Half a century ago, Hodgkin and Huxley developed an elegant theoretical model of excitability in nerves, which to date serves as the backbone for mathematical models representing the cardiac action potential. Evolution of such models, from the earliest effort of Noble in 1960, to the recent biophysically detailed generation of models, has been limited less by computational methods than by the state of the available biological data. Through technological advancements in patch-clamp and voltage-clamp techniques (both whole-cell and single-channel recordings), biophysical properties of different ion channels, contributing to different phases of the cardiac action potential, have been elucidated in the past 4 decades. Recent discoveries in genomics and proteomics have further propelled our understanding of channel structure and function and have shed light on gating mechanisms and drug interactions.

While early computational models were aimed at recapitulating the normal action potential using few ionic currents, the later generations consist of numerous channels, pumps, and exchangers (see Noble and Rudy for a historical perspective). Consequently, modern models allow us to pose complex hypotheses and to test these hypotheses in an integrative manner so as to probe the underlying mechanisms of the diseased state (Figure). It is important to emphasize the term “integrative,” because often the course of action is an iterative process where sophisticated biophysical data serve as an input to the computational models, and, in turn, these models answer questions that could not have been answered by experiments alone. This is partly due to experimental and practical constraints imposed either by the biological system at hand or by the state of technology in the instrumentation. For example, it is much easier to look at the effects of downregulation of a certain ionic current on action potential duration numerically than experimentally, especially if there are no specific blockers available for that particular channel. Therefore, the question of how an ion channel contributes to the state of the disease, or is altered as a byproduct of the disease itself, can be answered easily with this approach. In a similar manner, cardiac arrhythmias and long-QT syndrome, heart failure, and ischemic heart disease are among the conditions where mathematical modeling has enabled researchers to gain a better understanding of the channelopathies involved. Equally important is the emergence of nonintuitive insights from simulations of a complex system.

While the majority of the aforementioned models are focused on the electrophysiological properties of a “single cell,” researchers have been successful in simulating electrical properties of a cell in a 3-dimensional syncytium. This facilitates relating defects at the genetic level in a single cardiomyocyte to the phenotype at the tissue or whole-organ level. The elegant work presented in this issue of Circulation Research by Gima and Rudy exemplifies this approach. The authors were able to accurately reconstruct the phenotypic changes in the electrocardiogram measured experimentally in transmural wedge preparations, by numerical simulation. The novelty lies in their ability to reconstruct different modes of long-QT syndrome (eg, LQT1 versus LQT2) and to illustrate how different genetic defects or alterations in ionic current(s) would result in changes in the morphology of the T wave and duration of the QT interval of the electrocardiogram, all by using a simple geometric representation of the ventricular myocardium. Alterations in T-wave morphology due to changes in extracellular potassium and ST elevation during acute myocardial ischemia were also reproduced. Moreover, they were able to dissect the underlying mechanisms of the degree of severity in the Brugada phenotype, which results in different ST-segment and T-wave morphologies.

Although the degree of cell-to-cell coupling between myocytes, through gap junctions, can alter the transmural properties of action potential propagation, the way in which these cells are connected in the myocardial tissue (ie, myofiber and laminar sheet architecture), can also alter the properties of wave propagation in the heart. As the ability to image the detailed myocardial structure using diffusion tensor magnetic-resonance imaging improves, the accurate interpretation of 3-dimensional wave propagation recorded in the heart will increasingly depend on sophisticated computational models that use physical first principles to integrate biophysical knowledge with structural data. The recent work by Winslow et al and Nickerson et al are excellent illustrations of this new paradigm.

So, where are we in the journey from “computational biology” toward “computational medicine”? Are we already at the juncture where we can utilize sophisticated models of cardiac electrophysiology to select therapeutic interventions and to rationalize their outcomes? Well, we may be close. Recent advancements in gene therapy and viral gene transfer have opened the door to the possibilities of ectopically expressing a certain ion channel or regulatory subunit in the heart to regulate electrical and mechanical properties of the myocytes. In an example of the potential synergy of computational and biological approaches to guide gene therapy, we showed that regulatory
effects of a β-subunit (KCNE3) on endogenous potassium currents in the heart could be exploited to regulate action potential repolarization and the QT interval of the electrocardiogram. Moreover, using a computational model of transmural action potential propagation developed independently from that of Gima and Rudy, we were able to rationalize the degree of QT-interval shortening as a function of transgene transduction efficiency. The computational insights transcended the experimental ones in pointing out one important cautionary point. The model showed that, in order to achieve the same degree of QT-interval shortening without causing a higher degree of dispersion of repolarization, transgene transduction has to be homogeneous across the ventricular wall. A similar approach could be taken in conjunction with the present work; for instance, in the most severe case of Brugada syndrome, where both the transient outward current and the inactivation rate of the sodium current are augmented, what would be the best strategy for gene therapy to correct the phenotype? Because epicardial cells are affected the most in this case, should the therapy be focused in that layer of the ventricular wall? If so, what percentage of the wall need to be treated? These are the types of queries that cannot be answered easily using experimental methods. The novelty of computational medicine lies in its potential for discovery of novel therapeutic candidates. Future advancements in pharmacogenetics and computational medicine, and our ability to integrate the two, will enable us to segregate between different forms of a disease (eg, LQT1 versus LQT2), thereby providing an opportunity to tailor therapeutics to specific patients (aka, personalized medicine).

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References


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