Systems Biology: Will it Work?

Clare Sansom reports from a meeting of the Biochemical Society, held at the University of Sheffield.

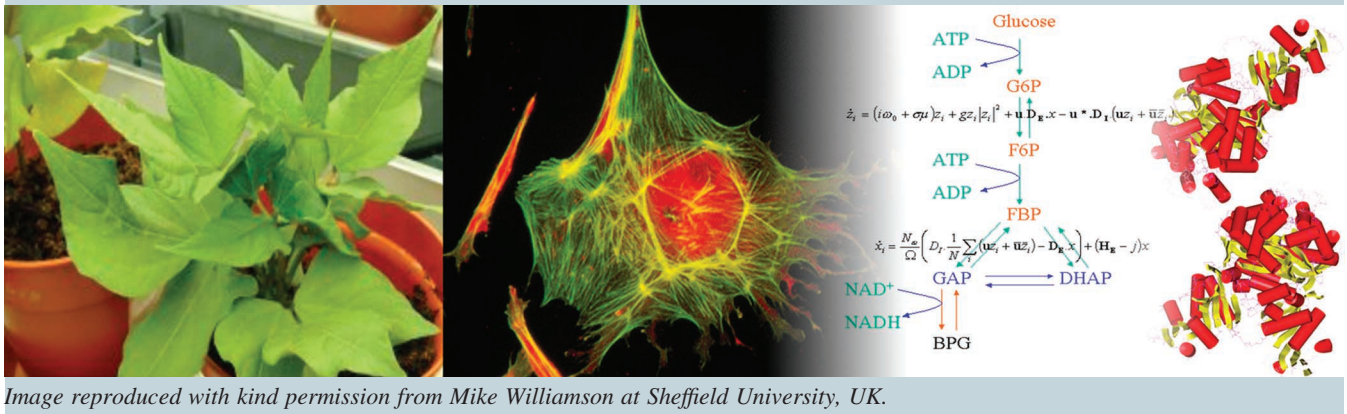
This was the intriguing name of a focused meeting of the Biochemical Society held at the University of Sheffield, UK from January 12–14, 2005. This series of Biochemical Society meetings, now in its third year, is designed to bring together relatively small groups of researchers with common interests. With an area as interdisciplinary as systems biology we expected – and got – some lively discussions and pointers to the future. What we did not get was a definite answer to the question.

Mike Williamson of Sheffield's Department of Molecular Biology and Biotechnology, one of the co-organisers of the event, gave an introduction to the meeting and its objectives. He said that the title was meant to be a question and that he expected it to yield several answers. The objectives of the meeting, he claimed, were for delegates to talk to each other, develop collaborations, and find some clear direction for systems research. Although there is a growing consensus of the importance of systems biology, which is borne out by an explosive growth of papers in this area of research, there are almost as many definitions of systems biology as there are practitioners. There is some consensus, however, that systems biology must aim to fill the gap from the molecular biology "parts list" to the physiological "whole". If systems biology is the modelling of biological systems from a parts list, then we first need to define and understand those parts. This is the task of the "omics" revolution, and it is far from complete. As Sir Peter Medawar said, "Science is the art of the possible"; we may need to simplify to concentrate on parts that we do understand. We may not need to understand every molecule to model a cell, or every cell type to model a tissue; we do need to pick the most appropriate level to model every system.

Olaf Wolkenhauer (University of Rostock, Germany) opened the debate by saying that systems biology needed to be more than a fashionable way of formulating problems in genomics. The characterisation of components – genes, transcripts or proteins – is a separate discipline, but one that is necessary for any understanding of biological systems. Systems biology is the use of mathematics, and modelling, to answer two questions: "how do cell components interact to bring about cell function?" and "how do cells interact to bring about tissue/organ function?". Models are not right or wrong, as much as accurate or inaccurate for a particular system.

Athel Cornish-Bowden (CNRS-BIP, Marseilles, France) delivered a lecture entitled "Systems biology may work when we learn to understand the parts in terms of the whole". Although the "omics" based disciplines are reductionist in nature, systems biologists must move beyond reductionism. Cornish-Bowden quoted Michael Savageau as saying, "If we are reductionists, we must also be reconstructionists". This is already working well in simple examples, such as metabolic pathway modelling. Applying perturbations to enzymes in the galactose pathway led to a model that can be used to understand phenotypic effects, and to an undoubtedly over-optimistic headline in *Nature* (December 2004): "Artificial cells take shape". This is one of the latest, and most respectable, examples of the media hype that has beset those working at the frontiers of biology for at least a hundred years.

Douglas Kell from the University of Manchester and **Jeremy Nicholson** from Imperial College, London, discussed metabolic profile modelling. Kell focused on closed loop machine learning for optimising measurements of the metabolome, a technique that may treble the number of peaks observed. Nicholson introduced the concept of the "superorganism". This is possibly the most complex system that could ever be studied by systems biology: the complex make-up of an organism (e.g. a mammal) and the population of microflora that inhabit its gut. The gut microflora in an adult human typically weighs about 1 kg, making it the third largest organ.



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Analysis of metabolites in rat urine using very high dimensional NMR techniques can reveal very subtle metabolic differences. When toxicology results from members of the Consortium on Metabonomic Technology were pooled, they were found to cluster by laboratory even when controlled for all other variables. Environmental differences in gut microflora are thought to be responsible for this surprising finding. There are also subtle differences in metabolism between dominant rats and the rest of the pack. As long as these subtleties are taken into account, it is possible to predict at least 90% of drug toxicity in rates from the profile of metabolites in urine. Nicholson concluded that metabonomics, or metabolite analysis, can provide a "real world" framework to integrate the other omics. This improves the chances that systems biology will work!

A number of talks focused on studies of proteins and the complexes and systems that they form. **Judy Hirst** (MRC-Dunn Human Nutrition Unit, Cambridge) described a single enzyme that can be studied as a very small system. Mitochondrial complex I is the first enzyme in the mitochondrial electron transport chain; it catalyses the reaction between NADH and ubiquinone, and pumps protons across the inner mitochondrial membrane. It is made up of 46 subunits, of which 14 are "core" subunits that have homologous equivalents in the bacterial complex, and the others can be described as supernumerary. Seven of the core subunits are membrane bound and extremely hydrophobic. Its L-shaped structure has been elucidated to 22 Angstroms resolution by electron microscopy, and it probably contains nine redox cofactors. The pathway for electron transfer through the enzyme is fairly well defined, but little is known about the mechanism of proton translocation.

Sarah Teichmann (MRC Laboratory of Molecular Biology, Cambridge) presented the dynamics of protein systems on a contrasting timescale: evolutionary time. She set up theoretical models of the evolution of protein complexes, and found gene duplication to be a major driving force for protein evolution, with partial duplication of complexes (incremental evolution) predominant. **Liisa Holm** (University of Helsinki, Finland) took a similar approach in applying mathematical modelling to protein interaction networks. A commonly used hypothesis called "guilt by association" assumes that a protein will have similar properties to those it interacts with. This is more accurate for some properties (e.g. subcellular location) than others (e.g. structure and function). The latter can be predicted more accurately by assuming that proteins are similar if they have similar sets of interaction partners. Interaction networks are already being produced for simple organisms such as yeast. But, with 30,000 genes in the human genome, and many different human proteomes, it will take years to catalogue human protein-protein interactions fully. Prioritising the "hubs" - those proteins with many interaction partners - is a useful strategy, but we first need to understand where these are. A directed search that explores the fringe of the interaction network known so far was shown to converge automatically on the hubs.

The British Biophysical Society lecture was given by **Jyoti Choudray** of the Sanger Centre, Hinxton, UK, with the title "Towards systematic biology of the mammalian nervous system" (see below).

Other speakers focused on novel experimental techniques for obtaining the data that will be used by future systems biologists. **Rob Beynon** from the University of Liverpool's Department of Veterinary Pre-clinical Science took the interesting title, "Is yesterday's proteome the same as today's?" The answer to this question, he said, was self-evidently no:

The British Biophysical Society lecture was given by Jyoti Choudhary from the Sanger Centre, Hinxton, UK.

Part of a group that is modelling the human nervous system, she described the subject area as "one of the most difficult and challenging biological systems", and has adopted an integrative approach - i.e. a systems approach - to understanding cognition and learning, using genomics, proteomics and bioinformatics to build up a picture of the gene products involved in these complex processes. Work on the molecular basis of learning goes back to the discovery, in 1949, that changes in electrical excitation in the brain underpin memory.

Choudhary is focusing on one poorly understood system, the NMDA receptor and the complex of proteins that surround it. Mutations in this receptor, and in proteins that are associated with it, are known to affect ability to learn. She has identified over 180 proteins associated with forms of this receptor complex using mass spectroscopy and Western blotting. Many of these have either rodent homologs known to be involved in learning, or have been associated with human cognitive disorders.

The NMDA receptor complex is, essentially, a molecular machine for taking up and passing on information. Enumerating the "long list" of proteins present in this complex is only the very first step in understanding how it works. Choudhary has used the protein-protein interaction database to build these proteins into an interaction network. She is probing the phosphorylation states of the proteins, and hopes, eventually, to integrate the data into a physiological model. But studying a few proteins at a time is slow work. "We need large scale approaches to tackle sets of proteins at once", she says.

Choudhary's work is funded by the Wellcome Trust's Genes to Cognition (G2C) initiative.

molecules in cells are always being renewed. "A mouse has a new liver every day. Has its proteome changed? Yes – and no." And proteins turn over at widely differing rates, leading to poor correlation between the transcriptome and the proteome. Beynon and his colleagues have developed a method of measuring protein half-lives using stable isotope labelled amino acids. He incorporated heavy leucine into yeast cells and measured the length of time it took the radioactivity in each protein to decay, finding a great variation in protein half-lives with some proteins being "effectively immortal", lost from the system only by dilution into daughter cells. Applying this technique to early chick development was harder, since it is impossible to make "all-heavy" chicks. Instead, chicks were fed a diet rich in heavy leucine and the incorporation of stable isotopes into proteins measured by mass spectrometry.

Bob Murphy (Carnegie Mellon University, USA) described an automatic technique for determining the subcellular location of proteins from fluorescence micrographs. Computer programs were trained to recognise subcellular locations from a set of morphological features defined in fluorescence patterns. Although most cell biologists predicted when the work began that it would not be possible for a machine to tell organelle locations apart, the computer model actually did better than human experts, recognising 90% of a set of test patterns against the experts' 83%. It was even able to distinguish between lysosomal and endosomal location, a task that is notoriously difficult for cell biologists. Building on this work, he described methods for clustering images of randomly tagged proteins that provide the first automated, objective grouping of proteins by their location patterns. He also described preliminary work on building generative models for location that can be incorporated into cell models.

An inspiring talk from **Denis Noble** (Department of Physiology, Oxford University, UK) gave delegates an insight into the roots of systems biology as well as a practical illustration that models of the heart are "already working" on a practical level for the pharmaceutical industry. Noble's models of the mammalian heart use cell models that he has been developing for over forty years. His initial models were of the dog ventricle, but he has now produced a model human ventricle, and drug companies are using it to present toxicology data to the FDA. The current generation of heart cell models includes about 200 proteins. But – if estimates that a third of human genes are expressed in the human heart are correct – this is only some 2% of those that would be included in a complete model of heart tissue. "Our work proves that even an imperfect model of an isolated module can produce good and useful results", said Noble.

Two poster presenters were chosen to give oral presentations from an excellent selection of abstracts. **Syma Khalid** (University of Oxford, UK), described a model of a "virtual outer membrane", and **Daryl Shanley** (University of Newcastle, UK), presented an innovative Web based tool to model ageing, which must be one of the most complex of all biological processes.

Molecular dynamics has been a useful tool for structural biologists for several decades. Models of the dynamics of one, or a few, molecules, often embedded in solvent, allow researchers to study the energetics of conformational transitions and drug binding. Khalid, working in Mark Sansom's group in Oxford, is extending this concept to a genuine molecular system: the outer membrane of Gram negative bacteria, which consists of proteins and lipopolysaccharides embedded in a phospholipid bilayer. Outer membrane proteins have beta-barrel folds: a handful of such structures are known and it is possible to model many others by homology. At present, the group is working on developing and automating the enabling methodologies for full-scale simulations, including developing accurate parameters to model lipopolysaccharides, and running test simulations of simplified systems. They are planning to use Grid technology, via the BioSimGrid project, to increase the computational resources available for this project.

Shankley presented a tool for the mathematical modelling of the ageing process that has been developed at the University of Newcastle. Ageing from the cellular to the organismal level is a complex, multifactorial process; it is not known, for example, why genetically similar animals kept in identical environments may have an enormous range of lifespans. Initially, the group has been concentrating on the level of the single cell. They have produced components of a model "virtual ageing cell" to study cellular processes involved in ageing such as telomere shortening and oxidative damage. The eventual aim is to scale up to incorporate models of ageing tissues and even organisms. This collaboration between biogerontology, mathematics and statistics departments is mounted on the web as http://www.basis.ncl.ac.uk; it has been set up as a pilot for the E-science Grid project, and all members of the systems biology and gerontology communities may register to browse and interact with the "public space" of published simulations. Registration for academic users is free.

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Research council funding for systems biology

Alf Game, from the Biotechnology and Biological Sciences Research Council, gave an update on the Council's plan to jointly fund Centres in Integrative Systems Biology (CISB) with the Engineering and Physical Sciences Research Council. He began by putting the scheme into the context of the BBSRC's ten-year vision. Systems biology holds a key place in this vision, entitled "Towards Predictive Biology". The centres are one part of a council-wide strategy that has also included setting up a strategic panel for integrative systems biology and building closer links with physical science organisations including the EPSRC.

The BBSRC has agreed to fund at least three of these centres immediately, and aims to increase the number to six within two years. Nineteen expressions of interest in the first round have been winnowed down to a shortlist of seven, with four more potential centres invited to resubmit in the next round. The first centres will be announced in March or April 2005. "We were pleased by the commitment and enthusiasm shown by the University sector", said Game. "However, we would have liked to see some more interest from industry. Furthermore, we did receive some bids that were not really "systems biology". Bids for little more than genomics and bioinformatics, or only for modelling microbial cells, stood no chance of receiving funding.

The EPSRC will be providing £1M of the £6M earmarked for each of the centres. This money is mainly for engineers and systems theorists to work in them alongside biologists and mathematicians. "It is essential that we ensure that engineers and physical scientists provide underpinning research into the technologies and methodologies of systems biology", comments Elizabeth Pyton, Life Sciences Interface Manager for the EPSRC.

"The UK's been a bit slow off the mark in this area", concluded Game. "We hope that this significant investment by the research councils will drive large-scale change in the UK biology community".

The two final talks gave two different philosophical perspectives on systems biology, and contrasting answers to the question "Will systems biology work?". **Hans Westerhoff** (Amsterdam, The Netherlands) answered the question with the title of his talk: a resounding yes! He began by defining what it meant to say that a science works: "[It] "works" when it enables us to describe, discover, engineer and understand natural phenomena, and when it has its own laws and principles". He then listed examples to prove that systems biology was already fulfilling these criteria: mathematical models of cells (including Noble's), and the use of network analysis to pick rate determining steps in metabolic pathways as drug targets. It has even helped understand and formulate laws such as those that define flux control through metabolic pathways. So systems biology, according to Westerhoff, is already working.

Walter Blackstock (University of Sheffield), the meeting co-organiser, gave a pessimist's – and a drug industry insider's – perspective. He quoted the book of Ecclesiastes: "Is there [any]thing whereof it may be said, See, this is new?" (Ecc. 1:10, KJV) in making the point that fashions come and go as much in molecular biology as in anything else. Productivity in the pharmaceutical industry is going down, with unprecedented research investment yielding disappointingly few new drugs. "The real question is, can "omics" and systems biology make a difference to this problem – and can we afford it?". Whatever systems biology is, it must be integrative. Many of the talks at this meeting still presented data and details. Systems biology needs this data (and we have seen a lot of the data that is necessary for systems biology to work) but we now need to be thinking more about the big picture. We're not there yet.

As Olaf Wolkenhauer said, "A cell is built of molecules, as a house is built of stones. But a heap of molecules is no more a cell than a heap of stones is a house." A well-known quote from Nobel laureate Ernest Rutherford has similar resonance here: "All science is either physics or stamp collecting". The "omics" technologies have been libelled as "stamp collecting", but we need to elucidate and understand the data they produce if we are to understand the physics of biology and to model genuine systems. Systems biology may be beginning to work – Noble's heart models are an exemplar – but it will be a very long haul. The future of systems biology depends on excellent young scientists as much as on building contacts between disciplines and, if the work selected for oral presentation from the submitted posters is typical (see examples on p. 3), the future is in good hands.

The proceedings of the meeting will be published in June 2005, as *Biochemical Society Transactions*, volume 33(3).

Dr Clare Sansom is a freelance science writer, and part-time Teaching fellow with the Department of Crystallography, Birkbeck College, University of London, UK.