Modeling the Heart

Models of the heart have been developed since 1960, starting with the discovery and modeling of potassium channels. The first models of calcium balance were made in the 1980s and have now reached a high degree of physiological detail. During the 1990s, these cell models were incorporated into anatomically detailed tissue and organ models.

Modeling excitable cells and systems took a giant leap forward when Alan Hodgkin and Andrew Huxley (21) published their equations for the squid giant axon, an achievement for which they received the Nobel Prize for Physiology or Medicine. It was the first model to use mathematical reconstruction of ion channel transport and gating, rather than abstract equations, and it correctly predicted the shape of the action potential, the impedance changes, and the conduction velocity. This was a brilliant demonstration of the need for biological modeling to respect the details of experimental results.

A “hole in one” is a rare phenomenon in theoretical biology. The squid axon is a relatively simple nervous mechanism. Most nerve cells are much more complex, and so are cardiac cells, with the added complexity of electromechanical coupling and mechano-electric feedback (39). Modeling the heart has therefore been more like driving into the rough and then working out how to get back on the fairway and onto the green. The “hole,” which I would identify as the ability to predict cardiac arrhythmias, is now on as high as the horizon at least. We are at last reaping the rewards in terms of understanding disease states.

Even in the physical sciences, modeling has usually been an iterative process of interaction between mathematics and experimentation, involving successive approximations toward predictive capability. The iterative process generates insights on the way, even when models are wrong or incomplete. In fact, the mistakes can be as illuminating as the successes (34). Models of complex biological systems should be judged as much by the insights they have given as by their predictive power. The theme of this article will be to ask what kinds of questions were resolved with modeling that could not have been answered without it.

Potassium Channels: Nature’s Pact with the Devil

The first questions to be resolved were fundamental to cardiac electrophysiology. Compared with nerve, where the total duration is only a millisecond or two, the cardiac action potential is exceedingly long. Hundreds of milliseconds are required for repolarization to occur, and when the resting potential has been restored, it is not necessarily stable. In pacemaker regions like the sinoatrial node, the atrioventricular node, and the Purkinje fibers, it immediately starts to depolarize again to generate spontaneous rhythm.

What is responsible for these differences? The answer lies primarily in the nature of the potassium channels in cardiac cells. The first experimental results (5, 23) showed the existence of two kinds of channels: the inward rectifier, \( I_{Kr} \), now known to be coded by Kir2.x, and the delayed rectifier \( I_{K} \). The delayed rectifier was later shown to be generated by multiple components (38, 48, 58), including the “rapid” \( I_{K1} \) (coded by HERG and MinK) and “slow” \( I_{Ks} \). We now know that there are many other K+ channels whose expression levels vary with spatial location (1). These include the transient outward \( I_{to} \), which shapes the early phases of the action potential.

The discovery of the inward rectifier was a surprise. On depolarization it closes so that the conductance changes in precisely the opposite direction to that of the potassium channel in squid giant axon, and it was natural to ask whether this could account for the long-lasting nature of the cardiac action potential. The model incorporating this mechanism (35) showed unambiguously that it could. In fact, it is a major energy-saving device, because by reducing the membrane permeability, very small inward currents (generated by sodium and calcium ions) suffice to maintain a long plateau of depolarization. The energy cost of a long action potential generated in this way is an order of magnitude less than it would otherwise be. The 1962 model also correctly attributed repolarization to \( I_{K} \) and identified its decay as an important contribution to pacemaker activity. FIGURE 1 shows the voltage dependence of these two kinds of potassium channels and how they are predicted to change with time during electrical activity in cardiac cells.

Evolution involves a playoff between competing factors, energy conservation and safety being two of them. Engineers are familiar with this concept in the context of constructing aircraft, bridges, spacecraft, elevators, and a host of other technologies. Evolution approaches these com-
Modeling of pacemaker activity is currently a hot topic, with the roles of a number of ion transporters being reassessed (7, 47) and variations in expression levels being incorporated (59). A major new focus of this work is the mouse, which is of great importance in correlating genetic information with electrophysiology (10, 27) and for interpreting the effects of genetic modifications (37, 43).

Calcium Balance: Calcium Channels, Sodium-Calcium Exchange, and the Sarcoplasmic Reticulum

Cardiac physiology owes an immense debt to Harald Reuter, who first discovered calcium channels in the heart (44) and discovered the sodium-calcium exchanger (45), and to Alex Fabiato, who first demonstrated calcium-induced release of calcium from the sarcoplasmic reticulum (SR) (16). The next major role for modeling was to integrate these three processes into the cellular web of interactions. Calcium currents were incorporated into models by McAllister et al. (30) and by Beeler and Reuter (2), but the first integrative models that addressed the key questions of calcium balance were those developed with DiFrancesco (13) and Hilgemann (20). These became the generic models.

Although the model illustrated in FIGURE 1 successfully represented the roles of \( I_{K1} \) and \( I_{K} \), it completely lacked calcium fluxes, and its representation of pacemaker activity was far too simple. There are many other mechanisms involved, including the hyperpolarizing-activated current \( I_{f} \) (12, 13) and various sodium and calcium channels (24).

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from which all of the modern models of excitation-contraction coupling derive (25, 28, 29, 39, 56, 57). The Hilgemann-Noble model addressed a number of important questions concerning calcium balance:

1. How quickly is calcium balance achieved? Net calcium efflux is established as soon as 20 ms after the beginning of the action potential (19), which was considered to be surprisingly soon. In the model this was achieved by calcium activation of efflux via the sodium-calcium exchanger, thus revealing the time course of one of the important functions of this transporter in the heart.

2. If the exchanger is electrogenic, where is the current that this would generate and does it correspond to the quantity of calcium that the exchanger needs to pump? Mitchell et al. (31) provided the first experimental evidence that the action potential plateau is maintained by sodium-calcium exchange current. The Hilgemann-Noble model showed that this is precisely what one would expect, both qualitatively and quantitatively. Subsequent experimental and modeling work has fully confirmed this conclusion (3, 14, 15, 26).

3. Could a model of the SR that reproduced the major features of Fabiato’s experiments be incorporated? The model followed as much of the Fabiato data as possible, but although it was broadly consistent with the Fabiato work it could not be based on that alone. Fabiato’s experiments were heroic, but they were done on fibers that had been skinned, which removes many of the relevant mechanisms. It is an important function of simulation to reveal when experimental data need extending.

4. Were the quantities of calcium, free and bound, at each stage of the cycle consistent with the properties of the cytosol buffers? The great majority of the cytosol calcium is bound so that, although large calcium fluxes are involved, the free calcium transients are much smaller, as they are experimentally.

The major deficiency of this model was that it could not account for graded release of calcium from the SR. Much more complex models, incorporating finer detail of the excitation-contraction process, including the communication between L-type calcium channels and the SR calcium release channels, are required to achieve this (17, 25, 46, 57).

**Modeling Disease States**

**Genetic mutations**

Connecting genetics to physiological function at cellular and other levels is an exciting new development in which simulation is helping to unravel complex behavior resulting from simple changes at the genetic level. For example, we can now simulate long QT syndrome, which refers to the prolongation of the electrocardiogram interval between excitation of the ventricles (Q) and their repolarization (T) and is a phenomenon that can indicate life-threatening arrhythmias. (Q, T, and other cardiac waves are defined in Figure 2.) The simulations shown in Figure 3 reveal the arrhythmogenic effects of two types of mutations in the sodium channel gene SCN5A (8). Figure 3A simulates a mutation that affects sodium channel inactivation and is associated with a congenital form of the long QT syndrome, LQT3. The simulations show that the mutant channel generates a persistent inward sodium current during the action potential plateau, and at long cycle lengths this generates an early afterdepolarization, thereby delaying repolarization and prolonging the QT interval. Figure 3B shows the effects in a guinea pig ventricular cell model of shifting the voltage dependence of sodium channel inactivation (40). A 12-mV shift (trace b) simply prolongs repolarization, but 18 mV produces an early afterdepolarization (trace c). This mimics part of the experimental effect of a missense mutation underlying the Brugada syndrome, an inherited condition in which sudden fatal ventricular fibrillation can occur in people who show no other manifestation of heart disease.
Ischemia is a multifactorial process, starting with interruption of the blood supply (FIGURE 4), leading to rundown of metabolites like ATP involved in driving energy-using mechanisms, with consequent changes in ionic concentrations. These processes have been partially modeled (6). Both the metabolic and the ionic changes in turn modulate the activity of channels and transporters. Thus some potassium channels, such as the ATP-dependent potassium channel ($I_{\text{K}}$), are activated by the fall in ATP (41), thus shortening the action potential. Extracellular accumulation of potassium ions also contributes to this shortening through changes in $I_{\text{K1}}$ and $I_{\text{K2}}$. Meanwhile, the development of sodium and calcium overload may generate oscillatory changes in intracellular calcium that may initiate ectopic beating. These are the acute changes. Long-term changes create scar tissue that can contribute to determining the pathways for reentrant arrhythmia. Unraveling the ways in which all of these processes interact to generate major arrhythmia (56) and in showing that the major factor involved is the changes in calcium balance.

Congestive heart failure

The ability to track multiple changes in gene expression levels using cDNA arrays, real-time PCR, and other methods has revolutionized the range and quantity of data available on disease states. A major problem, however, is to distinguish those changes that are primary from secondary changes attributable to remodeling in response to the disease state. Computer modeling can help in this distinction because it can identify those changes that explain the disease effect, such as cardiac arrhythmia. An excellent example of this approach is the modeling of congestive heart failure. Experimental data show that $I_{\text{K1}}$ and $I_{\text{K2}}$ are downregulated, leading to a prolongation of the action potential, whereas the SR calcium pump SERCA is also downregulated, leading to a reduction and slowing of the intracellular calcium transient. Sodium-calcium exchange is upregulated, which may be a secondary response to the other changes in calcium handling. Introducing these changes into cardiac cell models succeeds in reproducing failure of repolarization and multiple reexcitations of the kind that generate major arrhythmia (56) and in showing that the...
life-threatening arrhythmia is a problem that requires modeling. The interactions are too complex to be understood without quantitative study. However, at present, all of the model studies are partial ones, and they have mostly been carried out at the cellular level, although Rudy and colleagues (49, 54) have done important studies on one-dimensional multicellular models and an ectopic focus has been simulated in two- and three-dimensional models (55). Computations at the whole organ level have yet to appear. These will be important because reentrant arrhythmia and fibrillation are properties of the whole ventricle.

Linking Levels: Putting Cell Models Into Tissue and Organ Models

Life-threatening arrhythmias depend on molecular and cellular mechanisms, but they are fatal because of their actions at the level of the whole organ. Anatomically detailed models of the ventricles, including fiber orientations and sheet structure (9, 22), have been used to incorporate the cellular models in an attempt to reconstruct the electrical and mechanical behavior of the whole organ.

FIGURE 5 shows frames from a simulation in which the spread of the activation wave front is reconstructed (33, 50). This is heavily influenced by

Left ventricular endocardial surface

FIGURE 5. Spread of the electrical activation wavefront in an anatomically detailed cardiac model

As shown from left to right, the earliest activation occurs at the left ventricular endocardial surface near the apex. Activation then spreads in the endocardial-to-epicardial direction (outward) and from apex toward the base of the heart (upward). 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 (33, 50).
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. Accurate reconstruction of the depolarization wavefront promises to provide reconstruction of the early phases of the ECG to complement work already done on the late phases (1), and as the sinus node, atrium, and conducting system are incorporated into the whole heart model 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 (4), including the electrical conducting properties of the different tissues, to extend the external field computations to reconstruction of multiple lead chest and limb recording. Incorporation of biophysically detailed cell models into whole organ models (9, 33, 36, 53) is still at an early stage of development, but it is essential to attempt to understand heart arrhythmias. So also is the extension of modeling to human cells (42, 52).

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References


