The beating heart of virtual engineering

As the human genome project nears completion, the problem of how to use genomic information in clinical medicine imposes new demands on computational hardware and software. For the beating heart, and some potentially lethal arrhythmias, it is already possible to create a computational pathway from genetic abnormalities to clinical outcome. Using virtual reality techniques, it may soon be possible to ‘hold’ a beating heart in your hands and feel the irregular writhing and squirming as it begins to fibrillate.

A major problem for computational molecular biology is to work out how the three-dimensional structure of a protein emerges, for the sequence of bases in DNA encodes only the linear sequence of the protein’s amino acids. However, the practical problems are not with how genetic information determines molecular structures but with how it determines functional behaviour: of cells, tissues, organs, and systems within the organism.

Empirically, quantitative data exists on the behaviour of some proteins, even though the way this behaviour emerges from molecular structure is still speculative. For example, the behaviour of the membrane proteins forming the channels, pumps, and ion exchangers that determine the electrical behaviour of the heart is known in adequate detail to allow the reconstruction of the heartbeat. The function of the heart is simple enough – it is basically a pulsatile pump – for it to be an ideal test-bed for the application of computational functional genomics. It is an important application: ventricular fibrillation is a common cause of death, and most cardiac deaths are premature as they could be avoided by a changed lifestyle or postponed by interventions. Experimental cellular physiologists, histologists, anatomists, bioengineers and clinical cardiologists in laboratories throughout the world have now characterised the mechanisms and structures of the heart in great detail. Here at Leeds University’s Computational Biology Laboratory we have gone beyond mere simulation and visualisation of this data to the point where our computational techniques amount to virtual tissue and organ engineering (http://www.cbiol.leeds.ac.uk/epsrc-network-home.html).

Within such a virtual heart, the effects on its electrical and mechanical activity of changed protein dynamics, due to drug actions, inherited diseases or pathological processes, can be computed. For example, at Leeds we have used virtual ventricular tissue to compute the life time for re-entrant arrhythmias for the different long-QT syndromes produced by mutations in the HERG, KVLQT1 and hminK genes that are expressed as rapid and slowly activated K+ currents, and in the SCN5A gene that is expressed as incomplete inactivation of the Na+ channel. We have correlated these to the clinically observed differences in cell behaviour.

The pulsatile ejection of blood by the heart depends on the synchronous contractions of its muscular chamber walls, triggered by waves of electrical excitation. These start in a specialised pacemaker region, whose cells are autorythmic, and spread rapidly through the heart muscle, at a speed of up to half a metre a second. The mechanisms generating the electrical activity of single cardiac cells have been analysed and modelled in detail by different electrophysiological laboratories in Europe, Japan and North America, and so there are competing families of models for the different cell types and for different species. Currents flow across the cell membrane through ion-selective channels that open and close with voltage-dependent kinetics; or by ion exchangers; or active mechanisms that require the use of metabolic energy. Each of these channels, exchangers, or pumps, is a transmembrane protein, with a specific structure and kinetics. Different parts of the heart, which differ in their overall behaviours, have different densities of these transmembrane proteins, and these quantitative differences account for the qualitative differences in cell behaviour.

The electrical behaviour of any one cell can be described by a system of about two dozen differential equations, where the different variables describe the kinetics of the channel opening and closing control processes (reflecting changes in shape of channel proteins) and ion concentrations. This high-order system of equations is stiff, with time-scales ranging from fractions of a millisecond to seconds, and can be solved in real time on a PC. These current generation models of cell excitation are being coupled to models of intracellular biochemical pathways and cell metabolism to allow detailed simulations of the behaviour during acidosis and ischaemia, where metabolism as well as membrane properties are altered.

However the heart is not one cell, but some hundred thousand million coupled cells, each slightly different in its properties, and perhaps radically different in its state. In the early 1990s, computations of propagation in a sheet of cardiac tissue with an area of a few square millimetres on the Connection Machine used one node to represent each cell: this obviously could not be extended to the whole heart, a volume of hundreds of cubic centimetres. Since the coupling between cells is by a simple linear resistance, cardiac tissue can be represented by a partial differential equation, with voltage and all the kinetic variables changing in time and space, as a reaction-diffusion equation. The reaction terms represent the non-linear properties of excitability and the diffusion terms the linear coupling between cells.
inside and outside surfaces of the heart can be visualised from magnetic resonance images with a pixel size of 0.33mm x 0.33mm. To compute the electrical activity for a single heart beat (just under a second of real time) takes about a week of CPU time on a 0.1Mflop workstation. Use of more efficient variable step methods offers practical simulation of the electrical activity of the whole heart for illustrative examples rather than systematic research. However, for a few cubic centimetres of tissue, virtual cardiac tissue can be used as research tools, for the design, and virtual pre-screening, of drugs that prevent or lead to the rapid termination of arrhythmias. This forms one component of a suite of Enabling Technologies for the loop analysis of a disease process that are being developed under an MRC Co-operative at Leeds. (http://www.bmb.leeds.ac.uk/enabling_technology). The heart is composed of muscle and connective tissue within a complicated anatomy, within which the heart muscle fibres have an orientation. The local fibre orientation is functionally important, as propagation of electrical activity along the fibre axis is faster than across the fibre axis. The three dimensional surface anatomy of an individual heart – its geometry – can be reconstructed by using a robotic measurement arm to locate surface point co-ordinates, and a model constructed by Computer Assisted Design methods for reverse engineering. This method, originally developed in Auckland, New Zealand, is now being applied by Andrew McCulloch to the pig heart in the University of California at San Diego: the pig will be an organ source if xenotransplantation becomes possible. The resultant tissue ischaemia alters local measures of how much of the blood in the heart chambers is ejected.

Propagation of electrical activity occurs within this three dimensional geometry, with the local velocity faster along the muscle fibre orientation. In the reaction-diffusion model the ‘diffusion coefficient’ is a tensor, obtained from histological measurements of fibre orientation. Computation of normal propagation within an anatomically realistic heart reproduces the pattern of cardiac excitation. If this excitation is coupled, via intracellular changes in calcium ion concentration, to a simple model of cellular contraction the rhythmic beating of the heart can be simulated and visualised. The onset and development over several seconds of cardiac arrhythmias can be computed, along with quantitative measures of how much of the blood in the heart chambers is ejected.

Figure 5: Endocardial and epicardial surfaces of a beating human ventricle before and after ejection of blood, frame from a movie reconstructed from magnetic resonance imaging of the beating human heart.