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An Introduction to Computational Modeling of Cardiac Electrophysiology and Arrhythmogenicity

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Abstract

Mathematical modeling is a powerful tool to study the complex and orchestrated biological process of cardiac electrical activity. By integrating experimental data from key components of cardiac electrophysiology, systems biology simulations can complement empirical findings, provide quantitative insight into physiological and pathophysiological mechanisms of action, and guide new hypotheses to better understand this complex biological system to develop novel cardiotherapeutic approaches. In this chapter, we briefly introduce in silico methods to describe the dynamics of physiological and pathophysiological single-cell and tissue-level cardiac electrophysiology. Using a “bottom-up” approach, we first describe the basis of ion channel mathematical models. Next, we discuss how the net flux of ions through such channels leads to changes in transmembrane voltage during cardiomyocyte action potentials. By applying these fundamentals, we describe how action potentials propagate in models of cardiac tissue. In addition, we provide case studies simulating single-cell and tissue-level arrhythmogenesis, as well as promising approaches to circumvent or overcome such adverse events. Overall, basic concepts and tools are discussed in this chapter as an accessible introduction to nonmathematicians to foster an understanding of electrophysiological modeling studies and help facilitate communication with dry lab colleagues and collaborators.

Keywords

Cardiac electrophysiology; Systems biology; Quantitative systems pharmacology; Models of disease; Ion channels; Torsades de pointes; Arrhythmias

1 Introduction

1.1 Why Do We Need Mathematical Models in Basic and Translational Research?

Biological processes exhibit different layers of complexity that obscure the interpretation of experimental findings. First, many biological phenomena are nonlinear, whereby small changes in one system component can lead to large changes in overall behavior. Second,

biological processes are multiscale, which means that the translation of behavior from one spatial scale (e.g., the cell) to another (e.g., the organ) is not always straightforward. Such complexity forces experimentalists to utilize a simplified representation, or a model, of a given system in order to address a biological question. Independent of one's biological interests, three fundamental questions are commonly asked [1]: (1) what mechanisms regulate my biological process? (2) how do my findings translate in a multiscale context? and (3) how can I extract meaningful biological information from my big data set? Each of these issues can be addressed with computational methods.

Experimentalists utilize conceptual models to develop causal relationships; computational models use mathematical equations to describe such relationships. Both types of models help build intuition, contextualize data, and generate hypotheses [1]. Together, these two approaches provide complementary information and can yield greater insights than either strategy used in isolation [2, 3].

A typical flowchart to incorporate mathematical modeling into an experimental study involves a well-defined research question, model development/refinement, and experimental validation, leading to refined hypotheses or answers to biological questions (Fig. 1). In this chapter, we discuss methods to incorporate mathematical modeling into experimental cardiac electrophysiology under healthy and diseased conditions.

1.2 Multiscale Characteristics of Cardiac Electrophysiology Models and Their Applications

Like other biological processes, cardiac electrophysiology has complex nonlinear and multiscale characteristics (Fig. 2). By integrating experimental data from key components of cardiac electrophysiology, systems biology simulations can complement empirical findings, provide quantitative insight into physiological and pathophysiological mechanisms of action, and guide new hypotheses to better understand this complex biological system and develop novel cardiotherapeutic approaches.

Fine-tuned movements of ions into and out of the cardiomyocyte are at the core of cardiac electrophysiology. Individual cardiomyocytes have distinct ion channels, each with their own kinetics and properties that regulate the magnitude and rate of ions fluxing into and out of the cell (Fig. 2, item 1). The activity of a given ion channel can be mathematically modeled with sufficient voltage clamp data obtained by measuring ion channel activity while holding a cell's transmembrane voltage for a set amount of time at a range of values (for more details, see Subheading 2.1). Tireless efforts and collaborations between experimentalists and dry lab colleagues have led to models of each key ion moving through compartments of the cardiomyocyte. By accounting for the net effects of all key ion channels/pumps/exchangers in cardiomyocytes, mathematical modelers have been successful in simulating whole-cell electrophysiology (Fig. 2, item 2; for more details see Subheading 2.2). Experimentally, cellular electrophysiology can be assessed via single cell imaging and microelectrodes, whereas tissue-level measurements are commonly made with electrode arrays and optical mapping. Higher-order models can be subsequently developed by accounting for electrical excitation through image-based anatomical representations of tissue comprised of *in silico* single-cell models (Fig. 2, items 3–5).

Throughout this chapter, we sequentially demonstrate that each order of model—from ion currents to whole cell to tissue level—has its own utility and contributes to modeling and predicting specific types of physiology and pathophysiology (Fig. 2, right panel).

1.3 Chapter Overview

In the remainder of this chapter, we briefly introduce *in silico* methods to describe the dynamics of physiological and pathophysiological single-cell and tissue-level cardiac electrophysiology (Fig. 2, items 1–3), aiming to provide a primer that will enable nonmathematicians to better communicate with computational modeling colleagues and understand the related scientific literature. Following a brief review of the basics of human ventricular cardiomyocyte electrophysiology (Subheading 1.4), we adopt a “bottom-up” approach that starts by describing the basis of ion channel mathematical models (Subheading 2.1). Next, we discuss how the net flux of ions through key channels leads to changes in transmembrane voltage during cardiomyocyte action potentials (Subheading 2.2). By applying these fundamentals, we describe how action potentials propagate in models of cardiac tissue (Subheading 2.3). Finally, for each of these latter sections, we also provide case studies and applications of simulating single-cell and tissue-level electrophysiological pathology (Subheadings 3.1 and 3.2, respectively).

1.4 Brief Overview of Adult Human Cardiomyocyte Electrophysiological Properties

As a reference for the nonelectrophysiologist, we first provide a brief overview on cardiomyocyte electrophysiology. As illustrated in Fig. 3, the human adult ventricular cardiomyocyte (hCM) has five phases of the cardiac action potential: (0) upstroke; (1) early repolarization notch; (2) plateau; (3) late repolarization; and (4) diastole. Specific ion channels dominate each of these respective phases: (0) sodium current; (1) transient outward potassium current; (2) L-type calcium current; (3) rapid and slow delayed rectifier potassium currents; and (4) inward rectifier potassium current. Figure 3 illustrates how these channels contribute to the action potential, and when they are active during the ventricular action potential.

Myocytes from different regions of the heart (e.g., atria compared with ventricles) contain different ionic current constituents, and, as a result, exhibit different action potential shapes. Similarly, important differences in ion channels and action potential waveforms are observed between mature adult human cardiomyocytes and human stem cell-derived cardiomyocytes (hiPSC-CMs) that are often used in the experimental setting. More specifically, hiPSC-CMs have prominent funny currents, or pacemaker currents, which contribute to hiPSC-CM automaticity that is not evident in adult ventricular myocytes (Fig. 3) [4]. Mathematical models can describe these differences, and even help predict how findings from hiPSC-CMs may translate to healthy and diseased adult ventricular myocytes [3]. Below, we describe how to mathematically model individual families of ion currents; specifically, we use the hERG rapid delayed rectifier K^+ current (I_{Kr}) as a case example.

2 Methods

2.1 How to Model Ion Channel Activity

Cellular electrophysiology depends on the movement of sodium, potassium, calcium, and other ions across semipermeable cellular and intracellular membranes. However, the lipid bilayer has an extremely high resistance that acts as an electrical insulator; transmembrane ion channels control the flux of specific ions across cell membranes [5].

Ions flow through an ion channel down an electrochemical gradient—that is, ion flux is influenced by both diffusional and electric field forces. When ion x 's movement in one direction of a channel due to diffusion is equal and opposite to the rate of movement due to the electric field, equilibrium is achieved. This occurs when the transmembrane voltage (V_m), defined by present-day convention as intracellular minus extracellular voltage, is equal to the Nernst equilibrium potential (E_x) that can be calculated using an equation derived by the physical chemist and Nobel Laureate, Walther Nernst, in the late nineteenth century:

$$E_x = \frac{RT}{zF} \ln \left(\frac{[x_o]}{[x_i]} \right) \quad (1)$$

That is, for an ion with a known charge z at constant temperature T , E_x increases in magnitude when the disparity between intracellular and extracellular concentration ($[x_i]$ and $[x_o]$, respectively) of a given ion x increases. Note that R and F are the ideal gas constant and Faraday's constant, respectively. Mathematical modelers can therefore keep track of intracellular and extracellular concentrations of ions to calculate E_x over time. Using the present-day convention, the logarithmic term in E_x is positive if the extracellular concentration of an ion is greater, and negative if the intracellular concentration of an ion is greater.

When deviating from equilibrium, the net driving force of ion x outward (based on convention) can be defined as ($V_m - E_x$). If $V_m > E_x$, the outward diffusion forces (e.g., K^+ is higher intracellularly than extracellularly) outweigh inward electric forces, leading to a net flux of a given ion out of the cell through its channel (this is common in several cardiomyocyte K^+ ion channels, as E_K is approximately -90 mV, and a cardiomyocyte's V_m ranges from approximately -90 mV to $+40$ mV). Conversely, if $V_m < E_x$, the inward diffusion forces (e.g., Na^+ is higher extracellularly than intracellularly) outweigh outward electric forces, leading to a net flux of a given ion into the cell through its channel (this is common in the cardiomyocyte Na^+ ion channel, which leads to Phase 0 depolarization as in Fig. 3).

Using this framework, the current I of ion x is proportional to the electrochemical driving force ($V_m - E_x$), with the proportionality coefficient g_x , defined as the conductance, or the ability of electrical charge to flow through the ion channel. The conductance is generally not modeled as a constant, but rather simulated to account for the average number of channels within a cell membrane that are open at a particular time.

Macroscopically, the number of open voltage gated channels changes over time in response to V_m . Computational electrophysiologists describe these changes mathematically using macroscopic channel kinetic equations. In a simple case, a channel can be modeled as switching between active and inactive states using first-order rate processes. The average percent of open channels (x_1) over time can therefore be described by two variables: (1) its steady state value, $x_{1,\infty}$, defining the average percent of open channels over a sufficiently extended period of time; and (2) its time constant, τ_{x1} , defining how quickly x_1 approaches $x_{1,\infty}$. Based on these definitions, $x_{1,\infty}$ ranges between 0 and 1, where it increases at higher transmembrane voltages. Mathematically, x_1 obeys the differential equation:

$$\frac{dx_1}{dt} = \frac{x_{1,\infty} - x_1}{\tau_{x1}} \quad (2)$$

That is, the instantaneous change in x_1 is such that it approaches $x_{1,\infty}$ (i.e., if x_1 is less than $x_{1,\infty}$, there is a positive instantaneous change in x_1 to approach its steady-state value $x_{1,\infty}$; on the other hand, if x_1 is greater than $x_{1,\infty}$, there is a negative instantaneous change in x_1 to approach its steady-state value $x_{1,\infty}$) at a rate proportional to $1/\tau_{x1}$ (i.e., the smaller the τ_{x1} , the faster it will approach the steady-state value). Importantly, both $x_{1,\infty}$ and τ_{x1} are functions of transmembrane voltage, as demonstrated in Fig. 4. Numerical methods are used to update x_1 values over time, thereby simulating the temporal evolution of ion channel gating at a given voltage, by: (1) discretizing changes in time (e.g., time increments of 0.0025 ms); (2) calculating the right hand side of the differential equation—recall that $x_{1,\infty}$ and τ_{x1} are functions of transmembrane voltage, so this value must be known; (3) multiplying the values from the previous two steps; (4) adding step 3 to the previous value of x_1 ; and (5) repeating steps 1–4.

In more complex cases, a channel can again switch between open and closed states; however, in addition, it can also be inactivated—or blocked—by specialized subunits of a channel, adding another layer of complexity. The switch between the two states—inactivated or not inactivated—can be modeled using similar first-order rate processes. However, the steady-state values typically decrease, rather than increase, at higher transmembrane voltages. Nevertheless, the same differential equation typically applies to model inactivation.

This approach was utilized by Tong et al. to model the hERG delayed rectifier current (I_{Kr}) [6]. To formulate such a model, it is necessary to develop relationships between the transmembrane voltage and steady-state activation, activation time constant, steady-state inactivation, and inactivation time constant. This was done by Tong et al. [6] by extracting data from full length hERG clones expressed in different expression systems [7–10], as shown in Fig. 4a–d, respectively.

The theory behind gating kinetics motivates the use of the sigmoidal-shaped function to relate voltage and steady-state variables, as shown in Fig. 4a, c. On the other hand, normal distribution-shaped functions (as in Fig. 4b, d) or exponential decay-shaped functions (not shown) are commonly used to relate voltage and time constants. The parameters within each

equation are typically found through algorithms to minimize the error between the function outputs and experimental data points. Both activation and inactivation variables obey the differential Eq. (2) previously shown; in this case, the resulting conductance (g_{hERG}) was defined as the product of the maximum conductance constant, activation variables (each a function of time and voltage, as previously described), and the inactivation variable (a function of time and voltage, as previously described), which can be inserted into the hERG ion current equation, $I_{\text{hERG}} = g_{\text{hERG}}(V_m - E_K)$.

More sophisticated models have been developed to refine the hERG model specifically for its contributions to the cardiomyocyte action potential. For example, using a similar methodology to that described herein, O'Hara et al. [11] developed a more complex, but more cardiomyocyte-specific, representation of the delayed rectifier potassium current. As shown in Fig. 4e, f, it is highly representative of experimental hERG activity throughout the cardiac action potential.

In the next section, we demonstrate how O'Hara et al. [11] used their hERG model (and other key action potential ion channel/pump models) to simulate whole-cardiomyocyte action potentials. While other human ventricular models have been successfully developed [12–14], we focus on the O'Hara et al. model [11] for its current use as an *in silico* component of the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative, which we describe further in Subheading 3.1 [15].

2.2 How to Model Whole-Cardiomyocyte Electrophysiology

As outlined in Subheading 1.4, several key ion channels are active at different phases of the cardiac action potential. Each of these channels can be modeled using the framework described in Subheading 2.1, with slight modifications to account for unique properties of each channel. The net flux of ions (I_{total}) through key channels (for a schematic of all channels/pumps/etc. involved in the O'Hara et al. human adult cardiomyocyte model, *see* Fig. 5a) [11] leads to changes in transmembrane potential (V_m) over time, obeying the following differential equation:

$$\frac{dV_m}{dt} = - \frac{I_{\text{total}} + I_{\text{stim}}}{C_m} \quad (3)$$

where C_m is the constant capacitance of the cell (proportional to cell size) and I_{stim} is the artificial stimulus provided in the simulation (adult ventricular myocytes do not excite on their own, thus requiring artificial activation in the model). Note that the negative term in front of the right hand side of the equation is due to the present-day convention of current previously described. Similar to the differential Eq. (2), numerical methods can be used to update V_m values over time (allowing for simulations of the transmembrane voltage over time) by (1) discretizing changes in time (e.g., time increments of 0.0025 ms); (2) calculating the right hand side of the differential equation (recall each ion channel has its own gates, so for each gate, the numerical methods for solving respective gating differential equation (Subheading 2.1) must be used); (3) multiplying the values from the previous two steps; (4) adding step 3 to the previous value of V_m ; and (5) repeating steps 1–4.

By doing so, the O'Hara et al. model [11] was able to successfully simulate adult cardiomyocyte action potentials (Fig. 5b) that look remarkably similar to experimental action potentials from three select adult cardiomyocytes (Fig. 5c) and was within experimental variability for several characteristics of the action potential, including resting membrane potential, peak voltage, and maximum rate of voltage increase (Fig. 5d–f). Furthermore, by accounting for net fluxes of calcium into and out of four key cellular compartments—such as bulk myoplasm (myo), junctional sarcoplasmic reticulum (JSR), network sarcoplasmic reticulum (NSR), and subspace (SS)—the O'Hara et al. model [11] could also simulate intracellular calcium (in myo) over the duration of the action potential, which was also remarkably similar to experimental calcium transient characteristics (Fig. 5g–i).

2.3 How to Model Cardiac Tissue Strands

Myocardium is made up of individual cardiomyocytes connected by intercalated disks, embedded within the extracellular matrix; in the context of cardiac tissue electrophysiology, gap junctions play a key role by allowing for intercellular propagation of action potentials throughout the myocardial tissue. To simulate tissue-level electrophysiology, mathematical modelers extend the single-cell model (Subheading 2.2) by accounting for ion flow through gap junctions between neighboring cells. Figure 6 illustrates this method and the resultant simulations in the simplest tissue case—a one-dimensional strand of myocytes, also referred to as a “cable model”.

In this example, cells are connected end-to-end through gap junctions. Gap junctions contain proteins called connexins, and these form channels that connect the intracellular spaces of two adjacent myocytes. As a result of the connexin proteins, gap junctions allow the flow of electrical charge (i.e., they are conductive). To this end, flow between two cells can be modeled analogously to an ion channel. Just as there was an electrochemical driving force ($V_m - E_x$) for a single-cell's ion channel, there is a driving force through a gap junction between cells 1 and 2 of ($V_{m,1} - V_{m,2}$); if cell 1 has a higher voltage than neighboring cell 2 (i.e., $V_{m,1} > V_{m,2}$), then cation flux is driven from cell 1 to cell 2 (Fig. 6a). This gets scaled by the constant gap junctional conductance, g_{gap} , to compute the gap junctional current. Keep in mind, each cell has its own electrophysiological properties that can be described by whole-cell models (Fig. 6b). Altogether, each cell within the tissue strand can be mathematically approximated as:

$$\frac{\Delta V_{m,\text{cell } n}}{\Delta t} = - \frac{I_{\text{total},n} + I_{\text{stim},n} + g_{\text{gap}}(V_n - V_{n-1}) + g_{\text{gap}}(V_n - V_{n+1})}{C_m} \quad (4)$$

where, for a given cell n with transmembrane voltage $V_{m,\text{cell } n}$, the change in voltage over time can be approximated as single-cell changes (from $I_{\text{total},n}$ and $I_{\text{stim},n}$), in addition to the fluxes through gap junctions to neighboring cells to the left ($g_{\text{gap}}(V_{m,n} - V_{m,n-1})$) and right ($g_{\text{gap}}(V_{m,n} - V_{m,n+1})$) of cell n . Yet again, as an extension to the whole-cell calculations (Subheading 2.2), numerical methods can be used to update voltage values of all cells in a tissue over time by: (1) discretizing changes in time; (2) calculating the right hand side of

the differential equation (recall each cell has its own voltage and channels, so for each cell's gates—which are dependent on voltage—the numerical methods used to solve each gating differential equation (Subheading 2.1) must be implemented); (3) multiplying the values from the previous two steps; (4) adding step 3 to the previous value of V_m for each cell; and (5) repeating steps 1–4. Note that I_{stim} does not necessarily need to excite all cells at once, as we discuss below.

Figure 6c illustrates simulation results of action potentials propagating from cell 1 (the only excited cell) to cell 100 connected in series. Note a delay in activation from cell-to-cell, which reflects the intrinsic resistance to ionic flux through the gap junctions. A typical metric used to characterize this delay is called the conduction velocity (CV); the greater the conduction velocity, the less the delay. Measuring the difference in time of activation between a cell near the beginning of the strand and the end of the strand (defined as Δt) and the spatial distance between these two cells (defined as Δd), conduction velocity is calculated as $CV = \Delta d / \Delta t$ (Fig. 6c). Physiologic CV along the fiber direction in healthy adult human myocardium can decrease appreciably in the setting of fibrosis or other pathologies or interventions that diminish the integrity or expression level of gap junction proteins, leading to irregular heartbeats. Therefore, CV is recognized as a valuable metric when attempting to predict myocardial arrhythmic potential.

3 Applications of Cardiac Electrophysiology Models

3.1 Applications of Single-Cell Models: Predicting Torsadogenic Drugs

In this section, we provide an example of the utility and promise of computational approaches to model whole-cell electrophysiological pathology and emerging drug toxicity screening technologies.

Torsades de pointes (TdP) is a rare but lethal form of polymorphic ventricular tachycardia [16]. In addition to congenital long QT syndrome, antiarrhythmic and noncardiac drugs have been implicated in causing TdP [17]. Drug-induced TdP is a leading cause of drug relabeling or withdrawal from the market, second only to drug-induced hepatotoxicity [18, 19]; this has led to the establishment of regulatory cardiotoxicity testing [20–22]—including in vitro measurements on hERG current inhibition, animal model QT assays, and clinical examination of QT interval in healthy volunteers—that is both expensive and of limited predictive value for subsequent clinical trials [23, 24]. Given early drug development attrition rates of 80–90% and only 10% commercial success [25, 26] with development costs on the order of two to three billion dollars [27], it is of great interest for pharmaceutical companies to economically and effectively screen whether a drug under development is likely to be torsadogenic [28].

Recent work has demonstrated the promise of integrating systematic simulations with machine learning to successfully predict pharmacological toxicity [29]. Lancaster and Sobie [29] simulated the individual effects of a panel of 86 drugs on cardiomyocyte action potential and calcium transient metrics by incorporating each of their empirical inhibitory effects on hERG delayed rectifier K^+ channel, L-type calcium channel, and sodium channel activity (Fig. 7a). This was accomplished by scaling the maximum conductance as a

function of the half-maximal inhibitory concentration (IC_{50}) value, and the effective free therapeutic plasma concentration (EFTPC).

By inputting the simulated effects of each drug on 13 action potential (Fig. 7a) and calcium transient (Fig. 7b) metrics into a support vector machine (SVM) learning algorithm (SVM divides the input metrics into two regions—e.g., torsadogenic and nontorsadogenic—separated by a linear boundary), Lancaster and Sobie [29] were able to classify drugs as torsadogenic or nontorsadogenic with superior sensitivity and specificity (Fig. 7c) and lower misclassification rates (Fig. 7d) in comparison to conventional methods [e.g., using IC_{50} values from hERG channel inhibition assays (hERG IC_{50} /EFTPC), or from simulations of action potential duration alone (APD₉₀)].

These promising quantitative systems pharmacology approaches are gaining traction; currently, *in silico* modeling of human ventricular electrical activity is an integral part of the CiPA initiative to more effectively detect and avoid drug-induced TdP for new drugs seeking regulatory approval from the Food and Drug Administration (FDA) [15].

3.2 Applications of Tissue-Level Models: Predicting Stem Cell Effects on Electrical Properties of Fibrotic Heart Tissue

In this final section, we provide an example of using computational approaches to model tissue-level electrophysiology pathology and therapeutic interventions.

Human bone marrow-derived mesenchymal stem cells (hMSCs) offer a promising approach to treat heart failure [30]. To date, clinical benefits of hMSC therapy have achieved statistical significance, but typically remain modest in effect and not long lasting [31–34], representing an opportunity for improvement. A better understanding of underlying cardioactive mechanisms could help optimize future hMSC-based therapies. These mechanisms involve antifibrotic and ion channel remodeling effects of hMSC paracrine signaling, as well as direct hMSC–myocyte heterocellular coupling [3].

In our recent study [3], *in silico* findings provided insights that help resolve disparate reports of potential proarrhythmic risks of hMSCs *in vitro* [35] that contradict *in vivo* reports of hMSCs having no effect [36] or even favorable cardioprotective effects [34] on arrhythmogenesis in preclinical animal studies and clinical trials. To do so, we extended one-dimensional tissue strands to two-dimensional tissue sheets (Fig. 8a), with cells coupled end-to-end in the *x* direction, as well as side-to-side in the *y* direction. Heterogeneous cell populations comprised of cardiac myocytes and fibroblasts were used to simulate cardiac tissue with either low levels or high levels of fibrosis. The former is more representative of *in vitro* cell culture with minimal fibrosis, whereas the latter represents *in vivo* models where hMSCs are used therapeutically post-myocardial infarction. Note that myocyte–myocyte gap junctional conductances are higher than myocyte–fibroblast gap junctions (i.e., there is more resistance in myocyte–fibroblast coupling), leading to slower CV when adding fibrosis into cardiac tissue simulations.

Slowed conduction could lead to arrhythmogenesis, warranting a systematic method to test arrhythmic responses. In the context of cardiac tissue, a metric called the vulnerable window

(VW) is often used [3]. A typical protocol for VW analysis is shown in Fig. 8b; a higher VW corresponds to a higher risk of arrhythmogenesis.

In simulations more closely representing healthy myocyte monolayers (Fig. 8c), both hMSC paracrine signaling (PS) and heterocellular coupling (HC) are predicted to increase arrhythmogenicity compared to hMSC-free control conditions. However, in VW simulations of highly fibrotic cardiac tissue (Fig. 8d), hMSC paracrine signaling-only conditions were predicted to be antiarrhythmic by decreasing VW compared to control, whereas HC between hMSCs and cardiomyocytes caused the VW to increase [3]. VW analyses further predicted that hMSC supplementation (involving both PS and HC mechanisms) did not adversely impact fibrotic cardiac tissue arrhythmogenesis, and may even be antiarrhythmic [3]. These simulations could help explain why hMSCs are often reported as safe [36] or even antiarrhythmic [34] in clinical trials where paracrine effects are present despite low cell engraftment.

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Fig. 1.

Typical flowchart for incorporating mathematical modeling into an experimental study to answer biological questions. (a) Well-defined research questions lead to (b) the development of hypotheses and (c) appropriate modeling approaches. Iterating through (d) model development, fine-tuning, and (e) experimental validation can lead to refined hypotheses (b) or answers to biological questions (f). Figure redrawn from [1]

Fig. 2.

Multiscale integration of experimental data into mathematical models to predict healthy and diseased cardiac electrophysiology. From bottom to top: (1) voltage/patch clamp data are used to develop models of cardiac ion channels; (2) the net effects of all cardiac ion channels/pumps/etc. are used for single-cell cardiomyocyte models; together, these models can be perturbed to simulate physiologic and pathophysiologic single-cell electrophysiology. (3–5) tissue-, organ-, and body-level simulations utilize image-based anatomical models; incorporating single-cell models with electrical excitation through tissue allows for higher-order predictions of arrhythmia. The right panel illustrates in silico applications for each respective scale. Figure adapted from [37] with permission

Fig. 3.

Overview of cardiomyocyte action potential electrophysiology. Human adult ventricular cardiomyocytes have distinct action potential waveforms with unique underlying ion current contributions. Phases 0–4 of an excited adult ventricular cardiomyocyte action potential (looking at transmembrane potential over time) correspond to upstroke (mainly due to the sodium current, I_{Na}), early repolarization notch (mainly due to transient outward K^+ current type 1, I_{to1}), plateau (mainly due to L-type calcium current, $I_{Ca,L}$), late repolarization (mainly due rapid and slow delayed rectifier K^+ currents, I_{Kr} and I_{Ks} , as well as the inward rectifier K^+ current, I_{K1}), and diastole (mainly due to I_{K1} and others not shown), respectively. Adapted from [38] with permission

Fig. 4.

Modeling the hERG rapid delayed rectifier ion channel. Tong et al. [6] developed a model of the hERG delayed rectifier channel by determining relationships between the transmembrane voltage (V) and (a) steady-state activation (ss_{act}), (b) activation time constant (τ_{act}), (c) steady-state inactivation (ss_{inact}), and (d) inactivation time constant (τ_{inact}) using data from full length hERG clones expressed in different expression systems [7–10]. Lines represent best fit equations to experimental data points. Note two different activation gates were incorporated into the Tong et al. [6] hERG model by using the same steady-state activation equations from Panel (a), each with different activation time constants τ_{hn1} and τ_{hn2} from Panel (c). (e, f) Other models (e.g., O'Hara et al. [11]) have been developed to better reflect the hERG delayed rectifier current (I_{Kr}) contribution during an adult human cardiomyocyte action potential. Panels (a) through (d) adapted from [6] with permission. Panels (e) and (f) adapted from [11] with permission

Fig. 5.

Modeling the human adult cardiomyocyte action potential. (a) Schematic of the types of ion channels/ pumps/exchangers modeled; the net effects of these channels/pumps/exchangers in their given compartment are used to model whole cell electrophysiology. Four main compartments are accounted for, including (1) bulk myoplasm (myo), (2) junctional sarcoplasmic reticulum (JSR), (3) network sarcoplasmic reticulum (NSR), and (4) subspace (SS); for details, see [11]. Comparison of the (b) simulated and (c) three select experimental adult cardiomyocyte action potentials during electrical pacing with varying cycle length (inverse of frequency). (d–f) Comparison of simulated and experimental characteristics of the action potential, including resting membrane potential (V_{min}), peak voltage (V_{peak}), and maximum rate of voltage increase (dV/dt_{max}), respectively. (g) By accounting for net fluxes of calcium into and out of each key cellular compartment, O'Hara et al. [11] could also simulate intracellular calcium ($[Ca^{2+}]_i$) over the duration of the action potential (top);

comparison to experimental $[Ca^{2+}]_i$ transients (bottom). **(h, i)** Comparison of simulated and experimental characteristics of the calcium transient, including peak $[Ca^{2+}]_i$ and decay time constant (τ_{ca}), respectively. Adapted from [11] with permission

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Fig. 6. Modeling action potential propagation in a one-dimensional tissue strand. **(a)** Schematic of action potential propagation when cells are coupled to each other—cell 1 is excited, leading to depolarization; $V_{m,1}$ therefore has a higher voltage than neighboring cell 2, driving cation flux from cell 1 to cell 2, and so forth. **(b)** This can be represented with electrophysiological models, where each cell has its own whole-cell model (e.g., O’Hara et al. cell model [11]), and ions flow down the electrochemical gradient through gap junctional channels with constant conductance, g_{gap} . **(c)** Simulation results of action potentials propagating from excited cell 1 to cell 100. The speed of propagation from one cell to the next can be calculated by the conduction velocity (d / t). Panel **(b)** adapted from [11] with permission. Panel **(c)** adapted from [39] with permission

Fig. 7.

Using single-cell models to predict drug-induced arrhythmias. By simulating effects of 86 drugs on 13 metrics (inset) from human adult ventricular myocyte (a) action potentials and (b) calcium transients, Lancaster and Sobie were able to classify drugs as torsadogenic or nontorsadogenic with superior (c) sensitivity and specificity and (d) misclassification rates compared to conventional methods [e.g., using IC_{50} values from hERG channel inhibition assays (hERG IC_{50} /EFTPC), or from simulations of action potential duration alone (APD_{90})]. Figure adapted from [29] with permission

Fig. 8.

Modeling hMSC electrophysiological effects on 2D fibrotic cardiac tissue. **(a)** Schematic of two-dimensional cell–cell coupling between human adult ventricular myocytes (hCMs) and fibroblasts. In this case, action potentials can propagate both in the x and y directions, rather than just along one dimension as in Fig. 6. **(b)** Steps for performing two-dimensional vulnerable window (VW) analysis by observing electrical wavefront propagation patterns in a 5×5 -cm square region of simulated cardiac tissue. VWs of **(c)** low fibrotic and **(d)** high fibrotic cardiac tissue with varying levels of human mesenchymal stem cell heterocellular coupling (HC) and/or paracrine signaling (PS) interventions. Panel **(b)** adapted from [40] with permission. Panels **(c)** and **(d)** adapted from [3] with permission