

**Scottish Industrial Networking Initiative in Mathematical
Sciences (SINIMS) Workshop**

***Applications of Mathematics in
Medicine and Biotechnology***

Wednesday 13th February 2002

International Centre for Mathematical Sciences
14 India Street, Edinburgh EH3 6EZ

Delegates:

Dr Jonathon Bard	Biomedical Sciences, Edinburgh University
Dr Stephen Blythe	Inverness Medical Ltd
Dr David Burt	Roslin Institute
Dr John Byatt-Smith	Edinburgh University
Prof. Jack Carr	Heriot-Watt University
Ms Tracey Dart	International Centre for Mathematical Sciences
Dr Hermann Eberl	Edinburgh University & German National Research Centre
Prof Chris Eilbeck	Heriot-Watt University
Dr Paul Fotheringham	Centre for Mathematical and Computational Science in Medicine (CMCSM)
Mr Joseph Gallagher	BioSil Ltd
Dr Michael Gordon	Hycor Biomedical
Dr Sandy Gourlay	CMCSM
Prof Nick Hill	Glasgow University
Dr Ralf Jacobs	Strathclyde University
Mr Daniel Jefferson	Heriot-Watt University
Dr Gabriela Kalna	CMCSM
Prof Andrew Lacey	Heriot-Watt University
Dr Robert Leese	Smith Institute
Dr Qiangyi Li	Scottish National Blood Transfusion Service
Dr Gabriel Lord	Heriot-Watt University
Dr Tom Mackay	Edinburgh University
Mr John McIntosh	Edinburgh University
Prof Sean McKee	University of Strathclyde
Ms Bethany McLemore	Edinburgh University
Dr Andrew Mearns Spragg	Aquapharm Technologies
Dr Paul Moseley	Smith Institute
Prof David Parker	Edinburgh University
Dr Yiqi Qui	Heriot-Watt University
Prof. Elmer Rees	Edinburgh University
Dr Heather Tewkesbury	Smith Institute
Dr Keith Vass	Cancer Research UK, Beatson Institute
Dr Sarah Waters	Nottingham University
Mr Andrew Waugh	Heriot-Watt University
Dr Stephen K. Wilson	University of Strathclyde

Delegates will be referred to by their initials.

Programme:

- 10:30 Registration / Coffee
- 11:00 Welcome & Introduction to Faraday Partnerships (Paul Moseley)
- 11:10 Smith Institute Faraday Partnerships (Robert Leese)
- 11:20 A bioinformatics approach to investigating genetic networks (Jonathan Bard)
- 11:50 Some recent applications of mathematics in medicine (Sean McKee)
- 12:20 Buffet Lunch
- 13:00 *Roslin Institute* (David Burt)
- 13:40 *Inverness Medical Ltd* (Stephen Blythe)
- 14:20 *Beatson Institute* (Keith Vass)
- 15:00 Tea
- 15:30 *Aquapharm Technologies* (Andrew Mearns Spragg)
- 16:10 *Hycor Biomedical* (Michael Gordon)
- 16:50 Concluding Remarks (Paul Moseley)
- 17:00 Close

Meeting Notes

1. PM welcomed attendees to the workshop and introduced the programme for the day (see above). He explained that the objectives for the day were:
 - to provide information for industrialists about the idea of Faraday Partnerships in general, and in particular, the Smith Institute Faraday Partnership.
 - to provide an overview of the range of applications of mathematics in the medicine and biotechnology industry over the last 30 years
 - to listen to industrialists and provide academics with some ideas of the type of problems which are important in their businesses
 - PM then gave an introduction to Faraday Partnerships (FPs) and their principles. These evolved from a series of Government white papers and investigations into maximising the potential of the UK research base for the benefit of the country's industry and academia, with specific attention being given to the industrial sectors identified by Foresight as of strategic importance to the economy. A full list of FPs is available on www.faradaypartnerships.org.uk. The Faraday principles are:
 - To promote active flows of people, industrial technology and innovative business concepts amongst the science and technology base and industry
 - To promote the partnership ethic in industrially relevant research organisations, business and the innovation knowledge base
 - To support core research that will underpin business opportunities
 - To promote business-relevant postgraduate training, leading to lifelong learning.

2. RL spoke briefly about the Smith Institute Faraday Partnership, and the way it aims to promote the use of mathematics and computing in industry with the aid of its team of Technology Translators (including PM and HT). The Smith Institute covers the whole of the UK, and is in contact with a large network of academics interested in industrially motivated mathematical problems. Some funding routes were highlighted including the Engineering and Physical Sciences Research Council (EPSRC) CASE and post-doctoral research awards, TCS (Teaching Company Scheme), LINK (several companies and universities collaborating) and SMART. Details of CASE awards which the Smith Institute have available to allocate can be viewed on www.smithinst.ac.uk/news. RL described some of the current activities of the Smith Institute, involving 30 projects with 70 companies and 25 Universities.

A number of forthcoming events were also highlighted:

 - Flexible Photovoltaics – in collaboration with TechniTex, INREB and EPPIC Faraday Partnerships, 21st March, Cambridge

- Applications of Mathematics in Food and Agriculture, 25th February, ICMS
- Applications of Mathematics in Oil and Gas, 11th March, ICMS
- Applications of Mathematics in Semiconductors, 24th April, ICMS
- 43rd European Study Group with Industry (ESGI), 2-5th April, Lancaster University (further details are given at www.smithinst.ac.uk/projects/study_groups)

People requiring further details on these events should contact HT, RL or PM, on the details given at the end of this report.

3. JB talked about the bioinformatics approach to investigating genetic networks. Congenital abnormalities arise when single genes involved in normal development mutate. Of the 3000 such disorders known, the key genes are only known for a few hundred - there is much work to be done to complete the knowledge base. Key sources of candidate genes for humans comes from our knowledge of the genes expressed in mouse tissues as they develop and of the effect of gene mutation on them. The numbers of genes involved in any developmental event is very large. These genes are arranged in tissue-based networks. A mutation in any gene causing an abnormality. The amount of expression data for many tissue is so great that it can only be stored in databases. There are now two gene-expression databases for the mouse embryo that can be searched for candidate genes, GXD (Gene expression Database, a text data base) and GENEX (a graphical database) which is partly in place. Both are based on mouse developmental anatomy.

Other people involved in this project are Martin Ringwald, Janan Eppig etc at The Jackson laboratory (USA), Duncan Davidson, Richard Baldock etc at MRC Human Genetics Unit and Matt Kaufman, Jonathan Bard, Cecilia Oram etc at Biomedical Sciences (Edinburgh University). The underlying mathematics involved in bioinformatics include: database design and informatics, graph theory in designing ontologies, differential equations and elastic theory for making 3D models, set theory for handling 3D querying and a lot of programming, but the user of such a database needs to know nothing of the underlying mathematics. JB then went on to describe the structure of this knowledge base (ontology). GXD can be found at the Jackson Laboratory homepage. GENEX can be found at <http://genex.hgu.mrc.ac.uk>, which has advantages over GXD as it can be used to compare tissues spatially and geometrically, whilst not demanding that the users know developmental anatomy in the first instance. Graphical databases can also reconstruct 2-D images into 3-D volumes, then these completed models stored in an object oriented database. Gene expression data can then be painted onto these models, and the whole system be used in the teaching of developmental anatomy and gene expression. The networks also provide candidate genes that when mutated will lead to congenital abnormalities, thereby speeding up the identification of genes responsible for such abnormalities.

4. SMcK talked about his (mathematical) work in medical devices and related topics, giving four examples (below) after describing the process of mathematical modelling in terms of encapsulating the essentials of the system and comparing known results with initial model estimates until sufficient refinement made the model practical and useful.

- 4.1 Pregnancy testing kits are essentially antigen-antibody testing kits, with two chemical reactions going on. Mathematically, the problem can be thought of as a diffusion problem to solve for the rate of reaction expected in the three minute testing time. Other questions which mathematics helped to answer were how small can the device be? and how much of the specific antibody needs to be attached to the dipstick? The quantitative modelling gave an advantage over the qualitative biological knowledge.
- 4.2 Intestinal disease in chickens (caused by parasites) was another problem where mathematics had been used to provide some qualitative analysis of the solution. Due to public concerns over the effect of drug residues in meat and the high cost of an anti-parasitic feed, the model centred on minimising the amount of special feed required to keep the birds healthy.
- 4.3 A device for measuring cardiac output was described, where the problems were multiple: the method was to introduce a 10cc cold bolus into the blood stream and measure the temperature change as the bolus mixes with the blood. This temperature change can be back-calculated to a cardiac output. However, this requires hand-delivered injections for patients, only gives a snapshot of the cardiac output, there is

increased infection risk and staff time is expensive. Instead, a catheter placed in the pulmonary artery with two temperature sensors can relate the temperature difference and the power output to the blood flow. But SMcK warned of the difficulties in modelling blood flow, as it is pulsatile, non-newtonian, in essentially elastic tubes and can be slowed by the very presence of the catheter.

- 4.4 Flow of anaesthetic from a needle into the lumbar region was described in particularly graphic detail! The objective is that there needs to be adequate concentration of anaesthetic to block the spinal nerves for the duration of the surgery, but fast recovery is also required. The questions which mathematics helped to answer included: what is the concentration and distribution of anaesthesia around the spinal nerve, how does that depend on the type of needle used, the angle of injection, the angle of the patient to the horizontal and how does the temperature of the drug affect the flow?

5. DB spoke about functional genomics at the Roslin Institute, the farm animal biotechnology research centre, where 5 main disciplines are used: Molecular Genomics, Functional Genomics, Quantitative Genetics, Bioinformatics and Numerical Genomics, the last of these bridging the gap between Bioinformatics and Quantitative Genetics. These are used in the study of medicine development and agriculture, particularly animal breeding and health (e.g. growth, obesity, fertility, behaviour, osteoporosis, disease resistance, immune response and vaccines), with particular attention paid to quantitative traits. One aim is to develop bioinformatics tools to isolate trait genes and construct genome maps, but an inherent problem with such bioinformatics tools is the handling of huge quantities of data. He noted that comparisons between chicken, mouse and human genes showed that it is possible to start to identify particular gene traits. The biggest benefit he could see from mathematics and statistics in the near future is the handling of large data sets, including filtering of data to remove non-informative data (he pointed out that some early experiments could have been better designed).

6. SB talked about mathematical and statistical issues in biosensors. In particular, Inverness Biomedical make self-test blood glucose testing kits, which return to the user a reading in mg/dl of glucose in blood plasma. They make single use test strips, which incorporate a small (1 μ l volume) electrochemical test cell for measuring the potential difference across the sample of blood. The electrochemical reaction produces a measure of current with time, and this metric has to be processed to give the best estimate for glucose level. Therefore questions exist around the optimal tuning method for the processing of this metric, and also about understanding the electrochemical response variation with time. He said that modelling was already part of the system design: computational fluid dynamics is used to analyse the fluid mechanics of the (non-newtonian) blood inside the test cell. However it would be useful to combine the fluid dynamics calculations with a calculation of the electrochemical reaction in the test cell in order to understand better the variation of current with time, and enable an accurate measure of blood glucose to be calculated. One of the problems already identified from the CFD calculations was the occurrence of air bubbles in the test cell, which can undoubtedly cause spurious results in blood glucose level. The company is looking at ways of introducing baffles into the test cells to reduce the occurrence of these air bubbles. Blood is chemically complex; many substances can interfere with the reaction, e.g. painkillers, which lead to uncertainty in some parameters. The strips are manufactured in lots, so strips are tested lot by lot (after manufacture) for variability due to supplies, but still the meter needs to know how to convert the current measured to a glucose level. This is done by assigning a code which characterises a current / glucose relationship for a particular lot. The system can be calibrated using clinical data, but the safety and quality of the system is of primary importance. Top of the "mathematical research wish list" would be an integrated fluid dynamics and electrochemical reaction model. More use of statistical methods could also prove beneficial for optimisation issues.

7. NV circulated a paper called "Correlation between transcriptome and interactome mapping data from *Saccharomyces cerevisiae*", by H. Ge, Z. Liu, G.M. Church & M. Vidal, (Nature genetics, volume 29, December 2001 edition, <http://genetics.nature.com>). His work is at the messenger RNA level of control. Genes copied into mRNA are subject to a variety of control systems. He encouraged mathematicians to look at Biology as an area

needing mathematical solutions. NV talked about a Tuberculosis Growth curve data set consisting of an acute growth phase followed by a stationary dormant phase. Antibiotics won't work on bacteria in the dormant phase so the aim is to find genes as potential drug targets for this stage of the disease. The process of finding genes can give rise to raw data that is very messy, and there is a need to allow for variation between experiments. One way of data analysis is to look for neighbour genes that behave similarly, and NV showed a correlation map method of visualising such large data set comparisons. Using this it is possible to see areas of similarity and difference by colour scales. It was noted that this method of comparing neighbouring genes may give correlations, but they are not all necessarily biologically interesting. Ideally it would be possible to add in descriptions of the genes, which might result in suggested causal effects. Any arrangement is also possible by chance: with a 95% significance level between experimental results over 4 time points, 7-800 genes correlate by chance.

8. AMS, the CEO from a spinout company from Heriot Watt University described the development of marine biotechnology in relation to drug discovery, with less than 1% of some 10,000 marine compounds having been commercially exploited. Some of those not yet exploited, it was thought, have potential for anti-cancer drugs (compounds which block microtubial production), dietary antioxidants and novel nutraceuticals. One area which required a mathematical approach to drug discovery was the management of microbial genomics databases, solutions to culturing previously "uncultured" microbes (those which for some reason resist laboratory growth conditions), and a mathematical approach to drug design.

9. MG from Hycor Biomedical (19 employees, no mathematicians or statisticians) talked about development of Enzyme Linked Immuno Sorbent Assays (ELISA), a method for detection of autoimmune diseases, infectious diseases and allergies, e.g. Rheumatoid Arthritis, Systemic Lupus Erythymatosus, measles and mumps. The mathematics in use at the company is mainly statistics and curve fitting: calculating assay cutoffs by normal distributions, analysis of background noise levels, sensitivity and specificity and antibody binding. Potential further uses of maths were identified in analysis of enzyme activity, enzyme characteristics, receiver operating characteristics and comparison of effectiveness of 2 assays, but the limiting factors were resources and time.

10. PM summarised the day's presentations and identified the overwhelming theme of the need for management of huge datasets.

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Some useful websites:

www.dti.gov.uk
www.epsrc.ac.uk
www.faradaypartnerships.org.uk
www.foresight.gov.uk
www.ma.hw.ac.uk/icms
www.sbs.gov.uk/smart/
www.smithinst.ac.uk
www.tcsonline.org.uk

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