Modelling the brain: the last frontier?

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Pioneering systems biologist Denis Noble initially trained as a cardiac physiologist. He started using differential equations to model the flow of ions, and thus current, into and out of cells as a graduate student in the early 1960s. These small beginnings have led to the development of computational heart models that are accurate enough to be used to predict which potential drugs are likely to cause cardiac side effects.

Models of this type can be thought of as building blocks in a computational project that dwarfs the genome projects in its complexity: the Physiome Project, which is defined as "an integrated program whose mission is to archive and disseminate quantitative data and models of the functional behaviour of biological molecules, cells, tissues, organs, and organisms". Models of the heart – the 'cardiome' – are the most sophisticated and highly developed of these organ models. Perhaps surprisingly, one reason for this is the relative simplicity of cardiac physiology. Denis Noble acknowledges that he was lucky to choose to study a system so amenable to mathematical modelling, with relatively few cell types that, at least in healthy hearts, act in a predictable, cyclical way. The central nervous system (CNS), which includes the brain, is, in contrast, widely regarded as the most complex of all human systems; the US-based Society for Neuroscience defines it in its educational material as "the most complex living structure known in the universe". Fifteen years after the word "physiome" was first coined, it is useful to survey the state of the art in CNS modelling, and to speculate on how long it will be before computational models of the brain are as comprehensive, and as useful, as the cardiac models of today.

In one sense, however, computational models inspired by the brain have been used in bioinformatics for decades. The phrase "neural network" has two meanings. Biological neural networks are groups of neurons in either the central or peripheral nervous system that are linked together and that, together, perform a particular function. Computer programs that mimic the function of biological neurons are termed artificial neural networks. They are used for pattern recognition and modelling relationships between data, which are very common generic bioinformatics tasks: any biochemist who has spent more than a few minutes using programs to predict the location of transmembrane helices, or to find functional domains within protein sequences, is almost certain to have used a neural network at some point.

Yet although it is perfectly possible to use artificial neural networks to model biological ones, the majority of neural network programs in biology model much simpler systems. Full-scale projects to model the CNS are still relatively few and far between. The EU Framework VII has funded a Network of Excellence, the Virtual Physiological Human, to support European research into modelling and simulations of the human body. It maintains a list of present and past EU-funded and related projects in this area. Currently, this list includes only one CNS-specific project, and that is a very specialized one. The recently completed @neurIST project, funded under Framework VI, has aimed to develop an integrated IT tool for the diagnosis and treatment planning of cerebral aneurysms. This is perhaps more useful than most systems biology projects could hope to be, but it is a long way from the type of integrated simulation represented by models of the cardiome.

However, the worldwide physiome projects do not tell the whole story. Neuroinformatics has been defined by analogy with bioinformatics as a field that encompasses "the organization of neurological data and application of computational models and analytical tools". Some of today's most interesting large-scale neuroinformatics projects have similar aims to the physiome projects without being linked to them. Among them is Blue Brain, established in Lausanne, Switzerland, in 2005.

Blue Brain is an ambitious project to model the mammalian brain down to the molecular level. Its name derives from the massively parallel supercomputer system on which it runs, IBM's Blue Gene. The first stage of this project, now completed, has involved modelling a single neocortical column. This tiny structure, not much larger than the head of a pin, is formed from a group of neurons that function together in a mini-circuit; the number of such columns in the human cortex has been estimated as about two million. Blue Brain's neocortical models consist of thousands of 3D digital images of rat neurons, encompassing a number of different cell types and with each potentially connected to thousands of its neighbours. The electrical connections between the neurons are simulated through ion channel models, much as in the heart models developed first by Denis Noble.

Blue Gene's scientists have estimated that modelling one neuron and its connections takes approximately the computer power of one high-end laptop. The pinhead-sized neocortical column contains about 10000 neurons, with millions of potential connections or synapses between them. Estimates of the total number in the human brain vary, with numbers of 100 billion (10^{11}) neurons and 100 trillion (10^{14}) synapses often quoted. A supercomputer with the power of 100 billion of today's laptops is still in the realms of science fiction. Blue Brain's aim to build a functioning model of the human brain within a decade is a very ambitious one: it is uncertain whether it is realizable. I suggest, however, that increasing collaboration between these and other neuroinformatics groups involved in CNS modelling, and the worldwide physiome project, could be of great benefit to both. ■

Best of the web

Gotcha!

Mark Burgess (Executive Editor)

On 1 April last year, *The Guardian* announced that it would become "the first newspaper in the world to be published exclusively via Twitter, the sensationally popular social networking service that has transformed online communication." and even promised to give the same treatment to its archives, giving examples such as: "OMG Hitler invades Poland, allies declare war see tinyurl.com/b5x6e for more"; and "JFK assassin8d @ Dallas, def. heard second gunshot from grassy knoll WTF?"

This is innocuous stuff compared with the Romanian newspaper *Opinia* which claimed in its 1 April 2000 edition that prisoners were to be granted early release from Baia Mare prison. Sixty people made the long journey to the prison, only to learn that the paper had played an April Fool's joke on them. *Opinia* later published an apology.

The Museum of Hoaxes is a website (www.museumofhoaxes.com) devoted to the preservation and discussion of hoaxes. It has its own online encyclopaedia which collates hoaxes, pranks, urban legends and scams.

An interesting section of the site is the gallery of photographs. The site's owner, Alex Boese, identifies six basic techniques for faking a photo:

1. Inserting details – an early example (late 1860s) is *Lincoln's Portrait*, where the head of Lincoln was pasted on to the body of Southern leader John Calhoun in order to create a heroic-style presidential portrait.
2. Deleting details – this was the specialty of the former Soviet Union, where those who fell from favour, such as Trotsky, were purged from all photographs and it became as if they had never existed.
3. Manipulating elements within the photograph – a modern example of this is *Bush Reads Book Upside-Down*, which dates from 2002. In the original version, the book is the right way up.
4. Falsifying the caption – this occurs early in the history of photography with *Portrait of the Photographer as a Drowned Man* (1840): Hippolyte Bayard pretending to be a suicide victim. (This is probably the first fake photo ever created.)
5. Staging the scene – a particularly vice in photojournalism and, again, one with a long history. In *The Valley of the Shadow of Death* (1855), cannonballs were strewn across a road to enhance the drama of the scene.
6. Taking a photograph at a trick angle – most commonly to use forced perspective and make things appear larger.

Digital trickery is obviously a new phenomenon. One of the first high-profile examples was in February 1982 when *National Geographic* magazine moved the pyramids closer together to fit within the frame of the cover.

The site is also home to the Hoaxipedia, an online encyclopaedia of hoaxes, and hosts a community message board. ■

Now you see them, now you don't: Trotsky, Kamenev and Khalatov retrospectively fail to appear at the 7 November 1919 celebration of the second anniversary of the October Revolution in Red Square.