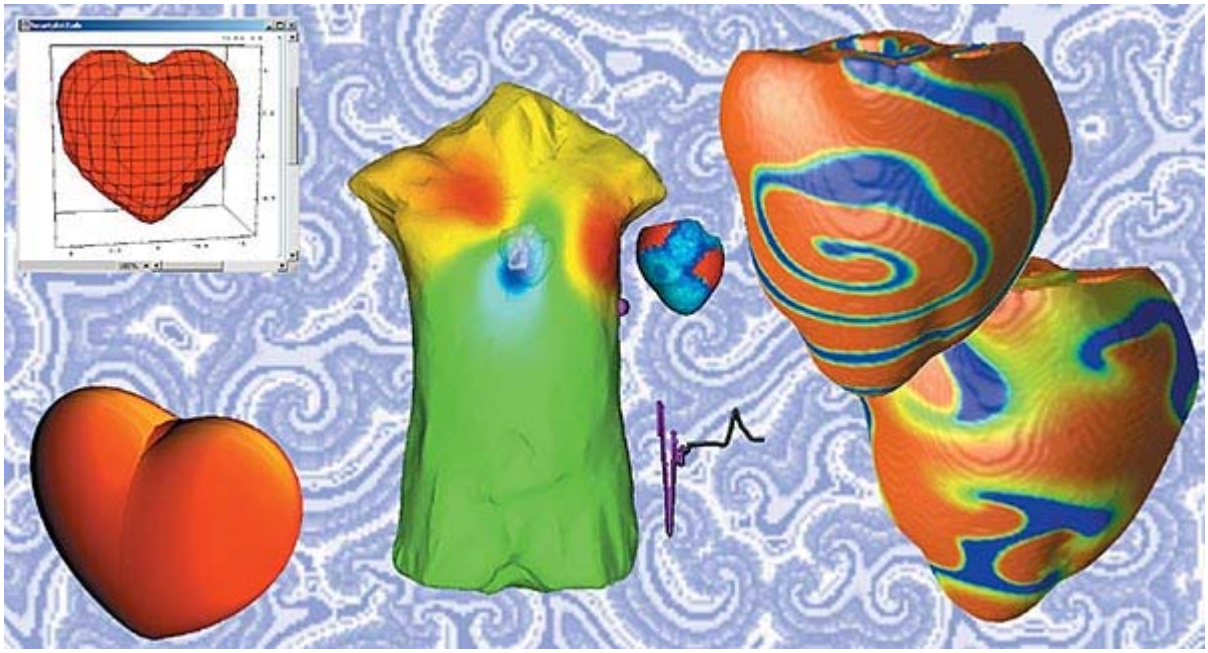
FIBRILLATION

THE BEAT GOES ON

A well (or badly!) timed baseball to the chest can cause cardiac fibrillation. *Ray Girvan* explores how science is unlocking the secrets of the human heart

Some article topics lead inexorably to the thesaurus, dictionary of quotations, and store of bad puns. Heart of the matter? Heart for heart's sake? The beat goes on? Whatever ... the nearness of this issue to Valentine's Day provides an ideal opportunity to explore in more detail the field of cardiac simulation featured in the Summer 2004 issue of our *Life Science IT* supplement. Clare Sansom's article **'The Virtual Human'** reported the pioneering career of Professor Denis Noble. From his early models of electrical Purkinje cells, 40 years of work led to a full 'virtual heart', co-developed by teams at Oxford and the University of Auckland, to predict drug reactions. This achievement highlights an area of study with a wealth of interesting facets.

The impetus for simulation is the heart's unique status. It's a vital organ of crucial medical interest. Naturally, physicians want to know why it goes wrong and how to repair it - but investigation causes huge problems. Observation and experiment involve danger, inaccessibility, and ethical difficulties, particularly in emergencies when there's only one chance to get things right. Hence the appeal of a virtual heart.



Left: The stylised heart symbol (Mathematica code from MathWorld) was popularised by the Victorians, though its origin is obscure. Theories include the Sacred Heart of Roman Catholic symbology; the hieroglyph for the ancient Egyptian 'ab' heart-soul; an erotic anatomical image; and the seed of Silphium, a fennel-like plant used for contraception in ancient Cyrene.
Centre: Diffpack simulation of the location on the torso of cardiac electrical impulses (courtesy of Cardiac Computation Project, Simula Research Laboratory).
Right: Excitation patterns in a simulated rabbit ventricle, the stable spiral of 'flutter' above, the chaotic state of fibrillation below (courtesy of Dr Flavio Fenton, Center for Arrhythmia Research). Background: Spiral waves in the Hodge Podge cellular automata model.

A recap of the biology helps explain why this isn't an easy brief. The heart is a four-chambered muscular pump whose two sides serve separate circuits for the lungs and body. The upper smaller chambers, the atria ('auricles' seems to have gone out of fashion) feed two big lower chambers, the ventricles, that provide the major pumping action. This description is traditionally credited to William Harvey's 1628 *De Motu Cordis*, but at least partial credits now properly go to the 11th century Persian Ibn Sina and the 13th century Arab physician Ibn Al-Nafis. Baffling though the mechanics were historically, there's even greater complexity in its electrical system, the pathway of conductive tissue - picturesquely-named structures such as Purkinje Fibres and the Bundle of His - mapped out piecemeal over the 19th to early 20th century. Starting from the semi-auricular (SA) node that normally initiates heartbeat, this tissue acts as a 'delay line' to trigger atria and ventricles in the correct phase. The heart muscle itself, the myocardium, is also electrically active, propagating excitation and contraction in a smooth wave.

All this leads to a fiendishly difficult multiphysics model. Macroscopically, the heart is a moving 3D structure, both mechanically and electrically anisotropic, pumping a non-Newtonian fluid. Microscopically, its contraction is governed at a cellular level by voltages (action potential) generated by electrochemical process of ion pumping in multi-state cells that go through a sequence of excitable, active and refractory states. Modelling action potential alone involves coupling two equation systems - an ODE such as the Luo-Rudy Phase I model for the cellular ionic activity, and a PDE governing the electrical propagation between cells. Unsurprisingly, major simulation projects, even focusing purely on the physical, fluid, or electrical aspects, have involved supercomputers.

Fortunately, some simplification is possible. General models for excitable media, such as cellular automata (CA) or the Fitzhugh-Nagumo PDE model for wave propagation, give good qualitative simulation. Some workers have ongoing projects to refine such approaches; Tran, Jordan, and Luebke at the University of Virginia have used a CA that reflects the shape and connectivity of real cardiac cells, using a graphics processing unit (GPU) to provide the computing power. This, I think, will catch on as an unconventional route to supercomputing.

That crazy rhythm

There are obviously a variety of areas where modelling is useful. An important one is to aid the design of artificial heart valves, which are made to avoid the turbulence and stagnation (hence clot formation) that plagued early ones imitating those used in plumbing. A classic example was Peskin and McQueen's simulation in 1994, to improve design of an artificial aortic valve. This used the Immersed Boundary Method, modelling the heart as directional fibres in a fluid lattice, and calculated the fibre forces in parallel with a Navier-Stokes solver for the blood. This method is applicable to other purely fluid aspects of the heart; the Oak Ridge National Laboratory has used it to model cardiopulmonary resuscitation (CPR), when the heart may be operating as a 'valveless pump'.

However, if there's a dominant area in cardiac modelling, it's tackling arrhythmias: disorders where the heart fails to beat correctly. Usually this is due to conduction faults either in the electrical system or the myocardium itself, but arrhythmia can also occur in situations when there's no structural problem. Some types aren't dangerous in the short term: the ventricles have a backup pace-making node that keeps them going, irregularly, in case of atrial faults. Ventricular fibrillation, in contrast, is quickly lethal; the ventricle tissue loses co-ordination, writhing rather than pumping. Defibrillation, the administration of a shock to restore a normal rhythm, is well-known; no hospital drama would be complete without it. But less urgent arrhythmias can be corrected by less heroic measures: drugs, a smaller shock, or microwave ablation via catheter of the dysfunctional tissue (Tony Blair, the British Prime Minister, underwent this procedure, cardioversion, in 2004). Again, simulation plays a part. Programs such as Comsol's Femlab have been used to model local damage to tissues, and virtual reality systems such as Medtronic's LocaLisa to map points for ablation.

It's now generally accepted that fibrillation is due to re-entrant waves; electrical excitation that sweeps backward into tissue that's supposed to be inactive until the next beat. A typical onset involves the formation of stable spiral waves: 'flutter', when the heart still pumps, but inefficiently. These can break down into smaller interacting waves: fibrillation proper. There are many groups working in this field; a notable one is the Center for Arrhythmia Research, Department of Physics, Hofstra University, whose website (see references) is worth a visit for its excellent collection of explanatory material. Such waves are ubiquitous in excitable media, and are familiar from popular 2D cellular automata toys and reaction-diffusion systems. Developments such as voltage-sensitive dyes have revealed them in flat cultures of cardiac tissue. But a glance at current papers shows the difficulty of modelling their dynamics in the 3D non-homogeneous medium of the heart muscle. The recent PhD thesis by Kirsten ten Tusscher of the University of Utrecht, *Spiral Wave Dynamics and Ventricular Arrhythmias*, is an interesting analysis of the processes by which spirals break up. Fibrillation, it seems, can involve only half a dozen re-entrant sources. The difference between a normal and chaotic heart is far less than was thought previously.

Chaos may apply literally. James Gleick's book *Chaos: Making a New Science* describes how, in the 1980s, chaos theory became an influential slant on mathematical cardiology. It provides an explanation for some paradoxical aspects of the heart. One oddity is heart rate variability. For a healthy heartbeat, the ECG waveform shows a broad spectrum of variation, which diminishes in many pathological states (contrary to the expectation that a faulty heart ought to be more erratic). Another is that despite being highly fail-safe in the face of major malfunctions, the heart can be thrown out of kilter by quite subtle influences. A chest blow in a 20 millisecond window, typically from a baseball, can induce fatal commotio cordis - mechanically induced ventricular fibrillation. A suitably-timed electrical impulse can do likewise: the death in 1913 of cardiologist George Ralph Mines may have been caused by self-experimentation with this effect.

Chaos theorists interpret such phenomena as signs that the heart is a mathematically chaotic system. In phase space, it follows a strange attractor, a cycle that never repeats exactly, but whose dynamics can be shifted by precise intervention to follow cyclic attractors. These are generally pathological: the repetitive spirals of flutter and fibrillation. This raised the interesting possibility of novel means of cardioversion that would be less traumatic than large shocks. A classic work by Garfinkel, Spano and Ditto suggested the use of OGY (Ott Grebogi York) and similar algorithms to stabilise chaotic behaviour by feedback to a monitored parameter. Such techniques have been shown to work in chemical, electronic and mechanical systems. So far, despite hype in the mid-1990s, they haven't lived up to their initial promise in cardiology.

Simulation meets diagnosis
Cardiac simulation slots in as a component of broader projects to model the body, but it also leads to useful crossover between simulation and traditional means of diagnosis.

While auscultation (listening with a stethoscope) is still useful, the standard clinical technique is the electrocardiogram, a recording of the myocardial signal by external electrodes. The five traces of the ECG (called PQRST) correspond to known portions of the heart; for instance, the P-wave shows the atrial signal. Traditionally, ECG interpretation is a skilled, and partly subjective, task based on recognising typical waveforms. Increasingly, though, automatic dataprocessing is making inroads. Dr. Steven Evans, of Long Island Jewish Medical Centre, has used the DADiSP engineering spreadsheet from DSP Development Corporation to extract waveform information for passing to a neural network that classifies arrhythmia types. Wavelet, Fourier and other derived data are being used; long-term statistics on interbeat interval can be particularly diagnostic.

Correlating ECG with cardiac status can be approached from two directions. The Simula project, Lysaker, Norway, is an example of 'forward' simulation: modelling electrical wave propagation out to the chest surface where the ECG electrodes go (the model is a showpiece application for Diffpack, the C++ objected-oriented finite element library from inuTech of Nuremberg). Conversely, the Image Synthesis Group, Trinity College Dublin, has developed a 'reverse' simulation that processes ECG input, via waveform analysis, to recreate wave propagation on a 3D virtual heart model.

Neither has yet reached clinical usefulness, but I don't think it's too far-fetched a prediction that such approaches will eventually converge. Soon, if your heart misses a beat when your baby kisses you, or leaps up on seeing a rainbow in the sky, it may well be routine for cardiologists to use, rather than an ECG trace, a real-time visual diagnostic display that shows exactly what part of your myocardium is missing or leaping.

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