Modelling the Virtual Physiological Human

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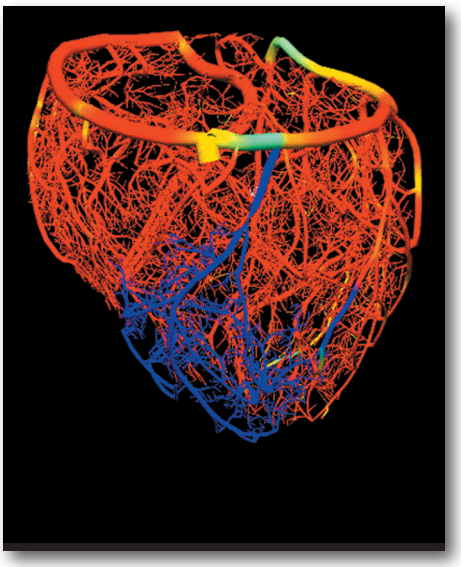
Systems biology – the theme of this issue of *The Biochemist* – can be thought of as more a philosophy of biology than a distinct set of techniques. It arose out of, but is distinct from, the genome projects and associated initiatives. The 'catalogues' of genes and proteins produced in recent years have generated enormous advances, but they do not tell the whole story. Nobel Laureate Sydney Brenner said in 2001 that "I know one approach that will fail, which is to start with genes, make proteins from them and try to build things bottom-up"[1]. In contrast with the reductionism of genomics, systems biology is 'integrative': as another Nobel Laureate, David Baltimore, writes, "it seeks to understand the integration of the pieces to form biological systems"[2]. Thus a typical systems biology study will involve both experimental analysis and computational modelling of a biological system at a number of levels: theoretically, at least, including the molecule, the pathway, the organelle, the cell, the tissue or organ, and the organism.

One of systems biology's most ambitious goals for the next decades is that of modelling human physiology. This is a mammoth task, but one that can, self-evidently, be broken down into small pieces. To start with, some organs and systems are much easier to model than others. The very first research that would now be termed 'systems biology' may be Denis Noble's models of heart muscle cells, first published in 1960[3]. These led eventually to the development of multi-level models of heart physiology that are sophisticated enough to predict cardiac side effects of drugs in development. One reason why this research has proved so successful is the relative simplicity of the heart as a system. Our knowledge of the mathematics behind some other organs and systems is much more primitive.

Modelling the whole of human physiology – coined the 'physiome' by analogy with 'genome' and 'proteome' – is an enterprise that exactly fits the tag of 'Grand Challenge' previously attached to the Human Genome Project and to physical science projects such as climate and ocean current modelling and, outside the computational sphere, the Large Hadron Collider. These challenges are too large for any single scientific community to solve: they must be international as well as multi-disciplinary. Solving complex simulations involves the collaboration of experts from a wide variety of backgrounds. Much of the impetus for supporting collaboration between modelling (and experimental) groups is coming from international scientific organizations such as the International Union of Physiological Societies.

The European Commission has been involved in funding the emerging discipline of physiome research since the Framework Six programme, which ran from 2003 to 2006. In the current Framework Seven, which runs until 2013, this support has been consolidated into the Virtual Physiological Human (VPH) initiative. This funds large and medium-sized collaborative research projects: 15 of these are up and running and another 12 are in the pipeline. Just as importantly, however, it provides support and co-ordination for all physiome-related research projects within Europe or involving European researchers. This generous support for the development and integration of computational models of physiology fits well within the much broader framework of the European Union's 'vision for e-health in 2020', in which future healthcare was described as being 'personalized, predictive and preventative'.



A coronary circulation model has been subjected to a constriction of one of the main branches leading to blocked blood flow in the regions coloured blue. The colour code shows rapid flow in red, low flow in blue. This model forms the basis for identification of regions of ischaemia, which are modelled at a cellular level. Illustration Denis Noble, from *The Biochemist* Vol. 27 (2), April 2005.

Research projects funded under the Framework Seven VPH Initiative are focused on a variety of human organs, systems and, very importantly, diseases. Much research in physiome modelling is very deliberately clinically led, and clinicians and biotech companies are participants in many of the projects. There are two projects involving the heart and two involving the vascular system, but cancer, with four projects, is the best-covered disease. These include the ContraCancrum project (Latin for 'against cancer'), which is developing a tumour simulator that can be adapted to model different solid cancers, and projects to diagnose cancer and to detect recurrence in specific tumour types. Another VPH project, PredictAD, is using computer modelling to develop tools and biomarkers for the early diagnosis of Alzheimer's disease.

Most of the European human systems biology community, however, is not involved in any of the funded VPH projects.

The Network of Excellence has been set up to benefit that whole community. Besides its 14 core member institutions, drawn from seven European Union countries and from New Zealand, the network currently has well over 40 'general' and 'associate' members. The only difference between these categories is that general membership is open to academic institutes and associate membership to commercial and some other organizations. People from all member organizations can benefit from conferences and networking events, training activities, and the development of a 'VPH Toolkit' of computer methods and models. This is a shared resource for the whole VPH community, with members encouraged both to submit and to use tools. Members may also apply for funding for small 'exemplar projects', perhaps to pump-prime a larger grant application, and some conference bursaries are available for junior researchers.

The VPH is co-ordinated from University College, London, led by Peter Coveney in the Department of Chemistry there. More information is available at www.vph-noe.eu/. ■

References

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2. www.systemsbiology.org/Intro_to_ISB_and_Systems_Biology/Systems_Biology_--_the_21st_Century_Science
3. Noble, D. (1960) Nature **188**, 495–497

Best of the Web

Life on the screen

Mark Burgess (Executive Editor)

In 1970, the mathematician John Horton Conway developed his famous *Game of Life*. It simulates the simplest aspects of life with three sets of rules covering birth life and death. It is played on a large grid (Conway used a Go board) with a number of counters, which are placed on it randomly. Each square had eight neighbours, four adjacent orthogonally, four adjacent diagonally. These are the rules:

- Birth. Each empty square adjacent to exactly three neighbours is a birth square and a counter is placed on it at the next move.
- Life. Every counter with two or three neighbouring counters survives for the next generation.
- Death. Each counter with four or more neighbours dies (is removed) from overpopulation. Every counter with one neighbour or none dies from isolation.

The whole board changes with each move; 'dead' counters are removed and counters are placed on 'birth' squares.

Conway showed the game to his friend, Martin Gardner, who wrote in up in the October 1970 issue of *Scientific American*. The *Game of Life* was an immediate success, and was soon programmed for a computer, in ALGOL_68 for the DEC PDP-7, by Mike Guy and Stephen Bourne.

It was the computer's ability to perform iterative tasks quickly that brought out the complexity of *Life*. As well as patterns, certain 'organisms' became apparent. Simple static patterns ('still lives') and repeating patterns ('oscillators') were obvious from the game's board game/blackboard stage. The computer reveal that a particular five cell pattern, the 'f' (now 'r') pentomino takes 1103 generations to stabilize, by which time it has a population of 116 and has fired six escaping 'gliders' (an arrangement of five cells that traverses the board).

Conway originally thought that no pattern can grow indefinitely and offered a prize to the first person who could prove or disprove the conjecture before the end of 1970. It was won in November by a team from the Massachusetts Institute of Technology, led by Bill Gosper; his 'glider gun' produces its first glider on the 15th iteration, and another glider every 30th iterations from then on.

Of course, the *Game of Life* is not simply a desktop toy for geeks; it models emergence and self-organization and demonstrates how patterns emerge from the application of a few simple rules. Scientists and economists, even philosophers, have found much to ponder.

Life is probably the most commonly programmed computer game in existence; Paul Callahan's page (www.radicaleye.com/lifepage/) is a good guide to the bewildering number of varieties and implementations, whereas www.collidoscope.com/modernca/welcome.html is a spectacular showcase of the different types and rules. ■