The beating heart of virtual engineering

Thanks to virtual reality, it is now possible both to visualise and feel the rhythmic beating of a virtual heart. Arun Holden reveals how the fusion of 3D visualisation with computational simulation of functional behaviour can help the development of cardiology, where detailed biophysical descriptions of electrical propagation can be combined with accurate cardiac anatomy

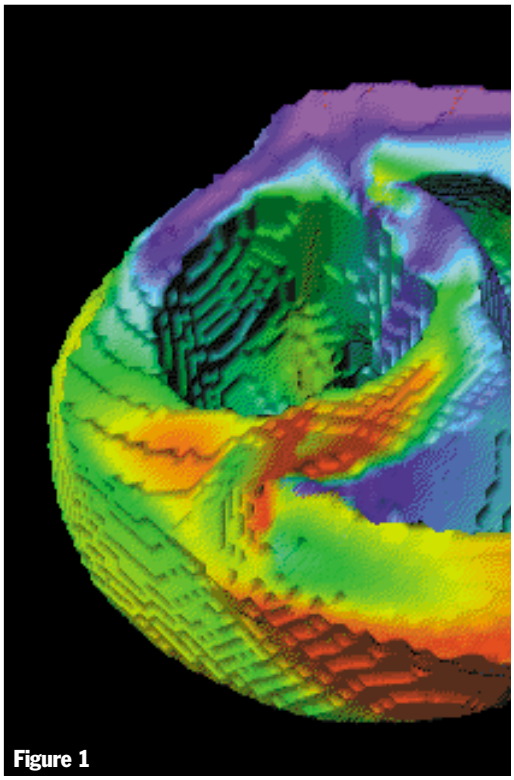
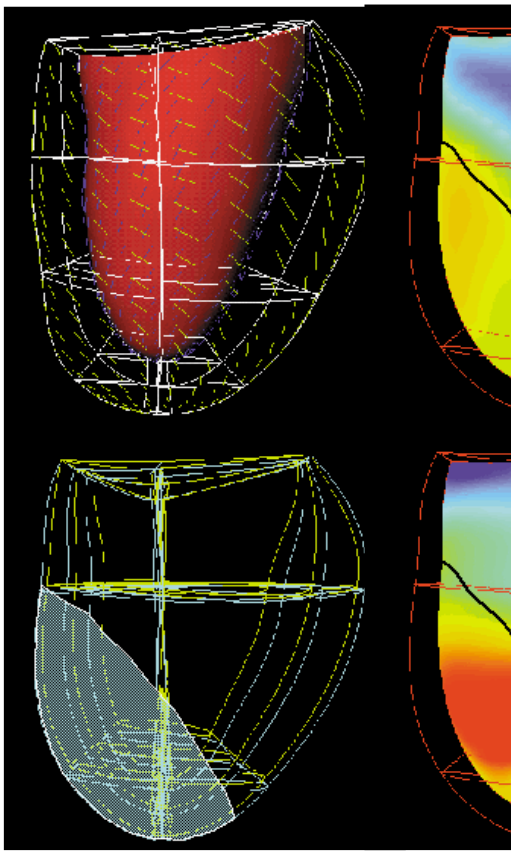


Figure 1

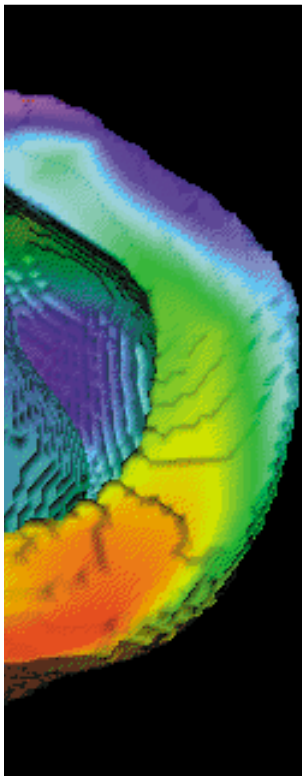


As the human genome project nears completion, the problem of how to use genomic information in clinical medicine imposes new demands on computational hardware and software. For the beating heart, and some potentially lethal arrhythmias, it is already possible to create a computational pathway from genetic 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).

The CardioModel2000 workshop held at the Institute for Biomedical Technology at Karlsruhe, Germany in mid-September and published as a special issue of a free electronic journal *International Journal of Bioelectromagnetism* (http://www.tut.fi/ijbem) brought together biophysically detailed computational simulation of cardiac excitation, propagation, and contraction, with clinical visualisation of cardiac electrical activity and motion. The components for virtual engineering the beating heart are all available in the published literature, or from electronic archives – http://www.ibet.etec.unikarlsruhe.de, http://www.cbiol.leeds.ac.uk, http://bionome.ucsd.edu.



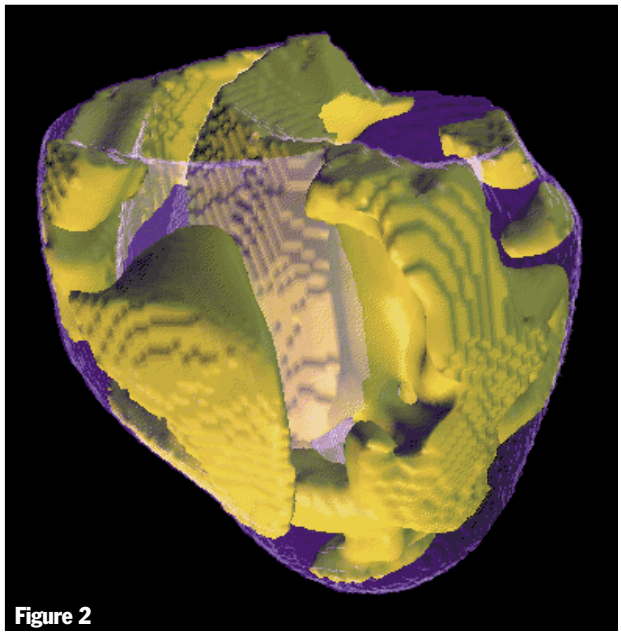


Figure 2

Figure 1: View of the ventricles of a canine heart, looking down into left and right ventricular chambers. The muscle fibre orientation is colour coded. Figure 2: Frame from a movie of irregular propagation during the onset of ventricular fibrillation in an anatomically detailed model of the canine heart: the excitation wave is yellow.

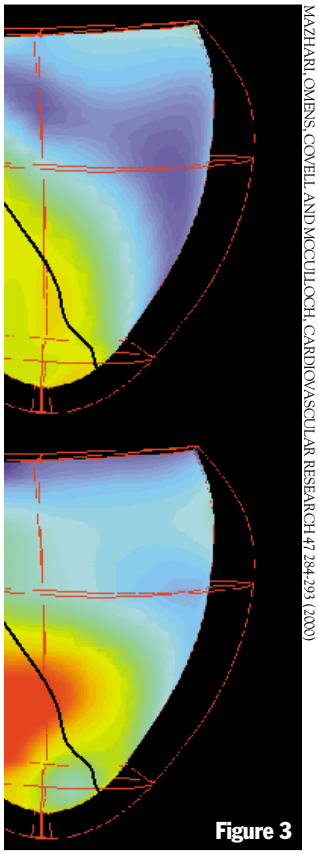


Figure 3

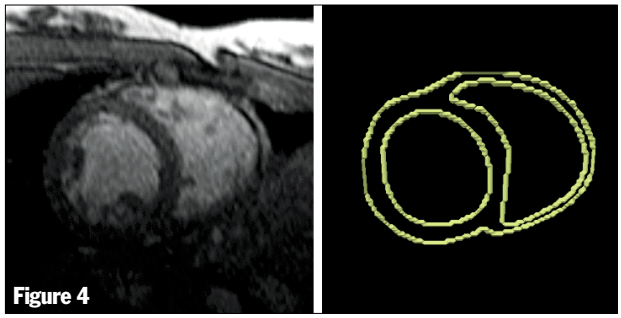


Figure 4

Figure 3: Strain along and across the heart muscle fibres of a computational model of a canine heart where the left anterior descending artery is acutely occluded, causing localised ischaemia. Figure 4: Frame from a movie of magnetic resonance images of a slice through a beating human heart, and the epicardial and endocardial boundaries of the right and left ventricles extracted from the image. The surfaces of the ventricles, and the volume of blood ejected, can be constructed from a stack of such images.

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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 differential mortalities of the different phenotypes for these arrhythmias.

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 autorhythmic, 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.

Numerical solution of such stiff, high-order, partial differential systems, where the tissue properties (equation parameters) vary in space is just becoming practical on fast workstations. Since the kinetics are fast, small time and space steps (typically 0.01 ms and 0.1mm) are necessary. 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 xenotranplantation techniques are applied. Alternatively, the surfaces can be reconstructed from digitised serial sections, as from the US National Library of Medicine Visible Human Project databases. In this way, Frank Sachse at Karlsruhe has reconstructed a female heart from images with a pixel size of 0.33mm x 0.33mm. Static geometry datasets are available for human and other mammalian hearts.

As the heart beats, it contracts and its shape and position changes. The moving geometry of the beating human heart can be visualised from magnetic resonance images, where a temporal resolution of about 80 milliseconds and a spatial resolution of about a millimetre are possible. The inside and outside surfaces of the heart can be reconstructed, along with quantitative measures of how much of the blood in the heart chambers is ejected.

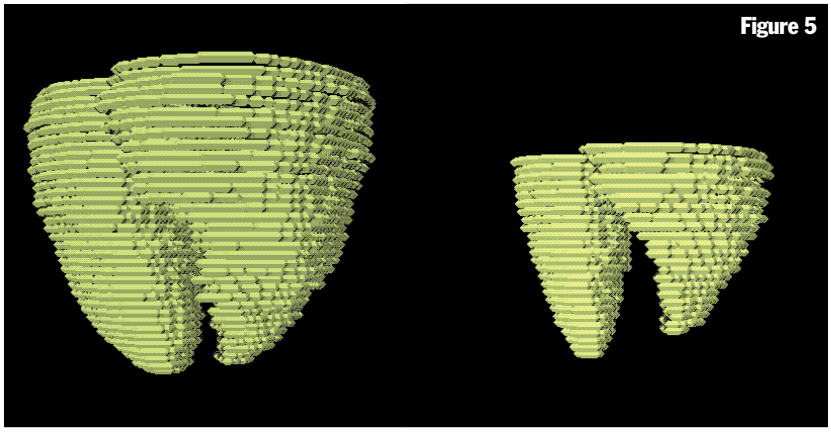

Figure 5

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.

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. The three dimensional behaviours visualised reproduce the surface patterns of excitation seen on experimental arrhythmic fibrillating hearts, or recorded from the surface of the human heart during open chest surgery.

'The three dimensional surface anatomy of a heart can be reconstructed by using a robotic measurement arm and a model constructed by CAD methods'

These are major computations, requiring at least modest supercomputing facilities; we use a cluster of Silicon Graphics 4-processor Origin 200s for computations, and an Onyx 2 InfiniteReality graphics engine for visualisation. The output, the pattern of activity of tens of variables over a complicated and moving geometry, requires high performance graphics, and is visualised as a movie: a sequence of two-dimensional images. However, what is computed is a three-dimensional movie, which can be viewed in three dimensions using switched polarised spectacles on an appropriate graphics display. Such a sequence of three-dimensional images can be exported in a virtual reality format, say in VRML, and viewed on a PC with a VRML browser (http://fly.hiwaay.net/~crispen/vrml/get_browser.html). In collaboration with Open Computer Finance (http://www.ocf.co.uk) we are applying sophisticated visualisation tools such as Opus and Eon (a suite of software tools developed for commercial virtual reality engineering) to export our high-resolution fusions of clinical visualisation and computational simulation into a form accessible by a standard desktop PC. Within the virtual environment, you can move your viewing position and so explore around and inside the beating heart, where what is displayed in colour may be electrical excitation, or ionic concentrations, or mechanical variables such as strain.

Virtual reality techniques allow interaction with the physics of the virtual environment. In principle, it is now possible, using a VR pressure glove with haptic feedback, both to visualise and feel the rhythmic beating of a virtual heart. Then press on a branch of coronary artery and so deprive of blood the area of heart it perfuses, watch how the resultant tissue ischaemia alters local excitability and contractility, leading to an arrhythmia, and feel the irregular writhing and squirming of the virtual heart as it begins to fibrillate.

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