The heart of the matter

In silico biology: Better tools, and more data, mean that creating virtual organs by computer is no longer a pipe-dream. How will this help the drug industry?

ALTHOUGH he is a mild-mannered academic, Peter Hunter is quick to reveal his heart. It pulses and surges for all to see. Give it a shock and watch it race; disturb its balance and see it beat wildly out of control. And like some men, Dr Hunter, who works at the University of Auckland in New Zealand, has an unerring ability to switch his heart on and off at will.

But Dr Hunter carries this heart on a laptop, not his sleeve. It is an astonishingly life-like representation of the ventricles—the pump room—of a human heart, from the fine net of blood vessels that surround the organ to the specific proteins of individual cells within it. This "virtual" organ is the work of the Cardiome Project, a consortium of bioengineers, physiologists and computer scientists who are knitting together the complex anatomy, mechanics and electro-physiology of the heart into an interactive model.

Unlike video or animation, the on-screen organ is not simply a picture of a heart. In essence, it is a heart whose intricate structure and function has been translated into thousands of mathematical equations and millions of datapoints that are programmed into a computer and run as simulations. As such, it is a spectacular example of *in silico* biology, an emerging discipline that brings computing power to bear on a wide range of biological problems—from analysing genomes to recreating neural networks.

Computer modelling may be standard practice in, say, designing an aircraft or studying planetary motion, but it is only now taking off in physiology. Simple descriptive models—the heart as a pump, or the lungs as bellows—have been used by biologists for centuries. More sophisticated quantitative models describing, for example, the movement of molecules across a cell membrane—in terms of mathematical equations based on fundamental laws of physics—have also been employed for decades.

But there is only so much insight, and so many hypotheses, to be gleaned from simple models. Over the past quarter of a century, molecular biology has begun to reveal the amazing complexity of molecules and biochemical interactions within cells, tissues and organs. And yet what has been revealed so far is a mere trickle of information compared with the deluge that will flow from work on the human genome. Making sense of this information, and understanding how the various pieces interact to produce such complicated biological activities as heartbeats, requires more complex ways of thinking about physiology than can be done on the back of an envelope. Hence the promise of "computational physiology".

Model behaviour

Creating computer models of even single cells, let alone whole organs, is a tricky business. While other complex phenomena, such as climate modelling, pose similar challenges of collecting millions of bits of data and converting them into mathematical models, physiology also brings the problem of scale. Biological entities range in size from single proteins one-billionth of a metre long to bones the length of one's thigh. Biological processes, such as enzymatic reactions, can flash by in milliseconds or, in the case of a heart attack, take place over hours. Fitting this range of events into a single model stretches computing power to the limit.

Dr Hunter's virtual heart forms part of a larger initiative, called the Physiome Project, launched four years ago by James Bassingthwaighte of the University of Washington in Seattle. The grand plan comprises two parts. One is to catalogue physiological information, from previously published research and continuing experiments, into digital databases. The other is to organise this information into a hierarchy of quantitative models that will integrate the activity of one organ—from genes up to whole collections of tissues—to another.

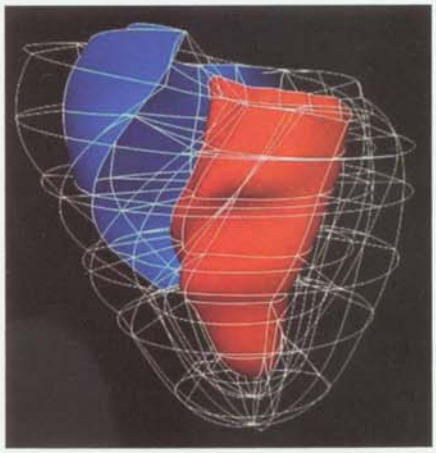
Forget all thoughts of science fiction: the Physiome Project is not an attempt to recreate a "virtual human" on computer. A complete model of everything in the body would not be a model at all, but rather a clone of the real thing. That would leave researchers back where they had started—in need of models of individual organs to help them understand how they work. Nor is the Physiome Project intended to replace messy experiments. What it will be is a tool to help researchers refine their ideas before even reaching for a test-tube, and to improve their understanding of the result afterwards.

Combine and conquer

The virtual heart is a union of form and function on a computer screen. Its gross shape was determined by analysing thousands of wafer-thin slices of a dog's heart. These measurements were then digitised and fed into a computer. The three-dimensional arrangement of the cells and muscles within each slice was determined by microscopy, and that information added to the geometric data in the computer. Also included in the model was a sequence of mathematical equations to represent the physical properties of the tissues involved—defining such things as how the heart tissue behaves when stressed.

All this information was tied together in a program called CMISS, developed by researchers at the University of Auckland to create a structural framework of the heart. On to this framework, Dr Hunter's team was then free to attach "functional components" that represent mathematically many of the activities within the heart—for example, ion channels opening and closing during a surge of electrical current through the heart. The result is a visual simulation that looks and behaves much like the real heart it mimics.

This was a mammoth task, but many ▸▸



Start with a framework

"Computer modelling may be standard practice in designing an aircraft or studying planetary motion, but it is only now taking off in physiology."

of the mathematical tools, modelling tricks and analytical instruments used to create the virtual heart can be used on other organs. Indeed, the Auckland group, with Denis Noble at Oxford University and researchers at the University of Bordeaux, have started modelling the lung. Already, they have created an anatomical model of its branching airways, which includes a representation of how oxygen is exchanged for carbon dioxide.

Modelling how lungs work is even more complicated than simulating the heart, because lungs also depend on the activity of adjacent structures, such as muscles and ribs. Still, models of these are also in the works. Dr Hunter's team has scanned all the bones of the body by laser and created anatomical models of them on a computer. Meanwhile, making models of muscles—which draw on the MRI (magnetic resonance imaging) methods used in hospitals—is also under way.

Yet another organ model under the Physiome Project's umbrella is the microvasculature—the vast network of tiny blood vessels that penetrate deep into almost all the nooks and crannies of the body. Aleksander Popel and his colleagues at Johns Hopkins University in Baltimore are building a model of the micro-vasculature to get a better understanding of how molecules and cells interact in these narrow channels where physical experiments are hard to perform. Although it is still early days, attempts are even being made to model the pancreas, bladder and kidney.

As well as the whole organ modelling under way, other groups are focusing on single cells and trying to mimic their myriad processes using computers. Bernhard Palsson of the University of California at San Diego, who is also head of a local start-up firm called Genomatica, is using a different mathematical technique called "constraint-based" modelling to re-create hundreds of metabolic reactions within *Escherichia coli*, a common bacterium found in the gut. Dr Palsson and his colleagues at Genomatica are now applying the same modelling methods to other micro-organisms, including human pathogens and micro-organisms used in industrial processes.

At Keio University in Tokyo, Masaru Tomita heads an entire institute devoted to *in silico* biology. To date, he has created computational models of the metabolism of a single-celled bug called *Mycobacterium genitalium* as well as human red-blood cells. Another promising cell project is the Alliance for Cellular Signalling, recently launched by America's National Institutes of Health. Its goal is to map the complex network of signalling reactions which cells use as an internal messaging system, and then feed this information into other computational models.

The Physiome Project has some signalling problems of its own. Few of the physiological models and their associated databases can communicate with one another. That is because they tend to be written in different programming languages. Fortunately, help is at hand. A new version of XML (the extensible mark-up language used to define the actual content as well as the layout of web pages) has been developed by Dr Hunter's group with Physiome Sciences, a company based in Princeton, New Jersey.

The new language, CellML, offers a standard way of representing, and exchanging, the wealth of information contained in a variety of organ and cell models. This means that users who are interested in a particular function or part of an organ can import this information from another model over the web, and incorporate it into their own models using their own programming language. In return, the information that they generate from their experiments and include in their models can also be encoded in CellML and similarly used by modellers elsewhere.

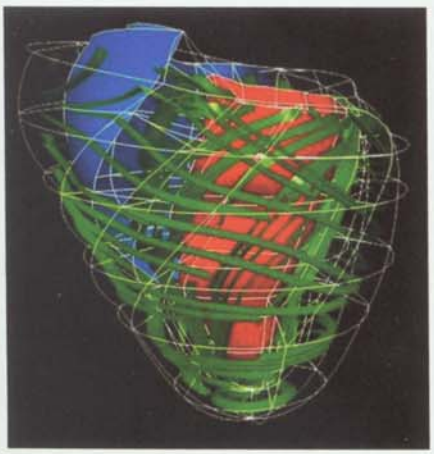
Show me the money

Computational physiology is more than an academic exercise; it excites commercial interest in many quarters. One obvious beneficiary is the information-technology industry. Already, IBM has staked its claim in the biological sciences, forging links with companies working in genomics and proteomics. To reinforce its position, IBM has now moved into computational physiology, licensing know-how from Physiome Sciences to help it integrate information from gene to organ. Along with Compaq and Sun Microsystems, IBM has joined an industry consortium that is seeking to speed the development of CellML.

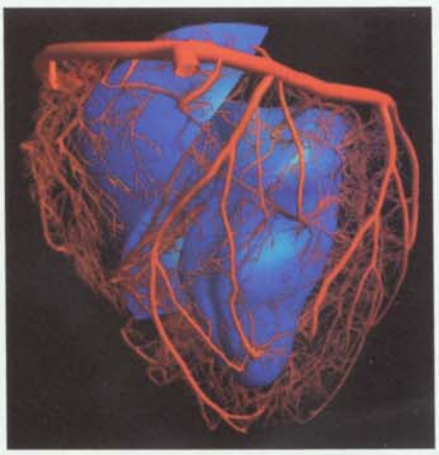
Another firm with an interest in computer modelling is LifeFX of Newton, Massachusetts. It produces "stand-ins"—life-like images of human faces that represent the user over the Internet in, say, reading an e-mail message aloud to an acquaintance, delivering company information or making sales pitches for online retailers. Although a number of other companies have also developed online avatars, LifeFX gets its version from Dr Hunter's laboratory, where many of the same modelling techniques are used in the virtual heart.

The Auckland group has described the complexity of the human face using "finite-element" techniques borrowed from engineering to build a mathematical mesh, over which skin texture and other features are rendered. The model is given life by incorporating data gleaned from analysing videos of a real face doing such things as moving its lips to pronounce specific sounds. This digital model is translated into software which, when downloaded to a user's computer, simulates a face in action.

Medical-device makers, too, have been quick to see the benefits of computational physiology. In orthopaedics, for example, the musculo-skeletal models developed by Dr Hunter's group could be used not only by surgeons planning pre-



Add the functional components



Clothe it in a mesh of blood vessels

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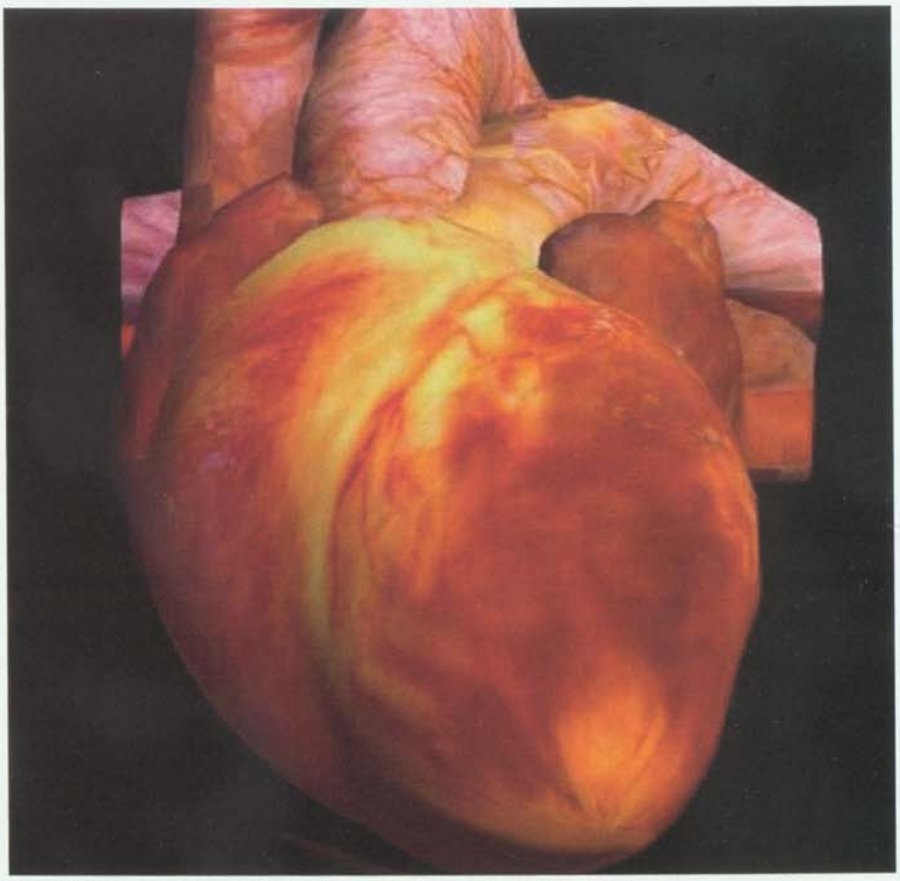
cisely where to make their cuts, but also by prosthetics makers seeking to tailor their devices to suit a patient's specific needs. Tweaking the bone-and-muscle models to take account of, say, an individual's knee shape or bone density would allow braces to be made that support the leg just where the stresses were critical. America's Food and Drug Administration (FDA) now requires physiological simulations of all implantable devices before they can be released on to the market.

Pharmaceutical firms are also looking to computational physiology for ways to improve the design and development of new drugs. Companies need to make hard choices about which of the millions of compounds and targets they should pursue. Picking the wrong ones brings heavy opportunity costs.

Novartis, Aventis and several other firms are testing cellular simulations to see how useful they might prove in developing promising drug candidates, or for rescuing molecules that may have fallen by the wayside in earlier attempts. Entelos, an *in silico* biology company based in Menlo Park, California, has an asthma model which helped one drug firm to redirect its research from drugs acting on one type of inflammatory cell to another. Physiome Sciences' model of blood coagulation showed yet another drug firm why flooding the body with one clotting factor would actually have the unexpected effect of blocking coagulation rather than speeding it up.

Pharmaceutical firms are more sceptical about how useful whole organ models will prove. The developers of such models hope that they might one day be used routinely to assess drug safety and efficacy before firms move into the expensive and lengthy business of clinical trials. The pharmaceutical industry certainly needs new ways of forecasting adverse drug reactions. In recent years, a number of potential blockbusters have failed to meet regulatory requirements, or have been pulled from pharmacy shelves, because of unexpected side-effects.

In fact, the virtual heart has already been put to practical use. Three years ago, it helped Roche to gain approval from the FDA for its calcium channel blocker. It demonstrated that the drug was not causing a particular sort of unusual behaviour (even though the medicine, Posicor, was later withdrawn because of kidney complications). But because computer models are, by definition, stripped-down versions of reality, Paul Herrling, head of research at Novartis, reckons they will have limited use in revealing side-effects compared with conventional animal testing, unless they become as complex and unwieldy as the real thing.



Portrait of a few thousand equations and a million data points

Although some models may have a clearer commercial future than others, they all have a role to play in gaining a better understanding of the body's intricate ways. Unlike the Human Genome Project, which had a defined goal—a complete DNA sequence—the Physiome Project will always be a work in progress. The more that researchers use the models, the more experimental data there will be to feed back into them, and the better they will become, attracting still more researchers to experiment with them. But, as Dr Noble notes, many biologists are frankly intimidated by the complex mathematics in computational physiology. The crucial step of creating tools that allow physiologists to model biological functions without having to grapple with equations and computer code is already in the works.

One such tool being developed by Physiome Sciences and Leslie Loew's group at the University of Connecticut at Farmington allows biologists to create models of how cells function by simply selecting from a menu of pre-defined biochemical pathways and specific locations inside the cell. Do you want to know how changing the level of calcium at the cell surface might influence a signalling pathway that is known to be involved in Alzheimer's disease? Just click and drag.

Modelling that friendly depends on engineers, physicists and physiologists who can handle mathematics with ease. Such people are in short supply. Both the National Institutes of Health in America and the Medical Research Council in Britain have launched recruiting drives to train students who can bridge the gap between mathematics and physiology. Although many who have crossed that divide complain that a shortage of computing power and good biological data are the main stumbling-blocks, for the time being brains, rather than bytes, will determine how far computational physiology can really go. ■