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Computational modelling of biological systems: tools and visions

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We are currently witnessing the advent of a revolutionary new tool for biomedical research. Complex biochemically, biophysically and pharmacologically detailed mathematical models of 'living cells' are being arranged in morphologically representative tissue assemblies, and, using large-scale supercomputers, utilized to produce anatomically structured models of integrated tissue and organ function. This provides biomedical sciences with a radical new tool: '*in silico*' organs, organ systems and, ultimately, organisms. *In silico* models will be a crucial tool for biomedical research and development in the new millennium, extracting knowledge from the vast amount of increasingly detailed data, and integrating this into a comprehensive analytical description of biological function with predictive power: the Physiome.

Our review will illustrate this approach using the example of the cardiovascular system, which, along with neurophysiology, has been at the forefront of analytical bio-mathematical modelling for many years, and which is about to deliver the first anatomico-physiological model of a whole organ. Already, electrophysiologically detailed cardiac cell models have been incorporated into mathematical descriptions of representative ventricular tissue architecture and anatomy, including the coronary vasculature, and assimilated to realistic representation of ventricular active and passive mechanical properties. This is being extended by matching atrial models and linked to an artificial torso to compute the body surface electrocardiogram as a function of sub-cellular activity during various (patho-)physiological conditions.

We will illustrate the utility of *in silico* biological research in the context of refinement and partial replacement of *in vivo* and *in vitro* experimental work, show the potential of this approach for devising patient-specific treatment strategies, and try to forecast the impact of this new technology on biomedical research, health-care, and related industries.

Keywords: Physiome; mathematical model; heart; ion current; *in silico*

1. Introduction

(*a*) *Do we need another -ism?*

Since the advent of the 'molecular revolution' in biology, there has been an ongoing argument about the interrelation of *integrationism* and *reductionism*. Integrationism

represents the effort to comprehend biological function in its greater context, notably via recognition of the dynamic interactions between a system's components. Reductionism, conversely, focuses on understanding a system's capacity via the detailed description of its constituent parts.

The two apparently contrasting views were expressed in almost aphoristic form during the recent Novartis Foundation meeting on '*The limits of reductionism in biology*' by Professor Lewis Wolpert and Professor Gabriel A. Dover, who said, respectively: '... there is no good science that doesn't have a major element of reductionism in it...'; and '... we have imagined we have explained something merely by describing its parts, but all we have done is create an excuse for not to think about it...' (Bock & Goode 1998).

This leaves us with the question of whether or not the two directions are irreconcilable, or, to put it more positively, whether or not we may resolve the apparent controversy by developing a new framework for life sciences, a new concept, a new logic.

Physiology *is* 'the logic of life'; see also the collection of seminal essays published under that title for the 32nd World Congress of the International Union of Physiological Sciences (Boyd & Noble 1993). The logic of life will neither be recognized without precise understanding of the manifold of components that give rise to biological function, nor without a clear conception of the dynamic interactions between individual components on every level of functional integration. Likewise, the logic of life lies exclusively neither in the most incredible detail, nor in the most sweeping synopsis. Neither of the two—*integrationism* and *reductionism* (and this shall be the last time we affront the reader with an '-ism')—is self-sufficient, and both are obligatory to our quest for knowledge.

This concept of a natural interdependence of opposites that seemingly exclude each other but, equally, cannot survive without the other, is not new at all. It is the central part of modern dialectics—'the soul of all knowledge which is truly scientific'—as taught by Hegel (see his *Shorter logic* in the *Encyclopaedia of the Philosophical Sciences* 1830) and Engels (see *Dialectics of Nature* 1879). And, to go back in time even further, 'combined opposites'—Yin and Yang—are central to old Chinese philosophy and ancient popular wisdom.

As an illustration, we would like to reflect on an old Chinese proverb.

> The wise man walks from the village to the top of the nearby mountain and, after a brief and peaceful rest, strides back to the village. There he stays for a short while, before he returns to the mountain, and so on. Asked why he does this, he replies that he wants to understand his people. But when he dwells inside the village, he can't see the whole of it, and when he is on the summit, he is out of touch with the villagers. So he continues his pilgrimage for eternity.

Can we hope to break the vicious cycle by having a wise man on the mountain top and another one in the depth of the valley? Probably. But only if we can inspire the two to communicate and if we develop tools for their efficient interaction!

(*b*) *The Physiome as route and vision*

The attempt to incite effective communication between scientists at all levels of biological function was publicly initiated at the 33rd World Congress of the International Union of Physiological Sciences in 1997 in St Petersburg, where the *Phys-*

iome Project was officially launched (see http://www.physiome.org). The Physiome Project represents a worldwide effort to organize, systematically, the huge data mass on biological function into a 'quantitative description of the physiological dynamics and functional behaviour of the intact organism' (Bassingthwaighte 1995). The Physiome Project, therefore, sets a vision that will be much harder to accomplish than that of the Human Genome Project, an international 15-year effort, formally begun in October 1990, to discover all the 60 000–80 000 human genes and to make them accessible for further biological study (Hudson 1998). By the time this review is published (i.e. ten years into the project), some 15% of the human genome will have been completely sequenced. Still, at the current rate of increase, it would appear that the target for completion of the project by 2005 will be met two years earlier than originally expected. The new target date in 2003 will also mark the 50th anniversary of the fundamental description of the DNA structure by Watson and Crick.

The Physiome Project should be viewed as both a vision and a route. It has been portrayed as consisting of two parts (Bassingthwaighte *et al.* 1998):

(i) the databasing of biological information (the 'village touch'); and

(ii) the development of descriptive and, ultimately, analytical models of biological function (the 'mountain view').

These are by no means sequential stages of the development.

The Physiome Project will undoubtedly benefit from lessons learned during the progress of the Genome Project, in particular, that big visions and small steps (at least initially) are not necessarily a contradiction. It will, however, have to develop a completely different approach to problem solving than that used for the Genome Project, as neither the total dimension of the task (there are 'only' 23 human chromosome pairs), nor the size of the smallest component that needs investigating (DNA bases), can be defined at the outset of the Physiome Project.

Another difference from the Genome Project is that there will not necessarily be a concerted effort along the whole breadth of the problem. Biological function may be modelled at any level of functioning—from protein folding (Onuchic *et al.* 1997) to neuronal networks (Kotter & Wickens 1998)—and for any tissue, organ or organ system. Examples range from hepatocytes (Cuthbertson & Chay 1991), and pancreatic beta cells (Chay 1997), to muscle fibres (Cannon *et al.* 1993) and neurons (Chay 1996), etc. Despite this breadth, the Physiome Project has developed its first significant foundation in the cardiovascular field. The reasons for this are diverse, and will be addressed in more detail below. Here, we would like to stress that:

(i) models of cardiac cellular activity were among the first cell models ever developed;

(ii) analytical descriptions of most cardiac cell types are now available; and

(iii) large-scale integration of cardiac organ activity is helped immensely by the high degree of spatial and temporal regularity of functionally relevant events and structures.

The Physiome Project will build on linking the descriptions of biological function and structure. On a macroscopic level, this will benefit from another ongoing

large-scale research effort: the *Visible Human Project*. This is an expansion of the US National Library for Medicine's long-range plan of 1986 that aims to create anatomically detailed, three-dimensional representations of the human anatomy. The project is based on collecting transverse computer tomography, magnetic resonance, and cryosection images at 0.5–1 mm intervals. This spatial resolution is sufficient to develop initial models of biological function, in particular where these are related to macro-mechanics or passive electrical properties (Kauppinen *et al*. 1998). A finer resolution may, however, be required in the context of anatomico-functional modelling at tissue level, and, almost certainly, when addressing intercellular or sub-cellular events.

So much for the vision, what about the route? The Physiome Project will, like the Genome and Visible Human projects, crucially depend on the ability to develop the necessary tools for its own successful implementation. Apart from obtaining useful data and building representative databases, this primarily includes the ability to devise appropriate algorithms to model physiological function.

Why model? *The concise Oxford dictionary of current English* defines a model as '*a simplified... description of a system, etc., to assist calculations and predictions*' (Thompson 1995). One can apply this definition in its wider sense to any intellectual activity (or its product) that tries to make out the components of a system and predict the outcome of their interaction. Thus, to think is to model (beware, though, that the reverse is not necessarily true).

To implement the Physiome Project, a lot of 'good science' (Wolpert) and 'thinking' (Dover) will be required. The tools that will ultimately define the success of the project are analytical models of biological processes that have predictive power: *in silico* models.

(*c*) *In silico models as the tool*

The Physiome Project's *in silico* models are to be based on and validated against solid experimental data. Much of the 'input' data is already available, and, with the development of new tools and technologies, the insight into sub-cellular and molecular levels of biological activity will become increasingly detailed. *In silico* biological systems will be produced by quantitatively describing the constituent parts and their interrelation on the basis of the laws of conservation of energy, mass and momentum (Hunter & Smaill 1989; Hunter 1995; see also the review by Kolston in this issue).

These models can be used to perform *in silico* experiments by monitoring the response of a system or its components to a defined intervention. Model 'output'—predictions of biological behaviour—is then validated against *in vitro* or *in vivo* data. Confirmation of modelling-derived predictions will lead to new *in silico* experiments with a higher degree of confidence and/or at a higher level of functional integration. Hypothesis rejection will first define the requirement for new input data and/or model improvement and then allow repetition of the *in silico* experiment with a higher degree of confidence. This is a steady iterative process whose prime objective is the development of our understanding of the system and the improvement of its *in silico* description. Through this multiple iteration the model matures towards a tool that can be used for research and development by scientists and clinicians who are not necessarily specialists in model development or validation.

In the case of cardiac modelling, 'maturation' has already proceeded to a level where models possess predictive power. Examples range from theoretical work on the sodium–calcium exchanger that, in 1980, predicted its stoichiometry some five years before the experimental confirmation (for details see Noble (1995)); over the demonstration of the reciprocal roles that the hyperpolarizing-activated current and the background sodium current play in the control of sino-atrial node (SAN) pacemaker frequency (Noble *et al.* 1992); to recent forecasts on the effect of cytosol dilution on pacemaker mechanisms, which have since been experimentally validated (Lei & Kohl 1998); to name but a few.

Cardiac computer models already play a variety of roles, including the performing of 'test series' for verification of suitability of experimental designs, identification of targets for more detailed research, interpretation of experimental data, and description of causal relationships in complex biological responses. We will illustrate this in § 2, before addressing, in § 3, the significance of *in silico* work for biomedical research in general.

2. Example: cardiac model development

Over the past decade or so, three major developments have occurred that have made attempts to devise comprehensive mathematical models of cardiac function feasible.

(1) Our understanding of cellular and sub-cellular processes in the various populations of cardiac cells is now sufficiently complete to produce very detailed mathematical models of the individual cell types.

(2) Histo-anatomical studies have benefited from new techniques, like the combination of confocal microscopy with immuno-histochemistry, to provide highly accurate information on the fine architecture of extended three-dimensional cardiac-tissue areas. This includes the spatial distribution of cell sub-populations and the different gap junctions (proteins that connect adjacent cells).

(3) The development of new numerical algorithms and a massive increase in computing power have provided the basis for combining anatomically detailed models of cardiac structure with accurate descriptions of function. These models compute organ activity on the basis of simulating ionic and molecular processes on the sub-cellular level.

Before illustrating the state of *in silico* organ models, we will first describe their constituent parts—cardiac single-cell models with different degrees of functional detail—and how the electrical interaction of these can be investigated using lower-order tissue models.

(*a*) *Biophysically detailed single cell models*

(i) *Membrane potential models*

Modelling of cardiac electrical activity has a long history. Back in 1928, the heartbeat was described mathematically by van der Pol & van der Mark as a relaxation oscillator. This gave rise to a whole family of models of excitable cells. Their common denominator is the attempt to represent cellular electrical activity by describing, with a minimal number of equations, the time-course of changes in membrane

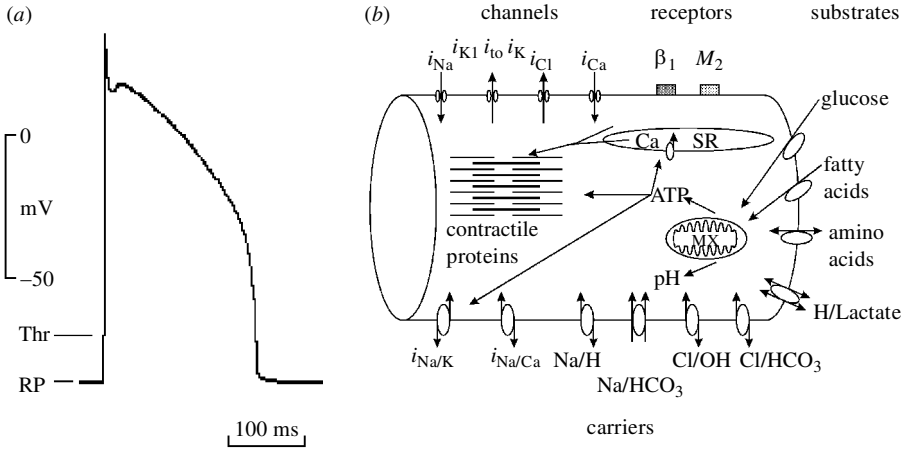

Figure 1. Scheme of a ventricular action potential (*a*) and sub-cellular mechanisms that give rise to it (*b*). (*a*) Cardiac contraction is controlled by an electrical waveform called an action potential. Action potentials are induced by depolarization of cells from their resting potential (RP) towards the threshold for excitation (Thr). Once the threshold is reached, an action potential is initiated, characterized by a swift upstroke (depolarization), followed by a plateau and slow repolarization to resting membrane potential levels. The well-ordered spread of this waveform lays basis to the regular contraction of the heart. Membrane potential models (§ 2 *a* (i)) simulate action potentials (*a*) with a deliberately small number of equations; ionic current models (§ 2 *a* (ii)) reproduce the action potential on the basis of calculating the sub-cellular processes that give rise to it (*b*). (*b*) Example of constituent parts of a detailed ionic current model (here Oxsoft Heart v4.8). The model incorporates essential intracellular structures like the contractile proteins, sarcoplasmic reticulum (SR) or mitochondria (MX), and computes the action potential as a function of ion movements through channels (see a selection of channels present in the model, top left), exchangers and pumps (bottom). This makes it possible to predict the cell's electrical and mechanical activity, and to account for effects of receptor stimulation (see selection at top right: adrenergic, β_1, and cholinergic receptors, M_2), or changes in substrate transporter activity, cell metabolism and pH (right-hand side). Most importantly, (patho-)physiological behaviour may be simulated as it develops in time.

potential (figure 1*a*). Important developments of this approach were the description of excitability, threshold, plateau and refractoriness: key determinants of a cell's ability to respond to stimulation (FitzHugh 1960; Nagumo & Sato 1972).

Models along this hereditary line are continually developed and applied to the simulation of various populations of excitable cells like neurons and cardiomyocytes (for some recent examples see Gan & Wei (1992), Knudsen *et al.* (1997) and Tuckwell & Rodriguez (1998)). Since they are compact, models of this type were the first to be used in investigations of the spread of excitation in multi-dimensional 'tissue' representations consisting of relatively large numbers of interconnected excitable elements (see, for example, Gul'ko & Petrov 1972; van Capelle & Durrer 1980). Their role in assessing biophysical behaviour like cardiac impulse propagation is undiminished (Panfilov & Holden 1993; Panfilov & Keener 1993; Holden 1997; Holden & Panfilov 1997).

One drawback of these models, however, is their lack of an explicit reference between model components and constituent parts of the biological system (e.g. structures like ion channels, transporter proteins, receptors, etc.).

(ii) *Ionic current models*

A major breakthrough in cell modelling was the work of Hodgkin and Huxley as, for the first time, *ionic current mechanisms* that lay the basis to cellular electrophysiology (as expressed, for example, in the action potential waveform, figure 1*a*) were modelled (Hodgkin & Huxley 1952). In contrast to the pre-existing models that merely portrayed membrane potentials, the new generation of models calculated the ion fluxes that underlie specific resting and action potential behaviour.

Hodgkin and Huxley's work (for which they were, jointly with Eccles, awarded the Nobel prize in 1963) provided the core foundation for mechanistic description of cell function. Their concept was applied to cardiac cells by Noble (1960).

Since then, cardiac cellular electrophysiology has made immense progress, as have the related 'ionic' mathematical models (DiFrancesco & Noble 1985; Hilgemann & Noble 1987). There are now various ionic representations of SAN pacemaker cells (Brown *et al.* 1984; Noble *et al.* 1992; Wilders *et al.* 1993; Demir *et al.* 1994; Boyett *et al.* 1997), atrial myocytes (Earm & Noble 1990; Lindblad *et al.* 1996; Nygren *et al.* 1998), Purkinje fibres (Noble 1962; Varghese & Winslow 1994), ventricular myocytes (Beeler & Reuter 1977; Luo & Rudy 1994; Wilders *et al.* 1996; Jafri *et al.* 1998; Noble *et al.* 1998) and cardiac connective tissue cells (Kohl *et al.* 1994; Kohl & Noble 1996). This is an incomplete illustration of examples only, and the catalogue of available models continues to expand. Descriptions of metabolic activity and its relation to cell electrophysiology have been developed (Ch'en *et al.* 1998), and excitation–contraction coupling (Hilgemann & Noble 1987; Rice *et al.* 1999) has been complemented by descriptions of the appropriate feedback mechanisms (Sachs 1994; Kohl *et al.* 1998; Rice *et al.* 1998). Drug–receptor interactions (Cuthbertson & Chay 1991; Noble & Varghese 1998), and even the effects of modifications in the genetic information on cardiac ion-channel proteins, have been computed (Hancox *et al.* 1998; Noble & Noble 1999).

Principal components of cell models developed by the Oxford Cardiac Electrophysiology Group (Oxsoft models of v4.8, Noble *et al.* (1998)) are illustrated in figure 1*b*. We will provide two illustrations of how these models can be used to study processes like myocardial ischaemia (a reduction in coronary blood flow that causes undersupply of oxygen to the cardiac muscle), or effects of genetic mutations on cellular electrophysiology.

(iii) *Cellular effects of ischaemia*

Models of metabolic activity and the effect of energy substrates and metabolites on cell electrophysiology are a relatively recent development (Ch'en *et al.* 1998). Figure 2 illustrates the effect of ischaemic inhibition of cell metabolism on cardiomyocyte function.

In the model, triggered electrical activity (top trace) causes contraction (bottom trace). This process utilizes energy, as becomes particularly evident from the breakdown of the 'high-energy substrate' creatine phosphate into creatine and inorganic phosphate during simulated total ischaemia (see top three labels of the middle section). Concurrent inhibition of the sodium–potassium pump (by acidification and phosphate accumulation) causes sodium overload (curve labelled [Na]). This reduces the cell's ability to extrude calcium via the sodium–calcium exchanger. As a conse-

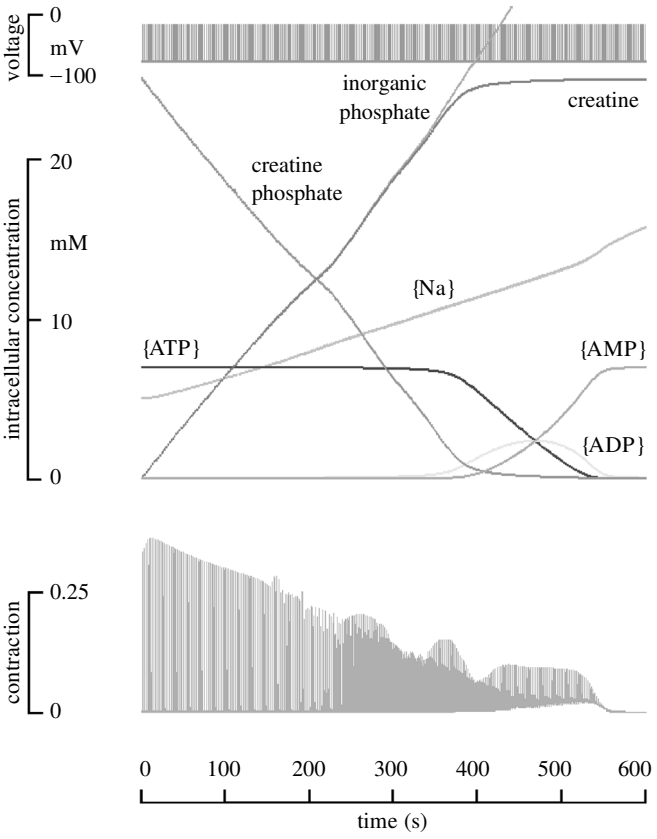

Figure 2. Oxsoft Heart v4.8 computation of metabolite changes during simulated termination of oxygen supply for aerobic energy production. Top panel: triggered electrical activity. Middle panel: concentration changes of selected intracellular metabolites and ions. Bottom panel: contraction. For an explanation see text. Reprinted by permission of Elsevier Science from Ch'en *et al.* (1998).

quence, the intracellular calcium concentration rises, and, eventually, causes calcium-induced arrhythmic contracture (see irregular mechanical activity in bottom trace).

The model reproduces arrhythmic behaviour caused by ischaemia. Interestingly, the arrhythmic interval commences *before* a significant reduction in ATP levels occurs (see middle panel). This is in keeping with key metabolite changes observed in nuclear magnetic resonance studies during total ischaemia (Clarke & Willis 1987). Thus, contemporary models of cardiac cell function during ischaemia allow one to compute a whole range of patho-physiologically relevant events, ranging from changes in oxygen supply to arrhythmic contracture.

(iv) *Cellular effects of sodium channel gene mutations*

The interpretation of human genome data, whether associated with physiological or pathophysiological behaviour, is difficult. Still, a number of pathologies have been successfully related to specific mutations. This is the case, for example, for the human

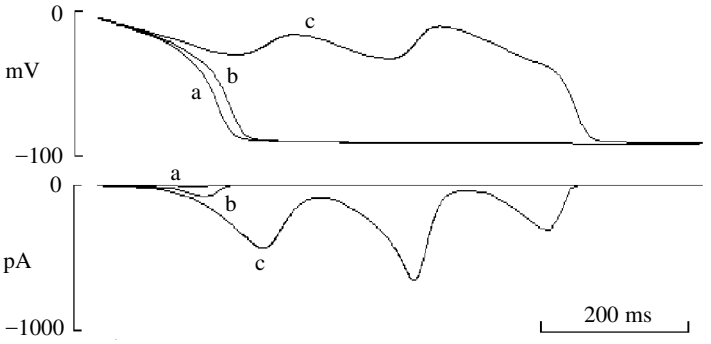

Figure 3. Reconstruction of the arrhythmogenic effects of *SCN5A* gene mutation. Action potential repolarization (top) and sodium current (bottom) are shown in three different conditions: a, normal sodium channel; b, model of *SCN5A* gene mutation, expressed by a moderate positive shift in sodium channel inactivation curve; c, as before, but with a more severe shift of inactivation. Reprinted by permission of The Physiological Society from Noble & Noble (1999).

SCN5A gene, mutations of which have been linked to increased susceptibility to ventricular fibrillation and long QT syndrome (Bennett *et al.* 1995; Wang *et al.* 1995).

The human *SCN5A* gene is a member of the voltage-gated sodium channel gene family. Cardiac sodium channels underlie the fast membrane depolarization at the beginning of each cardiac cycle (figure 1*a*). The link between sodium-channel structure and function has recently been reviewed (Marban *et al.* 1998), and it has been suggested that mathematical models are needed to determine the effects of small changes in ion-channel subunit function on whole-cell activity (Jongsma 1998). This has been approached by implementing the experimentally observed changes in sodium-channel function into a recent version of the Oxsoft guinea-pig ventricular cell model (Noble *et al.* 1998).

The modelled mutation is primarily based on data from Chen *et al.* (1998), who studied the effects of mutations in the *SCN5A* gene of three idiopathic ventricular fibrillation (IVF) families. Electrophysiological studies, using expression of wild-type and mutated sodium channels in oocytes, showed that channels with the mutation recover from inactivation more rapidly. This is apparently caused by a positive shift in the steady state inactivation curve of the channel. Such a shift would delay inactivation and be expected to increase the so-called sodium 'window' current (Attwell *et al.* 1979), a current that could give rise to early after-depolarizations (EADs).

As shown in figure 3, an adequate positive shift in sodium current inactivation may indeed cause EADs, or, during smaller changes in the channel's inactivation behaviour, prolong the action potential (Noble & Noble 1999). This general type of response conforms well with the changes in cellular electrophysiology expected in patients with long QT syndrome and could explain their increased susceptibility to ventricular arrhythmia.

There are, of course, more open questions than answers, and detailed modelling of the impact of the cellular effects on the ECG will further require whole-heart and torso modelling. The present results, however, show that models of cardiac electrophysiology are now sufficiently detailed to allow representation of changes that are induced by arrhythmogenic mutations and to reproduce the cellular mechanisms underlying the fatal arrhythmias they cause.

(*b*) *Multi-dimensional grid-structured tissue models*

Clearly, cardiac function may not be addressed exclusively on the basis of describing the working mechanisms of single cells. Both normal and pathologically disturbed spread of excitation (like re-entry) are based on pathways of hundreds and thousands of cells in length. Much of the biophysics of this behaviour may be addressed in multi-dimensional grid-structured cardiac models (see, for example, Winslow *et al.* 1993; Cabo *et al.* 1995; Zhang & Patel 1995; Biktashev & Holden 1996). Out of the many different applications, we will illustrate the utility of simple two-dimensional and three-dimensional tissue models.

(i) *Two-dimensional grid-structured ionic models of atrial tissue*

Two-dimensional sheets that incorporate thousands of cells, interconnected by model gap junctions, are a versatile test-bed for investigations into the biophysics of conduction of cardiac excitation. Models may be composed of different cell types (pacemaker, atrium, connective tissue, etc.), and experimental conditions (e.g. ischaemia, stretch), cell-to-cell coupling (gap junctions), structural inhomogeneities (pacemaker cells inside an atrial net, or cardiac scars, etc.) may be freely defined.

To illustrate the utility of such models, figure 4*a* shows a two-dimensional sheet of 128×128 atrial myocytes with a small, centrally located, round SAN, 25 cells in diameter. All cells in the sheet are resistively coupled to their nearest neighbours, simulating electrical interaction via gap junctions. The coupling values inside the node are ten times lower than those in the atrium to reflect physiological differences in conduction velocity (Winslow *et al.* 1993, 1995; Cai *et al.* 1994; Winslow & Varghese 1994; Noble & Winslow 1997).

In figure 4*a*, spontaneous pacemaker activity does not succeed in triggering a spreading wave of atrial excitation, as SAN activity does not create a sufficient current density at the SAN–atrial border to depolarize atrial myocytes beyond their excitation threshold. The atrial 'electronegative load' on the pacemaker–atrium boundary is too large (Winslow & Jongsma 1995).

This situation could be overcome by a number of changes in model parameters, like increasing the number of pacemaker cells, or using unrealistic coupling parameters. A more physiological way, however, is to introduce additional structural detail. It has been known for some time that strands of atrial tissue invade the pacemaker area, and vice versa (Opthof *et al.* 1987; Meijler & Janse 1988; Oosthoek *et al.* 1993; Trabka-Janik *et al.* 1994). Simulating simple interdigitations of atrial and nodal tissue at the boundary between the two cell populations is enough to ensure that pacemaker excitation *does* invade the atrial tissue model (see figure 4*b*).

Note that *none* of the parameters that describe electrophysiological or coupling properties of the model have been changed. The interdigitations merely improve the pacemaker's 'driving force-to-passive atrial load' ratio, in particular in the central clefts of the interdigitations, where relatively few atrial myocytes are surrounded by a relatively large number of pacemaker cells. This situation did not occur at the smooth boundary of the node in the previous simulation, where pacemaker and atrial cells were facing each other roughly on a 1:1 basis. The localized increase in current density is enough to depolarize the 'innermost' atrial cells beyond their threshold; once reached, this sets off a spreading wave of atrial excitation.

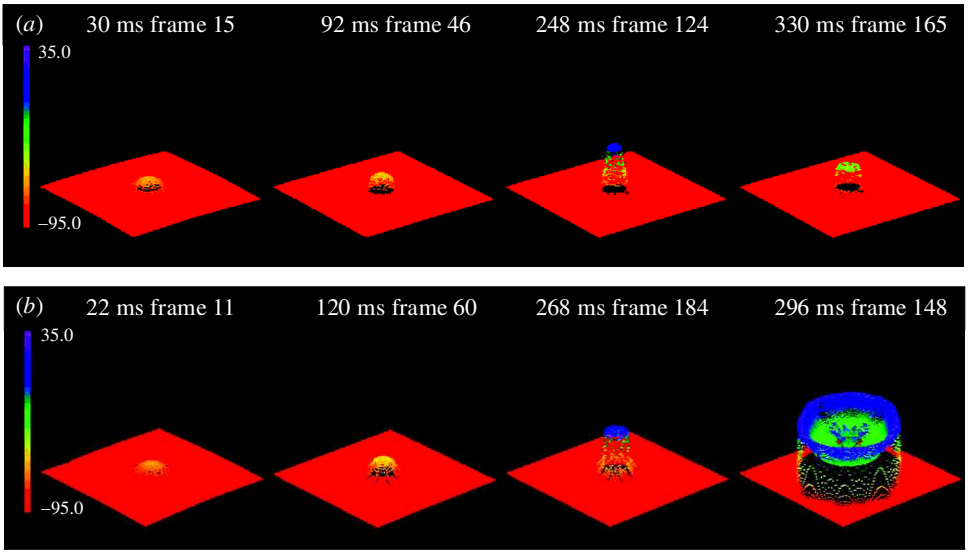

Figure 4. Simulation of pacemaker activity within a two-dimensional grid of 128 × 128 atrial cells (Oxsoft v4.6 models, interconnected by simulated gap junctions). Membrane potentials of individual cells (one pixel equals one cell) are colour and altitude coded (red, −95 mV; blue, +35 mV). (*a*) Maximum diastolic potentials in pacemaker cells are less negative than in atrial myocytes (left). Therefore, during diastole, the pacemaker region slightly depolarizes adjacent atrial cells, while atrial myocytes impose a hyperpolarizing impact on the periphery of the node. Progressive spontaneous depolarization of pacemaker cells (middle frames) causes an action potential in the central node, but this does not spread into the atrium (right). (*b*) Same general conditions as in (*a*), with the exception that sino-atrial node and atrial tissue interdigitate (see second frame). Under these conditions, the balance between electrotonic driving force of the pacemaker and passive load imposed by the surrounding 'electronegative' atrial tissue is changed. At the innermost junctions between node and atrium, pacemaker excitation invades the atrial grid and leads to complete activation of the atrial tissue model (right).

The patterns of SAN–atrial interactions are far more complex in reality, and aspects of preferential gap junctional distribution are not accounted for in this model. Still, the above may serve as an illustration of how basic aspects of the interrelation between structure and function may be investigated in relatively simple two-dimensional models.

(ii) *Two-dimensional anisotropic electromechanical models of ventricular tissue*

The above model is based on equi-directional conduction with no mechanical properties simulated. Cardiac tissue is anisotropic, however, and mechanical activity affects electrical behaviour via mechano-electric feedback (Lab 1982).

In figure 5, a two-dimensional electromechanical ventricular tissue model with a centrally located area of ischaemically damaged tissue is simulated. In the damaged region, intercellular gap junctional coupling is reduced by a factor of ten, cardiomyocytes are slightly sodium and calcium overloaded, passive mechanical compliance is increased, and contractility is reduced. This is to reflect typical changes as they occur in local ischaemia (Ursell *et al.* 1985; Janse & Wit 1989).

Such an ischaemic focus, while morphologically inconspicuous, may act as an obstacle to the normal propagation of electrical excitation. Consequently, a plane wave (triggered along the left edge of the two-dimensional model; see figure 5, frame 1) propagates through the sheet and circumvents the ischaemic area (frames 2 and 3). This causes partial reversal of the direction of wavefront propagation: the ischaemic area is initially invaded from right to left (frame 4).

Retrograde impulse propagation is, in this case, initiated by geometric factors that (i) decrease the electrical load on the ischaemic focus at its proximal edge where the propagating wavefront splits; and (ii) increase the load at the distal edge of the ischaemic focus as that is being hit by two wavefronts of considerable 'depth' (Kohl *et al.* (1997); for further information on the effects of geometrical factors on impulse propagation, see Sahakian *et al.* (1992), Fast & Kléber (1995), Grindrod (1995) and Winslow & Jongsma (1995)).

These purely electrotonic effects are further enhanced by cardiac mechanical activity. The normal wave of excitation activates the healthy tissue that surrounds the damaged area and leads to active contraction (see movement of grid lines in figure 5). As a consequence of increased mechanical compliance and delayed activation, the ischaemic focus is being distended by the mechanical action of surrounding cells (frames 2–4). This passive distension causes, via stretch activation of ion channels, depolarization, and leads to an ectopic focus of excitation (frame 5). The emerging mechanically induced wave of excitation propagates into those tissue regions that first regain their excitability, i.e. again in retrograde direction initially, before re-entry of excitation occurs (frames 6–8).

Such simulations may help to explain mechanisms of arrhythmogenesis in ischaemic foci, to assess parameters (like dimensions and orientation of ischaemic areas) that determine the occurrence of ectopic excitation or re-entry, and to suggest targets for experimental validation. This example shows how re-entry may develop as a consequence of changes in functional parameters, i.e. in the absence of a clear, histologically verifiable substrate (such as regions of necrosis or scar tissue (Kohl *et al.* 1999)).

(iii) *Three-dimensional grid-structured ionic models*

Re-entry of excitation is a most common source of cardiac arrhythmia and fibrillation (Janse 1997). While two-dimensional investigations of propagation prove useful, the behaviour of cardiac conduction in three dimensions is significantly more complex (Winfree 1994; Winslow *et al.* 1995; Holden & Panfilov 1997).

One of the early examples of massive three-dimensional ionic tissue models addressed the question of the minimal size of an ischaemic focus, simulated by sodium overload in a defined tissue region, which would be arrhythmogenic (Winslow *et al.* 1995). A sodium-overloaded cell group was placed in a 20-cell-diameter spherical volume in the centre of a three-dimensional network of $128 \times 128 \times 32$ atrial cells of the Oxsoft type (i.e. more than 500 000 ionic cell models were used). This relatively small 'ischaemic' focus—in real terms, the tissue volume would be of the order of no more than 1 mm^3—is capable of triggering a spreading wave of excitation in the whole tissue model (figure 6).

The above examples illustrate that both qualitative and quantitative conclusions may be drawn from investigations based on multi-dimensional, grid-structured car-

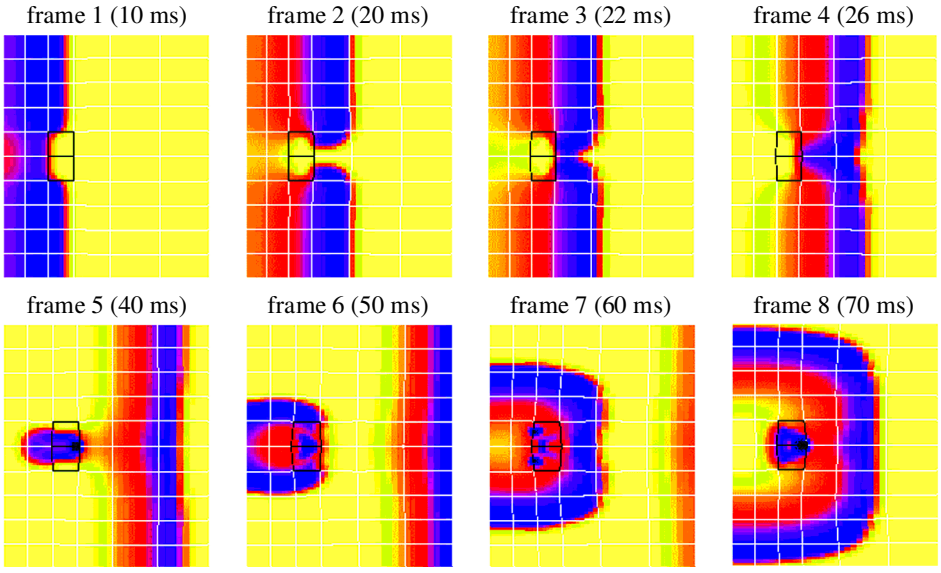

Figure 5. Two-dimensional electromechanical model of an ischaemic focus inside ventricular tissue. Membrane potentials are colour coded, yellow indicating resting, and dark blue indicating peak action potentials. Grid lines illustrate the movement of material points, visualizing active contraction (shortening of grid) and passive distension (elongation of grid). The ischaemic focus is outlined by black grid lines. Reprinted by permission of Elsevier Science from Kohl *et al.* (1999).

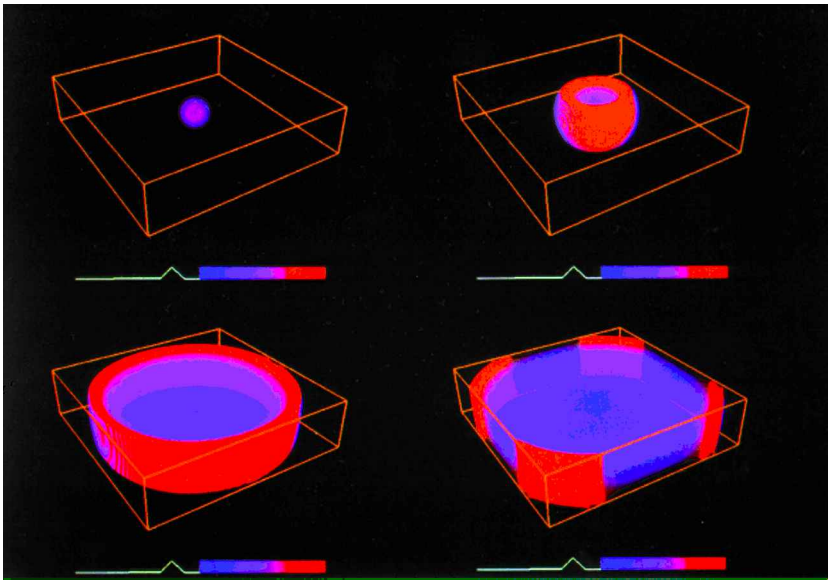

Figure 6. Three-dimensional atrial model with centrally located small sodium-overloaded ischaemic focus. The dimensions of the atrial tissue block are outlined in orange, while the action potential wavefront and plateau are colour coded (red and magenta, respectively). Reprinted by permission of Elsevier Science from Winslow *et al.* (1995).

diac models. On the other hand, these simulations also show that geometrical factors, tissue (in)homogeneity, cell-to-cell coupling, etc., are critical to the utility of cardiac models. Thus, while grid-structured cardiac-tissue models clearly have their place in biomedical research, more sophisticated 'anatomical' models are required to progress beyond the reproduction of biophysical behaviour and towards the provision of physiologically and clinically relevant new insights.

(*c*) *Anatomical models*

(i) *Electrical models*

Simulating myocardial excitation in three-dimensional anatomically detailed models of the heart began with the work of Panfilov and co-workers (Panfilov & Holden 1993; Panfilov & Keener 1993), who mapped finite-difference models of FitzHugh–Nagumo equations to experimentally determined cardiac geometry and fibre distribution data (Nielsen *et al.* 1991).

The first solutions of ionic current models used finite-difference techniques and non-deforming anatomical heart geometry (Winslow & Scollan 1997). Later, ionic current models were linked to material points of a moving finite-element mesh (see § 2 *c* (ii), and Sands (1998)). This allowed simulation of the electromechanical coupling between the activation process and the mechanically deforming finite-element model in both directions: the solution of the electrophysiological equations described the calcium current that initiates contraction, and the shape changes caused by cardiac-contraction-influenced electrical propagation (Hunter *et al.* 1997). Extensions of this work to accommodate more sophisticated models of cardiac ion channels (Luo & Rudy 1994; Noble *et al.* 1998) and cellular electromechanical coupling (Hunter *et al.* 1998) are well underway.

(ii) *Mechanical models*

Initial attempts to analyse myocardial stresses and strains during the cardiac cycle used simplified geometric models of the ventricles (cylinders, spheres or prolate spheroids), often with some variation of fibre orientation through the wall, but always assuming symmetry about a central axis (Dieudonne 1969). Later came linear elastic finite-element models, which allowed a more accurate representation of geometry and used commercial engineering packages to compute stress and strain distributions in the heart (Gould *et al.* 1972). An increasing awareness of the importance of anisotropic and nonlinear tissue properties of the heart soon led to the development of large-deformation finite-element models (Janz & Grimm 1973).

The first quantitative measurements of fibre orientation through the heart wall were made by Streeter & Bassett (1966). They found a smooth transmural variation of fibre orientation and argued that the myocardium was a continuum rather than an assembly of discrete fibre bundles, as had been postulated before (Mall 1911). The first attempt to measure and comprehensively model the detailed fibrous structure of the ventricular myocardium came in 1991 (Nielsen *et al.* 1991).

It was later realized that myocytes are tightly coupled into sheets by the extracellular collagen matrix (ECM) of the heart and that the ECM creates a second material axis, named the 'sheet' axis, which was defined to be orthogonal to the fibre direction in the undeformed state (LeGrice *et al.* 1997). For a more detailed account

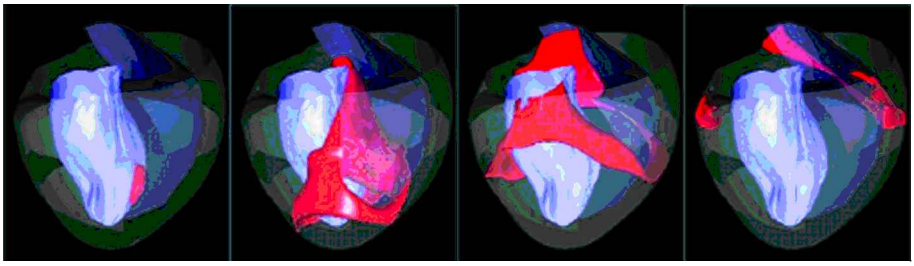

Figure 7. Spread of the electrical activation wavefront in an anatomically detailed cardiac model. Earliest activation occurs at the left ventricular endocardial surface near the apex (left). Activation then spreads in the endocardial-to-epicardial direction (outwards) and from the apex towards the base of the heart (upwards, middle frames). The activation sequence is strongly influenced by the fibrous-sheet architecture of the myocardium, as illustrated by the non-uniform progression of excitation. Red, activation wavefront; blue, endocardial surface.

on the fibrous-sheet structure of the heart and the theoretical framework for the modelling of mechanical deformation of the right and left ventricles see Costa *et al.* (1996) and Hunter *et al.* (1997).

(iii) *Electromechanical models*

In the following examples, we will illustrate the utility of mathematical models of the heart that are based on the combined representation of anatomy and cellular biophysics. These models currently include myocardial activation, myocardial contraction, coronary perfusion, and, to some extent, the coupling between these different physical processes.

Ventricular geometry is based on measurements of the epicardial and endocardial surfaces of both ventricles of a canine heart, fitted with a finite-element model to an accuracy of *ca.* 0.5 mm (Nielsen *et al.* 1991).

In addition to general geometry, the fibrous-sheet structure of ventricular myocardium (LeGrice *et al.* 1997) is also represented by finite-element model parameters, yielding a continuous description of fibre and sheet orientations throughout the myocardium.

Fibre direction and sheet orientation determine passive and active mechanical properties, as well as key electrical characteristics, including patterns of conduction (see figure 7). Active contraction is triggered in the model via excitation–contraction coupling. The underlying electrical properties of cells can be defined to represent any of the single cell models discussed in § 2 *a*.

Furthermore, the first six generations of the coronary tree, starting with the large epicardial vessels and ending with vessels of the order of 100 μm diameter, are represented discretely (figure 8; see also Kassab *et al.* 1993; Smith 1999). A black box model of the capillary bed is used to connect arterial and venous vessels in the model.

Solving this anatomically representative, electromechanical model of the heart requires powerful supercomputational equipment. We will illustrate two examples of such studies, performed on a Silicon Graphics 16-processor (R10000) shared memory Power Challenge.

In the first example, the spread of ventricular activation is modelled (figure 7). As indicated above (see § 2 *a* (i)), elementary membrane potential models are well

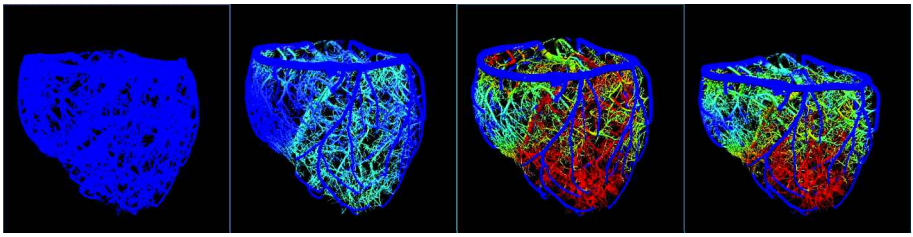

Figure 8. Flow calculations coupled to the deforming myocardium. The colour coding represents transmural pressure acting on the coronary vessels from the myocardial stress (dark blue, zero pressure; red, peak pressure). The deformation states are (from left to right) zero pressure, end-diastole, early systole, and late systole.

suited for this task, and cell electrophysiology is represented here by a FitzHugh–Nagumo-type model. Excitation is initiated by a stimulus point on the left ventricular endocardium near the apex (earliest breakthrough point). Spread of the activation wavefront is heavily influenced by cardiac ultra-structure, with preferential conduction along the fibre direction (Sands 1998).

The second example combines contraction and coronary-tree architecture in one model that allows simulation of changes in intra-luminal coronary pressure during the cardiac cycle. The coronary tree moves with the cardiac tissue into which it is embedded, and the transmural pressure acting on the vessels is calculated from the difference between fluid pressure in the coronaries and external stress. The external pressure is shown to affect the deforming coronary vessel tree in figure 8 (Smith 1999).

Thus, complex electromechanical models of ventricular anatomy and function allow one to describe coronary perfusion during the cardiac cycle. By linking this to the above models of cell metabolism and electromechanical function, the whole sequence from a simulated disturbance in coronary blood supply to depression in ventricular-pressure development may be computed. This possesses an immense potential, not only for biomedical research but for clinical applications, including patient-specific modelling of therapeutic interventions. This approach could, for example, be used for the prediction of optimal coronary bypass procedures, as modelling of a patient's cardiac anatomy is feasible on the basis of nuclear magnetic resonance data (Zerhouni *et al.* 1988; Young *et al.* 1996), and three-dimensional coronary angiography can provide data on coronary-tree architecture.

(*d*) *The heart in the thorax*

(i) *Simulation of the ECG*

The most common tool for clinical assessment of cardiac electrical function is the electrocardiogram (ECG). It is a dynamic representation, usually obtained from the body surface, of the changes in cardiac electrical vector directions and amplitudes.

While the ECG is an invaluable tool for the observation of cardiac rate and rhythm—as well as for the diagnosis of various conduction abnormalities, ischaemia and infarct regions—its detailed interpretation is not without pitfalls. One reason for this is that different changes in cardiac (cellular) electrophysiology may give rise to similar effects on the ECG. This makes it difficult to draw conclusions from ECG waveform changes to the specific underlying sub-cellular behaviour (the 'inverse problem').

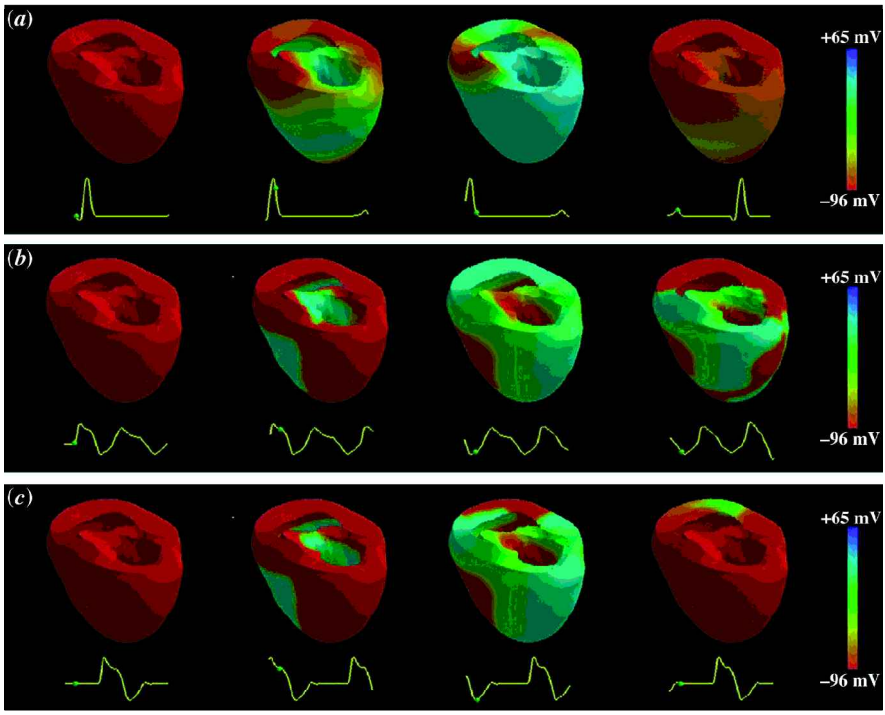

Figure 9. Simulation of the spread of excitation in canine ventricles. Ventricular cell models are based on a simplified version of the Oxsoft v4.6 ionic models. Membrane potentials are colour coded (red, −96 mV; dark blue, +65 mV) and ECG equivalents are computed (yellow lines). Note the absence of a 'P-wave', as no atrial excitation is modelled. The small green dot on the ECG indicates the position of the particular three-dimensional 'snapshot' relative to the cardiac cycle. (*a*) Normal spread of excitation. Frames illustrate the normal sequence of excitation and repolarization during one cardiac cycle (from left to right). (*b*) Spread of excitation in a CHF model. The initial activation sequence (frames 1 and 2) is followed by irregular re-entrant excitation (frames 3 and 4). Note the typical, for this pathology, sawtooth-shaped ECG. (*c*) Simulation of the effect of ATP-modulated potassium-channel openers on the spread of excitation in the same CHF model. The first three frames are closely reminiscent of those leading to re-entrant excitation in (*b*), with the sawtooth-like ECG shape still apparent. Due to the drug effect, however, the heart does reach a resting state before a new cycle of cardiac excitation is triggered (frame 4). This allows time for diastolic filling and permits effective pumping action of the heart.

While today's heart models do not yet possess the power to solve explicitly the inverse problem from body-surface measurements to cell function, they do help in understanding and interpreting the ECG by simulating the forward effects of specific modifications of the cellular models (figure 9*a*). For this, anatomical models of the heart are coupled to a volume conductor that simulates the human torso. This *in silico* chest can be used as a test-bed for studying the effects of defined (patho)physiological changes in cell activity on the ECG (Bradley *et al.* 1997), or to address issues like the optimization of defibrillation electrode placement (Malik *et al.* 1997).

Tools such as this clearly have considerable potential for the interpretation of clinically relevant ECG patterns, as, for the first time, ECG changes can be related

to and derived from alterations in cell electrophysiology. This opens new perspectives for the simulation of clinical manifestations of pathologies and the assessment of drug actions. We will illustrate this using the example of arrhythmias generated during congestive heart failure (CHF), and their pharmacological termination.

(ii) *The pathologically disturbed ECG*

Reconstruction of the normal ECG is the first step towards developing a better understanding of the information 'hidden' in it. As discussed above, approaching the inverse problem of the ECG can be greatly helped by solving a manifold of 'forward problems', to gain insights into causal links between local (cellular) electrophysiological changes and their representation in the ECG.

Here, we illustrate work on simulating CHF. CHF is a primary cardiac disease, characterized by decreased myocardial contractility and reduced cardiac output, which affects *ca.* 1% of the population in Western countries. While therapeutic advances have reduced mortality from pump failure, they have been relatively ineffective in reducing the incidence of sudden cardiac death caused by disturbances in cardiac electrical activity (CONSENSUS Report 1987; Packer *et al.* 1996).

At a cellular level, heart failure is accompanied by changes in the genetic expression of proteins governing electrical repolarization and intracellular calcium handling. These molecular changes prolong the action potential, decrease the peak amplitude of the intracellular calcium transient, and slow down the removal of calcium from the cell. This threatens orderly repolarization of cardiac tissue by increasing the likelihood of EADs that can trigger arrhythmias.

Heart failure is further accompanied by structural changes at the whole-heart level, each of which affects electrical conduction. These include cell hypertrophy, ventricular dilatation, wall thinning, and interstitial fibrosis (for a detailed account on modelling pathologically disturbed cardiac cellular electrophysiology, see Winslow *et al.* (1998, 1999)).

Figure 9*b* illustrates the effect of simulating changes in cardiac cellular electrophysiology that are typical for CHF (down-regulation of transient outward potassium current, inwardly rectifying potassium current and sarcoplasmic calcium uptake, together with up-regulation of the sodium–calcium exchanger) on the spread of cardiac excitation and the ECG. These changes, introduced at the cellular level, lead to the typical pattern of rhythm disturbance in the model, as observed in CHF patients: sawtooth-like ECG patterns, circulating waves of re-entrant excitation, and lack of regular electrical diastole.

Thus, anatomical models of the heart allow one to close the gap between changes in cellular electrophysiology and whole-organ behaviour, as assessed, for example, by the ECG. This type of simulation can be conducted for any pathology whose (sub-)cellular effects are known. Thus, *in silico* technology can provide forward estimations of clinically relevant ECG changes, and, therefore, assist in approaching a solution for the inverse problem of the ECG.

(iii) *Drug effects and the ECG*

Drug effects on single cells differ significantly from those observed in tissues and organs, as cellular interaction principally affects electrophysiology. The analysis of

this discrepancy can benefit from modelling studies, as recently shown on the example of lidocaine (Noble & Varghese 1998), where computer modelling provided the first successful explanation for the large difference in drug efficacy at single-cell and tissue levels.

Modulatory effects of neighbouring cells on drug actions are even more complicated (and important) in the whole organ, where anatomical detail (like preferential conduction pathways), anisotropic tissue architecture (fibres, sheets, etc.), and differences in coupling parameters (types of cardiac gap junctions) affect key electrical behaviour. As discussed before, this is clearly a field where detailed anatomico-physiological models are of great utility.

This is illustrated in figure 9*c*, where application of ATP-modulated potassium-channel openers at a concentration sufficient to increase channel open probability from 0 to 0.0002 was simulated in the above CHF model. This leads to termination of EADs at the cellular level without appreciable action potential duration shortening, and allows the whole heart to regain a stable diastolic resting potential. Thus, while the pattern of impulse conduction in the heart has not entirely normalized, the development of fatal re-entry is terminated by the drug.

Anatomically detailed models of the 'heart in the thorax' provide a useful tool for the simulation of cardiac pathologies, their effect on the ECG, and the consequences of drug administration. Drug discovery and assessment will be one of the first fields where *in silico* technologies will reform research and development in a whole industry.

(*e*) *Summary: cardiac model development*

Analytical models of the heart are a reality. They are based on detailed descriptions of cardiac tissue architecture and anatomy, including the coronary vasculature. *In silico* cardiac tissue possesses realistic passive mechanical properties, and both electrical and contractile activity can be simulated with a very high degree of biophysical detail. Descriptions of key components of cellular metabolism have been introduced, as have models of drug–receptor interactions.

The individual modules of the *in situ* heart can be coupled together to compute a whole sequence from ventricular-pressure development, coronary perfusion, tissue supply of metabolites, cell energy consumption, and electrophysiology, to contractile activity and ventricular-pressure development in the subsequent beat. The 'starting point' (here chosen as ventricular-pressure development) can be freely selected, and drug effects on the system can be simulated. 'Inserted' into a virtual torso, these models allow one to compute spread of excitation, its cellular basis, and the consequences for the ECG under normal and pathologically disturbed conditions.

Ongoing work is devoted to the accurate description of the origin and spread of excitation from the natural pacemaker in the right atrium, via the atria, atrioventricular node, bundle of His, and Purkinje system, to the ventricular myocardium. Computations of ventricular-pressure development are being extended to account for blood-flow dynamics in extra-cardiac vessels. The thorax representation is being extended to allow simulation of respiratory movement, and the computation of pulmonary ventilation and gas exchange is well underway.

Thus, *in silico* cardiovascular tools are among the most detailed biomedical models currently available. Their advantages for biomedical research and development are as follows.

(i) Complex investigations can be performed in a fraction of the *time* required for 'wet' (*in vivo* or *in vitro*) studies.

(ii) The *costs* involved are much smaller than for traditional research. This applies not only to direct financial aspects, but also to requirements in terms of human resources, and to ethical matters, related, for example, to the origin of 'wet' tissue or organ samples.

(iii) The *quality* of information benefits from the fact that interventions and observations can be specifically targeted at any component or mechanism represented in the model, and at any desired temporal and spatial resolution.

(iv) While the first three points improve the quantity and quality of information, *in silico* models benefit further from their (theoretically unlimited) potential for customized presentation of results. This allows addressing aspects like individual preferences in information gathering, remote usage of models, interactive teaching and training, etc.

So much for the advantages. *In silico* tools clearly have one major drawback: they are models. While this very nature of *in silico* technology is *the* core foundation for the benefits listed above, it also calls for a word of caution. It is imperative for *in silico* tools to be seen in the context of a whole range of scientific and research tools, as theoretical considerations need experimental validation.

Thus, *in silico* models are by no means self-sufficient. They are irreplaceable for the future progress of biomedical research. They do not aim to replace biomedical research, which will keep being indispensable for model development and validation.

3. *In silico* technologies: an outlook

(i) *Drug development*

We conclude this review by considering the immense potential of *in silico* technology for biomedical research and development. A recent report by industry analysts PricewaterhouseCoopers, titled 'Pharma 2005: an industrial revolution in R & D', highlighted the following.

> Emerging *in silico* techniques and technologies... will enable the industry to identify targets with the ideal physiological and pathological characteristics... Computer modelling will even provide the tools with which to perform *in silico* clinical trials, based on whole organ body models that test for everything, including side effect profiles, and drug–drug interactions—although it is doubtful that the regulators will accept such evidence for some time. In short, within a few years, the industry will be able to move straight from the test tube to man, if not to the marketplace.†

The drug industry's current approach to R & D is largely based on trial and error. Some of these errors have proved quite costly (see, for example, CAST Investigators

† The detailed models of the heart described here have, in fact, already been accepted by the FDA to explain drug effects on the ECG in the context of a new drug application by Hoffman–LaRoche (Noble 1997; Winslow 1998).

1989). Analytical computer models clearly have the potential to reduce the risk of clinical testing.

There are a number of levels in the drug development process at which *in silico* technologies will be of great benefit to the industry.

First, in duplication of the current 'trial and error' approach, *in silico* models can be used for primary scans through the huge database on compounds developed by combinatorial chemistry, to assess the potential usefulness of specific substances. This will help to accelerate the progress of newly synthesized substances into the pre-clinical testing stage.

Second, as only an estimated 10% of pre-clinically tested lead compounds are likely to ever reach the market, it is important to identify the most promising compounds at an early stage. *In silico* models will speed up and simplify the assessment of complex pre-clinical data and predict (patho)physiological (side)effects of drugs.

Third, as most substances lack strict organ specificity, interactions with receptors in other cell populations or cross-reaction with other drugs tend to give rise to unexpected behaviour. This is another area for the application of analytical models of organs, organ systems and organisms, right up to the *in silico* patient.

The applications listed above will not, however, bring about the crucial change in the industry's approach to drug development. What is needed is, fourth, a shift towards identification of the desired drug effect and description of the sub-cellular target for pharmacological intervention *before* compound synthesis or testing commences. This may well include counter-intuitive leads, as recently demonstrated for the direction of change in sodium–calcium exchanger that is implicated to reduce arrhythmogeneity during ischaemia (Ch'en *et al*. 1998).

Thus, one consequence of the traditional approach to drug discovery is that the pharmaceutical industry appears to accept the dogma that the overwhelming majority of drug-development programmes fail. It is likely, however, that the adoption of the new technologies described here will reverse this trend by making drug discovery and development more predictive. This will allow the industry to re-address complex diseases, such as cardiac arrhythmia, that represent an important therapeutic need and a large worldwide market, but have been notoriously difficult to tackle with the trial-and-error approach.

(ii) *Device development*

Like the pharmaceutical field, the world of medical devices is also entering a new and very challenging phase in its development. Successful products will be those that are increasingly tuned to flow with the stream of human physiological function, even to mimic it in fine detail. Modelling and computation are set to make major contributions for several reasons.

First, as devices become increasingly intelligent, with their on-board computing power, they can be designed to mimic the way in which human organs function. For this, analytical descriptions of organ function are required.

Second, accurate and efficient modelling of organ function provides a test-bed for the development of devices that are energy efficient and less invasive. This is badly needed in the cardiac field since defibrillators, for example, use excessive levels of energy. They would be better tolerated if the applied energy could be reduced even modestly, let alone by an order of magnitude. This should be achievable, as is

evident from the fact that mechanical cardioversion (chest thump) consumes about two orders of magnitude less energy than electrical defibrillation (Zoll *et al.* 1976). The great majority of the energy delivered in electrical cardioverters/defibrillators is consumed in ways that, at present, we cannot control. Similarly, pacemaker devices need to become more intelligent, capable of detecting when they are really required, thus avoiding unnecessary 'kick-in'.

Third, as specialist equipment is easier to (re-)produce and more portable than specialist expertise, it is likely that future medical training, diagnosis and (even surgical) treatment will be performed remotely. The combination of sophisticated sensory devices with micro-manipulation equipment of a high number of degrees of freedom, together with three-dimensional 'interactive feedback' models, will provide further tools and novel approaches for the medical profession.

(iii) *Benefit for society*

'*The proper study of mankind is man*' (Alexander Pope, *An essay on man* 1733; see Brady (1965)). *In silico* technology is set to produce a quantum leap in understanding the nature of man, for it is only through the identification of information in the vast amount of data on 'man' that we will arrive at a genuine comprehension of our biological nature.

Analytical bio-modelling is also set to make major practical contributions and to transform the pharmaceutical and device industries on which future developments in health-care depend. The 'added benefits' of *in silico* technologies for health-care include the following.

(i) New interactive *in silico* teaching and educational tools will be available for doctors and the greater public. This will help improve professional skills and general health awareness. Future health-related implications of behavioural patterns or treatment strategies can be assessed and compared on the basis of longitudinal case predictions.

(ii) *In silico* technologies will help acute decision making and long-term health-care policy development. Decision making will be based on improved access to expert information, statistics, case reports, etc. Medium-term decisions will benefit from the early recognition of epidemiological patterns, etc. Long-term policies can be based on detailed investigations into the cost–benefit relation of restorative versus preventative strategies, which will ultimately lead to the triumph of preventative medicine.

(iii) *In silico* models will aid both the standardization and individualization of medical care. Standardization of diagnoses, drug and device descriptions, procedures, etc., will make relevant information more readily available. On the other hand, advanced models will allow development of patient-specific procedures for diagnosis and treatment. This will move the focus from the treatment of diseases to the curing of patients.

(iv) All the above effects will ultimately lead to reduction in morbidity and mortality and an improvement in the quality of life.

This would seem to be fitting logic for life.

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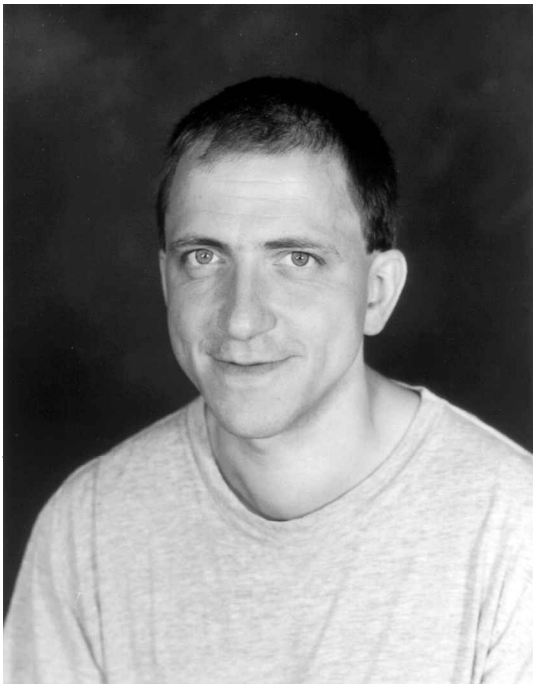

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Denis Noble, 63, is the British Heart Foundation Burdon Sanderson Professor of Cardiovascular Physiology at the University of Oxford and a Fellow of Balliol College. In the early 1960s, he developed the first 'ionic' cell models of cardiac excitation and rhythm generation and has been at the forefront of computational biology ever since. As the Secretary-General of the International Union of Physiological Sciences, he has been pivotal to the initiation of a worldwide effort to describe human physiology by analytical models: the Physiome Project. In 1998 he was honoured by the Queen for his services to Science with a CBE. Denis Noble enjoys playing classical guitar, communicating with people all over the world in their mother-tongue, and converting the preparation of a meal into a gastronomic celebration.

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Peter Hunter, 51, is a NZ Royal Society James Cook Fellow and Chair of the Physiome Commission of the International Union of Physiological Sciences. He founded the Biomedical Engineering Group at Auckland University, which, in close collaboration with the Auckland Physiology Department, uses a combination of mathematical modelling techniques and experimental measurements to reveal the relationship between the electrical, mechanical and biochemical properties of cardiac muscle cells and the performance of the intact heart. A similar approach is also being used by the Auckland group to analyse gas transport, soft tissue mechanics and blood flow in the lungs with the aim of producing an anatomically detailed, biophysically based coupled heart–lung model for use in drug discovery and the clinical diagnosis and treatment of cardiopulmonary disease.