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Elastic Theories of Biological Cells >>>


Samuel A. Safran

[Editor's note: Samuel A. Safran[1] holds the Fern and Manfred Steinfeld chaired professorship in the Department of Materials and Interfaces at the Weizmann Institute of Science, Israel. His research interests include the theory of soft matter and biomaterials. He visited the IMS during the period 13–16 November 2011 and participated in its program Multiscale Modeling, Simulation, Analysis and Applications (November 2011–January 2012). During the visit, he also delivered a public lecture titled "Order and Rigidity Sensing by Biological Cells". He contributed this invited article to Imprints *as a follow-up to his public lecture.]*

The application of concepts from the quantitative sciences to biology represents a stimulating new quest that can take several different directions. One of these[2] (pursued by an interdisciplinary group of physicists, physical chemists, materials scientists, and materials/mechanical engineers) focuses on the mechanics, structure, and dynamics, of entire cells and tissues. Such materials-science approaches to biological matter can also be useful in the understanding and eventual design of synthetic systems composed of biomolecules or cells. The goal, as summarized by the NSF program on the physics of living systems[3], is to "emphasize the physical principles of organization and function of living systems, including the exploration of artificial life. While the problem under study must be important to advancing our understanding of the living world in a quantitative way, particular emphasis will be placed on those projects in which lessons learned from the biological application also expand the intellectual range of physics."

Biological physics research at the Weizmann Institute of Science in Rehovot[4] encompasses studies of both cellular and synthetic systems, with a focus on the physical properties of biomaterials. Examples include: synthetic gene chips that contain DNA brushes, artificial neural circuits in one or two dimensions, bio-lubrication, DNA transport through the nucleus, protein folding in the presence of excluded volume constraints, AFM studies of the elasticity and morphology of cells, and polymer network theory applied to evolutionary dynamics.

My own research focuses on a theoretical understanding of the elastic response of biological cells adhered to an elastic substrate. A dramatic example of the importance of understanding cell elastic response are experiments[5] that show that the differentiation of stem cells can be guided by the mechanical or adhesive properties of their substrate. These and related studies of cell mechanics can pave the way to new applications in regenerative medicine and

[1]sam.safran@weizmann.ac.il
[2]Ana-Sunčana Smith, *Nature Physics* **6** (2010) 726.
[3]http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=6673
[4]http://www.weizmann.ac.il/Biological_Physics/
[5]A. J. Engler, S. Sen, H. L. Sweeney, and D. E. Discher, Cell 126 (2006) 677.

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tissue engineering, because physical signals are easier to control and more permanent than biochemical or genetic manipulations. On the scientific side, however, the fundamentals of these processes are puzzling and not yet well understood, despite their importance in development, health and disease.[6]

The study of the physical properties of living systems is difficult due to their molecular complexity. However, this has recently changed due to the maturation of soft matter physics[7] into an independent and very active research area. While soft matter such as polymeric macromolecules and lipid membranes comprise the building blocks of biological cells, their behaviour crucially depends on a unique feature of living systems: their ability to actively remodel their structures as controlled by genetic and signaling networks. Meeting the challenge of combining the physics of soft matter with active processes that describe living matter will enable insight into many biological processes.

For the purposes of understanding their mechanics, cells can be idealized as composite, soft materials whose outer envelope is a fluid membrane that is coupled to an internal gel (a cross linked polymer network called the *cytoskeleton*) within the cell. The resulting elastic modulus of the cell is about 6 orders of magnitude smaller than that of solids such as aluminum or glass. This soft composite can deform under a variety of conditions determined by the cell and its environment, such as the elastic substrate to which the cell attaches. If subjected to mechanical forces, the biological material initially responds like a passive elastic body; thus, elasticity theory is an essential element of the physics of cells and tissue. At longer time scales, the cell can respond to either external or internal mechanical perturbations by actively reorganizing the structure of its cytoskeleton. In some cases, this can lead to flow of the internal, polymer gel[8] that drives cell motility. What is even more unique is that the structure and dynamics of even non-motile cells is often dictated by active processes, in which energy consumption is used to change molecular conformations of "molecular motors" that generate internal forces within the cell. For adherent cells, this activity-driven, intracellular contractility translates itself into lateral forces that allow the cell to mechanically explore its environment. These forces exist in addition to the usual normal forces that result from the adhesion of both "dead" and "live" matter to a substrate.

The understanding of the mechanical activity of cells is important for wound healing, muscle growth, tissue assembly, and development. Biological cells sense their mechanical environment[9] (i.e., its rigidity and the presence of external strains) and respond to these factors in an active manner. Cells respond differently to static or quasi-static strain (on the scale of many minutes) compared with rapidly varying cyclic strain (on the scale of 1 Hz). When the matrix in which the cells are embedded is subjected to a static or quasi-static strain, some cells tend to orient along the direction of applied stretch while others show almost no responses. However, for rapidly varying strains, cells tend to orient away from the stress direction[10]. In addition, the organization of the cellular cytoskeleton is sensitive to the rigidity of its elastic environment. More recent experiments show maximal cytoskeletal alignment of stem cells (along the long axis of the cell) when the substrate rigidity is approximately matched to that of the cell[11]. The degree of alignment is a function of the global cellular shape anisotropy (and is thus zero in a cell with a circular cross section). These two findings suggest that long-range[12] interactions are important in organizing the cellular cytoskeleton. Furthermore, the combination of ordering and rigidity sensing may be a cue that triggers muscle development[13] when stem cells are plated on substrates with the optimal substrate rigidity[5].

Theoretical understanding of the mechanical response of cells can begin with a molecular approach in which one focuses on the effects of external and substrate-induced stresses on the various macromolecules comprising the cellular cytoskeleton, the molecular motors, as well as those molecules that couple the cell to the substrate. Such models may provide detailed understanding of specific situations and may be able to predict how biochemical changes may affect the system. Another way to tackle the problem is to use a "coarse-grained", continuum approach in which the cell is modeled as an elastic body that is coupled to an elastic substrate. The molecular motors are accounted for by the presence of internal, cellular forces whose origin is not derived from the model since they are related to the non-equilibrium processes that drive the motors. In the case of

[6]P. A. Janmey and R. T. Miller, Journal of Cell Science 124, (2011) 9.

[7]Systems such as polymers, gels, colloidal dispersions and membranes in which the intermolecular interactions are of the order of the thermal energy so that small changes in conditions such as composition or temperature can lead to large responses. "Soft Matter: Nobel Lecture", P.G. de Gennes, *Ang. Chemie Int. Ed.* **31** (1992) 842.

[8]J. F. Joanny and J. Prost, *HFSP Journal* **3** (2009) 94.

[9]D. E. Discher, P. Janmey, and Y. Wang, *Science* **310** (2005) 1139.

[10]J. H.-C. Wang, et al., *J. Biomech.* **34** (2001) 1563; S. Jungbauer, et al., *Biophys. J.* **95** (2008) 3470; U. Faust et al., *PLoS One* **6** (2011).e28963

[11]A. Zemel et al., *Nature Physics* **6** (2010) 468.

[12]As opposed to molecular-scale.

[13]Muscle cells have highly aligned cytoskeletons and are thereby able to exert large, contractile forces.

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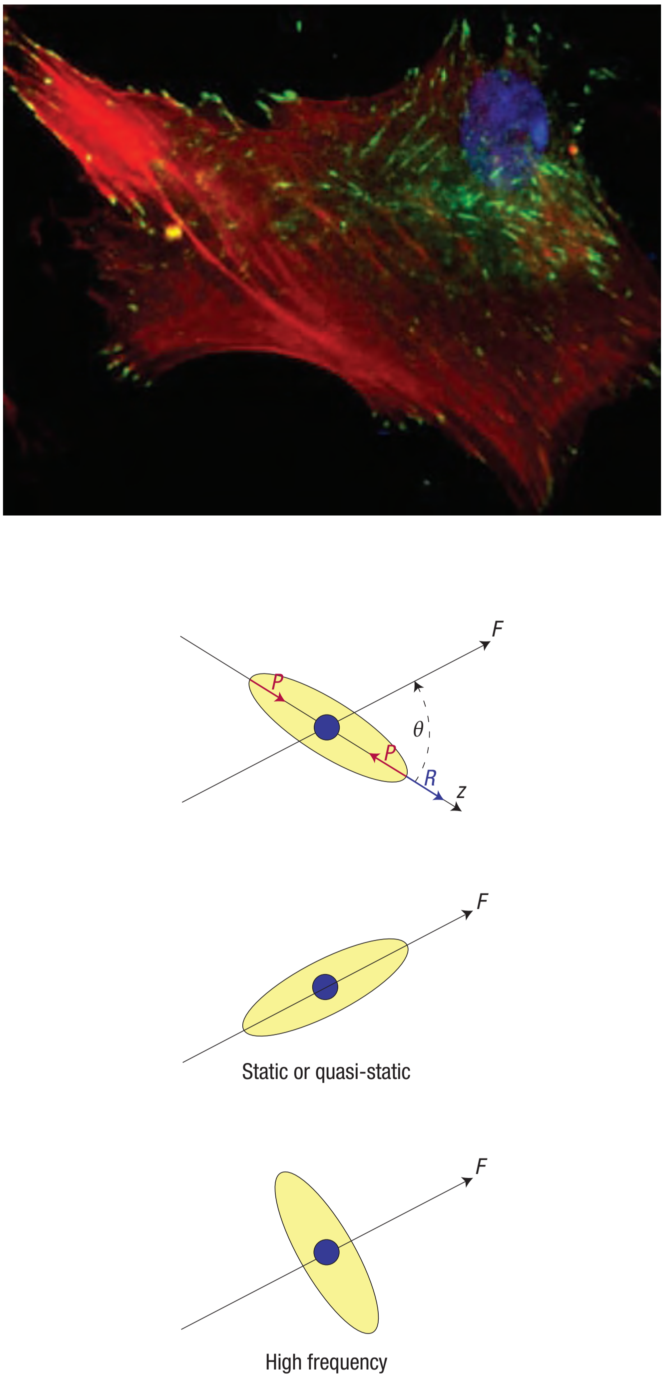

Fig. 1: Stem cell and coarse-grained dipole model. The fluorescence image (courtesy of A. Engler) shows the cytoskeletal actin fibres that generate stress (red), the sites of adhesion to the substrate (green) and the cell nucleus (blue). The model described in the text consists of a contractile force dipole *P* along the z-axis oriented at an angle to the direction of an external force field *F*. *R* is the reaction stress in the adjacent elastic matrix due to the cell's contractility. In the static and low-frequency case, the cell aligns parallel to the strain; at higher frequencies, the cell orients nearly perpendicular to the oscillating stretch. [From F. Rehfeldt and D. Discher, Nat. Phys., **3** (2007) 592.]

well-adhered cells, the relevant motors result in localized, contractile forces that are exerted on the cytoskeleton. These can be included in the theory by introducing into the elastic body a distribution of pairs of equal and opposite forces known as force dipoles. On average, an ensemble of such dipoles results in a macroscopic contraction of the cell, as indeed observed for cells distributed in gel-like surroundings. At a finer scale, the deformation of the cytoskeleton by one dipole gives rise to stresses and strains that propagate to large distances; a dipole located at some distance from the first interacts with these strain fields. This represents an effective, long-range interaction between the dipoles that is mediated by the elastic medium. Taking into account the entire ensemble of motor-driven dipole forces and the fact that the elastic interactions are long-ranged, means that the emergent order of the dipoles subject to these internal interactions can depend on global properties such as the cell shape and substrate rigidity as observed. We have used such models [10,14,15] to understand and predict the elastic response of cells to both externally applied and substrate-induced stresses with results that are consistent with the observations described above.

This approach, while generic and not dependent on specific molecular models, raises many interesting questions that are the focus of current research. For example, how can strain-stiffening (that is a property of biopolymers found in the cytoskeleton), be incorporated into a non-linear elastic theory of force dipole interactions and cyoskeletal ordering? Initial theoretical studies[16] indicate that such non-linear effects give rise to interactions that are even stronger than the usual, long-range strains predicted by linear elastic theory. In addition, given the fact that the cytoskeleton can remodel and sometimes flow in response to force, what is the time regime for which one can assume that force dipoles that are a micron or more apart can indeed interact elastically as described above? Finally, what are the implications of mechanically-induced ordering for multicellular[17] systems? This question, of importance for tissue formation and development, is an interesting area for future research.

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Weizmann Institute of Science

[14] R. De, A. Zemel, and S. A. Safran, *Nature Physics* **3** (2007); 655 R. De and S. A. Safran, *Phys. Rev. E* **78** (2008) 031932.
[15] B. Friedrich and S. A. Safran, *Soft Matter* **8** (2012) 3223.
[16] Y. Shokef and S. A. Safran, *Phys. Rev. Lett.* **108**,(2012) 178103
[17] S. Douezan, J. Dumond and F. Brochard-Wyart, *Soft Matter* **8** (2012) 4578.

People in the News >>>

Joan Birman, Russel Caflisch and Ruth Williams — Newly Elected Academicians

The Institute offers its congratulations to Professors Joan Birman (Columbia University) and Russel Caflisch (University of California, Los Angeles) on their election to membership of the American Academy of Arts and Sciences in 2012, and to Professor Ruth Williams (University of California, San Diego) on her election to membership of the US National Academy of Sciences in 2012.

Professor Birman was a member of the Organizing Committee and one of the conference principal speakers of the IMS program Braids (14 May – 13 July 2007). Professor Caflisch was a member of the Organizing Committee of the IMS program Hyperbolic Conservation Laws and Kinetic Equations: Theory, Computation, and Applications (1 November – 19 December 2010). Professor Williams was the Chair of the Scientific Program Committee of the 7th World Congress in Probability and Statistics (14 – 19 July 2008), which was jointly organized by the NUS Department of Statistics and Applied Probability, NUS Department of Mathematics and IMS; she was also a member of the Organizing Committee and an invited speaker of the conference From Markov Processes to Brownian Motion and Beyond: An International Conference in Memory of Kai Lai Chung (held at Peking University, 13 – 16 June 2010), of which the IMS was one of the sponsors.

Zuowei Shen honored with the Wavelet Pioneer Award

Congratulations to Professor Zuowei Shen (NUS Department of Mathematics), who has recently received the Wavelet Pioneer Award 2012 from the international society for optics and photonics SPIE for his "contributions in MRA wavelet frame applications". Professor Shen is a serving member of the IMS Management Board. He also served in the organizing committees and was an invited speaker of several IMS programs and activities.

Programs & Activities >>>

Past Programs & Activities in Brief

Multiscale Modeling, Simulation, Analysis and Applications (1 November 2011 – 20 January 2012) and Winter School (12 December 2011 – 13 January 2012)

*... Co-sponsored by Institute of High Performance Computing, A*STAR*

Website: http://www2.ims.nus.edu.sg//Programs/011multi/index.php

Co-chairs:

Weizhu Bao, *National University of Singapore*
David Srolovitz, *Institute for High Performance Computing and National University of Singapore*

With recent advances in both the mathematical understanding of multiscale modeling and the advent of multiscale computational methods, multiscale modeling and simulation are becoming key approaches to investigate complicated and advanced scientific problems in applied sciences and to support future technology development in both academia and industry.

The objective of this program was to bring applied and computational mathematicians, theoretical physicists, computational materials scientists and other computational scientists together to review, identify, develop and promote interdisciplinary research on multiscale problems that often arise in science and engineering. In addition, the Winter School aimed to train junior researchers and graduate students by exposing them to a broad spectrum of mathematical knowledge and computational techniques through tutorial lectures, public lectures, research seminars and collaborations.

The interdisciplinary program attracted speakers and participants from various disciplines, including mathematics, physics, chemistry, material sciences, among others. The program consisted of three workshops with one on "Challenge and Modeling of Multiscale Problems in Mechanics and Materials" (14 – 18 November 2011), another on "Multiscale Modeling and Simulation for Defects and Their Dynamics" (19 – 21 December 2011), the third on "Mathematical Theory and Computational Methods for Multiscale Problems" (9 – 13 January 2012); a Winter School (12 December 2011 – 13 January 2012); two public lectures; extensive special lectures and seminars (16 – 18 January 2012); the 1st SIAM Student Chapter, NUS Symposium on

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Applied and Computational Mathematics (5 January, 2012); a few working seminars; and collaborative research during the whole period.

Distinguished researchers gave tutorial lectures on topics in physical modeling, mathematical theory, computational methods and applications related to multiscale modeling, simulation, analysis and applications. The Winter School provided an opportunity for graduate students and junior researchers to present their recent work in front of world leading experts in their fields, learn the state-of-the-art knowledge, and interact with overseas participants. A total of 136 participants attended the program.

A multiscaled gathering


Winter school participants


Max Gunzburger on nonlocal phenomena and methods


In conversation: (From left) Frédéric Legoll and Mitchell Luskin


Introduction to multiscale analysis by Weinan E

Workshop on Nonlinear Partial Differential Equations: Analysis, Computation and Applications (7 – 10 March 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012wnpde/index.php

Organizing Committee:
Weizhu Bao, *National University of Singapore*
Weiqing Ren, *National University of Singapore and Institute for High Performance Computing*

The objective of the workshop was to bring together applied mathematicians and scientists from different disciplines to exchange the latest developments in the study of nonlinear PDEs and computational sciences, identify future directions and unsolved questions, and actively initiate collaborations. The topics of the workshop included multiphase fluid dynamics, complex fluids, solid mechanics, computational biology, multiscale methods, and numerical analysis of PDEs.

During the 3-day workshop which comprised 15 invited talks and a one-day discussion, the participants exchanged the latest developments of their research. Several interesting scientific problems and new research directions were identified through the workshop, and some new collaborations and professional relationships were formed. The graduate students and postdocs attending the workshop learned new knowledge in the inter-disciplinary research area.


Smooth lecture on rough surfaces: Xiao-Ping WANG

The workshop attracted 25 participants from various disciplines, including mathematics, fluid dynamics, biology and other applied sciences.

A nonlinear PDE working group

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Branching Laws (11 – 31 March 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012law/index.php

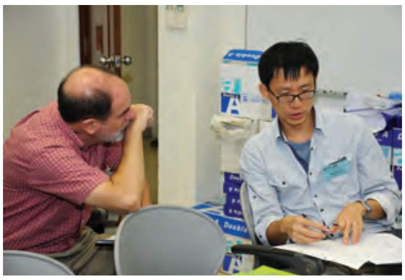
Chair:
Chengbo Zhu, *National University of Singapore*

The aim of the program was to bring together the world's leading experts and promising researchers to examine important recent progress on branching problems, with special attention to topics such as invariant theory and toric deformation; unitary representations and branching laws; and Gross-Prasad conjectures.

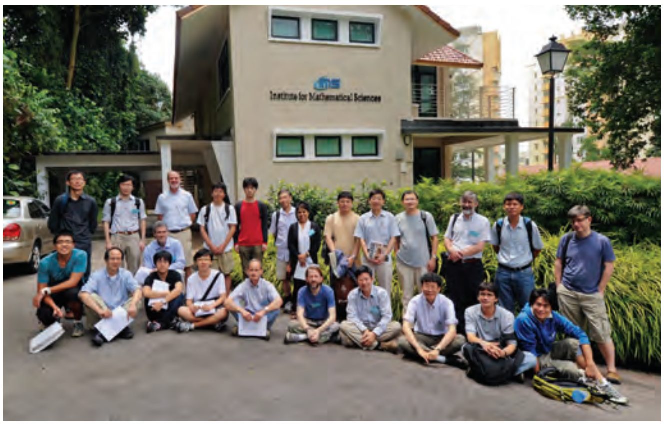
The timely program attracted an impressive roster of overseas participants, including Jeffrey Adams (University of Maryland), Joseph Bernstein (Tel Aviv University), Michel Brion (Université de Grenoble), Benedict Gross (Harvard University), Roger Howe (Yale University), Toshiyuki Kobayashi (University of Tokyo), Erez Lapid (Hebrew University of Jerusalem), Jian-Shu Li (HKUST), and David Vogan (MIT).

The following topics were covered in this program: (a) Invariant theory and toric deformation — multiple flag varieties, coherent cohomology, Schubert varieties, branching algebras, path models for branching; (b) Unitary representations and branching laws — Dirac cohomology, finite multiplicity theorems, Kazhdan-Lustig theory, estimation of automorphic periods, Ranking-Selberg for real groups, Chevalley involution, and local theta lifting; (c) Gross-Prasad conjectures — local theta correspondence and Gross-Prasad conjecture, stabilized trace formula, p-adic L functions, ext-analog of branching laws, formal degree conjecture, and Speh representations.

The program consisted of 30 invited talks with most of the afternoons free for discussions. The informal structure of the program provided significant periods of time for actual mathematical discussions and collaborations. There were a total of 34 participants.


Working out the branches: (From left) Benedict Gross and Wee Teck GAN


Parabolic and parahoric subgroups: Benedict Gross


Branching out at IMS


Hibi algebras and iterated Pieri algebras: Roger Howe


A bunch discussing branches: (From left, facing camera) Chengbo ZHU, Wen-Wei LI

Workshop on Mathematics for Defence (13 April 2012)

... Jointly organized with The Defence Research & Technology Office (DRTech)

Website: http://www2.ims.nus.edu.sg/Programs/012wmathd/index.php

The purpose of this workshop was to provide a platform for defence scientists and mathematicians to discuss their research and exchange ideas, with a view to possible future collaboration between the two groups of researchers as well as on funding opportunities for such joint interdisciplinary research.

The workshop focused on four areas, namely computational PDE, cryptography, high dimensional data analysis, and imaging. The speakers included four defence scientists from DSO National Laboratories and four mathematicians from IHPC, NUS and NTU. There was also a panel discussion on enhancing collaboration between the two groups of researchers as well as on funding opportunities for such joint interdisciplinary research. A total of 96 people attended the workshop.

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Math plays defence

Exchanging ideas over break

Panel discussants (From left): Zuowei SHEN, William LAU Yue Khei, Chi Tat CHONG, Chye Hwang YAN (moderator), Tong Boon QUEK, Louis CHEN

Workshop on Non-uniformly Hyperbolic and Neutral One-dimensional Dynamics (23 – 27 April 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012whyperbolic/index.php

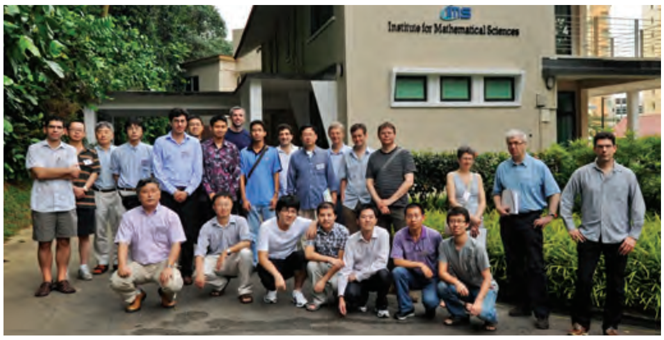
Co-chairs:
Juan Rivera-Letelier, *Pontifical Catholic University of Chile*
Weixiao Shen, *National University of Singapore*
Mitsuhiro Shishikura, *Kyoto University*

The aim of the workshop was to bring together some of the leading experts working on parabolic renormalization, statistical properties and thermodynamic formalism of one-dimensional dynamical systems and related topics, to disseminate and explore possible research collaborations.

The workshop featured 22 invited talks and was attended by 27 participants. Among the invited speakers were leaders in the field, including Michael Benedicks (Royal Institute of Technology), Arnaud Cheritat (Mathematics Institute of Toulouse), Mitsuhiro Shishikura (Kyoto University), Sebastian van Strien (Imperial College London and Warwick University) and Masato Tsujii (Kyushu University).

The talks in the workshop covered various aspects of non-uniformly hyperbolic and neutral one-dimensional dynamical systems, including the theory of (nearly) parabolic renormalization and its application to holomorphic dynamics with indifferent fixed points, the thermodynamic formalism of interval maps and complex polynomials, typicality of non-uniformly expanding one-dimensional maps, statistical properties of systems with non-uniform hyperbolicity, the monotonicity conjecture of topological entropy of interval maps defined by polynomials, the topological equivalence of certain non-uniform expanding condition, dynamics of rational maps, the topological complexity of wild attractors, and skew-product systems constructed from one-dimensional maps.

There were many informal discussions among the participants during the workshop. The workshop enhanced existing research collaborations and established some new ones.



Dynamicists captured in a static moment

A dynamical audience enthralled

Fixed points of holomorphic functions: Mitsuhiro Shishikura

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School and Workshop on Random Polymers and Related Topics (14 – 25 May 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012randompoly/index.php

Co-chairs:
Frank den Hollander, *Leiden University and EURANDOM*
Rongfeng Sun, *National University of Singapore*
Nikos Zygouras, *University of Warwick*

During the last few of years, the probability community has witnessed a burst of groundbreaking developments centered around the theme of random polymer models. These models, originating from the physical and the chemical sciences, show fascinating behavior and pose formidable challenges (both at the rigorous and the non-rigorous level).

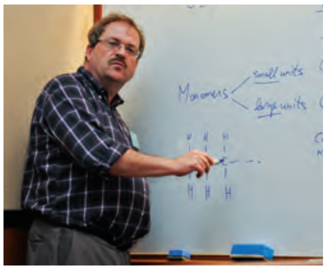
During the week of the school, there were three tutorials by world experts in the field. Frank den Hollander (Leiden University and European Institute for Statistics, Probability, Stochastic Operations Research and its Applications) explained the general framework of random polymers, presenting in a three-hour tutorial their physical, chemical and biological origins, and outlining some of the major challenges. These lectures paved the way for the two, more specialized, seven-hour tutorials given by Francesco Caravenna (University of Milano-Bicocca) and Timo Seppalainen (University of Wisconsin). Seppalainen's lectures focused on the study of fluctuation exponents of directed polymers with bulk disorder while Caravenna's lectures focused on pinning and copolymer models. The school was attended by 31 participants, the majority being PhD students or early stage post-doctoral researchers.

The program culminated in the workshop, which took place during the second week. Twenty-four talks were scheduled, each one lasting forty-five minutes, thus leaving ample time for discussions. In the workshop, the speakers presented interesting new results on a number of topics, including the Kardar-Parisi-Zhang (KPZ) universality class and exactly solvable directed polymers, non-exactly solvable directed polymer models, branching random walks and branching Brownian motions, pinning and copolymer models, the Potts model, the Fleming-Viot process, and the contact process. The workshop was attended by 46 participants.

The program provided the venue for many ongoing collaborations among the participants, and many new collaborations were initiated as well.

Workers on a common thread

Looking at random polymers



Introducing random polymers: Frank den Hollander

Directed polymers in random environments: Timo Seppalainen

Public Lecture:

The adventures of Carbon: Boris Yakobson

Professor Boris I. Yakobson (Rice University) delivered a public lecture titled "Carbons: from diamonds to space elevator and future electronics" at NUS on 10 January 2012. In the lecture, Professor Yakobson introduced a cornucopia of different forms of carbon which have been in focus

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of research. He gave a brief description of some interesting research topics on them, including the fundamental strength of carbon fibers and their ultimate incarnation — nanotubes, the adsorption area of graphene and its curved three-dimensional surfaces for hydrogen energy storage or for batteries, the gapless electronic structure and how to engineer it for electronics use. He also gave a fascinating account of how mathematical models, rooted in physicochemical principles and enhanced by computing, have guided the progress in this rich field of knowledge and applications.

Next Program

Financial Time Series Analysis: High-dimensionality, Non-stationarity and the Financial Crisis (1 – 22 June 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012hidim/index.php

Co-chairs:
Ying Chen, *National University of Singapore*
Piotr Fryzlewicz, *London School of Economics*
Qiwei Yao, *London School of Economics*

The program will invite world-leading experts in the areas of stationary and non-stationary modelling of low- and high-dimensional financial time series, and encourage them to use data covering the period of the recent financial crisis to discuss the impact of the crisis on their proposed models, methods and theories.

Activities
- Workshop I: 4 – 7 June 2012
- Special Lecture Series and Graduate Student Poster Presentation: 11 – 18 June 2012
- Workshop II: 19 – 22 June 2012

Upcoming Activity

Asian Initiative for Infinity (AII) Graduate Summer School (20 June – 17 July 2012)

... Jointly funded by the John Templeton Foundation

Website: http://www2.ims.nus.edu.sg/Programs/012aiiss/index.php

The Summer School bridges the gap between a general graduate education in mathematical logic and the specific preparation necessary to do research on problems of current interest in the subject. The main activity of the AII Summer School will be a set of four intensive short courses offered by leaders in the field, designed to introduce students to exciting, current research topics. The invited lecturers are Ilijas Farah (York University), Ronald Jensen (Humboldt-Universität zu Berlin), Gerald Sacks (Harvard University) and Stevo Todorcevic (University of Toronto).

Programs & Activities in the Pipeline

Random Matrix Theory and its Applications II (18 June – 15 August 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012random/index.php

Chair:
Ying-Chang Liang, *Institute for Infocomm Research*

The two-month program will provide the mathematicians and engineers a unique platform to discuss interesting fundamental problems, results and explore possible solutions related to random matrix theory and its applications in wireless communications and statistics.

Activities
- Informal seminars, ad hoc talks and discussions: 18 June – 6 July 2012
- Tutorial 1: 10 – 16 July 2012
- Workshop 1 — RMT Applications in Wireless Communications: 18 – 25 July 2012
- Tutorial 2: 30 July – 2 August 2012
- Workshop 2 — RMT Applications in Statistics: 8 – 15 August 2012

Meeting the Challenges of High Dimension: Statistical Methodology, Theory and Applications (13 August – 26 October 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012statheory/index.php

Co-chairs:
Peter Hall, *University of Melbourne*
Xuming He, *University of Michigan*
Yingcun Xia, *National University of Singapore*

The topic of high-dimensional data analysis has many aspects, motivated by many applications, sometimes relying

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heavily on dimension reduction and variable selection, and sometimes co-habiting happily with more conventional multivariate methods. The program's first workshop (13 – 24 August 2012) will address all of these aspects. They lie at the frontiers along which statistical methodology, the applications that motivate it, the questions that it answers, and the theory that underpins it, are advancing today. The program's second workshop (1–12 October 2012) will continue to address challenges of high dimensional data analysis with more focuses on the methods and applications where sparsity is present.

Activities
- Workshop 1: 13 – 24 August 2012
- Tutorials: 25 & 27 September 2012 and 16 & 18 October 2012
- Workshop 2: 1 – 12 October 2012

Joint Workshop of IMS and IMI on Mathematics for Industry: Biological and Climatic Prospects (3 – 7 September 2012)

... Jointly organized with Institute of Mathematics for Industry, Kyushu University

Website: http://www2.ims.nus.edu.sg/Programs/012wind/index.php

Organizing Committee:
Robert S. Anderssen, *CSIRO*
Kenji Kajiwara, *Kyushu University*
Tomoyuki Shirai, *Kyushu University*
Kim Chuan Toh, *National University of Singapore*
Masato Wakayama, *Kyushu University*

This workshop will help create/enhance the awareness on the applicability and importance of mathematical sciences in industry and foster closer interactions among industrial researchers/practitioners and mathematical scientists to solve contemporary industrial problems. It will also help find new directions in mathematics.

Optimization: Computation, Theory and Modeling (1 November – 23 December 2012)

Website: http://www2.ims.nus.edu.sg/Programs/012opti/index.php

Co-chairs:
Defeng Sun, *National University of Singapore*
Kim Chuan Toh, *National University of Singapore*

This program will provide a platform for exchanging ideas in solving large scale conic optimization problems including semi-definite programming (SDP) and symmetric cone programming (SCP), report on the latest exciting developments in complementarity and beyond and discuss on another closely related theme — optimization under uncertainty. Additionally, exciting applications of optimization models involving uncertainty from engineering, data mining, financial economics, supply chain management, and etc. are highly anticipated in this program.

Activities
- Workshop I — Large Scale Conic Optimization: 19 – 23 November 2012
- Workshop II — Optimization under Uncertainty: 10 – 14 December 2012
- Workshop III — Complementarity and Its Extensions : 17 – 21 December 2012

Algorithmic Game Theory and Computational Social Choice (7 January – 8 March 2013)

Workshop on Topological Aspects of Quantum Field Theories (14 – 18 January 2013)

Modular Representation Theory of Finite and *p*-adic Groups (1 – 26 April 2013)

Nonlinear Expectations, Stochastic Calculus under Knightian Uncertainty, and Related Topics (3 June – 12 July 2013)

...Jointly organized with Centre for Quantitative Finance, NUS

Complex Geometry (22 July – 9 August 2013)

Mathematical Horizons for Quantum Physics 2 (12 August – 11 October 2013)

...Jointly organized with Centre for Quantum Technologies, NUS

Inverse Moment Problems: the Crossroads of Analysis, Algebra, Discrete Geometry and Combinatorics (11 November 2013 – 25 January 2014)

Mathematical Conversations

Huzihiro Araki: Mathematics and Physics, A Tale of Two Cultures >>>

Huzihiro Araki

Interview of Huzihiro Araki by Y.K. Leong

Huzihiro Araki made pioneering and fundamental contributions to axiomatic quantum field theory, statistical mechanics and the structure of von Neumann and C* algebras.

After obtaining a postgraduate diploma from Hideki Yukawa, he arrived in Princeton University in 1957 during what could be considered as the formative years of the development of axiomatic quantum field theory and statistical mechanics using the operator algebra approach. During his short period of study in Princeton, he made fundamental contributions to a wide range of areas in theoretical physics, even before he was formally awarded a PhD in theoretical physics in 1960 (the first Japanese to have been so awarded in the United States). He was also awarded the Doctor of Science by Kyoto University in 1961.

After a short sojourn in Europe and United States, he returned to Japan in 1964, having been recruited by Y. Akizuki to join the then newly established Research Institute for Mathematical Sciences (RIMS) of Kyoto University. He became full professor in 1966 and was Director of RIMS from 1993 until his retirement in 1996. He continues to contribute his expertise and experience as professor emeritus at RIMS and professor in the Faculty of Science and Technology of Tokyo University of Science.

His extensive work in physics include deep results in local quantum physics, scattering theory, relative entropy in quantum statistical mechanics, variational principles on quantum lattice models, theory of algebras of local observables, KMS states and uncertainty of quantum measurement. Though his interest in operator algebras was initially sparked by quantum physics, his work (with E.J. Woods) on ITPFI (infinite tensor product of finite type I) factors had an influence on the classification of von Neumann algebras and could be considered a precursor of the fundamental work of Alain Connes (Fields Medal 1982). In recognition of his far-reaching influence on mathematical physics, Araki was awarded the Henri Poincaré Prize (together with E.H. Lieb and O. Schramm) by the International Association of Mathematical Physics in 2003. His mathematical legacy is evident in the school of operator algebras that is flourishing in Japan today.

Araki's work generated more than 150 single and jointly written research papers and he wrote *Mathematical Theory of Quantum Fields* (1999). He is the founder of *Reviews in Mathematical Physics*. He was on the Advisory Board of *Communications in Mathematical Physics* when it appeared in 1965 and has been on its editorial board since 1973. He also serves on the editorial boards of the journals *Letters in Mathematical Physics, Reports on Mathematical Physics, Nuovo Cimento B, Journal of Mathematical Physics, Open System & Information Dynamics* and of the series Springer Lecture Notes in Physics and the Birkhäuser Monographs in Mathematics.

He is known for his boundless energy and capacity for scientific organization. He was Vice-Chairman of Kyoto University's Committee for International Exchange and on the board of the Yukawa Foundation. He was instrumental in the founding of the International Association of Mathematical Physics, of which he was the first president. He was one of the representatives of the International Mathematical Union, and was primarily responsible for the organizing and holding of the International Congress of Mathematicians held in Kyoto in 1990.

In addition to promoting mathematical sciences in Japan, he is untiring in his efforts in promoting international cooperation and understanding among mathematical scientists. He was program coordinator of the Institute's program "Mathematical Horizons for Quantum Physics" (28 July – 21 September 2008) jointly organized with the Centre for Quantum Technologies of the National University of Singapore. He also gave a joint colloquium talk on "Points of Contact between Mathematics and Physics". During his visit to NUS, *Imprints* had the opportunity to interview him on 3

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September 2008. The following is an edited transcript of this interview in which his recollections of his younger days and early years of research give us a sense of excitement of the vicissitudes of discovery and even missed opportunities. It also offers us an insight into the fruitful interaction between two apparently incompatible disciplines, mathematics and physics, by one whose heart is in mathematics and passion is in theoretical physics.

Imprints: You published a paper on atomic spectroscopy with your physicist father when you were an undergraduate. Did it ever occur to you to pursue your career as an experimentalist?

Huzihiro Araki: No. From my younger days, I thought the only profession for which I will be good at is mathematics or theoretical physics. I'm not very good [at other things]. When I was young and went with my parents to buy something, I was very much afraid to talk with somebody. I am not good in communicating with others or negotiating something. So it would not be good for me to work in companies. Among academic subjects, I was not very good in humanistic subjects [humanities]. This was also due to the fact that there were no books except [books] on physics in the house. I already looked at some books on quantum mechanics when I was in school. I didn't look at books on other subjects. Science is okay. I am not very good with my hands or anything like that. My father is very good in working with his hands; he makes things by cutting anything. Sometimes my father wanted me to help, but then I made mistakes; sometimes I broke something. So I thought from that point on … later I also had similar experiences. For example, in university, in the first two years we had to do various subjects — in chemistry, for example. In analytical chemistry, you had to find out, given a solution in a test tube, what was inside the solution. But if I do it, then this becomes black. Also, in physics, I had to do three different experiments. I had chosen to build an electric computer, not electronic, using resistances. If you have a diode, you can do addition and some multiplication. When I built it, it didn't work very well. So I set up all these resistances. You had to connect some different parts together. I was not very good at it, and when I measured it there was a lot of resistance here and there where I made, and there should be no resistance. So I usually computed and certainly you can get the right answer. I could find out how I got the wrong answer. However, I was always good in writing reports. So that was my report. The theoretical part is okay, not the experimental part. So I wouldn't do any experiments.

I: Was your father an experimentalist?

A: No, he was a theoretical physicist. Up to my fifth grade in primary school, my father was appointed in the University of Tokyo until he moved to Kyoto. I was born in Tokyo. In Japan, before and during the war, there were only two planetariums — one was in Tokyo some distance from my house. I liked this planetarium and went there regularly during my second or third year in primary school. My father bought me at least two books; one was about the sun and the other about astronomy. One thing I remember about this book is that my father said that the explanation about relativity theory in this astronomy was incorrect. I liked astronomy.

I: Were the books in Japanese?

A: Yes, everything was in Japanese. I didn't even know the English alphabet until I went to junior high school. You see, this was during the war, so English was, of course, out. The only thing I knew about English in primary school was "C" and "P". I knew they were pronounced "pee" and "see". I never heard about "a, b, c". The reason I knew "C" and "P" was that they were used for combinations and permutations in a science book for children. Also, in Japan we had to remember the Chinese characters [Kanji] and write them. I'm not very good at it. Sometimes students had to present some writing. I couldn't do it because I didn't know what to write. But in arithmetic I was very good, especially in computation. There are three types of exercises — one is to just compute without doing something. For this I was the fastest in the class. The other type, you write and compute — I was fast but not the fastest. The third type, you had to use the abacus and I was not very good at that — you had to use your hands. So experiments were out of the question. I was also not very good in painting or music. For painting, only once my art teacher praised one of my paintings very much. At first, I didn't know why. We were free to paint anything. That was in Kyoto, in my sixth grade in primary school, or maybe junior high school. Near my house, there was some nice house with some trees which were not really Japanese. I wanted to paint it but it was very rough. After many times, it became a confusion [of colours]. The paint was not very good. I had to paint many times with different colors together. I like exact things like in mathematics, but it

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was not possible [in art]. Later, I understood that the teacher said that the trees I painted didn't have any branches or anything like that, but it was very much like the painting of a famous Impressionist painter. But I didn't know anything about Impressionist painting.

I: Did Yukawa have any influence on your choice of research area in your graduate studies?

A: I knew [Hideki] Yukawa [(1907–1981), Nobel Prize in Physics 1949] when I was in sixth grade of primary school. I have many stories to say. For example, he gave a talk on Dirac's theory. (He had written two books [on quantum mechanics], the advanced one has Dirac's theory.) He started to explain how to compute energy levels of hydrogen by using Dirac's equation instead of the ordinary energy potential for the relativistic equation. This was, of course, written in his book, but he was stuck in the middle. You had to use hypergeometric functions. I knew hypergeometric functions and so I just said you do this and do that to find the formula. So he was not extremely good in mathematics. At that moment he must have probably forgotten about it. But long, long time later, at some popular meeting he talked about it and remembered that class. I also met [Shinitiro] Tomonaga [(1906–1979), Nobel Prize in Physics 1965] in Tokyo. Tomonaga and Yukawa were completely different in character. Yukawa didn't tell graduate students what to do. In a discussion, when he heard somebody do something, he would want to say some opinion and the opinion would not be about computations but would be more conceptual, like Dirac. He said that he didn't like representations because it was mathematical.

I went to the United States on a Fulbright grant (it only provided travel expenses) and a Hayes grant which provided living expenses. I went to Princeton in '57 after two years studying in Kyoto. In those days, a person could bring out [of Japan] Japanese yen, I think, up to 10 dollars. I didn't bring out anything anyway. The first examination was a written one, together with an oral (sixth grade) examination. They selected a small number; then we had a second (oral) examination at the American embassy. The first step, I had to do it; but for the second step, I had a recommendation letter from Yukawa. That must be very good. They selected where I should go to.

I: Who was your thesis advisor in Princeton?

A: Professor [Rudolf] Haag. He was a visiting professor at Princeton; he just came exactly when I was there. He's German and was visiting Princeton for two years. I would have worked with [Arthur] Wightman but that year he was away in France. Wightman has been in Princeton for a long time.

I: Did your PhD work determine the direction of your subsequent research?

A: Not in particular. I was already in that direction. During my two-and-a-half years in Princeton, I wrote nearly 10 papers; my thesis [on Hamiltonian formalism] was only one of them. I presented my thesis in one year, maybe two years, anyway, in summer. I don't know whether Professor Haag or Professor Wightman was really my advisor. Haag was the person who supervised my paper. He went away after half a year. He came to Princeton on exchange visa and could not have some position in the United States immediately. He later came back to Illinois. After he went to Illinois, I went there.

I: Did Haag suggest a problem?

A: No, he didn't suggest, but we had a lot of discussions. What happened was that quite often when he wanted to establish some new theory, he thought about something and gave many physical examples. Well, of course, he had to transform them into mathematics. Either this must be true mathematically or he hoped that it was true; then his interpretation is correct. Always in quite a short time, sometimes immediately, it turned out to be incorrect — I gave counterexamples. He changed it slightly, and after some time when I couldn't find any counterexample then it was actually true. The first part was easy because I could easily find counterexamples.

I: Haag depends on intuition?

A: Yeah, it's very important the way Haag was doing it — first you have to use intuition to find out what could be true and then you have to realize it mathematically. You may not succeed initially but you try it repeatedly and finally you get what you want. This is what I learned from Haag. This is how you do physics mathematically. When I was in Yukawa's laboratory in Japan, there was also discussion by people, but nobody was doing things this way. Of course, some of the people in the laboratory, already with some position, reported what they did but with terribly difficult and complicated computations. He [Haag] used a lot of

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examples. Privately I was also interested [in what he did] and did some computations. So I knew what he wanted could be obtained very simply and neatly by using Fourier transforms. This was some kind of "eternal" conference in summer; there were also people coming from outside. There were many ways to find the right answer and Haag taught me many things. At some point Haag was studying the formulation of operator algebras and was talking about von Neumann algebras during our discussions. So I went to the library and read von Neumann's papers I, II, III, IV. Then Professor Haag lent me a book written by [M.A.] Naimark [(1909–1978)] in Russia; it was a German translation. I looked at the book. I finished it in a few days because what is written is exactly what is written in von Neumann's papers. That way I switched to doing things in von Neumann algebras. Then afterwards, he asked some questions, so I just tried to answer them and did more.

I: The theory of operator algebras is a purely mathematical field. Was your work on the theory of von Neumann factors of type III motivated by physics?

A: No. You see, I was already involved with von Neumann algebras. When I went to Princeton, Jim [E.J.] Woods was a student there but I didn't have any discussions with him. First of all, you have to take a general examination; then start to write a thesis. You need one year residency requirement. I went there in autumn and in spring I had the one year requirement, so I took the general examination on all topics and then I did the thesis. Woods is Canadian and he took more time. After I left Princeton, I went back to Japan. Just before I left the United States for Japan, I met Professor [Res] Jost [(1918–1990)] who was professor at ETH in Zurich. He was very much impressed by one of my papers which I had published when I was in the United States. He asked me to come to his place in Zurich, and I said "Yes". So the next academic year in Europe and United States, I went there. Some time when I was there, I received the thesis from Jim Woods. I looked at it. He was saying certain things that I needed, but it was incorrect, because in my thesis, apart from the main part, I dealt with some examples which I put in the appendix but I didn't publish that part of the thesis. From that study, I knew that what Woods was saying was incorrect. I didn't write a paper to correct it. After Zurich, I went to Illinois and again met Professor Haag. Around that time I met Woods and together we got some joint paper. This is not *the* Araki-Woods paper (which is a later one). This is about free Bose gas and this summarizes von Neumann algebras' point of view. This was the first time a physical model was summarized that way. This happened in the summer of '67. In those early days, he [Woods] was back in Alberta, Canada. After that, he went to University of Maryland.

In March '67, there was a conference at Baton Rouge organized by [R.V.] Kadison. In that conference a result of [R.] Powers, who was a physics graduate student in Princeton, was presented. Up to that time mathematicians could display only 3 different type III and 3 different type II factors. Powers proved that a 1-parameter family of von Neumann algebras exists. This was a central paper in that conference and he was the first speaker. There was a preprint brought by Tomita and distributed there. This has much more interest later because of the general theory and it also has physics connections. It later became known as the Tomita-Takesaki theory, also called the modular theory of von Neumann algebras. Then I arrived at Maryland to meet Woods and I said that we should put Powers' paper and Tomita's paper together. Powers classified this thing which is a tensor product Type I factors, which was introduced by von Neumann, but this 1-parameter family is only a very small part of infinite tensor products. I proposed to classify these infinite tensor products generally. Later I found out that he [Powers] was also trying to classify them. The motivation, at the Baton Rouge conference anyway, was Tomita's paper and a paper by Haag, [N.M.] Hugenholtz [and M. Winnink] in statistical mechanics. These two preprints were distributed to friends. We were very much surprised because one is pure mathematics, the other is statistical mechanics. The equations are exactly the same equations. These were further developed later by Takesaki, and the theory is called the Tomita-Takesaki theory. It has great influence in statistical mechanics too. That was the beginning part, but in Tomita's papers, he didn't write proofs.

I: Mathematicians usually like proofs. Is Tomita a mathematician?

A: [Minoru] Tomita is a pure mathematician. There are a lot of algebraists in Japan, including [Masamichi] Takesaki, but Tomita is a completely different kind of person, very "singular". Anyway, I thought this was a very important thing and one should find a general theory and try to classify the tensor products. Then we started generalizing Powers' paper and we found very interesting things in one of his lemmas. So we developed a theory out of this lemma. We

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were successful and I forgot about using Tomita's [paper]. We just used tensor products instead of the invariants he introduced in his modular theory. This was '67, and Takesaki completed his wonderful theory in '70. Then in '71 Takesaki gave a lecture in summer school in Seattle. To this Alain Connes came from France as a student. Then in '72 he started to write a lot of papers. What he did was to produce the invariants, which we used to do classical things, out of the Tomita-Takesaki theory. We should have looked into that direction instead of the other direction. But then he [Connes] just did it in '76.

I: I believe that the great physicist Paul Dirac said something to the effect that a physical theory should be mathematically beautiful. With the trend to resorting to computer simulations, do you think that the element of conceptual beauty and simplicity is now being sacrificed or at least relegated to a lower priority?

A: No. In the area where I'm working, I do not look for phenomena generated by the computer. In my institute, some mathematicians use computers. When you use computers together with mathematics, then it is a theory. First you try what could be true. When you are computing this way and do not get something correct, then you have to do something else. If you do the right thing, then it goes like this. So you understand what is going on. The computer helps you to find the right direction, and from there you do mathematics and prove things. In that way you can use it. I never use it because I'm not very good at using computers. I'm not solving any equations or something …

I: Is there a difference between a mathematical physicist and a theoretical physicist?

A: There is a difference although the boundary is not clear cut. It all depends on how a researcher considers himself or herself. The theoretical physicist, as I understand, does not care about rigor, only about the process. If he gets the right result, that's okay. The mathematical physicist would like to prove it and enjoys proving things. If you get the right result, the process can be anything. If you get the really correct things, then quite often anybody can prove it. The most difficult part is to find out what is the right thing, what is the aim. If you have a good aim, then of course, you can find things out, normally; it's not terribly difficult, but different.

I: Theoretical physics or at least mathematical physics is becoming more and more demanding in terms of the mathematics needed to understand the theory. Is there any danger that physical insight and intuition may be eclipsed by mathematical technicalities?

A: No, I don't think so. The situation in which mathematics was not used in physics before or was quite new at that time, appears in physics. This situation existed before. For example, when the theory of complex variables was developed in Princeton, the analytic properties of regions were not widely known to mathematicians, but physicists used them to compute things. The result is not so spectacular, but at least for some regions, some parts succeeded in some way. This was used by the mathematician [Mikio] Sato (then in Princeton) to develop hyperfunction theory; that partly came from physics.

I: Experimental physics and even theoretical physics seem to have become such a colossal collective enterprise that it may be very difficult for one single person to grasp the intricacies of different areas and their interconnections. Do you think that this spells the demise of the single intellectual "giant" capable of revolutionizing physics in the way that Newton and Einstein did?

A: This has been the case in the past. When I was a student, theoretical physicists were divided into two groups – one was working in nuclear physics of elementary particles and the other in solid state physics. Even though they are using the same mathematical processes, they are using completely different terminology and therefore they cannot talk to each other. Of course, mathematicians and physicists also don't talk to each other. Physicists say that the mathematics given by mathematicians is not useful, and the mathematicians say that what the physicists are doing does not have any mathematical rigor, therefore incorrect. I know areas in both physics and mathematics. Quite often I have to be an interpreter. But the only thing lacking is that they don't believe what the other one is saying. If they just try to listen to each other, there are a few things they can learn from each other. At the beginning I was not considered a mathematician. For example, one of the professors, who was teaching functional analysis, was telling me at some point that in the case of the rotation group, if you take the tensor product then it decomposes into irreducibles. This is well-known and also used in physics. When I was a student there were at least three books on group representations and applications to physics, for example, [B.L.] van der Waerden

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[(1903–1996 and [Eugene] Wigner [(1902–1995) Nobel Prize in Physics 1963]. This professor wanted to do this for the inhomogeneous Lorentz group including translations and so forth. So I said that at least for this representation (and also for other representations) this is well-known and very much used by physicists in scattering theory. I started to explain what the result is and how I can prove it, but this professor didn't believe me. You have to listen to see what other people are doing.

I: What advice would you give to graduate students who wish to pursue basic theoretical research in science?

A: I have one story to tell. You see, I am a graduate from the physics department and I am also involved in teaching mathematical physics in the physics department. A professor in the physics department once sent a student to me with two difficult mathematical questions. Quite often, the student said the following (he had studied this area of mathematics very much, meaning he had read one book, and wanted to find some problem to work on) — "Please give me some problem where I can use it." One example is category theory. What I would say is the following. This is not the attitude of the researcher in mathematical physics. The researcher first finds the problem and starts analyzing that problem. Then you always find some mathematical problem you should solve before attacking this. Then you look for what is known in mathematics — find some book, read it and apply it. But often you don't find what you need anywhere. Then you have to develop it yourself. That's the way to do mathematical physics. If you just do category theory and then try to find a problem in mathematical physics to use it — that's not a good way.

I: Do you have many students?

A: Not so many. I'm already retired more than ten years now. I used to have one or two students a year in Kyoto. I had many [students] who were at the front of research.

I: You mentioned you were Director of RIMS [Research Institute of Mathematical Sciences]. For how many years?

A: For three years, before retirement. Usually the director is an older person, often from Kyoto University, but sometimes there are exceptions. The Director's job is an administrative job. I was in some research role but not as director. The Director of Research Institute of Mathematical Sciences mainly has to do administration with people outside the institute. In the university, there are no scholars who are administrators. Some administrators come from the Ministry of Education and so forth. Also the university has many different sections. What our institute couldn't do well was to get a new building. But that's a completely different thing — that has to do with matters outside the institute. Some person is needed to take care of the internal things. I did not have an official position but it is a kind of chairman. It is the mathematics department that has a Chairman. The institute has a director – somebody who is like the chairman. I did this job. Also inside the university, I was for a long time Vice-Chairman of the University Committee for International Exchange. When the building for visitors' stay was to be built, I was first in the planning committee. From the time the building was built until my retirement I was Vice-Chairman. The Chairman changes one every one or two years and is usually an older person. But the Vice-Chairman has to do the real things. All the way I was Vice-Chairman.

I: You must have been very capable of doing things.

A: For example, we had the International Congress of Mathematicians in Kyoto [in 1990] and I was the executive secretary. I did everything, every preparation in Kyoto. I claimed at the beginning that that I would not able to collect money (donations). I didn't like to collect money (I didn't say that), and I'm not good at it. All other things I can do. I wrote, for example, a proposal to IMU [International Mathematical Union] and planned everything inside.

I: Did you manage to get any donations for the conference?

A: That was done by people in Kyoto. Professor [Kunihiko] Kodaira, an earlier Fields medalist [(1915–1997), Fields Medal 1954] and retired, was president of the committee. He graduated from Tokyo University. His classmates went to different fields; many went to the financial sector. They thought Kodaira could collect money. They suggested that mathematicians collect money from themselves and say that they collected so much; then they can very easily collect from other sources. This was done; I also donated. On the other hand, we were not sure how to proceed from there. Normally you ask some company to do various things. I did it all by myself. By myself, I mean I had ten secretaries for general purposes — housing, accounting, collecting fees from participants and so on. They were all in my office and we worked together. All we required was some administration. It was handled by us and not by a company.

Andrew Barbour:
Cambridge and Zürich, Probability and *Stochastik* >>>

Andrew Barbour

Interview of Andrew Barbour by Y.K. Leong

Andrew Barbour has made extensive and important contributions to probability theory and biomathematics.

He made significant contributions to Stein's Method for distributional approximation by introducing the so-called "generator interpretation", and adapted Stein's Method to Gaussian and Poisson processes. He has successfully applied modelling and data analysis in mathematical epidemiology. He has also done important work in branching and population processes and in combinatorial and geometrical probability. Some of the probabilistic methods that he applied to problems in computational molecular biology have contributed to the design of algorithms in genetics. In addition to contributing to about 150 research papers and two research monographs, *Poisson approximation* (with L. Holst and S. Janson) and *Logarithmic combinatorial structures: a probabilistic approach* (with R. Arratia and S. Tavaré), he has devoted much time to consulting and has shared his expertise unstintingly with biologists and statisticians.

Barbour was educated at Trinity College in Cambridge University, and received the Rayleigh Prize in the course of his PhD work. He was Fellow of Gonville and Caius College from 1973 to 1983 and Director of Studies in Pure and Applicable Mathematics from 1976 to 1983. Subsequently, he took up a position at the University of Zürich, Switzerland and was Professor of Biomathematics until his retirement in 2011. He continues to be active in research, particularly in collaborative work with biologists and mathematical scientists in various countries, and holds an honorary professorial fellowship at the University of Melbourne.

He is a Fellow of the Royal Statistical Society, the Cambridge Philosophical Society, the London Mathematical Society and the Institute of Mathematical Statistics (US). He has served on the editorial boards of a number of international journals on probability and statistics, notably *Annals of Probability, Annals of Applied Probability, Probability and Related Fields, Mathematical Proceedings of the Cambridge Philosophical Society, Random Structures and Algorithms*.

He is an ardent organizer, having been actively involved in numerous scientific meetings in Switzerland, Oberwolfach and Singapore. In particular, he was co-organizer of the International Congress of Mathematicians held in Zürich in 1994. He was co-founder of the Swiss Statistical Society and founded the Swiss Probability Seminar. He headed the Biomathematics and Applied Probability Group at the University of Zürich until his retirement.

In his long association with the National University of Singapore, he has given talks and conducted seminars on his research and collaborated with statisticians and probabilists here. In particular, he was the chair of the Institute's program "Progress in Stein's Method" (5 January-6 February 2009) and co-chair of the program "Probability and Discrete Mathematics in Mathematical Biology" (14 March-10 June 2011). During his visit to the Institute for the first mentioned program, Y.K. Leong interviewed him on 29 January 2009 on behalf of *Imprints*. The following is an edited and vetted transcript of the interview. Here he gives us a fascinating, if only brief, account of the statistical tradition in Britain, and shares his enormous enthusiasm for the theoretical (probability) and the applied (probabilistic modelling). We also get to catch a glimpse of the mind and working of a passionate applied probabilist.

Imprints: At what stage of your university education in Cambridge University was your interest directed towards probability and statistics? Who was your PhD supervisor?

Andrew Barbour: When I was doing my undergraduate at Cambridge, I found that probability and statistics were the courses that I enjoyed most, but there was then very little of it in the Tripos. At the end of the third year, I had become quite bored with mathematics. I felt that I wanted to do research, but I had no feel for where I should be doing it. I applied for jobs with various consulting companies and the like. And it was actually an advisor at the Cambridge Careers Service who asked if I knew that there was such a thing as a Diploma in Statistics, where you can spend a year doing probability and statistics and obtain a postgraduate qualification. I confessed that I didn't know about it, and promised to find out about it, and so I did the Diploma in Statistics, and that was delightful. So I had actually developed my interest instinctively, but it was the careers

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consultant who told me how to go about pursuing it. He did a very good job.

I: That was after your first degree?

B: Yes. He advised me in the middle of my final year. I was pretty bored with mathematics at that time, but there was this one bright spot, which unfortunately was a rather small one in the curriculum. My PhD advisor originally was David Kendall [(1918–2007)]. He was my supervisor for a year; then he went on leave and he passed me on to Geoff Eagleson, who was my supervisor for two of my three years.

I: What was the topic of your thesis?

B: It was called "Limit theorems for Markov population processes", and this was the main content, though there was other stuff too, about the convergence theory for tail sums, and some martingale theory. I guess my interest in probabilistic modelling came from this. Markov population processes are widely used as a mathematical framework for modelling processes in biology.

I: Was there a strong tradition in probability and statistics in Gonville and Caius College during your years in the college?

B: Actually no; the college is by tradition a medical college. John Caius himself was once Royal Physician. William Harvey [(1578–1657)], who was educated at Caius and also at Padua [in northern Italy], discovered the circulation of the blood (a fact also discovered by and known to the Chinese much earlier), and also became Royal Physician. The medical tradition persists to this day. However, colleges take a broad cross section of students, from all subject areas, and provide teaching in all of them. So you wouldn't expect necessarily to have a large concentration of mathematicians in one college. Trinity has a lot of mathematicians, Caius has a lot of medics but, in general, students should be spread out. But for various historical and political reasons, most people who did probability and statistics while I was in Cambridge were actually in Churchill College. Caius was sort of an outlier. I won one of their research fellowships; it was where I was appointed.

I: Gonville and Caius College, at more than 650 years old, is one of the oldest colleges of Cambridge University (Cambridge itself is celebrating its 800th anniversary this year). After being associated with such a prestigious college for 10 years, you took up a position in the University of Zürich. Why Zürich?

B: Well, that was a complicated story. When I had been at Caius for about ten years, having been an undergraduate and postgraduate at Trinity for the seven years before that, I woke up one morning and thought, "If I go on like this, I shall have spent my whole life in Cambridge. Do I really want to do this?" And I decided that it might be a little more exciting to have at least some experience outside. So I started thinking about other places that I might like to be. Actually, if you are at Cambridge, there are not many places that look nicer, and have such a good academic environment. I didn't want to go to the United States, because I wanted to stay in touch with my family back in Britain. So that more or less meant continental Europe. And I like mountains; mountains are something that you just don't have in Cambridge. It is completely flat; you have marshes, but not mountains. Then I saw a job advertised in Zürich, and I thought it would be fun to apply. I was lucky.

I: Do you still go mountaineering?

B: I still walk in the mountains. I still go skiing. Yes, I love the mountains. I don't think that part of me will ever change. I grew up in the hills in the north of England.

I: Is Zürich University as old as Cambridge University?

B: Nothing like that. It was founded in 1833. The oldest university in Switzerland, I think, is Basel. It's certainly the most famous old university; it had people like [Leonhard] Euler [(1707–1783)] and the Bernoulli family [(17th and 18th century)] who were famous scientists there. Zürich became really important only in about the 19th century. It was important before then, in Swiss terms, but it was with its new importance as a commercial center in the 19th century that it became important to have a university, and so the university was founded.

I: At ICM 2006 in Madrid, two of the Fields medalists had close connections with probability theory, and in many of the talks and papers presented, probabilistic ideas and methods were widely used, even by pure mathematicians. Do you think that this marks the beginning of a golden age of probability theory?

B: No is the short answer. I think the golden age has been going on for a very long time. It has taken almost as long to persuade people in the International Mathematical Union that they should actually recognize this fact. It has been very, very slow. I don't understand what particular political reasons were invoked for not to encouraging probability. For a long time it was not considered to be proper mathematics. The AMS [(American Mathematical Society)] mathematics subject classification allots only about one twentieth of mathematics to probability and statistics together. Of course, probability and statistics are much, much bigger than that. It

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was exactly the same story when I was helping to organize the International Congress [of Mathematicians] in 1994, which took place in Zürich. There, the official amount of time allocated to probability sections was tiny compared to its importance. But just as in 2006 there were lots and lots of probability actually being presented, to judge from the titles of the talks. In my view, the golden age has been going on since the late 40s and early 50s, and it has taken 50 years for the rest of the mathematical world to wake up to the fact. It's the same problem with statistics. Statistics is flourishing, but it's not flourishing because of mathematics. I think that's bad for mathematics and bad for statistics. The two should be prepared to talk and to work together, rather than to try to win territory in dispute and to protect it from the others.

I: We also know that statistics is also heavily dependent on probability.

B: Yes. Mathematical statistics uses probability as a model, in order to provide the basis for inference from data. The other way round also works: the problems that arise in statistics motivate interesting problems for probability. It's a two-way process, and if you have people from both disciplines working together and talking to each other, then I think it's really good for both sides. There is a sort of dichotomy within universities, maybe even a trichotomy. There is the choice to have a combined department with mathematics and statistics together. There is the solution which has mathematics as one department and statistics as another. And the third, in some sense, is the solution whereby statistics is separate from probability, which is considered to be more mathematical, but still not part of mathematics proper. This all reflects the fact that statistics is about more than just mathematics, because it applies mathematics in the real world. You have to understand real problems, you have to have data, you have to confront problems that come from the real world. These are the things which can be nicely pushed aside in mathematics, and then mathematicians become rather reluctant to give credit for working on such problems. That's where the tension comes from.

To me, data is the essence of statistics, and it's the data that force you to ask the questions that become interesting for probability. Problems come to probability from the other direction, too: there are many problems in other branches of mathematics that can be formulated or approached in probabilistic terms. A big example at the moment is the analogy provided by random matrix theory for things like the distribution of the zeros of the Riemann zeta function. It's a marvelous interface to study, because it seems that the model is very good, but I don't think that anyone has any mathematical idea yet as to why it should be. That will perhaps come in time. It's a sort of cross-fertilization; I think it's good for both sides. It's the same between probability and statistics.

I: I notice that Cambridge has a Department of Mathematics and Mathematical Statistics. It's a rather strange combination, I thought.

B: Yes; well, again it's history. When I said that mathematicians have done their best to suppress probability for as long as possible, Cambridge is no exception. One remarkable story is that David Cox, who is by far the most eminent statistician of the latter half of the 20th century, was an Assistant Lecturer in the Cambridge University mathematics department, but was not given tenure and was asked to leave. This is absolutely astonishing. There was no professor of statistics in Cambridge for many years. Henry Daniels [(1912–2000)] was head of the Statistical Laboratory, but was not appointed professor; he eventually left in disgust and went to Birmingham. At that point, which I guess would be around 1960, they needed to find someone else to fill the job as head of statistics. Eventually, they persuaded David Kendall to consider the post; he was also an excellent mathematician. They thus found themselves able to go the whole hog, and offered him a professorship. I imagine that at that point he said he wanted to be in the pure mathematics department, rather than in applied mathematics, since that was more his spiritual home. That is my understanding. In any case, being Cambridge, they had nonetheless to invent a special word to distinguish probability and statistics from pure mathematics. They call it "applicable". So they have an applied mathematics department and an "applicable" section. Applied mathematics is a separate department and is in a separate building, I think, even now; it certainly was in those days.

I: I thought applied mathematics had a long tradition in Cambridge, more so than statistics.

B: Well, that is probably right, but there has been a very long tradition in statistics in Britain too. In fact, I think it is the oldest tradition in the world.

Applied mathematics in Cambridge would be called theoretical physics in Zürich. There was an enormous contribution to and interest in mathematical physics from British mathematics departments in the 19th century and the early 20th century. For instance, there was a big stimulus from the interaction between mathematics and quantum physics. I think the British attitude with respect to mathematics is rather more pragmatic and less fundamental than that of the French. You have quite different ways of looking at things. Certainly, there aren't that many British

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mathematicians that you can point to in the 19th century, although [George] Green [(1793 – 1841)] would be one that would come to mind. When you compare that with what was going on in continental Europe, it is clear that the developments in the mathematics departments then were firmly rooted in physics. I think that this tradition has remained until today.

But statistics was happening as well. You had people like Francis Galton [(1822 – 1911)], who was interested in the fundamentals of regression, and there were the Pearsons and, of course, [Ronald] Fisher [(1890 – 1962)] in the 1930s. No one else much in Britain was doing statistics at that time; there was the collection and recording of data, but relatively little analysis, except, perhaps, in relation to insurance. There was also a tradition of medical statistics in Britain, which went back a long way. In fact, statistics has been a very traditional subject in Britain, but didn't get connected to mathematics for a long time. Only Fisher thought like a mathematician; yet he was a geneticist and wasn't educated as a mathematician. The medical statistical tradition began with [John] Graunt [(1620 – 1674)], who collected the information needed to determine life and mortality tables. The collection of data went on for a long time, but only rarely was any attempt made to make inference from them. Of course, Thomas Bayes [(1701 – 1761)] was a British statistician, though I doubt if he would have called himself that. His name is now attached to his famous theorem and to a whole branch of statistics.

I: I understand that one of your important contributions to probability theory is an approach different to the original analytical approach to Stein's Method. Could you tell us something about it and about some of the latest developments in Stein's Method?

B: Yes. I guess my contribution to Stein's Method comes in two parts. The first was in connection with Poisson approximation, to use coupling. Here, you have an interesting distinction between a pure mathematician's view of probability theory and a probabilist's view. One of my colleagues in Zürich once said that, from his point of view, probability theory was measure theory with a finite measure. This entirely misses the point because, when you have probability, you have the concept of independence, and, since the 1940s and 50s, you have sample paths and all sorts of important things which are somehow invisible in the measure-theoretic formulation of the subject.

Coupling is an idea which was developed just before the Second World War by [Wolfgang] Doeblin [(1915 –1940)]. The gist of the idea is as follows. You want to show that two probability distributions are close to one another. Now, that is, in principle, a problem within the space of measures. But a probabilistic approach to it is to construct two random variables, one with each distribution, and to construct them together on the same probability space in such a way that their realizations are, almost always, very close to each other in the space in which the realizations live. You transfer the problem from the space of measures to the space of objects which result from the realizations. By doing that, you develop a whole lot of new possibilities. So, in the context of Poisson approximation, the characteristic of the Poisson process is that knowing what happens in the process at a particular point in time has no effect on what happens at other times: the rest of the process is completely independent. That is a very characteristic property of the Poisson process. Then it is natural to want to show that a process is close to being a Poisson process if knowing what happens in the process at a particular time changes the distribution of the rest of the process very little. In the coupling approach, you actually construct processes with the event happening at the particular time in both, and such that, with a high probability, they are also identical at all other times. This is the basis of using coupling in combination with Stein's Method to prove Poisson approximation. It has turned out to be extremely powerful and efficient. It's an approach which, if you had been doing measure theory, you would have never thought about. It's a different kind of thinking — one of the strengths of probability theory.

I guess the other contribution has to do with developing ways of dealing with distributions other than the Poisson and the normal, which are the two canonical examples analyzed by Stein's Method. There are lots of other distributions, and not just those of random variables in one dimension; you can even ask for the distributions of whole processes. It wasn't clear how to guess at equations for those. My idea derives from the equations in the normal and Poisson cases. The characteristic Stein equation, which you use as the basis of Stein's Method in normal or Poisson approximation, can actually be interpreted as a characterization for the equilibrium distribution of a Markov process. And then it's a small step from there. If I want to have the distribution of the whole process, I just have to show that its distribution is the equilibrium distribution of some more complicated Markov process, and from that more complicated process derive an equation which is to be used as a Stein Equation. A by-product of this is that it not only enables you to construct Stein Equations for many sorts of distributions, but also gives you a probabilistic characterization of the solution of the equation. This enables you to make computations to bound the solution, which can be very difficult if you have a completely general Stein's equation. So that has two advantages.

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I: Some of your early work on Poisson processes and random combinatorial structures had important implications for computational biology. Were you involved in any international consortium or group that worked on the human genome project?

B: Not directly. I used to talk to Mike Waterman and Simon Tavaré, who were very active in connection with these things. As far as the human genome is concerned, I am at one remove from it. I mean, I was interested in the mathematical questions that arose out of consulting problems. But I did work on computational molecular biology at about the time the human genome project was under way. One of the things that I looked at was ways of detecting very distant relationships between proteins, using sequence similarity. There is a sort of rule that there is a certain amount of information contained in the sequence itself, and it has its limits; this is well understood. We wanted to push these limits as far as possible, rather than to have to rely on other information that may be more expensive to obtain. We used something called "family profile analysis", which is a method that uses information not only from individual sequences but also from sequences in the standard database which are similar to them. In some sense, you use the other similar sequences to crystallize the important commonalities, and then try to recognize similar structures in the further removed sequences that are of interest to you. You actually build families for both the query sequence and the potential target sequence. So it is a family-family analysis, if you like. The procedure was put on the web, as all algorithms now are. I don't know whether people actually use it today, but it worked pretty well.

I: Your work is very mathematical in nature, but you have been involved in numerous interdisciplinary projects in anthropology, zoology, microbiology and systems biology. What motivated you to do interdisciplinary research?

B: Well, probably growing up in the statistics department actually [*laughs*], because in statistics you have the data. I don't believe in mathematical statistics, in a sense, as a field. I believe in doing mathematics, and, in particular, in attacking interesting mathematical problems that arise from statistics; but that, somehow, is mathematics, possibly probability theory, but not statistics. Statistics requires data. When I was doing my diploma in statistics, we all had to complete an applied project. I chose a project that concerned the analysis of parish records — demography. There's a marvelous collection of these in Britain, from 1537 to beyond 1800, I think. I was given a project involving this, and I was given data from 20 parishes; actually they had been cleaned up by somebody else beforehand. I only had the numbers really. Subsequently, I visited some of the parishes and looked at the actual registers, if I found things in the data that were surprising. I enjoyed working with the data, and the conclusion that resulted was also interesting, in that it didn't show what the demographers had been expecting. It was a negative conclusion, which is always a tricky one, if you want to publish it. On the other hand, it was quite significant for the demographers. The conclusion was as follows. If you look at the relative death rates as a function of season, you expect to find more people dying in winter than in summer; that was as true in Britain in 1969, in relative terms, as it was in 1537. The astonishing discovery was that the magnitude of the seasonal fluctuation, winter to summer, had not changed at all over that period. You would have expected that, in the poorer communities in earlier times, the fluctuations would have been much bigger — more people dying in late winter because of no food, and it's cold, and they die of disease. The demographers concluded from this that Britain in 1537 was relatively prosperous. Whether that was true or not, I don't know. It was a fascinating study in data.

The project subsequently stood me in very good stead with my younger daughter, who had done her PhD in history, socio-economic history. When I mentioned to her that I had worked with [E.A.] Wrigley, who was then leader of the Cambridge Population Group, she was very deferential afterwards, because Wrigley is one of the really big figures in this area. She was amazed that I could have spoken to him, let alone have worked with him.

And then, after I did my PhD on limit theorems in Markov population processes, I heard a talk about schistosomiasis at a conference. I thought that this would be a marvelous system in which to try out my limit theorems, to see if they worked in practice. I worked out how the Markov population process should look, and I worked out what my limit theorems would suggest, and then I decided to have a look at some data. I rapidly discovered that no one else who had been modelling the disease had taken the trouble to match the predictions of their models to the data. In fact, the classical model was saying completely different things to what the data were saying. I then got seriously interested, and started to try to work out what was really going on. In the end that was why I got my job in Zürich; they were looking for someone who was interested not only in mathematics but also in biology. By then, I really was. So it was a great decision to go into biology.

I: Since then you have talked to many people in other fields.

B: Yes. I'm always talking to biologists. When I got to Zürich, I had already become friends with one of the biologists there, as a result of the interview process and so on. He invited me

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to come to his colloquium every week, and I said I would do consulting for people in his group. This was the basis for collaboration which has persisted on and off since then with biologists in Zürich. They are very open-minded people, and like to present their problems to mathematicians. I like talking to them and it all worked out very well.

I: Among your numerous interdisciplinary collaborations, which one has given you the greatest satisfaction?

B: I think actually my first work on schistosomiasis. This was, in some sense, not a collaboration, I was working more or less alone. But I talked to a lot of people who were active in the field, to practitioners, to people who were public health specialists.

I: What kind of disease is that?

B: It's a parasitic disease. It's widespread in the tropics. It visibly causes mortality in the Philippines and Southeast Asia – the *japonicum* variety. The African variety *mansoni* is not so obviously lethal but is believed to be debilitating. It's very widespread, and certainly not good for you, but it's arguable whether it actually kills you. You can certainly see how badly the liver is swollen as a result of *mansoni* — that's one of the easy ways to detect it, if the infection has been going on for a long time. But it's very difficult to point to someone dying and say that the real cause of death is schistosomiasis, though it could be a contributing factor, for sure. It's a disease which is very widespread; after malaria, perhaps the next most widespread parasitic disease in the tropics. When I started working on it, in the mid-1970s, one of the things that the original model said was that what limited transmission, and enabled a roughly stable level of infection to be maintained, was the fact that there weren't enough snails to go around. The life cycle of the disease is a complicated process. The infection passes from the human being into a water snail and back from the water snail into the human being — actually, a four-stage life cycle with two hosts, the intermediate host (snail) and the definitive host (human being or ape or other mammal, depending on the variety). The assumption that the spread of the disease is limited by the availability of snails is at variance with the data that has been collected, which showed very, very low proportions of snails infected, even in highly infected areas. It was the proportion of human beings infected that was high, maybe 50 per cent or more. It was easy to deduce from a better model that the limiting factor had to be in the human host; probably some form of concomitant immunity. This was not accepted at all in the mid-1970s, yet, by the end of the century, I think almost every biologist would say that some form of immunity was important, even if they didn't know exactly what form it took. It is one case of mathematics having given the right answer 25 years before biology caught up.

But otherwise, the big satisfaction that I get out of consulting with biologists is getting involved enough in a problem to be asking questions which they haven't asked, or even thought to ask, or been able to answer. When you reach that point, you feel that you are making a real contribution. A lot of consulting is very effective, but it's getting the person with whom you're consulting to understand his own problem. When he understands his problem properly, he can usually see what the solution is. Nine times out of ten, it's a sort of self-realization process for the other person. But then, in the remaining 10 per cent, you reach the point where you are pushing them further, and they don't know the answers; then you tell them what they need to know, and they go and find out. Those are the consultations that provide the greatest satisfaction. Consultation is actually a fascinating business.

I: Consultation is not everybody's cup of tea. Does it depend on temperament?

B: I think you have to like data. You have to have a certain intellectual curiosity for problems not your own. I'm not saying that I'd like to spend all my life as a consultant. It's also very tiring, especially doing what I used to do; on a Wednesday afternoon, after two hours of lectures, I used to have two hours of consultation — two problems, one hour for each. You have to understand a totally new problem, to a point where you can say sensible things about it, all within an hour. It's a considerable effort. In my early days, this was all going on in German, and I had only learned the language in order to come to Zürich, so I didn't speak it very well. That was an added factor. At the end of the two hours, I would lie down for half-an-hour, dozing on a table in the office, before I could think about going back to mathematics or going home.

I: I believe that biomathematics has a tradition of research in Europe dating back to the 18th century, but it is only recently that mathematics has systematically been used to meet the challenges of the revolutionary discoveries in biology. How successfully has biomathematics met these challenges?

B: First to get back to the traditional research in Europe. Coming from Switzerland, I have to mention Daniel Bernoulli [(1700–1782)], who was one of the earliest examples of a mathematician who applied himself to solving a very practical medical problem – in that case, deciding whether or not to employ variolation; whether it would improve your life expectancy or not. It was a very nice piece of work, which was outdated maybe 5 or 10 years later by the discovery of the smallpox vaccine using cow-pox. It is

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a story which is interesting in connection with mathematics and biology nowadays, because it illustrates that a good mathematical solution to a problem may have relevance only for a very short time. This is something very much against the taste of a mathematician, who likes to prove a theorem which lasts for all time. I think that the way in which mathematics is being used in biology at the moment rather reflects that. The biologists have lots of problems which they cannot solve; they know they need people who can handle the problems for them in a mathematical way, or even just in a data handling way. Part of their problem lies in the volume of data that they are collecting — the human genome, 3×10^9 or 3×10^{10} base pairs, or whatever, and then you probably haven't got them all. You have to do something with the data, and so you need people who can deal with such things. You can make some simple statistics out of them, you can put them in a computer, you can make a database, or whatever. So lots of the actual solutions to their problems are carried out by computer scientists, by people who write algorithms, rather than by mathematicians. And it's probably a good thing, because these guys are more interested in finding a quick answer and getting the job done, and it's important that they do. Mathematicians, on the other hand, are more interested in getting it right; but there is little time to get it right before life must move on. But I think that now that the data handling business is pretty well under control (even when new sorts of data appear, they are better and better handled) the questions are becoming more sophisticated and require, for instance, real statistics. Then I think that a lot more impact from mathematicians and, in particular, from statisticians will go into the biology process. But I think that the big molecular revolution has, with notable exceptions, largely been handled by computer scientists up to now.

I: What exactly is biomathematics? Could you explain the term a little? It's a very vague sort of term.

B: It's a very vague thing. It's like systems biology, which is also a vague term. I think biomathematics you would describe either as the application of mathematics in biology, or as mathematics, in some sense, designed for, developed for or applied in biology. In practice, one obvious feature is modelling biological processes — the spread of epidemic diseases, which is a very classical application, or the flow of blood in the human body, as another example. In a sense, biomathematics is used to describe processes that are too complicated to be described in words. The biologists are fine if you can talk about a phenomenon in words. As soon as you have some complicated interacting nonlinear phenomenon, you can't make predictions using words. Mathematics gives you a framework to take a very local description of what is going on and, by solving equations, to demonstrate its global consequences; and then you can make global predictions. In a nonlinear setting, you really require mathematics. Personally, I tend to put into biomathematics the things that I don't put into biostatistics; I tend to leave out the statistics part, and put in modelling instead, and the understanding that comes from having a mechanism to explain things. But, in practice, it's always been that you have to combine this with statistics and data, in order to make progress.

I: I notice that you have made a number of visits to Australian universities of duration three to four months each. Is there a personal connection?

B: Actually, my first collaborative work was with someone in Australia, in Melbourne. That was in the days before e-mail, and we communicated by post. It was near Christmas, and it used to take 3 weeks for letters to get from Cambridge to Melbourne. This would seem unimaginable nowadays, in mathematics. How it ever worked out, I don't know. We wrote 3 papers together, and one was about 50 pages long. Anyway, the connection with Australia really happened because my PhD supervisor (my second one), Geoff Eagleson, was Australian, and at some point, about 1980, he returned permanently to Australia. A year or two later, he invited me to visit. Since there have also been a large number of Australians in the probability and statistics group in Cambridge, partly because of the connection through Peter Whittle, and partly because Joe Gani in Sheffield made sure that the good ones came to Britain and studied there, I already had a lot of friends in Australia. When I went to Australia, I found it to be a nice place to visit and started working with people there anyway, and one thing led to another. I kept on being invited back and I accepted with

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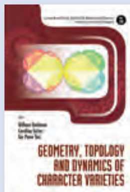

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glee. And then I met my now wife there. So I have a very strong personal connection, but this wasn't the original reason.

I: I believe that recently you have an even stronger connection with Melbourne University, isn't it?

B: In what way?

I: I believe they are offering you something or other.

B: That is true. You are very well informed. I have an honorary appointment (professorial fellow), but that doesn't start until a year's time. I have also had an honorary appointment at Monash University for a number of years. These are, in a sense, formal connections. They are nice for me, because it means that I have some sort of freedom to use their resources when I'm in Australia. I work with people at both universities on a regular basis. It's just a way of facilitating collaboration, as far as the authorities are concerned, I think.

I: You have supervised a number of students in Zürich. Do you still supervise any more students now?

B: Indeed, I do. For the "Progress on Stein's Method" meeting, which we've just had, two of my current students are here. One started about a year ago and the other I inherited from Sándor Csörgő, who died at the beginning of last year. She is from Hungary. I have a third; he doesn't work on Stein's Method, but works on modelling in biology. He is, I think, now back in Zürich from Kyrgystan, working with his co-supervisor. I like to maintain a broad spectrum of interests in my research supervision as well as in my research. That is one way of keeping young, I guess.

I: Do you have any advice for graduate students in probability and statistics?

B: Yes. It's a great subject, very enjoyable. My personal advice would be: find some data, because it's fun. If you are doing probability theory, no harm in finding some data (which may be connected to your interests), because you learn a lot from it, and you find a lot of good questions.

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