavior, and diabetes that did relate to the development of CVD and which, if treated by drugs or addressed by life style modification, could possibly be changed and in turn reduce the chance of a CVD event.

Originally the risk factors were established individually as related to the development of CVD. Then there were examined in multifactorial manner. This, in turn led to the development of multivariate functions that included age, sex, systolic blood pressure, total cholesterol, HDL-cholesterol, smoking behavior and diabetes that produced for a given individual and his/her set of risk factor an estimate of the chance or likelihood the individual would develop a CVD within a given time period (for example, 10 year). These function were called Framingham Risk Functions (also called Framingham Risk Scores). Functions were developed to estimate coronary disease (include angina, myocardial infarction, and coronary death), stroke (fatal and non-fatal stroke), and total CVD (CVD death, coronary disease and stroke).

Internal Evaluation of the Framingham Risk Function

Once the function is developed there is need to evaluate how well it performs.

There are a number of measures for this, but the two principal ones are discrimination and calibration. Discrimination relates to how well the function discriminates between those who develop CVD versus those who do not. The major measure is the C statistic which is the probability that the function will assign a higher probability to a randomly selected person who does develop CVD over the follow up then a randomly selected person who will not.

A second measure is a calibration measure and it evaluates the probabilities computed by the function do correspond to the rate of occurrence. For example, if 20% of set of individuals with a particular set of risk factors develop CVD does the Framingham Function assign 20% risk to the individuals in the set?
The Framingham Risk Functions have good to excellent internal discrimination and calibration.

External Validation

Once a Framingham Risk Score is shown to have good properties it is essential that they be shown to be valid for use on other populations. This is called external validation. In the late 1990s there was a major work shop at the NIH Heart, Lung and Blood Institute where is was shown that a Framingham Risk Score for hard coronary disease (coronary death and myocardial infarction) had excellent validation (possibly with a simple recalibration for Japanese Americans)

Use of Framingham Risk Functions for Cholesterol Guidelines (ATP-III)
Because the Framingham Risk Functions were shown to have good validation they were used by the third Adult Treatment Panel ATP-III) as the means to estimate 10 years coronary risk in individuals without coronary disease and this risk was used as an important component in the determination of the use of statins in the individual. That is, the Framingham Risk Function was used explicitly in the treatment guidelines.

Other Framingham Risk Functions

In addition to the Framingham Risk Functions mentioned above there are numerous others that are in constant use. Some are for stroke, secondary coronary events, intermittent claudication, heart failure, stroke or death after atrial fibrillation and global CVD function (including CVD death, general coronary disease, stroke (including TIA), intermittent claudication and congestive heart failure). In addition there are Framingham Risk Functions for lifetime risk which estimate the chance of a CVD event over a lifetime or long term follow up (say, 30 or more years).

Addition of new variables to a Framingham Risk Score

The above mentions in the presentation the set of standard risk factors such as age, sex, systolic blood pressure, etc. Today there a multitude of new biomarkers

(such as calcium scores, inflammatory markers, genetic markers, etc.). There is the concern as to whether they add to the prediction and discrimination ability of the function. An obvious measure is whether the C statistics improves. In addition to this measures of improvement in classification measures (called for example, net reclassification) have been developed. These are useful when there are cut points in the risks for classifying people (such as mild, moderate and severe). These methods obviously apply to any risk score.

New serious challenge. Can we estimate validate functions on contemporary data and can we estimate now natural history? Where will we go?

As in any scientific endeavor there are challenges in the future. A major challenge now facing the validation of existing functions on new cohort data is whether the new cohort has already reacted to a previous function or knowledge that came from previous research. As an example, in 2013 new CVD risk functions were developed based on the pooling of a number of cohort studies (the Framingham Study, Atherosclerosis Risk in the Community (AIRIC) Study, the Coronary Artery Risk Development in Young Adults (CARDIA) Study and the Cardiovascular Health Study (CHS)). The data used for the development of the functions were from dates when there was not intensive treatment for CVD risk factors (that is, before the mid-1990s). So natural history was observed in the development of the new risk functions. However, the external evaluation employed some studies with data generated in time periods when there was intensive treatments (mid 1990s). The new functions appeared to overestimate risk in these new data sets when most likely the risk in the new validation data was reduced due to medication.

The above poses a problem for the development of new risk functions since there will be ethical problems in not treating a person with, what is now considered, high risk. This will impose restrictions and challenges. They will be met.

A Next Generation of Subsea Production System for Deepwater Oil and Gas Development

by Menglan Duan

Short Biography

Prof. Dr. of Solid Mechanics and Ocean Engineering, Director of Institute for Ocean Engineering of China University of Petroleum, Beijing, China.
Over 200 publications in high quality scientific journals.
Project Manager for over 150 Projects in Ocean Engineering, Mechanical Engineering and Petroleum Engineering.
Chairman of Subsea Technology Committee of the International Ships and Offshore Structures Congress (ISSC)
Chairman of China Branch of the Society for Underwater Technology (SUT)
Chairman of Industry-University Joint Committee of the Chinese Society of Theoretical and Applied Mechanics (CSTAM)
Visiting Professor at Federal University of Rio de Janeiro
Founding Editor-in-Chief of Frontiers in Fossil Fuel Engineering, Editor-in-Chief of Development and Application of Oceanic Engineering, and Editorial Board Members of 16 international journals
Member of the EU Academy of Sciences
Founding and Executive Chairman of the Annual SUT Technical Conference
Founding and Executive Chairman of the China-Brazil Deepwater Forum

The increase of oil and gas production has come from offshore fields in the globe in the past decade, and about 90% of the increase is from the deepwaters. Subsea production systems (SPS) including subsea pipelines and risers are the must equipment and facilities for the development of deepwater oil and gas fields. Their applications to deeper and remoter waters as well as arctic areas are challenging the scientists and engineers, especially in increasing safety and reliability. And, to reduce the CAPEX and OPEX of the deepwater fields by developing new technologies of subsea production systems is always the main concern of the industry. The technologies cover the whole period of life of the systems from initiation of concepts to design, manufacture, testing, transportation, installation, monitoring and inspection, maintenance, repair and decommissioning. Any technologies shall be all for the maximum oil and gas production, the minimum environmental impact, the minimum risk to assets and personnel, the maximum profit and the highest safety of the subsea systems, and their advances are progressing each year.

The subsea production systems cover all the equipment and installations below the sea surface of the ocean, including 1) subsea processing facilities like subsea X-trees, manifolds, valves, separators, boosting pumps, water or gas injectors, 2) power supplying units like electric distribution units, umbilicals, 3) transportation systems like subsea flowlines, jumpers, connectors, pipelines and risers, 4) subsea control systems and 5) subsea operation equipment and tools like ROVs for installation, inspection and monitoring, maintenance and repair, and decommissioning. The research of fields for innovation of such subsea production systems requires a very wide range of multi-

principles of mechanical engineering, petroleum engineering, risk and safety engineering, electrical and control engineering, material sciences, theoretical and applied mechanics, and ocean engineering. The Offshore Oil/Gas Research Center of the China University of Petroleum has devoted its group for ten years to innovative development of the SPS and the application to deepwaters of South China Sea, and obtained around 100 patents as well as published over 200 technical papers. To further reduce the hazards and risks by improving the reliability of the SPS, and also to look for the possibility of greatly reducing the CAPEX and OPEX of the deepwater oil/gas fields, a new concept for next generation of SPS has been defined by Dr. Menglan Duan and got identically supported by the oil industries and universities from China, Brazil and Portugal. The main points of innovation could be presented like:

1) Integrating the horizontally distributed subsea facilities of the conventional SPS of wet production into a vertical compact layout of all subsea facilities spaced by a chamber (called subsea space, shown in Fig.1) or one more if necessary for dry production. There will be no need of connections of the wet facilities saving the investment on jumpers, PLET/PLEM, manifolds and their connectors, and accordingly on their installation, maintenance and repair, inspection and monitoring, decommissioning (IMRIMD), etc. The dry production facilities are 10 or even 100 times cheaper than the wet ones, and much easier for IMRIMD by which the reliability of the SPS is greatly improved. The great amount of investment on individual installation and decommissioning of each subsea wet facility is avoided by only once for the integrated subsea space.

2) Connecting the subsea spaces of the wells to a floated manifold by risers acting also as mooring lines, as shown in Fig.2. The manifold acts as only a connector of all risers for the spaces, and from which the export pipelines go to the land terminals or a FPSOs or other floating units. It is floated to a position of about 100m high over the sea bed rather than fixed to the bed by suction piles which are very expensive and hard to install. The floated manifold can also be a share of subsea spaces respectively for separating, boosting or injecting systems, and make it true that all the subsea processing equipment or facilities could be in dry production. Such a three-dimension distribution of SPS greatly simplifies the development scenario of a deepwater oil field, reducing the CAPEX of the field up to 50%.

3) Making it possible that hydrate or wax will never be blocking the flow of oil and gas in deepwater fields. A lot of money is spent on the flow assurance of subsea pipelines and production systems. Hot water cycling, electric heating and chemical injecting are three ways to prevent hydrate or wax from blocking the flow of oil and gas. The new concept for the SPS is to make a mixed flow of hydrate or wax together with oil, gas, sand and water, limiting the size of developed hydrate or wax. The solution is to find out the conditions of size limit of hydrate or wax for flow assurance and how to maintain such conditions. We'll develop drying nano membrane to avoid hydrate, super-oleophobic nano membrane to avoid wax, and phase-change membrane to absorb heat from oil and release heat to control the temperature to a content of flow assurance. The thermo-physical engineering model of the inner coated nano phase-change materials and the thermodynamic prediction model for the nano phase change material inner laminated pipelines conveying multi-phase flow are the main theoretical investigations on the conditions of limit size of wax or hydrate for the mixed multiphase flow. The super-oleophobicity mechanism of nano membrane and its surface hydrophilicity are also basic problems

for such a new concept of Never-Blocked Oil-Gas-Water-Sand-Hydrate-Wax Mixed Flow.

4) Application of smart technologies to the development of smart subsea production system and its IMRIMD. Smart manufacture will be widely applied to the industry. For the new generation SPS, smart materials will be developed together with corresponding smart sensors to monitor the change of environment, parameters of flow in the SPS and its structure state for the whole servicing life. Smart prediction of any structure damages or hazardous events will be made by smart monitoring, and self-healing of the structure will be possible to improve the safety and reliability of the SPS. Smart management for the whole life of SPS by using of Big Data and Cloud Computing, will be performed for higher reliability.

The following fundamental research and engineering services detail the key methods and technologies for design, construction, testing, installation, monitoring, maintenance, repair and decommissioning for subsea pipelines/risers and subsea production systems.

- Dynamic analysis of ocean structures: theoretical investigation and numerical simulation by ABAQUS, ANSYS, SESAM, FLUENT, NASTRAN, SACS, AUTOPIPE, ORCAFLEX, etc. with special concerns on ice-induced vibration of installations, VIV of slender structures like deepwater risers and spanning pipelines in scouring, severe slugging induced dynamics of Risers, etc.
- Non-linear analysis of soil-structure interactions for structure dynamics: touch-down point details of the SCR fatigue, soil constraint on the global buckling of subsea pipelines, anchoring penetration with subsea pipelines by third-party activities, soil induced local buckling of suction piles, etc.
- Limit state analysis of ocean structures in extreme conditions: yielding, buckling, fatigue and fracture of beam, plate and shell structures, with special concerns on thermal global buckling/post-kuckling of subsea pipelines and combination with the local buckling/propogation with imperfection participation in HTHP conditions, collapse of deepwater shell/tube equipment by high pressure and thermal loads, ECA on damaged structures, configuration of deepwater riser systems, surface cracking of flexible composite pipelines, structure details of deepwater pipelines based on flow assurance and integrity management, etc.
- Installation analysis of subsea hardware and subsea pipelines/risers by applying hydrodynamics of multi-body system: parameter design for controlling the installation based on theoretical and numerical calculations, safety and integrity of the subsea pipelines/risers during installation in towing, S-lay, J-lay and R-lay, and integrity of suction structures being installed to seabed, etc.
- Inventive conceptual design of subsea production hardware, deepwater riser system, pipeline laying system.
- Safety and reliability of subsea production system including installation and decommissioning.
- Mathematical models for optimization of overall development program of offshore oil/gas fields and layout scenario of subsea production system.
- Integrity management of the ocean equipment and structures on the basis of risk based inspection and monitoring by using Big Data and Cloud Calculations.

- VR technology with application to underwater operations, emergency management and Big Data based decision-making information system, etc.
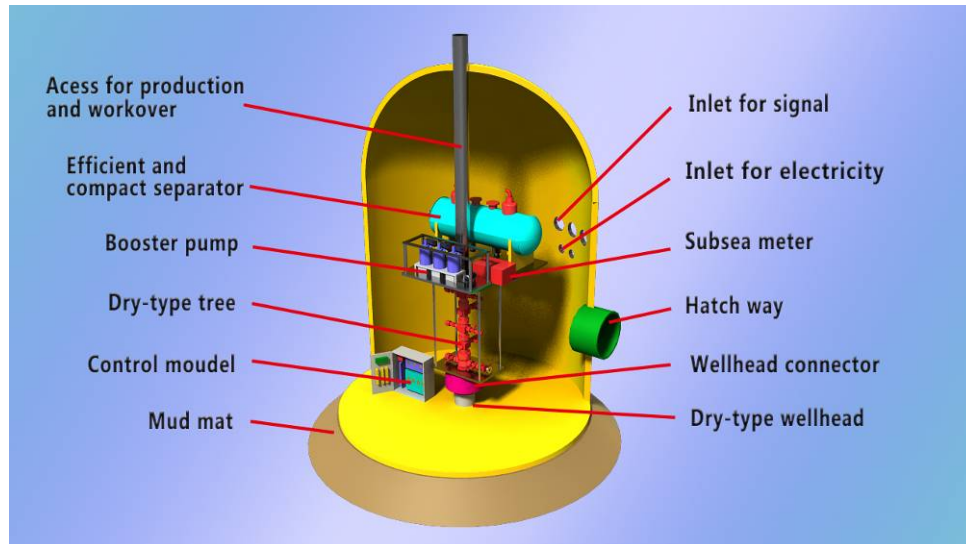
Fig.1 Subsea Space for Vertical Layout of Production Facilities in Deepwater
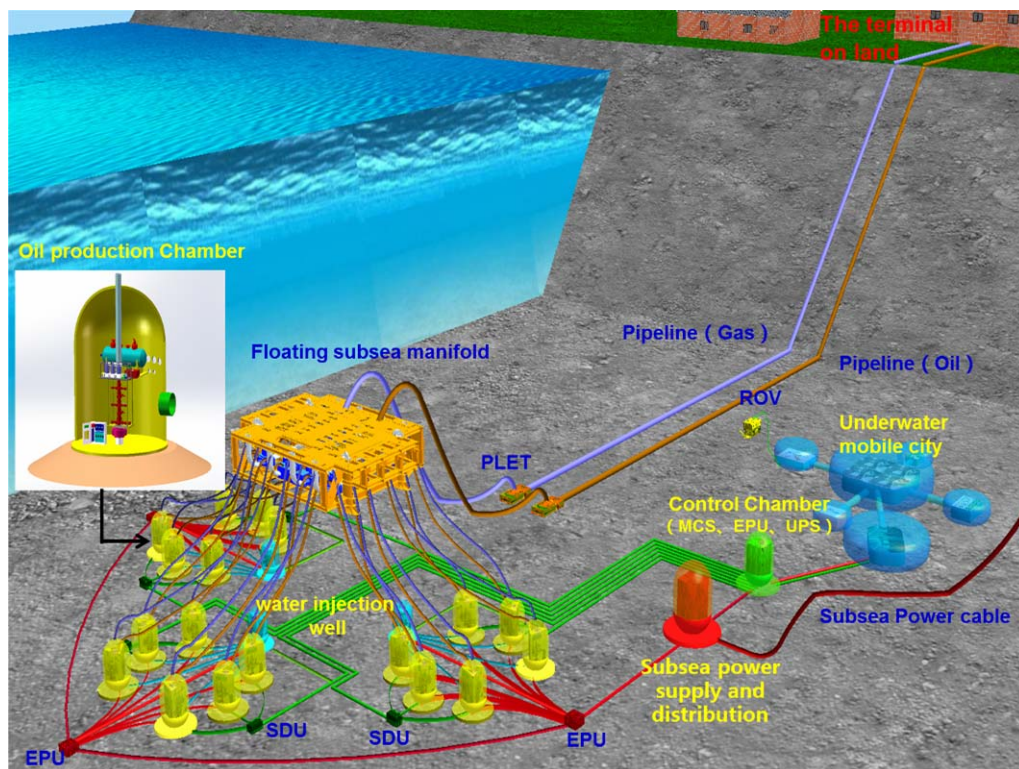
Fig.2 Development Scenario of a Deepwater Oil Field in Three-dimension Distribution of the New Generation SPS

# Innovation Starts with Materials Science

by Jeff Th. M. DeHosson

<u>Short Biography</u>

Professor Jeff Th.M. De Hosson holds a PhD in Physics from the University of Groningen, the Netherlands (with honours and highest distinction) and after his postdoctoral years in USA (Northwestern U. and UC-Berkeley) he was appointed professor in 1977 by the Crown (R.D. 101, H.M. Queen Juliana). His passion is to carry out innovative research in the field of materials, nanoscience and nanotechnology with particular emphasis on: advances in microscopy, in-situ transmission and in-situ scanning electron microscopy; nanostructured materials, e.g. nano-clusters, nano-foams, nano-objects, composite coatings and high power lasers for applications in transportation, communications, and data processing. He is elected member of the Royal Netherlands Academy of Sciences (KNAW), Royal Holland Society of Science and Humanities, editor of 4 international journals, member of editorial boards of 14 journals and Elected Fellow of various foreign scientific societies, including TMS-USA and ASM-USA. He acts as Honorary Professor of Tsinghua Un -Beijing, UST-Beijing and Port Elisabeth –SA. He holds several patents and received a number of renowned and illustrious international awards, including the prestigious European Materials Gold Medal in 2005 and the prestigious Nanostructured Materials Prize, NanoSmat prize 2009.He published more than 1000 publications in international scientific journals, including 190 papers in conference proceedings, 31 elaborate review papers /chapters in books and 19 books editor. See for details: *http://materials-science.phys.rug.nl/ and*

http://www.rug.nl/staff/j.t.m.de.hosson/cv

    We all live, play, work and study in a world of materials. Modern technology depends critically on the availability of advanced materials and tailoring these materials with a desirable set of structural and functional properties has always been a dream of materials scientists. The research efforts of the materials science field in general are devoted to make this dream to become true.

    With the emphasis on miniaturization stemming from the electronics industry, the same push has been seen in submicron- and nanosized mechanical systems. In medicine and biology, for example, there is a need for high-precision actuators and manipulators for work on fluid filtration and living cell manipulation. The increasingly-popular lab-on-a-chip technology takes advantage of highly-miniaturized mechanical systems – Micro-Electronic Mechanical Systems or MEMS – to fit efficient analysis systems in a very small space. For progress in these fields there is a necessity for the continuous development of both materials

with micro- and nanoscale functions and of tools that can facilitate the production and characterization of these materials.
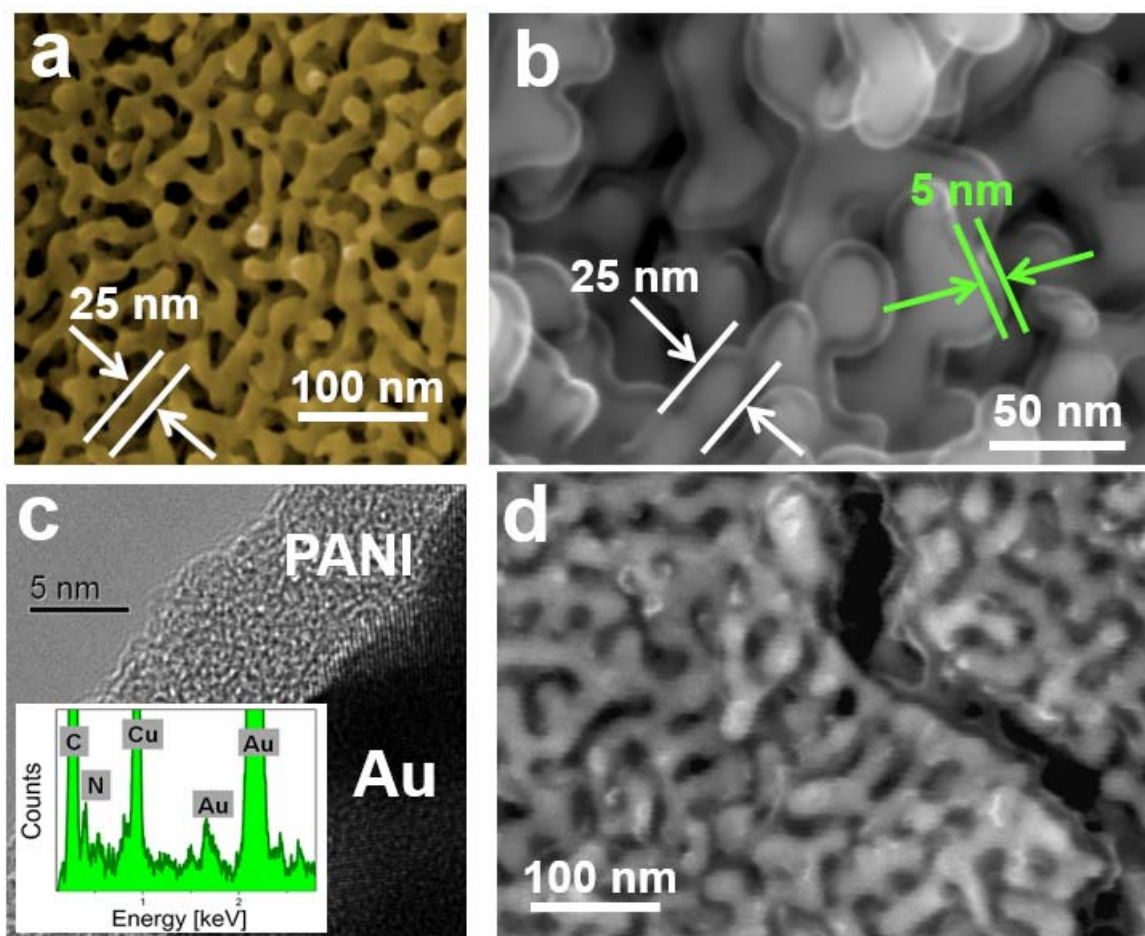
Figure 1: *Microstructural characterization of NPG/PANI. (a) Scanning electron micrograph showing the bicontinuous morphology of NPG. (**b, c**) Scanning and transmission electron micrographs showing a ~5 nm-thick PANI skin covering the ligaments of NPG. The inset of c displays the EDX spectrum of PANI. C and N come from aniline (C6H7N), Cu and Au come respectively from the Cu grid used as sample holder and the NPG. (**d**) Fracture cross-section of NPG/PANI; It can be seen that the polymer envelope covering the ligaments is present into the bulk of the composite material.*

Mechanical displacement that comes as a result of an electric signal passing through a material is called actuation. In materials that produce an actuation response, the reverse is often possible as well – an electric current can be induced to flow if the material is deformed. The most common type of material that shows such properties is described as piezoelectric, and of this class of materials quartz is the most well-known. Indeed, it is the piezoelectric property of quartz that allows it to be used as an oscillating pace mechanism in the common wristwatch. The typical piezoactuator delivers a ~0.2% strain at a high potential of 150V. Considering that it is desirable to see the use of actuation in low-voltage devices, such as MEMS, much

lower operational parameters are required for the modern actuating material. Polymer-based actuation materials have been developed that offer extraordinary capacity for induced deformation, but have the drawback of being weak and compliant.

In recent years together with my phd student Eric Detsi (see J. Mater Sci (2016) 51:615–634) now at UPENN Philadelphia, we have been exploring metallic nanofoams and have demonstrated the potential of nanostructured metals to act as actuators, creating so-called "metallic muscles," with the ability to demonstrate the properties required of the modern actuator: low throughput voltage requirements, high extension yield, strength and stiffness.

While the production of nanoporous metallic structures is well-documented, up until recently very little was known about their mechanical properties - at submicron scales. Nanoporosity has the possibility to produce a large effect on mechanical properties, where in macroporous foams cell size specifically does not have an influence on material strength. Nanofoams share many properties with their macrofoam counterparts, such as the high surface-area-to-volume ratio, but also including the capacity for cheap production and easy machinability. In addition, however, nanoporous foams have seen usage in many applications beyond those of macrofoams, including nanofiltration systems, drug delivery platforms, catalysis, sensing and actuation . A major advantage that nanoporous metals have is the ability to hold a lattice of nanoscale features whilst being able to be easily handled and transported, something metallic nanoparticles, for example, cannot provide.

Metallic muscles: why does it work ? The actuation mechanism in common artificial muscles makes use of microscopic phenomena in the bulk of the material such as dipoles polarization. In piezoceramics for instance, asymmetry in the crystal lattice structure gives rise to domains with electric dipole moments. These dipole moments are randomly oriented and they can be aligned with an external electric field. Dipole alignment through the bulk of the material results in macroscopic dimensional changes.

In metallic muscles, not only the bulk volume but also the interface surface area plays a central role during actuation. The fact that surface atoms in crystalline materials have a lower coordination than those in the bulk results in an excess bonds' charge at a newly created surface. This excess charge redistributes at the surface to strengthen the interatomic bonds and shorten the distance between surface atoms. This results in a positive surface stress (tensile stress) in the material at mechanical equilibrium of the material system (i.e. a tensile displacement to bring the atoms back to an equilibrium distances as in the bulk).

Although metal nanofoams share many properties with their macrofoam counterparts, they have many applications beyond those of macrofoams. One promising application corresponds to metallic muscles based on nanoporous metals

with high surface-area-to-volume ratios. For that specific application, in 2015 we have demonstrated a new electrolyte-free approach to generate work from metallic muscles by exploiting a nanoporous metal/polymer interface rather than the common nanoporous metal/liquid electrolyte interface (figure 1). In this actuation concept a doped polymer coating is grown onto the ligaments of a nanoporous metal and dopant counter ions present in the polymer coating matrix are exploited to modulate the electronic charge distribution at the nanoporous metal surface, resulting in surface stress changes and dimensional changes in the nanoporous metal. With this actuation approach, many of the drawbacks encountered in metallic muscles operating in aqueous electrolytes have been circumvented. In particular, the electrolyte-free actuator consists of a single-component hybrid material, in contrast to the three-component configuration required in nanoporous metal/electrolyte composite actuators; the nanoporous metal/polymer hybrid actuator is an all-solid-state device, like piezoceramic actuators, and its actuation rate is about three orders of magnitude higher than that of metallic muscles operating in aqueous electrolytes.

An interesting observation is that a thin polymer coating grown onto the metallic ligaments of nanoporous gold can be exploited to add a new functionality to nanoporous metals operating as electrochemical actuators. For example, a metallic muscle becomes a smart material because in addition to its reversible dimensional changes, it also undergoes a reversible change in color. This combination of electromechanical and optical changes could open the door to new applications in artificial muscles. A straightforward application includes a metallic muscle that can give feedback on the progress on its work simply by changing its color.

The exciting outlook for nanoporous metallic systems is not limited to the fields of sensors and actuators, however, where electrical or electrochemical energy is converted into mechanical work. The use of nanoporous metals and nanostructured materials in general in other energy-related applications has recently been demonstrated. For example, there is currently much interest in the sustainable production of hydrogen fuel by the decomposition of water-based solutions into hydrogen and oxygen as the only products using alkaline electrolyzers.

Overall we may conclude that metallic nanofoams sit at the centrepoint of a myriad of engineering disciplines, enabling a variety of applications because of their chemical and structural diversity. In particular, the exploitation of nanoporous metals in energy-related applications such as hydrogen fuel production and batteries opens novel avenues for fundamental and applied materials research .

Immunity and Cardiac Damage

by Stefan Frantz

<u>Short Biography</u>
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Professional Education

1989-91	*University of Regensburg, Germany*
1991-94	*University of Würzburg, Germany*
1994	*University of Western Ontario, London, Canada*
1996	*Thesis "Preservation of left ventricular mechanical function and energy metabolism in rats after myocardial infarction by the angiotensin-converting-enzyme inhibitor Quinapril"*

Postgraduate Training

1996-97	*Internship at the Medizinische Universitätsklinik Würzburg*
1998-2000	*Cardiovascular Division, Brigham and Women's Hospital/Harvard Medical School, molecular biology postdoctoral fellowship in laboratory of Prof. Ralph Kelly, MD*
2000-2007	*Resident in Internal Medicine, Medizinische Klinik Würzburg, Germany*
2005	*Board certification for Internal Medicine*
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2007	*Board certification for Intensive Care Medicine*
2007	*Consultant Internal Medicine/ Cardiology, University Hospital Würzburg*
2008	*Secretary of the Cardiovascular Center Würzburg*
2009	*Certification for Diabetology (German Diabetes Association)*
2009	*Director Emergency Medicine Department*
2010	*Implementation and director of the Chest Pain Unit*
2010	*Scientific Director CHFC (Comprehensive Heart Failure Center) Würzburg*
2010	*Deputy director Medizinische Klinik und Poliklinik I*
2011	*Associate professor "Translational Research"*
2014	*Chair/ director Internal Medicine/ Cardiology, Martin-Luther-Universität Halle/ Wittenberg*

Research Topics

Heart failure, healing, remodeling and activation of the immune system after myocardial infarction, ischemia/ reperfusion injury, heart brain interaction

In the early 1990ies it was first discovered that patients with heart failure have elevated levels of cytokines, a sign of an inflammatory reaction. This was rather unexpected since heart failure is a disease that is with the rare exception of an infective myocarditis not caused by infection. What could trigger the activation?

We recognized that all of the cytokines elevated in heart failure belong to the so called innate immune system. We therefore had the hypothesis that the innate immune system is activated upon cardiac injury. Indeed we were the first to show that receptors of the innate immune system like toll like receptors (TLR) are expressed in the heart [1] and are functional active [2]. It turned out that those innate immune receptors could not only be activated by microbes, but also by mediators released upon cell death or as a reaction to the injury like heat shock proteins or collagen. Downstream parts of the TLR signaling cascade like NF-κB (nuclear factor kappa B) were as well activated after myocardial infarction [3]. Inhibition of NF-κB was protective after myocardial infarction [4].

After a myocardial infarction different phases can be differentiated [5]: There is a first pro-inflammatory phase, where neutrophils infiltrate the heart and cardiac myocytes undergo necrosis and apoptosis. This is followed by the so called healing phase, where macrophages enter the heart and a solid scar is formed. These two phase heavily depend on the innate immune response. In the last phase, the so called remodeling phase, the remaining myocardium is reshaped and the innate immune response has to decrease for an adequate reaction. However, the mechanisms that switch off the innate immune response were largely unknown. We had the hypothesis that the adaptive immune system is activated by an immune response and controls its inactivation.

To investigate the role of the adaptive immune system we focused on the role of T-cells after myocardial infarction [6,7]. We were the first to describe that T-cells are activated after myocardial infarction, especially in lymph nodes draining the heart [8]. Activation of those T-cells is antigen dependent. In animals that lack T helper cells, severe healing defects developed after myocardial infarction. In a next step we found that especially regulatory T-cells are essential for healing after myocardial infarction [9]. Regulatory T-cells were able to increase the generation of so called pro-healing M2 macrophages, leading to improved healing after myocardial infarction.

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Contributions in the Prevention of Mammary Cancers

by Kirby I. Bland

Short Biography
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Former Fay Fletcher Kerner Endowed Professorship,
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Surgery, The Society of Surgical Oncology, Society of Surgical Chairs, Southern Surgical
Association, Southeastern Surgical Congress, First Vice President of the American College
of Surgeons
Senior Director, American Board of Surgery and the American Board of colon and Rectal
Surgery
Over 600 scientific journal publications, 45 textbooks,
Editorial Board member for15 peer-reviewed surgical journals
UAB Distinguished Faculty Lecturer (2014)
UAB Constance S. and James A. Pittman Lecturer (2016)

Conformationally Defined Rexinoids and Their Efficacy in the Prevention of Mammary Cancers

AtigaddaVR, *et al*. *Journal Med Chem* 2015 58 (19), 7763-7774.

UAB30 is a rexinoid that is derived from the structure of 9-*cis*-retinoic acid, except it contains a tetralone ring connected to a 9Z-tetraenoic acid side chain. Rexinoid agonists target exclusively the retinoid X receptors (RXRs) over agonists for the retinoic acid receptors (RARs). Bexarotene (Targretin) is the only clinically utilized rexinoid approved by the FDA. Recently the X-ray structures of each of these rexinoids were determined bound to the ligand binding domain of the human retinoid X receptor (hRXR*a-LBD)*. The binding of the rexiod agonists cause conformational and dynamical changes to the ligand binding domain enabling the recruitment of an amphipathic coactivator peptide containing the LLxxLL motif. Rexionids reduce proliferation and enhance apoptosis in mammary tumors and efficiently prevent mammary cancers in rodent models.

The X-ray crystallography structure of 4 methyl UAB30 or 7-methyl UAB30 bound to the hRXR*a*-LBD revealed that the methyl groups on the teralone ring interacts strongly with helix 7 residues, Phe346 and Val349; whereas the methyl

groups of the tetralone rings of 6-methyl-UAB30, 5-methyl-UAB30 and 8-methyl-UAB30 did not interact with these residues. This study also explore the ring-expanded homologue of UAB30, which contains a benzosuberone ring bonded to a 9Z-tetraenoic acid side chain.

Inhibition of Growth of MNU-Initiated Mammary Tumors.

Selective Estrogen Receptor Moderators (SERMS) are administered to humans with ER-positive and PR positive mammary cancer in an adjuvant or neoadjuvant setting in the clinic. Since rexinoids reduce proliferation in existing MNU-initiated mammary cancers, we next investigated if rexinoid treatment would slow the growth of existing mammary tumors. To investigate the effectiveness of rexinoids for therapy of ER-positive mammary cancers, rats (N=9) with small MNU-initiated tumors of about 200 mm^2 were treated with 200mg/kg diet of UAB30 with R_1 isopropyl Class I UAB rexinoids. The size of mammary tumors in control animals rapidly grew. The rate of tumor growth was different for each animal, which is consistent with chemically induced tumors containing different genomic instabilities. To account for slightly different sizes of tumors at day 0, the data were normalized to the size of the tumor at day 0 (just prior to rexinoid administration). The change in size of a tumor with time is reported as a percent change relative to the size of the tumor at day 0. After 7 days of rexinoid treatment, the average tumor size of the *untreated group* nearly doubled. After 14 days, the tumors from the control group rats were on average 4-fold larger (Figure 1). At this time point one rat was removed from the study to prevent death from a large necrotic tumor. At later time points, especially rapid tumor growth resulted in removal of three additional rats from the study in the control group to avoid death.

The average size of the tumors was reduced at time points of 21 and 28 days because of the smaller average size of the remaining tumors in control rats (since these are chemically initiated spontaneous tumor with different genetic mutations, tumors grow at different rates.) In contrast to tumors from rats fed only control diets, the average tumor size of rats fed R_1 isopropyl Class I UAB rexinoids principally decreased following 28 days of treatment (Figure 1). In one rat, the tumor completely disappeared at day 24; in four other animals the tumor size significantly decreased after 28 days of treatment with R_1 isopropyl Class I UAB rexinoid (30-55% decrease in size). In only one treated rat, the tumor growth was similar to that in the control rats. These data demonstrate that treatment with R_1 isopropyl Class I UAB rexinoids is potentially able to initiate regression of tumor growth for many cancer genotypes. Preclinical studies suggest R_1 isopropyl Class I UAB rexinoids could be used as an adjuvant or neoadjuvant agent of estrogen-positive tumors in addition to its use to prevent new cancers. Observance of similar results were evidenced for bexarotene treated MNU-mammary cancers. UAB30 was also studied, since this is the most potent and least toxic rexinoid developed at UAB. The average size of tumors from rats treated with UAB30 increased slightly relative to day 0 (40% increase in the average size of tumors between day 0 and day

14); whereas, tumors from control rats were 400% larger during the same time period (Figure 1).
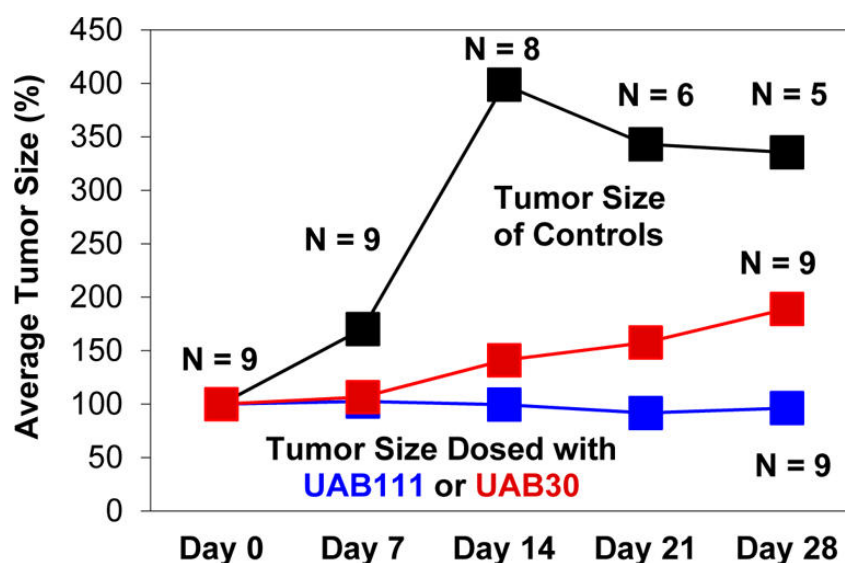
Figure 1. Treatment of small existing MNU-initiated rat mammary cancers with UAB30 (red) or class I rexinoid, R_1 isopropyl analog (blue), at 200 mg/kg diet versus controls (black). The size of the mammary cancers was normalized to 100% at day zero of treatment (N = 9). The change of the size of the cancer for controls or treated rats were measured once a week for 4 weeks and averaged at each time point. The average tumor size (y axis) was determined by the ratio of the average size at the indicated day to the average size at day zero. Nine animals (n = 9) survived in each treated group, and five animals (n = 5) survived in the control group after 28 days.

Conclusions

   Aromatase inhibitors block cell proliferation by downregulation of numerous genes (e.g., cyclins). We have demonstrated in prior data that rexinoids (bexarotene or UAB30) display significant capability to prevent MNU-initiated mammary cancer; they significantly decrease cell proliferation in MNU-initiated cancers as well as increase apoptosis.(Xia, *et al;* Boerma, *et al;* Grubbs*, et al;* Muccio*, et al;* Attigada *et al)*. RXR agonists are known to enhance signaling of retinoic acid or other RAR agonists through the permissive RAR:RXR heterodimer. Rexinoids have the advantage of stimulative additional signaling pathways that control cell proliferation besides those pathways mediated by the RAR:RXR herodimers. Studies by Bonofiglio *et al (Am J Pathol,* 2009;175:1270) demonstrate profound effects of low doses of RXR and PPAR*y* agonists in inducing apoptosis in human breast cancer cells but not in normal breast epithelial cells These observations suggest that rexinoids may in fact be preventing mammary cancer following synergy with endogenous PPAR*y* agonists.

   Papi *et al (J Cell Physiol,* 2014;229:1595) suggest PPAR*y* agonists and rexinoids

work synergistically to block inflammatory signaling cancer stem cells that surround and support growth of breast tumors. We remain uncertain if the profound effects that rexinoids have in the prevention of cancer are due to reduction of growth with induction of cell death in microscopic disease (transformed tissue) or if these effects result from prevention of transformed epithelial cells progressing from normal phenotypes to frank neoplasms. As cancer prevention in the high-risk population requires *chronic dosing* for extended periods (or even lifetimes), toxicity remains a real concern in drug development. Among class II rexinoids, UAB30 is the clear compromise between reasonable effectiveness and low toxicity.

Notable outcome of this study occurred when we changed the isopropyl group at R_1 of the cyclohexenyl ring to a cyclopropyl group. The effectiveness of cyclopropyl UAB8 analog in cancer prevention was less than R_1 isopropyl Class I UAB rexinoids, but levels of serum triglycerides were substantially mitigated. While cyclopropyl UAB8 analog is clearly less potent than R_1 isopropyl Class I UAB rexinoids, cyclopropyl UAB8 analog displays similar effectiveness to that of UAB30. On the basis of the results of these studies, UAB30, cyclopropyl UAB8 analog alone, or R_1 isopropyl Class I UAB rexinoids in combinations with SERMs appear to offer great promise for translational development in the prevention of human mammary carcinoma.