specificity of the effects of the second, encoding Krox-Engrailed, is attested to by the minor fraction of tested genes on which it had any effect whatsoever (*19*) and the fact that the only genes that were affected are required just where *krox* is expressed, even though the exogenous mRNA is present globally. The last, encoding an Elk-Engrailed construct, affects only three other genes out of all those tested (*19*) (Fig. 3). Elk plays a peripheral role in the network up to 24 hours, and its main importance may be for later events in development.
33. In such rescue experiments, if the effect is indirect via a second gene, then the introduction of mRNA generated from the second gene will suffice to correct the perturbation effect; but if it is direct, no rescue can be obtained by this route. For example, if gene A activates gene B, which in turn activates gene C, then the effect of a knockout of gene A expression is direct for gene B but indirect for gene C, and the effect of the gene A knockout on gene C would be rescued by the introduction of B mRNA. If, on the other hand, there are necessary target sites for the gene A product in the cis-regulatory elements of both genes B and C, then the effect on gene C of a gene A knockout cannot be rescued by the introduction of B mRNA.
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REVIEW

Modeling the Heart—from Genes to Cells to the Whole Organ

Denis Noble

Successful physiological analysis requires an understanding of the functional interactions between the key components of cells, organs, and systems, as well as how these interactions change in disease states. This information resides neither in the genome nor even in the individual proteins that genes code for. It lies at the level of protein interactions within the context of subcellular, cellular, tissue, organ, and system structures. There is therefore no alternative to copying nature and computing these interactions to determine the logic of healthy and diseased states. The rapid growth in biological databases; models of cells, tissues, and organs; and the development of powerful computing hardware and algorithms have made it possible to explore functionality in a quantitative manner all the way from the level of genes to the physiological function of whole organs and regulatory systems. This review illustrates this development in the case of the heart. Systems physiology of the 21st century is set to become highly quantitative and, therefore, one of the most computer-intensive disciplines.

The amount of biological data generated over the past decade by new technologies has completely overwhelmed our ability to understand it. Genomics has provided us with a massive "parts catalog" for the human body; proteomics seeks to define these individual "parts" and the structures they form in detail. But there is as yet no "user's guide" describing how these parts are put together to allow those interactions that sustain life or cause disease. In many cases, the cellular, organ, and system functions of genes and proteins are unknown, although clues often come from similarity in the gene sequences. Moreover, even when we understand function at the protein level, successful intervention, for example, in drug therapy, depends on knowing how a protein behaves in context, as it interacts with the rest of the relevant cellular machinery to generate function at a higher level. Without this integrative knowledge, we may not even know in which disease states a receptor, enzyme, or transporter is relevant, and we will certainly encounter side effects that are unpredictable from molecular information alone.

Inspecting genome databases alone will not get us very far in addressing these problems. The reason is simple. Genes code for protein sequences. They do not explicitly code for the interactions between proteins

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and other cell molecules and organelles that generate function. Nor do they indicate which proteins are on the critical path for supporting cell and organelle function in health and disease. Much of the logic of the interactions in living systems is implicit. Wherever possible, nature leaves that to the chemical properties of the molecules themselves and to the exceedingly complex way in which these properties have been exploited during evolution. It is as though the function of the genetic code, viewed as a program, is to build the components of a computer, which then self-assembles to run programs about which the genetic code knows nothing, although proteomics can show us some aspects of the grouping and interaction of proteins (*1*). Sydney Brenner (*2*) expressed this very effectively when he wrote: "Genes can only specify the properties of the proteins they code for, and any integrative properties of the system must be 'computed' by their interactions." Brenner meant not only that biological systems themselves "compute" these interactions but also that, in order to understand them, we need to compute them, and he concluded, "this provides a framework for analysis by simulation." In this review, I describe how far we have advanced in using simulation to understand these interactions in the case of the heart.

Cellular Models of the Heart

Models of heart cells have become highly sophisticated and have benefited from four decades of iterative interaction between experimental and simulation work (*3*). Models of all the main types of cardiac myocyte exist (in many cases there are multiple models of the same cell type), and we are now able to represent the variations in the expression of particular genes, for example, across the ventricular wall (*4*), between the center and periphery of the sinoatrial node (*5*), and within the atrium (*6*). These variations are of fundamental importance in understanding global phenomena such as the electrocardiogram (ECG, see Fig. 1), and for analyzing the way in which cardiac rhythm is generated. They are also fundamental to understanding disease states, some of which, like heart failure (*7*), can be characterized by alterations in gene expression profiles.

Linking to Genetics

An important strength of models based on reconstructing the functional properties of proteins is that it is possible for the models to reach down to the genetic level, for example, by reconstructing the effects of particular mutations when these are characterized by changes in protein function. An example of this approach is the use of multistate (Markov) models of the cardiac sodium channel (*8*) in which models of the wild-type and of a mutant sodium channel were formulated and validated. The simulated mutation was the ΔKPQ mutation, a three–amino acid (lysine-proline-glutamine) deletion that affects the channel inactivation and is associated with a congenital form of the long-QT syndrome, LQT3. The simulations showed that mutant channel reopenings from the inactivated state and channel bursting due to a transient failure of inactivation generate a persistent inward sodium current during the action potential plateau in the mutant cell. This causes major prolongation of repolarization and the development of arrhythmogenic early afterdepolarizations at slow pacing rates, a behavior that is consistent with the clinical presentation of bradycardia-related arrhythmogenic episodes during sleep or relaxation in LQT3 patients.

Another sodium-channel mutation that has been, at least partially, reconstructed is a missense mutation that affects the voltage dependence of sodium-channel inactivation; it is responsible for one form of idiopathic ventricular fibrillation [the Brugada syndrome (*9*)]. In this case, small shifts of the voltage dependence of inactivation generate early afterdepolarizations that may underlie fatal arrhythmia (*10*).

Early afterdepolarizations are also responsible for the arrhythmias of congestive heart failure. This process can be modeled on the basis of experimentally determined changes in gene expression for several of the transporter proteins involved (*7*).

These examples highlight the ability of cellular models to reconstruct the arrhythmogenic consequences of genetic and ion-channel abnormalities either of behavior or of expression levels. Given the present explosion of genetic information, such studies will continue to be at the forefront of modeling efforts in the next decade. Connecting the genome to physiology is one of the exciting prospects for computational biology.

Counterintuitive Predictions

Characteristically, the results of modeling complex systems are frequently counterintuitive. This occurs because, beyond a certain degree of complexity, armchair (qualitative) thinking is not only inadequate for understanding such systems, it can even be misleading. A good example of this comes from the extension of cellular models to include some of the biochemical changes that occur during ischemia (*11*). This work succeeds in reconstructing arrhythmias attributable to delayed afterdepolarizations that arise as a consequence of intracellular calcium oscillations in conditions in which intracellular concentrations of sodium and calcium become excessive. These oscillations generate an inward current carried by the sodium-calcium exchanger that can lead to premature excitation of the cell. This work has led to counterintuitive predictions concerning up- and down-regulation of sodium-calcium exchange in disease states involving metabolic damage, such as cardiac ischemia (*12*). This transporter is currently a focus of antiarrhythmia drug therapy. Simulation is playing an important role in clarifying and assessing the mechanism of action of such drugs, by unraveling the complex changes that occur as a consequence of the change in transporter activity.

Another area in which modeling has been

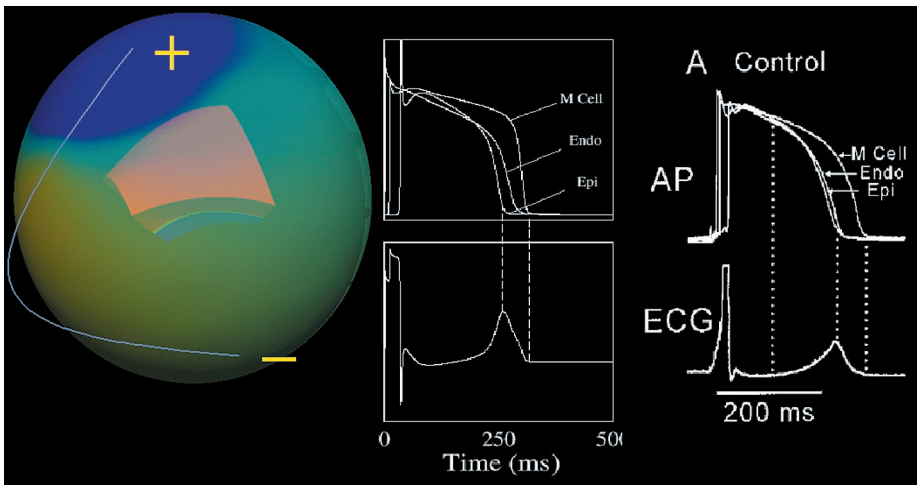

Fig. 1. Reconstruction of cardiac ventricular transmural action potential shapes attributable to variations in gene expression levels and the insertion of these cellular models into a 3D model of the ventricular wall capable of reproducing the T wave of the ECG. Left, supercomputer reconstruction of electrical field (color coded) when ventricular wall wedge is inserted into a conducting medium. Middle, in silico models of endocardial, mid-myocardial (M cell) and epicardial cells together with the reconstructed ECG obtained from the wedge model. Right, Experimental recordings of dog ventricle (*34*, *35*). The in silico records (left and middle) are from the CardioPrism cardiac safety assessment program of Physiome Sciences, Inc. (*36*).

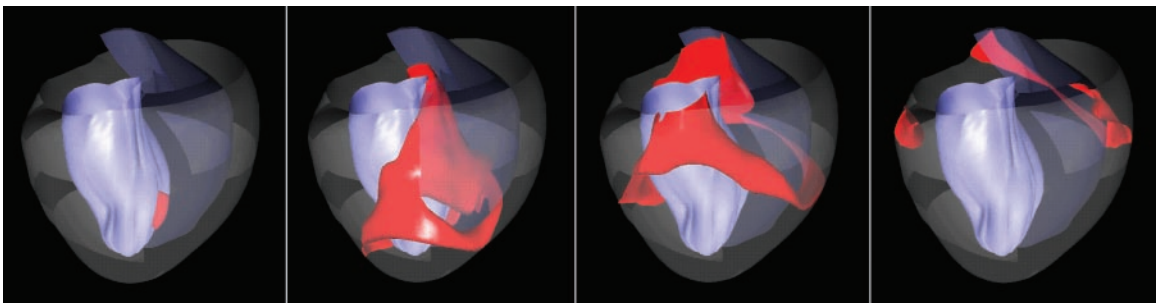

Fig. 2. Spread of the electrical activation wavefront in an anatomically detailed cardiac model (*21*). Earliest activation occurs at the left ventricular endocardial surface near the apex (left). Activation then spreads in endocardial-to-epicardial direction (outward) and from apex towards the base of the heart (upward, middle frames). The activation sequence is strongly influenced by the fibrous-sheet architecture of the myocardium, as illustrated by the nonuniform transmission of excitation. Red, activation wavefront; blue, endocardial surface.

rich in counterintuitive results is that of mechano-electric feedback, in which the contraction of the heart influences its electrical properties. This feedback mechanism has been unraveled in elegant experimental and computational work (*13*). Some of the results, particularly on the actions of changes in cell volume (which are important in many disease states) are unexpected and have been responsible for determining the next stage in experimental work. Indeed, it is hard to see how such unraveling of complex physiological processes can occur without the iterative interaction between experiment and simulation.

Assessing and predicting drug actions. Drugs act on proteins such as receptors, channels, transporters, and enzymes. Models that simulate effects of perturbing protein structure and function are therefore highly relevant to assessing and predicting drug actions. Simulations have already been used in assessing drug action by the U.S. Food and Drug Administration, and we can expect use of such biological models to increase greatly as their complexity and power grows (*14*, *15*). One obvious use in the case of the heart is in assessing the cardiac safety of drugs. It should be noted that half the drug withdrawals that have occurred since 1998 in the USA when drugs have come on the market have been attributable to cardiac side effects, often in the form of effects on the ECG and consequent arrhythmias. This is a large and very expensive form of attrition. Because virtually all the ion transporters involved in cardiac repolarization are now modeled and because very realistic simulations of the T wave of the ECG can be obtained when these models are incorporated into three-dimensional (3D) cardiac tissue models, it is clearly becoming possible to use in silico screens for drug development. One of the reasons that this is necessary is that the ECG is, unfortunately, an unreliable indicator of potential arrhythmogenicity. Similar changes in form of the QT interval and T waveform can be induced by very different molecular and cellular effects, some benign, others dangerous. We need to understand and predict the mechanisms all the way from individual channel properties through to the ECG. This goal is within reach, particularly as we acquire more experience of the incorporation of accurate cellular models into anatomically detailed organ models (see below).

Another use of simulation in drug discovery is screening drugs for multiple actions. Very few drugs that act on the heart bind to just one receptor. It is much more common for two, three, or even more receptors or channels to be affected. This is particularly true for drugs that act on the sodium-calcium exchanger (*16*). An important point to realize here is that multisite action may actually be beneficial. Many multireceptor drug actions are expected to be beneficial. I predict that this will be one of the ways in which more rational discovery of antiarrhythmic drugs may occur. In regulating cardiac function, nature has developed many multiple-action processes, particularly those regulated by G protein–coupled receptors. In seeking more "natural" ways of intervening in disease states, we should also be seeking to play the orchestra of proteins in more subtle ways. We need simulation to guide us through the complexity and to understand multiple action functionality.

Incorporation of cellular models into whole-organ models. There has been considerable debate over the best strategy for biological simulation, whether it should be "bottom-up," "top-down" or some combination of the two [see discussions in (*17*, *18*)]. The consensus is that it should be "middle-out," meaning that we start modeling at the level(s) at which there are rich biological data and then reach up and down to other levels. In the case of the heart, we have benefited from the fact that, in addition to the data-rich cellular level, there has also been data-rich modeling of the 3D geometry of the whole organ (*19*, *20*). Connecting these two levels has been an exciting venture (*21*, *22*). Anatomically detailed models of the ventricles, including fiber orientations and sheet structure, have been used to incorporate the cellular models in an attempt to reconstruct the electrical and mechanical behavior of the whole organ.

Still pictures from a simulation in which the spread of the activation wavefront is reconstructed are shown in Fig. 2. This is heavily influenced by cardiac ultrastructure, with preferential conduction along the fiber-sheet axes, and the result corresponds well with that obtained from multielectrode recording from dog hearts in situ. I referred earlier (Fig. 1) to work that reconstructs the later phases of the ECG using detailed reconstruction of the dispersion of repolarization. Accurate reconstruction of the depolarization wavefront promises to provide reconstruction of the ECG during the early phases of ventricular excitation, i.e., the QRS complex, and as the sinus node, atrium, and conducting system are incorporated into this whole heart, we can look forward to the first example of reconstruction of a complete physiological process from the level of protein function right up to routine clinical observation. The whole ventricular model has already been incorporated into a virtual torso (*23*), including the electrical conducting properties of the different tissues, to extend the external field computations to reconstruction of multiple-lead chest and limb recording.

Blood flow and the coronary circulation. Blood flow within the chambers of the heart, including the movement of valves, has been elegantly modeled by McQueen and Peskin (*24*) and this has been extended to the study of diastolic mechanical function (*25*). Blood flow within the coronary circulation has also been modeled (*26*).

Ischemic heart disease is a major cause of serious incapacity and mortality. It is also a good example of the multifactorial character of most disease states. Very few diseases are attributable to a single gene or protein malfunction. As noted above, cellular reconstructions of the metabolic and electrophysiological processes that occur following deprivation of the energy supply to cardiac cells have already advanced to the point at which some arrhythmic mechanisms can be reproduced. The initiating process in such energy deprivation is restriction or block of coronary arteries. This is another example where modeling at different data-rich levels is holding out the prospect of very exciting integration of function. Some of the spectacular modeling of the coronary circulation are shown in Fig. 3 (*26*). These are stills from a simulation in

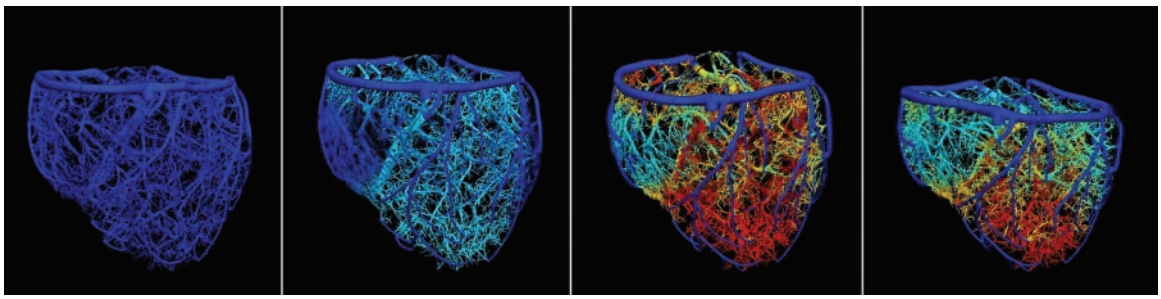

Fig. 3. Flow calculations coupled to the deforming myocardium. The color coding represents transmural pressure acting on the coronary vessels from the myocardial stress (dark blue, zero pressure, red, peak pressure). The deformation states are (from left to right) zero pressure, end-diastole, early systole, and late systole (*26*).

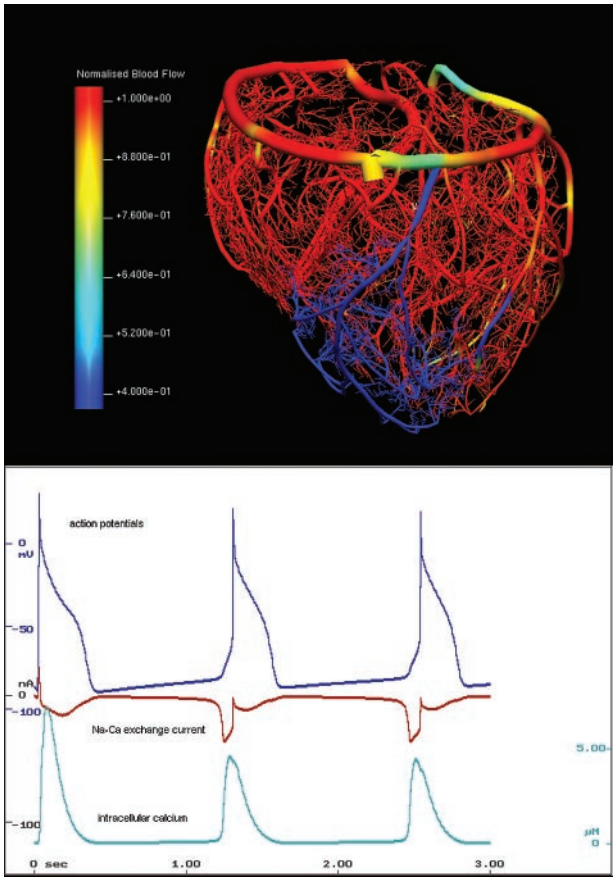

Fig. 4. Left, the coronary circulation model shown in Fig. 3 has been subjected to a constriction of one of the main branches leading to blocked blood flow in the regions colored blue. Right, simulation of ectopic beats in a Purkinje fiber model in conditions of calcium overload of the kind that occurs in ischemic tissue. Oscillatory calcium changes (bottom) induce inward sodium-calcium exchange current (middle) leading to initiation of action potentials (above). Linking these two levels of modeling to create a complete model of coronary heart attack is one of the grand challenges requiring massive computer power. [Top panel kindly provided by N. Smith. Bottom panel specially prepared for this review using the DiFrancesco-Noble 1985 Purkinje fiber model (*37*) as follows. To simulate sodium/calcium overload, $[Na]_i$ was increased from 8 to 12 mM. The first action potential is evoked by a current pulse. The second two are initiated by calcium oscillations. Note that the rise in $[Ca]_i$ and the flow of inward Na-Ca exchange current occur before the depolarization.]

which the blood flow through an anatomically detailed model of the coronary circulation is computed while the ventricles are beating. The simulation, therefore, also included the deformation that occurs as mechanical events influence blood flow.

This model has already been used to investigate the changes in blood flow that occur following constriction or blockage of one of the main arterial branches, and work is in progress to connect this to the modeling of ischemia at the cell and tissue level (see Fig. 4). If we can also connect the cellular mechanisms of arrhythmia to the processes by which regular excitation breaks down into the multiple wavelets of ventricular fibrillation (*27*) then yet another "grand challenge" for integrative physiological computation will come within range: the full-scale reconstruction of a coronary heart attack.

The term "grand challenge" is chosen deliberately. This kind of work requires massive computer power. The whole organ simulations described here require many hours of computation using supercomputers. (By contrast, the single-cell models can be run faster than in real time on a PC or laptop!) Future progress will be determined partly by the availability of computing capacity. It is significant therefore that attempts to break Moore's law (computing power doubles every 18 months) are in progress, notably that of IBM's blue gene project (*28*).

The Future: From Genome to Proteome to Physiome

The computer modeling of biological systems is an important technique for organizing and integrating vast amounts of biological information. Although this review has focused on modeling of the heart, it is important to note that biological simulation is now being done for a wide range of pathways, cells, and systems (*29*). The role of in silico biology in medical and pharmaceutical research is likely to become increasingly prominent as we seek to exploit the data generated through rapid gene sequencing and proteomic mapping (*1*) through to creating the physiome (*30*, *31*).

However, progress will be significantly enhanced by enabling ever greater numbers of researchers to use and verify models in the course of their everyday experimental work [for simulation and experiment must go together (*3*)]. It has been extremely difficult to transfer models between research centers, or to extend existing models so that more complex models can be constructed in an object-oriented or modular fashion. This process will be enhanced by the development of uniform standards for representing and communicating the content of models, and by the wide distribution of software tools that permit even nonmodelers to access, execute, and improve existing models. Increasingly, publication of models is accompanied by their availability on Web sites. Also, the process of establishing standards of communication and languages is developing (*32*, *33*).

Once this is achieved, we can confidently predict an explosion in the development of integrated model cells, organs, and systems. In a few years' time we shall all wonder how we ever managed to do without them in biological research. For drug development, there will certainly be a major change as these tools come on line and rapidly increase in their power. This will grow in a nonlinear way with the degree of biological detail that is incorporated. The number of interactions modeled increases much faster than the number of components. Biology is set to become highly quantitative in the 21st century. It will become a computer-intensive discipline.

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