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THE MAKING OF THE VIRTUAL HEART

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## Introduction

This essay is about the making of the most comprehensive computer model of a human organ to date: the virtual heart. It will beat, ‘consume’ energy or experience the lack of it, respond to stress or drug administration, grow and age – in short, it will behave like the real thing. Or, let’s say, close to. Because the virtual heart may be stopped without harm at any point in time, and dissected, inspected, resurrected, etc... We shall address this in more detail below, together with other enticing aspects of virtual organ development. In particular, we will try to:

- review the need for virtual organs in the context of contemporary bio-medical research;
- introduce the ideas behind the ‘Physiome Project’ – a world-wide research effort, similar to the Genome Project, to describe human biological function using analytical computer models;
- provide insights into some of the more technical aspects of the virtual heart; and finally
- address the utility and benefit of this new tool for biomedical research, drug & device development, and the wider society.

In order to understand the dimensions of the making of the virtual heart – let’s stand back, for a minute, and consider the difficulties of studying and describing any unknown complex system.

### ***Martians and the Highway Code***

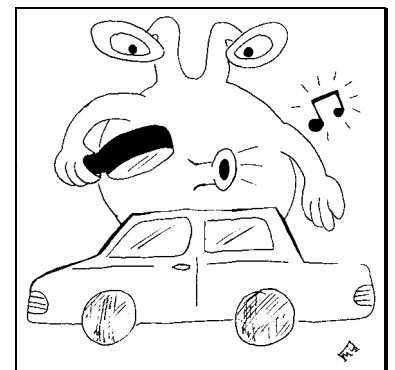
Imagine you are an alien. From Mars, to keep things simple. You are given the assignment, should you accept it, to report on the use of cars by humans. Please read on – this book will not self-destruct in a few seconds...

How would you go about it?

You could visit earth, hire a mechanical workshop in a remote area, car-jack a few specimens, and dissect them. You would observe that cars differ in their colour, shape, size and spec. Some may even contain a bar, cinema or swimming pool, but, perhaps, limousines are excluded from your exploration. On closer examination you would notice small ID-numbers imprinted on various strategic body parts. In short – you would find no two cars that are *exactly* the same.

Alternatively, you could focus on essential similarities between cars. For example that they *all* require one or the other kind of fuel to work.

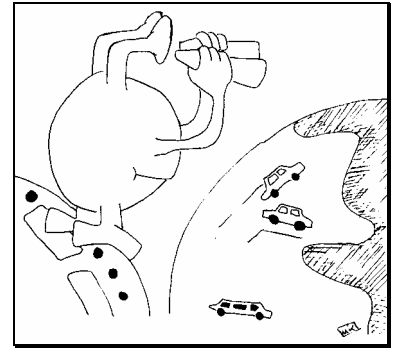
Or, you could stay in orbit and look down at the *movement* and interactions of cars. You would soon find that in some parts of the planet cars stick to the left side of the road, while elsewhere they prefer the right. You would notice that most cars stop at red lights, but others don’t. You would also see that there are complicated rules of ‘who goes first’ at crossings, although they would not appear



to be perfect. In short – you would discover a complex code for auto-motion.

Conversely, you might observe that – most of the time – all cars are *stationary*!

In your report you would summarise your observations. Your conclusions could range from ‘cars are all different’ to ‘they are all the same’, or from ‘cars are made for driving’ to ‘they are for parking’.



What a muddle!

To shed more light on this, you might try to generalise all findings. You could develop a model concept of car use by humans, based on apparent traffic rules.

This would be a challenging task as you would have to understand the Highway Code from the observed behaviour of other road users! However, you might come up with a reasonably close model of national traffic rules. And you would not need to give detailed descriptions of individual components of a car to do so.

If, however, all cars would stop as a consequence of an oil crisis, governmental budget, or other major disaster – you would realise that there is no way of fully understanding the rules of auto-motion without addressing how an engine works.

The same applies to the heart.

No two cells in the heart are *exactly* the same, but they are *all* made of rather similar components. Also, it is possible to study and model the general ‘traffic rules’ for the spread of the electrical signal that controls cardiac contraction and pumping, without addressing the workings of the individual cells that produce the electrical wave. However, this knowledge alone would be of little help for diagnosis and treatment of major energy crises like myocardial ischaemia, or heart attack.

## **The Need for Computational Modelling in Bio-Medical Research**

### ***What can we learn from Martians?***

Well, probably a lot. If they exist. What does exist for sure, though, is the challenge to understand in detail how the human heart works. And, similar to the above scenario, among the many different ways to advance this venture, there are at least two main directions: the top-down and the bottom-up route. Accordingly, bio-scientists tend to get pigeonholed into two schools of thought:

‘*Reductionism*’ is the direction that unites those guys who try to disassemble the parts of a biological system, and put them under a microscope (a laser-scanning quantum-leaping one, of course) to see the sparks of imagination hidden in the least of the components. The under-the-bonnet view, to stay

with the Martian's analogy.

'*Integrationism*', on the other hand, unites those who pride themselves for their holistic view of the complete system, without necessarily being burdened by a detailed understanding of structure and function of the minute components that make it work. The up-in-the-air perspective.

Reductionists might say that the division between the two schools of thought simply runs along the split between 'thorough' and 'not-so-thorough'. Integrationists would probably claim that the divide is nearer the categories 'geeky' and 'not-so-geeky'.

The two contrasting views were expressed at a higher level of sophistication during a recent Novartis Foundation meeting on '*The Limits of Reductionism in Biology*' by Professors Lewis Wolpert and 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 and Goode 1998).

This leaves us with the question of whether or not the two directions are irreconcilable.

We would like to think that the answer is a clear NO.

The logic of life will neither be recognised 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. Likewise, the logic of life lies exclusively neither in the most incredible detail, nor in the most sweeping synopsis.

### ***Combined Opposites***

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 (*Encyclopaedia of the Philosophical Sciences*, 1830) and Engels (*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.

Thus, common sense would suggest that 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 the quest for knowledge.

This view lays the basis of probably the most exciting new development in bio-medical research – the Physiome Project.

## The Physiome Project

### *The Vision*

The Physiome Project represents a world-wide effort to organise systematically the huge data mass on biological function into a ‘quantitative description of the physiological dynamics and functional behaviour of the intact organism’ (Bassingthwaighte). It was publicly initiated at the 33rd World Congress of the *International Union of Physiological Sciences*, 1997 in St. Petersburg (see <http://www.physiome.org>).

The Physiome Project sets a vision that will be much harder to accomplish than that of the Human Genome project – formally begun in October 1990 as an international effort to sequence, by the year 2005, all the 60,000 to 80,000 human genes in an attempt to make them accessible for bio-medical handling. By the time this essay is published, more than a third of the human genome will have been accurately sequenced. A decade into the project, this may seem little, but at the current rate of increase it would appear that the Genome project will be completed at least two years earlier than originally planned. The new target date in 2003 would fittingly coincide with the 50th anniversary of Watson and Crick's description of the DNA, the fundamental structure of our genes.

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 ‘Mechanic’s touch’), and ii) the development of descriptive and, ultimately, analytical models of biological function (the ‘Orbiter’s 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 to neuronal networks – and for any tissue, organ or organ system. Existing examples range from hepatocytes, and pancreatic beta cells, to muscle fibres, neurones, receptors, etc. Despite this breadth, the Physiome project has developed its first significant foundation in the cardiovascular field.

The reasons for this are diverse and include the fact that models of cardiac cellular activity were

among the first cell models ever developed. Analytical descriptions of virtually all cardiac cell types are now available. Also, the 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, as cells in the heart beat synchronously.

The Physiome project will build on linking descriptions of biological function and structure. On a macroscopic level, this will benefit from another on-going large-scale research effort – the *Visible Human* project. This is an expansion of the 1986 long-range plan of the US National Library for Medicine 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. A finer resolution will, however, be required in the context of anatomico-functional modelling at tissue level and, almost certainly, when addressing inter-cellular or sub-cellular events.

### **The Route**

So much about 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 capacity to devise appropriate algorithms to model physiological function.

But – 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*’. 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 to 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 – virtual cells, tissues, organs and systems.

This will extend, and partially replace, the traditional approach to bio-medical research that is based on studying ‘living’ cells or tissues *in vitro*, or on obtaining data from human volunteers *in vivo*, by introducing ‘*in silico*’ experiments (a term, derived from the currently prevailing silicon-based computer chips).

## **The Tools**

The Physiome project's *in silico* models are based on and validated against solid experimental data. Much of the 'input' data is already available from many decades of bio-medical research. More will follow and, with the development of new experimental tools and technologies, the insight into sub-cellular, genetic and molecular levels of biological activity is becoming increasingly detailed. Virtual biological systems will be produced by describing in great detail the constituent parts *and* their interrelation according to the laws of conservation of energy, mass, and momentum.

Such models can be used to perform *in silico* experiments, for example 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 from the real world.

A confirmation of the modelling-derived predictions would allow the performance of new *in silico* experiments, either with a higher degree of confidence or at a higher level of functional integration. Rejection of model output would help to pinpoint where the model needs refinement, either by providing new input data, or by direct model improvement. Subsequently, the *in silico* experiment could be repeated with a higher degree of confidence, until the model satisfactorily reflects reality.

This is a steady iterative process between the virtual organ and the real thing. Its prime objectives are the development of our understanding of a biological system like the heart, and the improvement of its *in silico* description. Through this multiple iteration, virtual organ models mature towards a tool that can be used with a high degree of confidence for research, development or clinical applications by scientists and doctors who do not need to be specialists in model development or validation.

## **The Virtual Heart\***

### **Science or Fiction?**

*...A patient who recently recovered from a minor heart attack is suffering from periods of ectopic ventricular beats, originating from what is believed to be a small area of post-ischaemic fibrosis in the free wall of the left ventricle. The extent and localisation of the area is investigated and confirmed, using catheter impedance tracking of ventricular wall tissue properties and non-invasive monitoring of cardiac dimensions and relative catheter location. A small area of increased fibrosis is diagnosed and mapped in real time to a patient-specific 3D virtual heart model. The model is then used to assess treatment strategies. A decision is*

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\* This will contain some of the more technical aspects of bio-mathematical modelling (in-depth information can be found in Kohl *et al.* 2000). The subsequent section on 'The utility of virtual organs' will address more general aspects that can be appreciated without knowledge of the detail presented next.

*taken by the surgeons to ablate the area. Using the virtual heart, optimal pattern and localisation for the tissue ablation are established with the aim of maximising the anti-arrhythmic effect while minimising the energy levels of the procedure. Using the same catheter, a minimal tissue area is ablated, obliterating the ectopic focus and terminating the arrhythmia. The whole, minimally-invasive procedure took only 12 minutes, and the patient made – as typical for 97 % of cases – a full recovery...*

Cardiac models are amongst the most advanced *in silico* tools for bio-medicine, and the above scenario is bound to become reality rather sooner than later. Both cellular and whole organ models have already ‘matured’ to a level where they have started to possess predictive power. We will now address some aspects of single cell model development (the ‘cars’), and then look at how virtual cells interact to simulate the spreading wave of electrical excitation in anatomically representative, virtual hearts (the ‘traffic’).

### **Single Cell Models**

The most prominent expression of cardiac activity is the rhythmical contraction of the heart – its pumping action. Less well known is the fact, that this mechanical activity is tightly controlled by an electrical process called ‘excitation’.

In the normal heart, electrical excitation originates in specialised pacemaker cells and spreads as an electrical wave throughout the whole organ. This electrical signal determines the timing and, to a degree, the force of cardiac contraction. Thus, the heartbeat is a consequence of an electrical process (which does, however, go completely unnoticed in day-to-day life).

Modelling of the heart’s electrical activity has a long history. In 1928, two Dutch mathematicians, van der Pol and van der Mark, described the heartbeat by comparing it to a simple oscillator. This approach, which was revolutionary at the time, gave rise to a whole family of models of the heartbeat and of the operation of other periodically active, electrically excitable cells (like neurones or skeletal muscle cells).

A common denominator of these models is the attempt to represent cellular electrical activity by describing, with a very small number of equations, the time-course of changes in the electrical potential in the cells (Figure 1A), but not of the ionic currents that gave rise to it.

This approach is, at the same time, the great advantage and a major limitation of membrane potential models. As they are rather 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; their role in assessing biophysical behaviour like cardiac impulse propagation is undiminished.

The major drawback of these models, however, is their lack of a clear reference between model

components and constituent parts of the biological system (e.g. structures like ion channels, transporter proteins, receptors, etc.). These models, therefore, do not permit the simulation of pathophysiological detail, such as the series of events that follows a reduction in oxygen supply to the cardiac muscle and, ultimately, causes serious disturbances in heart rhythm.

A breakthrough in cell modelling occurred with the work of the British scientists, Sir Alan L Hodgkin and Sir Andrew F Huxley, for which they were in 1963 (jointly with Sir John C Eccles) awarded the Nobel prize. Their new electrical models calculated the changes in membrane potential on the basis of the underlying *ionic currents*.

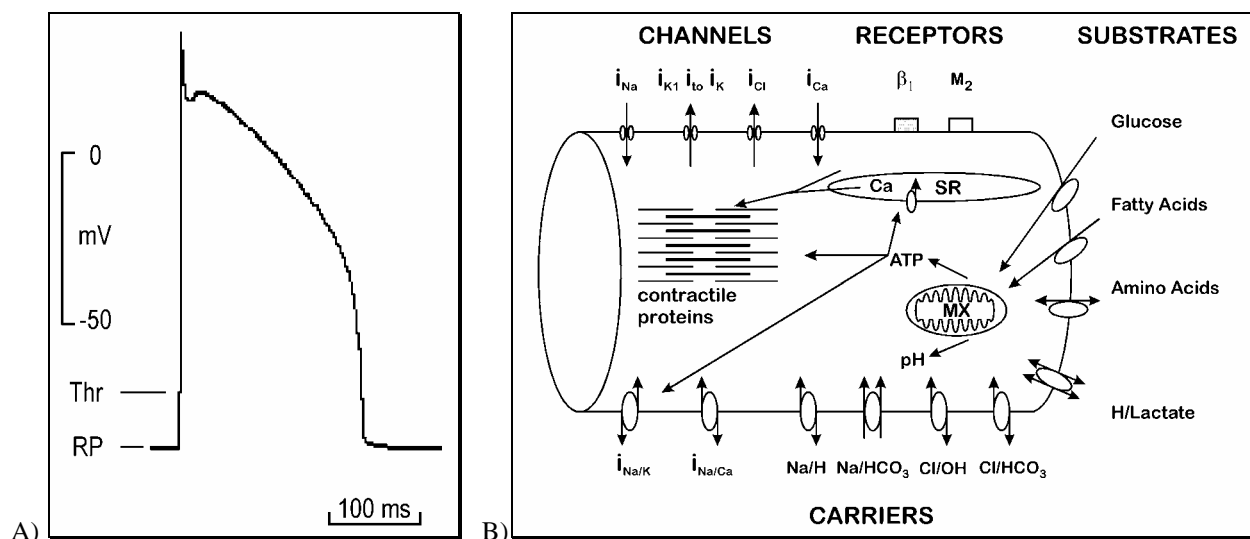


Figure 1: Scheme of a ventricular action potential (A) and sub-cellular mechanisms that give rise to it (B).

Membrane potential models simulate action potentials (A) with a deliberately small number of equations; ionic current models reproduce the action potential on the basis of calculating the sub-cellular ion movements that actually give rise to it (B).

- A) Cardiac contraction is controlled by an electrical waveform called action potential. Action potentials are induced by change in cell voltage to less negative values. Cells are said to ‘depolarise’ from their resting potential (RP) towards a threshold (Thr), at which automatic excitation occurs: an action potential is initiated. The action potential is characterised by a swift upstroke to positive cell voltages, followed by a plateau and slower return to RP levels. The well-ordered spread of this waveform lays basis to the regular contraction of the heart.
- B) Example of major 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, a calcium store) or mitochondria (MX, the powerhouse of the cell). It computes the action potential as a function of ion movements through channels (see a selection, 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 -  $\beta_1$ , and cholinergic receptors -  $M_2$ , that provide neural input), or changes in substrate transporter activity, cell metabolism and pH (right hand side). With this type of models, (patho) physiological behaviour may be simulated as it develops in time.

From Kohl et al., *Philosophical Transactions of the Royal Society A* 2000/358:579-610.

In contrast to the pre-existing models that merely portrayed membrane potentials, the new generation of models *calculated* the ion fluxes that give rise to the changes in cell electrical potential. Thus, the new models provided the core foundation for a mechanistic description of cell

function. Their concept was applied to cardiac cells by Denis Noble in 1960.

Since then, the study of cardiac cellular behaviour has made immense progress, as have the related 'ionic' mathematical models. There are various representations of all major cell types in the heart, descriptions of their metabolic activity, its relation to cell electrical and mechanical behaviour, etc. Drug-receptor interactions and even the effects of modifications in the genetic information on cardiac ion channel-forming proteins have begun to be computed. Principal components of cell models of this type are illustrated in Figure 1B on the example of work by the Oxford Cardiac Electrophysiology Group. As one can see, great attention is paid to the implementation of vital (sub)cellular mechanisms that determine function.

These detailed cell models can be used to study the development *in time* of processes like myocardial ischaemia (a reduction in coronary blood flow that causes under-supply of oxygen to the cardiac muscle), or effects of genetic mutations on cellular electrophysiology. They allow to predict the outcome of changes in the cell's environment, and may even be used to assess drug actions.

### **Organ Models**

Clearly, cardiac function may not be addressed exclusively on the basis of describing the working mechanisms of single cells. Both normal and disturbed heart rhythms are based on a *spreading wave* of electrical excitation, the meaningful investigation of which requires conduction pathways of at least hundreds if not thousands of cells in length.

These may be produced by grouping together multiple cell models to form virtual tissue segments, or even the whole organ. The validity of such multi-cellular constructs crucially depends on whether or not they take into account the heart's fine architecture, as cardiac structure and function are tightly interrelated.

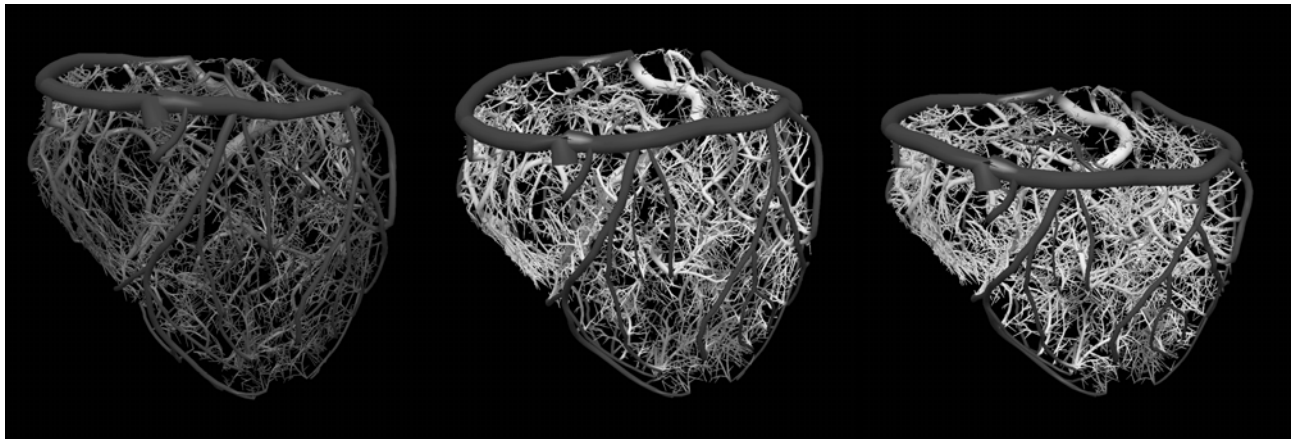
Modern representations of the virtual heart, therefore, describe structural aspects like muscle fibre orientation in cardiac muscle, together with the distribution of various cell types, active and passive electrical and mechanical properties, as well as the coupling between cells. This then allows accurate reproduction of the spread of the electrical wave, subsequent contraction of the heart, and effects on blood pressure, coronary perfusion, etc. It is important to point out, here, that all these parameters are closely interrelated, and changes in any one of them influence the behaviour of all others. This makes for an exceedingly complex system.

The example in Figure 2 illustrates a combination of 'only' two sub-systems to study the effects of cardiac contraction on coronary tree architecture and function. Models like this allow one to determine changes in coronary blood pressure during the cardiac cycle of contraction and relaxation.

Like in the real heart, the coronary tree moves with the cardiac tissue, into which it is embedded, and the pressure inside the vessels changes with the external compression by the contracting muscle. This external pressure is calculated and shown with the deforming coronary vessel tree in Figure 2.

Thus, current electro-mechanical models of ventricular anatomy and function allow one to describe coronary perfusion during the cardiac cycle. By linking this to the models of cell metabolism and electro-mechanical function, the whole sequence of the natural heartbeat may be reproduced.

The same applies to pathologically-disturbed function. A simulated reduction in coronary blood flow (heart attack) would lead to reduced oxygen supply to the cells in the virtual heart, which would reduce efficiency of cardiac contraction and possibly give rise to heart rhythm disturbances. Ventricular pressure development would be compromised, as would the blood supply to all organs of the body, including the heart. All these implications can be studied in a virtual heart.



**Figure 2:** Coronary vasculature (shown) coupled to the deforming myocardium (transparent). The grey-level coding represents the pressure acting on the coronary vessels from the myocardial contraction (dark - zero pressure, light - peak pressure). The deformation states are (from left to right): resting state, early contraction, and peak contraction.

Courtesy of Dr Nic Smith, University of Oxford.

This possesses an immense potential, not only for bio-medical research, but also for clinical applications, including patient-specific modelling of therapeutic interventions. For example, dynamic changes in a patient's cardiac anatomy can already be modelled on the basis of a non-invasive technique called Magnetic Resonance Imaging. The location of coronary vessels for that patient may be determined by 3D coronary angiography, a common procedure in the context of coronary surgery, and implemented into the virtual heart. Integrated patient-specific virtual hearts of this kind may, therefore, already be constructed – however not in real time yet. Once the interrelation between computational demand and computing power has sufficiently improved (and it does get better all the time), virtual hearts will be used for the prediction of optimal coronary bypass procedures, aid the surgeon's decision on the operative approach, and even predict the potential long-term consequences of various treatment strategies.

So – what about the prospects of powerful computational equipment? The calculations for Figure 2, for example, took about six hours on a 16-processor Silicon Graphics Power Challenge, which is a fairly powerful computer. Six hours to calculate a single heartbeat! However, there are already much more powerful systems that could cope with the same task in less than an hour. In December 1999, IBM announced the development of a new generation of super computers (Blue Gene), and other major systems manufacturers will have similar projects in the pipeline. The new computer generation is said to provide a 500-fold increase in maximum computing power over the next four to five years. Computation of the above model would then be possible in real time.

Such are the prospects.

Patient-specific and modelling-aided clinical treatment could, therefore, become a reality within the first decade of this millennium!

### ***Simulating the ECG***

To date, 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 behaviour.

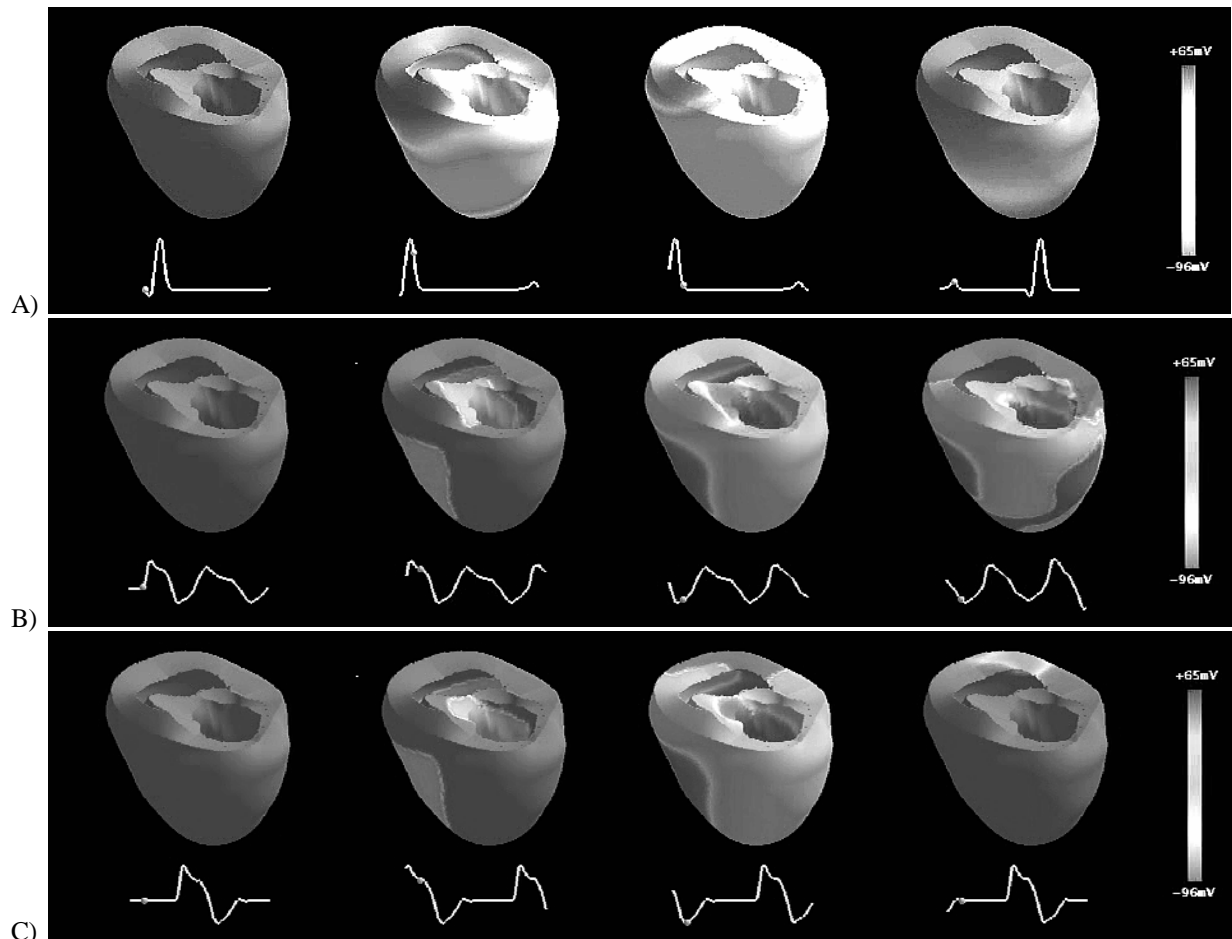
While the ECG is an invaluable tool for the observation of heart rate and rhythm, as well as for the diagnosis of conduction abnormalities, ischaemia, and infarcts, its detailed interpretation is not without pitfalls. One reason for this is that different changes in cardiac cellular behaviour may give rise to very similar effects on the ECG. This makes it difficult to draw conclusions from a patient's ECG to the underlying (sub-)cellular mechanisms. This issue is usually referred to as the 'inverse problem'.

Today's heart models do not yet possess the power to solve the inverse problem. They do, however, aid the understanding and interpretation of the ECG by repeatedly solving 'forward problems' to study the effects of cellular modifications on the calculated ECG. Model reconstruction of a normal ECG is therefore a necessary first step towards developing a better understanding of the information 'hidden' in it. Figure 3A illustrates this.

The same may be applied to simulations of the ECG in pathologies. Here, we illustrate work on simulating the typical ECG of patients with congestive heart failure (CHF), a disease that affects roughly 1% of the population in Western countries and causes a reduction in cardiac output. 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 the heart's electrical activity. The virtual heart can be used to identify promising targets for pharmacological interventions in CHF.

CHF is accompanied, at the cellular level, by changes in the content of proteins that govern electrical repolarisation and cellular calcium handling. This threatens orderly repolarisation of

cardiac tissue by increasing the likelihood of spontaneous ‘early after-depolarisations’ that can initiate an irregular heartbeat. Figure 3B illustrates the effect of CHF-typical cellular changes on the computed electrical activity of the heart and the ECG. The virtual heart shows the characteristic pattern of rhythm disturbance observed in CHF patients, together with the distinctive saw-tooth like ECG. The circulating waves of electrical excitation prevent the heart from relaxing between beats, which impedes the filling of the cardiac chambers and prevents effective pumping function.



**Figure 3:** Simulation of the spread of excitation in canine ventricles. Ventricular cell models are based on a simplified version of the Oxsoft v.4.6 ionic models. Membrane potentials are grey-level coded (dark - resting potential, light - action potential) and ECG equivalents are computed (curves below the images).

- A) Normal spread of excitation. Frames illustrate the normal sequence of excitation and repolarisation during one cardiac cycle (from left to right).
- B) Spread of excitation in a congestive heart failure 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, saw-tooth shaped ECG.
- C) Simulation of the effect of ATP-modulated potassium channel openers on the spread of excitation in the same congestive heart failure model. The first three frames are closely reminiscent of those leading to re-entrant excitation in B, with the saw-tooth 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 (‘dark’ cardiac chamber and ‘flat’ segment in the ECG, frame 4). This allows time for diastolic filling and permits pumping action of the heart.

From Kohl et al., *Philosophical Transactions of the Royal Society A* 2000/**358**:579-610.

Might this be reversed by pharmacological interventions? Figure 3C illustrates the application of a (virtual) drug that specifically activates one type of the potassium channels in the heart (the so-called ATP-modulated potassium channel, whose activity is increased in the model from 0 to 0.0002). This intervention leads to termination of the dangerous depolarisations at the cellular level and allows the whole heart to regain a stable resting state (compare last frames of the sequences in Fig. 3B and 3C). Thus, while the pattern of impulse conduction in the heart has not entirely normalised, the development of fatal re-entry is terminated.

Thus, the virtual heart may be used to simulate cardiac pathologies, their effect on the ECG, and the consequences of drug administration. It can be seen that drug discovery and assessment will be among the first fields where *in silico* technologies will reform research and development in a whole industry.

### **Summary: The Virtual Heart**

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 tissues possess realistic passive mechanical properties, and both electrical and mechanical activity can be simulated with high accuracy. 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 the spread of excitation, its cellular basis, and the consequences for an 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 to the rest of the heart. Computations of ventricular pressure development are being extended to account for blood flow dynamics in adjacent blood vessels. The thorax representation is being developed to allow simulation of respiratory movement, and the computation of pulmonary ventilation and gas exchange is well underway. Thus, the stage for patient-specific models is set.

## The Utility of Virtual Organs

### ***Added Value for Research***

Virtual organs will increasingly determine bio-medical research. Advantages of *in silico* models include:

- Complex investigations, for example on the (sub)cellular level, can be performed in a fraction of the *time* required for ‘wet’ (*in vivo* or *in vitro*) studies.
- 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.
- 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.
- While the first three points improve the quantity and quality of information, *in silico* models benefit further from their unrestricted potential for customised 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. Virtual organs clearly have one major drawback: they are models only. 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, and to never neglect that theoretical considerations will continue to need experimental validation.

Thus, *in silico* models are by no means self-sufficient. They are irreplaceable for the future progress of bio-medicine. They do not aim, however, to substitute but to improve bio-medical research, which will remain indispensable, not the least for model development and validation.

### ***Added Value for Drug and Device Development***

Drug development is currently largely based on trial and error. This is an exceedingly time-consuming process, and some of the associated errors have proved quite costly for patients involved. Even if distressing consequences of clinical testing could be avoided, the economical costs of bringing a new drug to market are prohibitive: close to \$ 0.5 billion.

Also, the fact that only an estimated 10% of pre-clinically tested lead-compounds are likely to ever reach the market must discourage companies from investing into new drug development, in particular for pathologies that are not deemed to constitute a profitable market. Thus, from the point of view of a commercial drug developer, ideal targets are chronic and non-lethal complaints that

affect people in the developed world at the prime of their financial viability. In other words, it is ‘more economical’ to come up with a treatment for obesity, baldness or impotence, rather than to tackle a rare but lethal disease that affects small patient groups.

Analytical computer models clearly have the potential to improve this situation, as they may help:

- to speed-up drug development by *in silico* screening for early identification of promising lead compounds;
- to simplify the assessment of complex pre-clinical data and predict (patho-)physiological (side-)effects of drugs;
- to cut the associated financial and ethical costs;
- to reduce the risk of clinical testing.

The above may not be enough, though, as it will be crucial to change the whole approach to drug development. What is needed is a method to identify the desired drug effect and (sub-)cellular target for pharmacological intervention *before* directed compound synthesis and testing commence. Virtual organs will form the basis for this novel approach.

Similar concepts apply to the world of medical devices. In future, successful products will increasingly be 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, since:

- devices become sufficiently ‘intelligent’, with their on-board computing power, to use analytical descriptions of (patho)physiological organ function;
- accurate and efficient modelling of body functions provides a test-bed for the development of devices that are energy-efficient and less invasive;
- specialist equipment is easier to (re)produce and more portable than the ‘specialists’ themselves.

Future medical training, diagnosis and – even surgical – treatment will increasingly be performed remotely. Thus, the combination of sophisticated sensory devices with advanced micro-manipulation equipment will, together with 3D ‘interactive feedback’ models, provide new tools and approaches for the medical profession.

### ***Added Value for Society***

*‘The proper study of mankind is man’* (Alexander Pope, *An Essay on Man*, 1733). *In silico* technology is set to produce a quantum leap in our understanding of the nature of man, for it is only through the identification of useful 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 way society handles health-related matters. The ‘added benefit’ of *in silico* technologies for health care includes:

- New, interactive *in silico* teaching and educational tools will be available for doctors and the greater public. This will help to improve professional skills and general health awareness. Future health-related implications of an individual's behavioural patterns or of various treatment strategies can be assessed and compared on the basis of long-term case predictions.
- *In silico* technologies will help health care policy development and acute decision making. The latter 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, undoubtedly, will consolidate the case of preventative medicine.
- *In silico* models will aid both the standardisation and individualisation of medical care. Standardisation of diagnoses, drug and device descriptions, procedures, etc. will make relevant information more readily and more widely 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.
- All the above effects will ultimately lead to reduction in morbidity and mortality and an improvement in the quality of life.

On this optimistic note we shall finish.

## Further Reading

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