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Mathematical modeling of physiological systems: An essential tool for discovery

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Abstract

Mathematical models are invaluable tools for understanding the relationships between components of a complex system. In the biological context, mathematical models help us understand the complex web of interrelations between various components (DNA, proteins, enzymes, signaling molecules etc.) in a biological system, gain better understanding of the system as a whole, and in turn predict its behavior in an altered state (e.g. disease). Mathematical modeling has enhanced our understanding of multiple complex biological processes like enzyme kinetics, metabolic networks, signal transduction pathways, gene regulatory networks, and electrophysiology. With recent advances in high throughput data generation methods, computational techniques and mathematical modeling have become even more central to the study of biological systems. In this review, we provide a brief history and highlight some of the important applications of modeling in biological systems with an emphasis on the study of excitable cells. We conclude with a discussion about opportunities and challenges for mathematical modeling going forward. In a larger sense, the review is designed to help answer a simple but important question that theoreticians frequently face from interested but skeptical colleagues on the experimental side: “*What is the value of a model?*”

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Introduction

“There are two possible outcomes: if the result confirms the hypothesis, you’ve made a measurement. If the result is contrary to the hypothesis, then you’ve made a discovery.”

- *Enrico Fermi*

“We often learn as much from the failures as from the successes of mathematical models.”

- *Denis Noble*

These words from the physicist Enrico Fermi and biologist Denis Noble strike at a strange but essential paradox in the pursuit of scientific knowledge. It is often an outcome we do not expect (i.e. desire) that leads to a breakthrough. Our challenge as scientists, then, is to embrace the unexpected in our studies. The central premise of this review is that this challenge is even greater but no less critical to studies involving mathematical modeling. Specifically, to realize the full value of a model, it is necessary to shift our thinking from one in which a good model simply confirms our expectations to a paradigm where the model is more central to the discovery process (Kohl et al., 2010, Noble, 2002). In other words, when the model produces unexpected results, we must resist the impulse to just ask “*What is wrong with the model?*” and instead pose the more difficult query “*What is wrong with the hypothesis?*”

Mathematical modeling and the scientific process

Before delving into a discussion of how models have been used to advance our understanding, it is worthwhile to briefly address the overall approach used in modeling. Similar to experimental studies, mathematical modeling begins with a well-formulated hypothesis based on previous observations. In fact, the mathematical model should really be viewed as a quantitative expression of a central hypothesis. Thus, one of the most difficult aspects of the modeling process is translation of a hypothesis into a set of mathematical equations (“model formulation”). Here, determination will need to be made regarding the components (e.g. pathways, reactions, reactants, etc.) that should be included in the model. Factors such as accuracy, availability of data, and computing time/resources will shape the choices made at this step. Furthermore, this step is often performed iteratively by developing an initial model, comparing results to experiment, and adjusting the model based on validity. Once a model has been settled upon (at least initially), the next step is model parameterization. Here, model parameters (e.g. channel conductances, ion concentrations, reaction rates) will be selected based on available experimental data (either published or original). In some cases, a value for a model parameter may be assigned based on a direct experimental measurement. Often, it may be difficult to directly measure a parameter and instead the value must be estimated to generate agreement between model and experiment with regards to an outcome that is directly measurable (“parameter fitting”). Following model parameterization, optimization may be performed where values for parameters related to solving the governing equations (e.g. time step, grid size) may be determined. Once model parameterization/optimization is completed, a validation step is important to evaluate

accuracy of the model. In this critical step, model output is compared to an experimental dataset that was not used in the parameterization process. As mentioned earlier, the steps outlined above will likely be repeated to arrive at a final model. Once the final model has been developed and validated, it is now ready for simulation/analysis to generate predictions regarding a phenomenon of interest. Ideally, the model prediction helps inform design of a new experiment that may be used to test the prediction and advance further model development.

The Birth of Quantitative Physiology - Hodgkin-Huxley and the Squid Giant Axon

Having addressed briefly the “*how*” of modeling, our focus now shifts to the “*why*” and begins with a historical survey of the evolution of mathematical modeling as a tool for discovery. Among the first, most successful, and best known applications of mathematical modeling to biological phenomenon (not just cell excitability) was the pioneering work of Hodgkin and Huxley, who in their seminal 1952 paper described a theory for action potential (AP) generation in the giant squid axon based on a set of coupled ordinary differential equations (Hodgkin and Huxley, 1952). In many ways, the work of Hodgkin and Huxley to understand the nerve AP remains the gold standard for how experiment and modeling should be used together to advance knowledge beyond what would be possible with either approach individually. Beginning with astute observations on the AP in a squid giant axon (which they first recorded just before the outbreak of World War II interrupted their work) and a simple model of the nerve cell membrane as a parallel combination of capacitive and resistive elements, they conducted a series of elegant experiments to separate and characterize transmembrane fluxes due to Na^+ and K^+ (resistive elements in their model) (Figure 1). Data from these experiments were used to determine rate constants for voltage- and time-dependent gating variables (control Na^+ and K^+ fluxes) in their membrane model. Finally, they demonstrated that by solving the set of equations describing the time-dependent changes in transmembrane potential and gating variables (four coupled, ordinary differential equations), they were able to accurately reproduce the nerve AP (Figure 1) (Hodgkin and Huxley, 1952). The work of Hodgkin and Huxley, for which they received the 1963 Nobel Prize in Physiology or Medicine (together with John Eccles), had an immeasurable impact on our understanding of electrophysiology not only by producing a robust theory for AP generation, but also by producing new experimental and mathematical tools that remain in widespread use today (Rall et al., 1992, Rinzel, 1990, Segev and Rall, 1998). On the experimental side, they perfected the technique of voltage clamp (building on advances of Dr. Kenneth Cole’s group) that remains an essential method for characterizing electrophysiological properties of excitable cells. On the modeling side, their efforts laid the foundation for modern quantitative physiology (not just in electrophysiology). In a more general sense, there is a great deal to be learned from the process followed by Hodgkin and Huxley en route to their great discovery. First and foremost is the fact that their experiments began and ended with a model, namely, the parallel conductance model of the axon membrane, coupled with a number of prescient assumptions about how ions traversed the membrane (Figure 1). The model helped inform their experiments and, in turn, results from their experiments informed the model. The work of Hodgkin and Huxley laid the foundation

for generations of researchers interested in understanding the activity of excitable cells from a wide range of systems.

Among the first researchers directly influenced by Hodgkin and Huxley were Richard FitzHugh and Wilfrid Rall. FitzHugh, working at the NIH, generated important insight into dynamics of excitability, especially threshold phenomena, by deriving a simplified two-variable system of equations based on the Hodgkin-Huxley equations (FitzHugh, 1960, FitzHugh, 1961). Rall, commonly considered one of the founders of computational neuroscience, utilized mathematical approaches based on cable theory to show that dendritic branching of neurons affect processing of synaptic input, developed the discretized version of cable theory (compartmental modeling), and was one of the first to use digital computers in neuroscience (Rall, 1962, 1964, Segev and Rall, 1998). Rall's work was among the first examples of how mathematical modeling can be applied to shift a paradigm. Before these studies, neurons were assumed to have uniform electrical potential and dendrites were not assigned any real electrophysiological importance (Segev and Rall, 1998). Through the use of mathematical modeling, Rall demonstrated the need to take current flow to dendrites into account when interpreting data recorded in the soma. Although it was not until much later that his ideas were accepted, ideas introduced by Rall, such as spatial summation and dendritic attenuation of synaptic input, are now considered integral to neuroscience.

Quantitative Physiology after Hodgkin and Huxley – The cardiac “explosion”

While Hodgkin and Huxley's influence may be felt across the broad spectrum of biology, nowhere is it more evident outside the nervous system than in heart. Around the same time Rall and FitzHugh were conducting their studies, the British biologist Denis Noble was beginning an ambitious effort to apply the Hodgkin-Huxley equations to understand the distinct morphology of the cardiac AP characterized by a relatively long plateau phase (Noble, 1960, 1962). These initial efforts generated important predictions about ion channel differences between neurons and cardiac myocytes that predated by several years the first successful voltage clamp experiments in cardiac myocytes (Noble and Rudy, 2001). In the wake of these early efforts, the cardiac field has generated a staggering number of cell models based in one way or another on the original paradigm established by Hodgkin and Huxley (Noble and Rudy, 2001, Rudy and Silva, 2006). Today, experimentally based mathematical models are available for the cardiac AP from virtually every region of the heart and across a wide variety of species, including human (based, in fact, on human data). Advanced models account for dynamic changes in intracellular ion concentrations (original work assumed these to be constant) (DiFrancesco and Noble, 1985, Hilgemann and Noble, 1987, Luo and Rudy, 1994, Rasmusson et al., 1990), complicated ion channel gating kinetics (Clancy and Rudy, 1999, Jafri et al., 1998, Silva et al., 2009), elaborate spatial organization of membrane ion channels (Greenstein and Winslow, 2002, Rice et al., 1999), mitochondrial energetics (Cortassa et al., 2003), and intracellular signaling pathways (Grandi et al., 2007, Hund and Rudy, 2004, Saucerman et al., 2003). Furthermore, cell models have been incorporated into multi-dimensional models of cardiac tissue based on realistic myocardial geometry (Trayanova, 2011).

Mathematical modeling to define congenital and acquired disease mechanisms

Mathematical modeling has been applied extensively to provide important insight into molecular/ionic mechanisms for both congenital and acquired disease. Central to this effort has been work from the lab of Dr. Yoram Rudy. Notably, the Luo-Rudy dynamic model and its variants remain among the most cited cardiac action potential models and are widely used to study cardiac electrophysiology principles (Faber and Rudy, 2000, Livshitz and Rudy, 2007, Luo and Rudy, 1994, Viswanathan and Rudy, 1999, Zeng et al., 1995). Moreover, studies using these models have demonstrated the power of computational approaches in generating new mechanistic insight into cardiac arrhythmia (Clancy and Rudy, 1999, Silva et al., 2009, Viswanathan and Rudy, 1999). An early example comes from elegant studies that used the Luo-Rudy dynamic model to link channel defects resulting from a genetic mutation in the voltage-gated Na⁺ channel (K⁺ deletion mutation in *SCN5A*, encodes for primary cardiac Na⁺ channel alpha subunit) to lethal cardiac arrhythmias (Clancy and Rudy, 1999). Subsequent studies have used a similar approach to study the mechanism responsible for a wide range of inherited arrhythmia syndromes (Roberts et al., 2012).

Beyond inherited, monogenic disorders, modeling has been applied to understand mechanism in the setting of complex acquired disease, including myocardial ischemia/infarction, heart failure, and diabetes (Christensen et al., 2009, Hund et al., 2008, Lascano et al., 2013, Luo et al., 2013, Roberts et al., 2012, Swaminathan et al., 2012, Swaminathan et al., 2011, Zang et al., 2013). For example, arrhythmia mechanisms in the setting of myocardial infarction have been studied extensively using a mathematical modeling approach (Cabo and Boyden, 2003, Christensen et al., 2009, Hund et al., 2008). Specifically, mathematical models of the cardiac cell and tissue have been used to study the role of the multifunctional Ca²⁺/calmodulin-dependent kinase II (CaMKII) in creating a substrate for arrhythmias following myocardial infarction in the canine (Christensen et al., 2009, Hund et al., 2008). Mathematical models have also been applied to determine the link between chronic CaMKII activation and sinus node dysfunction in the setting of cardiovascular disease (Luo et al., 2013, Swaminathan et al., 2012, Swaminathan et al., 2011). While these studies have provided insight into arrhythmia mechanisms, going forward, it will be important to account for the fact that cells have evolved a complex web of regulatory networks between genes, proteins and other cellular molecules. These networks between various components in a cell control crucial physiological processes which govern cell growth, differentiation, division and even cell death. A thorough understanding of these networks is crucial not only for appreciation of the underlying biology but also to develop efficient therapeutic interventions in diseased conditions. New, multi-scale models will be critical to discover new interactions among the existing cellular components and predict unfavorable interactions which may lead to diseases.

Mathematical modeling in drug discovery, development and screening

Mathematical modeling and computer simulation have also had a significant impact on multiple stages in the drug discovery and development process. For example, advanced modeling methods have been applied to virtually screen libraries of potentially active small

molecules against the three-dimensional structure of a target. *In silico* docking studies played an important role in the development of drugs like the HIV protease inhibitor, amprenavir, and the influenza neuraminidase inhibitor, zanamivir (Greer et al., 1994). Among the many challenges for development of new therapeutic drugs, cardiotoxicity remains a major obstacle, contributing to high drug attrition rates in the drug development process (Ferri et al., 2013, Roden, 2004). While guidelines have been developed to assist with prediction of cardiotoxicity, accurate assessment of pro-arrhythmia risk for a particular drug remains a major challenge for the industry (Roden, 2004). Mathematical modeling and computer simulations have increasingly been used in drug discovery and development and have potential to impact every stage of the process from target screening and validation, to lead generation and optimization, to toxicity analysis and pre-clinical testing (Amanfu and Saucerman, 2011, Mirams et al., 2012, Rodriguez et al., 2010). In fact, the effort to use mathematical models to screen drug effects on cardiac electrophysiology dates back almost four decades (Hondeghe and Katzung, 1980). The development of channel gating models that account for partial coupling between functional states (Markov models) allowed for improved representation of channel structure and drug binding leading to important new insights on mechanisms responsible for drug actions (e.g. use- and voltage-dependent drug block) (Liu and Rasmusson, 1997, Moreno et al., 2011, Starmer et al., 1984). Ivabradine and ranolazine are two examples of drugs whose successful development was supported by mathematical modeling (Mirams et al., 2012). Today, whole heart models that incorporate detailed representation of cellular electrophysiology, drug action, and three-dimensional heart structure have been developed and implemented to predict the effects of drugs on arrhythmias and heart function (Moreno et al., 2011). At the same time, with growing emphasis on the need for a personalized approach to medicine, new approaches will be needed to account for tremendous variability in biology even among healthy individuals (Sarkar et al., 2012).

Conclusion

An important goal of this review was to help answer the difficult but important question “*Why model?*” In light of this challenge, we have discussed the value of models in biological research, with a focus on cardiac electrophysiology. Using excitable cell biology as a reference, we have provided a brief historical survey of the evolution of mathematical modeling and have provided specific examples of areas in which modeling has played a critical role in the discovery process. We have also tried to provide some insight for the non-modeler into the process involved in modeling. In the final analysis, we hope that mathematical modeling is not viewed as the answer to all scientific questions but rather as one of many available tools that may be used in a synergistic manner to facilitate scientific discovery.

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Figure 1. Hodgkin-Huxley theory for action potential generation

(A–B) Parallel conductance model of the giant squid axon cell membrane representing the membrane as an electrical circuit with a capacitor in series with time- and voltage-dependent Na^+ and K^+ conductances (g_{Na} and g_{K} , respectively) and a constant leak conductance (g_{L}). V_m = transmembrane potential; E_{Na} = reversal potential for Na^+ ; E_{K} = reversal potential for K^+ ; E_{L} = reversal potential for leak. (C–D) Simulated action potential and Na^+ and K^+ conductances generated by numerically solving the Hodgkin-Huxley equations (Hodgkin and Huxley, 1952).