Modeling and Imaging of Bioelectrical Activity
Principles and Applications
BIOELECTRIC ENGINEERING

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University of Minnesota
Minneapolis, Minnesota

MODELING AND IMAGING OF BIOELECTRICAL ACTIVITY
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Bioelectrical activity is associated with living excitable tissue. It has been known, owing to efforts of numerous investigators, that bioelectrical activity is closely related to the mechanisms and functions of excitable membranes in living organs such as the heart and the brain. A better understanding of bioelectrical activity, therefore, will lead to a better understanding of the functions of the heart and the brain as well as the mechanisms underlying the bioelectric phenomena.

Bioelectrical activity can be better understood through two common approaches. The first approach is to *directly measure* bioelectrical activity within the living tissue. A representative example is the direct measurement using microelectrodes or a microelectrode array. In this direct measurement approach, important characteristics of bioelectrical activity, such as transmembrane potentials and ionic currents, have been recorded to study the bioelectricity of living tissue. Recently, direct measurement of bioelectrical activity has also been made using optical techniques. These electrical and optical techniques have played an important role in our investigations of the mechanisms of cellular dynamics in the heart and the brain.

The second approach is to *noninvasively* study bioelectrical activity by means of *modeling and imaging*. Mathematical and computer models have offered a unique capability of correlating vast experimental observations and exploring the mechanisms underlying experimental data. Modeling also provides a virtual experimental setting, which enables well controlled testing of hypothesis and theory. Based on the modeling of bioelectrical activity, noninvasive imaging approaches have been developed to detect, localize, and image bioelectrical sources that generate clinical measurements such as electrocardiogram (ECG) and electroencephalogram (EEG). Information obtained from imaging allows for elaboration of the mechanisms and functions of organ systems such as the heart and the brain.

During the past few decades, significant progress has been made in modeling and imaging of bioelectrical activity in the heart and the brain. Most literature, however, has treated these research efforts in parallel. The similarity arises from the biophysical point of view that membrane excitation in both cardiac cells and neurons can be treated as volume current sources. The clinical observations of ECG and EEG are the results of volume conduction of currents within a body volume conductor. The difference among bioelectrical activity originating from different organ systems is primarily due to the different physiological mechanisms underlying the phenomena. From the methodological point of view,
therefore, modeling and imaging of bioelectrical activity can be treated within one theoretical framework. Although this book focuses on bioelectric activity of the heart and the brain, the theory, methodology, and state-of-the-art research that are presented in this book should also be applicable to a variety of applications.

The purpose of this book is to provide a state-of-the-art coverage of basic principles, theories, and methods of modeling and imaging of bioelectrical activity with applications to cardiac and neural electrical activity. It is aimed at serving as a reference book for researchers working in the field of modeling and imaging of bioelectrical activity, as an introduction to investigators who are interested in entering the field or acquiring knowledge about the current state of the field, and as a textbook for graduate students and seniors in a biomedical engineering, bioengineering, or medical physics curriculum.

The first three chapters deal with the modeling of cellular activity, cell networks, and whole organ for bioelectrical activity in the heart. Chapter 1 provides a systematic review of one-cell models and cell network models as applied to cardiac electrophysiology. It illustrates how modeling can help elucidate the mechanisms of cardiac cells and cell networks, and increase our understanding of cardiac pathology in three-dimension and whole heart models. Chapter 2 provides a thorough theoretical treatment of the forward problem of bioelectricity, and in particular electrocardiography. Following a review of the theoretical basis of equivalent dipole source models and state-of-the-art numerical methods of computing the electrical potential fields, Chapter 2 discusses the applications of forward theory to whole heart modeling and defibrillation. Chapter 3 reviews important issues in whole heart modeling and its implementation as well as various applications of whole heart modeling and simulations of cardiac pathologies. Chapter 3 also illustrates important clinical applications the modeling approach can offer.

The following two chapters review the theory and methods of inverse imaging with applications to the heart. Chapter 4 provides a systematic treatment of the methods and applications of heart surface inverse solutions. Many investigations have been made in order to inversely estimate and reconstruct potential distribution over the epicardium, or activation sequence, over the heart surface from body surface electrocardiograms. Progress has also been made to estimate endocardial surface potentials and activation sequence from catheter recordings. These approaches and activities are well reviewed in Chapter 4. Chapter 5 reviews the recent development in three dimensional electrocardiography tomographic imaging. Recent research shows that, by incorporating a priori information into the inverse solutions, it is possible to estimate three-dimensional distributions of electrophysiological characteristics such as activation time and transmembrane potentials, or equivalent current dipole distribution. In particular, a whole-heart-model based tomographic imaging approach is introduced, which illustrates the close relationship between modeling and imaging and the merits of model-based imaging.

Chapter 6 deals with a noninvasive body surface mapping technology – surface Laplacian mapping. Compared with well-established body surface potential mapping, body surface Laplacian mapping has received relatively recent attention in its enhanced capability of identifying and mapping spatially separated multiple activities. This chapter also illustrates that a noninvasive mapping technique can be applied to imaging of bioelectrical activity originated from different organ systems, such as the heart and the brain.

The subsequent two chapters treat inverse imaging of the brain from neuromagnetic and neuroelectric measurements, as well as functional magnetic resonance imaging (fMRI).
Chapter 7 reviews the forward modeling of magnetoencephalogram (MEG), and neuromagnetic source imaging with a focus on spatial filtering approach. Chapter 8 provides a general review of fMRI, linear inverse solutions for EEG and MEG, and multimodal imaging integrating EEG, MEG and fMRI. Along with Chapters 4 and 5, these four chapters are intended to provide a solid foundation in inverse imaging methods as applied to imaging bioelectrical activity.

Chapter 9 deals with tissue conductivity, an important parameter that is required in bioelectric inverse solutions. The conductivity parameter is needed in establishing accurate forward models of the body volume conductor and obtaining accurate inverse solutions using model-based inverse imaging. As most inverse solutions are derived from noninvasive measurements with the assumption of known tissue conductivity distribution, the accuracy of tissue conductivity is crucial in ensuring accurate and robust imaging of bioelectrical activity. Chapter 9 systematically addresses this issue for various living tissues.

This book is a collective effort by researchers who specialize in the field of modeling and imaging of bioelectrical activity. I am very grateful to them for their contributions during their very busy schedules and their patience during this process. I am indebted to Aaron Johnson Brian Halm, Shoshana Sternlicht, and Kevin Sequeira of Kluwer Academic Publisher for their great support during this project. Financial support from the National Science Foundation, through grants of NSF CAREER Award BES-9875344, NSF BES-0218736 and NSF BES-0201939, is also greatly appreciated.

We hope this book will provide an intellectual resource for your research and/or educational purpose in the fascinating field of modeling and imaging of bioelectrical activity.

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1

FROM CELLULAR ELECTROPHYSIOLOGY TO ELECTROCARDIOGRAPHY

by Nitish V. Thakor, Vivek Iyer, and Mahesh B. Shenai

INTRODUCTION

Since many cardiac pathologies manifest themselves at the cellular and molecular levels, extrapolation to clinical variables, such as the electrocardiogram (ECG), would prove invaluable to diagnosis and treatment. One ultimate goal of the cardiac modeler is to integrate cellular level detail with quantitative properties of the ECG (a property of the whole heart). This magnificent task is not unlike a forest ranger attempting to document each leaf in a massive forest. Both the modeler and ranger need to place fundamental elements in the context of a broader landscape. But now, with the recent genome explosion, the modeler needs to examine the “leaves” at even much greater molecular detail. Fortunately, the rapid explosion in computational power allows the modeler to span the details of each molecular “leaf” to the “forest” of the whole heart. Thus, cardiac modeling is beginning to span the spectrum from DNA to the ECG, from nucleotide to bedside.

Extending cellular detail to whole-heart electrocardiography requires spanning several levels of analysis (Figure 1.1). The one-cell model describes an action potential recording from a single cardiac myocyte. By connecting an array of these individual myocytes (via gap junctions), a linear network (cable), two-dimensional (2D) network or three-dimensional (3D) network (slab) model of action potential propagation can be constructed. The bulk electrophysiological signal recorded from these networks is called the local extracellular electrogram. Subsequently, networks representing tissue diversity and realistic heart geometries can be molded into a whole heart model, and finally, the whole heart model can be placed in a torso model replicating lung, cartilage, bone and dermis. At each level, one can reconstruct the salient electric signal (action potential, electrogram, ECG) from the cardiac sources by solving the forward problem of electrophysiology (Chapter 2).

Simply put, cardiac modeling is equivalent to solving a system of non-linear differential (or partial differential) equations, though vigorous reference must be made to numerous
FIGURE 1.1. Levels of Analysis. One-cell models include the study of compartments and ion channels and their interactions. The basic electrophysiological recording is the action potential. Network models investigate the connectivity of one-cell units organized in arrays. An electrical measure of bulk network activity is the extracellular electrogram. Finally, many patches molded into the shape of a whole heart (in addition to torso variables) gives rise to the ECG. See the attached CD for color figure.

laboratory experiments which aim to determine the nature and coefficients of each equation. These equations provide a quantitative measure of each channel, each cell, and networks of cells. As more experiments are done and data obtained, the model can be made more complex by adding appropriate differential equations to the system. Thus, as more information about the cellular networks, tissue structure, heart and torso anatomy are obtained, a better reconstruction of the ECG becomes possible. Until recently, however, modeling efforts have primarily focused on accurately reconstructing normal behavior. But with the accumulating experimental history of cardiac disease (such as myocardial ischemia, long-QT syndrome and heart failure), modelers have also begun to revise and extend the quantitative description of these models to include important abnormal behaviors.

This chapter will first focus on the theoretical one-cell equations, which are only solved in the time domain. Subsequently, the one-cell model will be expanded to represent multiple dimensions with the incorporation of partial differential equations in space. At each level of analysis, the appropriate electrical reconstruction is discussed in the context of relevant pathology to emphasize the usefulness of cardiac modeling.
1.1 THE ONE-CELL MODEL

The origins of the one-cell model actually take root from classical neuroscience work conducted by A.L. Hodgkin and A.F. Huxley in 1952 (Hodgkin and Huxley 1952). In famous experiments conducted on the giant axon of the squid, they were able to derive a quantitative description for current flow across the cell membrane, and the resulting action potential (AP). This model mathematically formulated the voltage-dependent “gating” characteristics of sodium and potassium ion channels in the nerve membrane. Since similar ion channels exist in cardiac cells, this Hodgkin-Huxley formalism was applied to model the Purkinje fiber action potential by McCallister, Noble and Tsien (McAllister et al. 1975).

However, it was determined that the cardiac action potential is considerably more complex than the neuronal action potential, presumably due to a larger diversity of ion channels present in the cardiac myocyte, the intercellular connections, and its coupling to muscular contraction. With the addition of the “slow-inward” calcium current in 1976, Beeler and Reuter (Beeler and Reuter 1976) were able to successfully describe the ventricular action potential with the characteristic “plateau phase” necessary for proper cardiac contraction. Since then, numerous ion channels and intracellular calcium compartment dynamics have been added (DiFrancesco and Noble 1985; Luo and Rudy 1991; Luo and Rudy 1994), making the current AP model considerably more complex and robust. Nevertheless, many of these membrane channels still follow the same Hodgkin-Huxley formalism, reviewed below for the cardiac myocyte. In addition, the cardiac myocyte contains a prominent intracellular calcium compartment—the sarcoplasmic reticulum.

1.1.1 VOLTAGE GATING ION CHANNEL KINETICS (HODGKIN-HUXLEY FORMALISM)

At the most fundamental level of electrophysiology, an ion (K⁺, Na⁺, Ca²⁺) must cross the membrane via the transmembrane ion channel. Typically, the ion channel is a multidomain transmembrane protein with “gates” that open and close at certain transmembrane voltages, \( V_m = V_{in} - V_{out} \). The problem, however, is to characterize the opening and closing of these gates, a process symbolically represented by the following equation:

\[
\frac{d n}{dt} = k_1 n_{closed} - k_{-1} n_{open}
\]

(1.1)

where \( k_1 \) and \( k_{-1} \) are the forward and reverse rates of the process, respectively, and \( n_{open} \) and \( n_{closed} \) are the percentage of open or closed channels (which is proportional to channel “concentration”). Thus, by simple rate theory, one would expect the rate of channel opening \( (dn/dt) \) to equal (note that \( n_{closed} = 1 - n_{open} \)):

\[
\frac{dn}{dt} = k_1 n_{closed} - k_{-1} n_{open}
\]

(1.2)

The voltage dependence of these ion channels can be understood if these gates are treated as an “energy-barrier” model, described with Eyring Rate Theory (Eyring et al. 1949; Moore and Pearson 1981). Given the concentration of the charged particle on the inside and outside ([Cᵢ], [Cₒ]), an energy barrier \( \Delta G_0 \) located at a relative barrier position...
FIGURE 1.2. A Battery-Resistor-Capacitor model of a generic excitable membrane. Ions flow (current) to and from the extra- and intracellular domains, across a resistor (or conductance). The membrane has an inherent capacitance, due to its charge-separating function. The current relates to a transmembrane voltage, $V_m$.

(δ) along the transmembrane route, and a transmembrane voltage ($V_m$), Eyring Rate Theory predicts the forward and reverse rates for ion transfer as:

$$
k_1 = K \cdot \left( e^{-\frac{\Delta G_0}{R T}} \right) \cdot \left( e^{\frac{-zFV_m}{RT}} \right)
$$

$$
k_{-1} = K \cdot \left( e^{-\frac{\Delta G_0}{R T}} \right) \cdot \left( e^{\frac{zFV_m}{RT}} \right)
$$

(1.3)

where $K$ is a constant, $R$ is the gas constant, $T$ is the absolute temperature, and $z$ is the valence of the ion. While, the solution in Eq. (1.3) is an extremely simplified version of reality, it readily suggests that the forward and reverse rates are voltage-dependent (thus these rates can be represented as $k_{1}(V)$ and $k_{-1}(V)$).

While the “energy-barrier” model predicts voltage-dependence, it does not account for the time-varying features in opening and closing channels. A model that takes time-variance into account was developed by Hodgkin and Huxley in 1952 (Hodgkin and Huxley 1952). The Hodgkin and Huxley model likens the biological membrane to a Battery-Resistor-Capacitor (BRC model, Figure 1.2) circuit. The resistor (1/conductance) represents the ion channel, through which ions pass to create an ionic current ($I_{ion}$). Since the membrane confines a large amount of negatively-charged protein within the cell, it separates positively and negatively charged compartments, thus acting as a capacitor ($C_m$). Finally, as ions cross the membrane and enter (or leave) the intracellular compartment, electrical repellant charge begins to build that counteracts $V_m$. The $V_m$ at which a certain ion is at equilibrium ($I_{ion} = 0$) is termed the Nernst potential ($E_{ion}$), the “battery” which depends on valence, intracellular [C]$_i$ and extracellular [C]$_o$ ion concentrations:

$$
E_{ion} = \frac{-RT}{zF} \ln \left( \frac{[O]}{[C]_i} \right)
$$

(1.4)

Thus, from simple circuit analysis of Figure 1.2, the ionic current for a certain ion can be
written as:

$$I_{ion}(t) = g(V, t)(V - E_{ion})$$  \hspace{1cm} (1.5)$$

Where $g(V, t)$ is the voltage-dependent, time-varying ion channel conductance. To determine the dynamics of an individual ion channel, Hodgkin and Huxley assumed that the channel was a “gate” as described in Eq. (1.2), which can be rewritten solely in terms of open probability $n_{open}$ or simply, $n$ (the forward and reverse rates, $k_1(V)$ and $k_{-1}(V)$ are replaced with $\alpha(V)$ and $\beta(V)$, respectively):

$$\frac{dn(t, V)}{dt} = \beta(V)[1 - n] - \alpha(V)[n]$$  \hspace{1cm} (1.6)$$

Eq. (1.6) is a first-order differential equation, which has a particular solution under several boundary conditions. Following a voltage step $\Delta V(V_m = V_{rest} + \Delta V)$ from the resting membrane potential, $n(t)$ follows an inverted exponential time course with the following characteristics:

$$n_\infty(V_m) = \frac{\beta(V_m)}{\alpha(V_m) + \beta(V_m)}; \quad \tau_n(V_m) = \frac{1}{\alpha(V_m) + \beta(V_m)}$$  \hspace{1cm} (1.7)$$

The quantity of $n_\infty(V_m)$ represents the steady-state proportion of open channels after a step voltage has been applied for a near-infinite amount of time. The variable $\tau_n(V_m)$ characterizes the time the system takes to reach this $n_\infty(V_m)$. Rewriting Eq. (1.6) in terms of the quantities derived in Eq. (1.7), gives a differential equation that describes the time course of the open probability for a channel:

$$\frac{dn}{dt} = \frac{n_\infty(V_m) - n}{\tau(V_m)}$$  \hspace{1cm} (1.8)$$

Using an elegant experimental set-up that applied a voltage-clamp to a giant-squid axon (Cole 1949; Marmont 1949), Hodgkin and Huxley were able to define regression equations for $n_\infty(V)$ and $\tau_n(V)$, which represent the gating variables for the potassium channel. To obtain a suitable fit to experimental data, they arrived at the open channel probability of $n(V, t)^4$. Thus, by substituting the open probability into Eq. (1.5), the outward potassium current can be represented as:

$$I_K = C \frac{dV}{dt} = \bar{g}_K \cdot n(V, t)^4(V - E_K)$$  \hspace{1cm} (1.9)$$

An analogous equation can be written for the inward sodium current with the addition of an inactivation mechanism (Figure 1.3). Following the data fitting, the experimental sodium channel was represented by Hodgkin and Huxley as three voltage-activated gates similar to the potassium activation gates described by Eq. (1.8). As with the potassium channel, increased membrane voltages stochastically increase the probability that these three gates open. Inactivation follows the same kinetics as Eq. (1.8), except that the inactivation gate closes with increased voltages (Figure 1.4c). Thus, the sodium response to an applied voltage stimulation is biphasic. First, the faster activation gates rapidly open, allowing
FIGURE 1.3. Idealized ion channels. The potassium channel is generally modeled with four voltage-activation gates. The sodium channel is represented by three rapidly-activating voltage-sensitive gates, with an additional slowly acting voltage-sensitive inactivation gate. The lumped probability that all potassium gates will be open is \( n^4 \), while the probability that the activation and inactivation gates of the sodium channel is \( m^3h \).

FIGURE 1.4. Activation curves for (A) potassium channels, \( n \); (B) activation curve for sodium channel, \( m \); and (C) inactivation curve for sodium channel, \( h \).
inward current to develop. However, with increased voltage, the slower inactivation gates will close, forcing a decrease in the inward current. There is no conceptual change in the nature of the current equation—the activation gate \( n \) is simply replaced with \( m \) and \( h \) (though these gates all differ quantitatively, \( m \) and \( n \) both increase with more positive \( V_m \), while the value of \( h \) decreases with more positive \( V_m \)). The sodium current can be represented as:

\[
I_{Na} = g_{Na} \cdot m(V, t)^3 h(V, t)(V - E_{Na})
\]  

(1.10)

The biphasic nature of the inward sodium current is crucial to the rapid elicitation of an action potential and the characteristic biphasic shape of the action potential.

This simplified approach assumes that the cell membrane contains two distinct types of voltage-gated channels (Na\(^+\) and K\(^+\)) that conducting currents in the opposite direction. With the addition of other inward and outward channels (see later sections), a generalized differential equation can be written:

\[
\frac{dV}{dt} = \frac{1}{C_M} (I_K + I_{Na} + I_{other\ channels} + I_{stim})
\]  

(1.11)

where \( I_{stim} \) represents a stimulation current (provided from a stimulating lead or adjacent cells), and \( I_{other\ channels} \) is provided via many other channels that vary among cell-types (atrial vs. ventricular cells) and various excitable tissues (heart vs. nervous system). Note that \( I_K, I_{Na}, \) and other channels are represented by non-linear terms (i.e. \( n^4 \) and \( m^3 h \)), and are both voltage and time-dependent. Thus, Eq. (1.11) coupled with gating equations for each channel (Eq. (1.8)), represents a system of non-linear differential equations that must be solved using techniques of numerical integration.

1.1.2 MODELING THE CARDIAC ACTION POTENTIAL

While the model of an action potential was originally described for a neuron, the methods were quickly adapted to represent the cardiac action potential. Although there are slight differences in the quantitative description of the sodium and potassium channels described above, the cardiac myocyte also exhibits a considerable inward calcium current that is responsible for the distinguishable “plateau” phase—which coincides with the muscular contraction in the ventricular myocyte. Additionally, the cardiac myocyte uniquely expresses a diverse set of ion channels—which give unique electrophysiological properties to different types of heart tissue, in normal and diseased heart function.

Within the heart, there exist a variety of cell types that require different considerations when developing a model. Pacemaker cells in the sino-atrial node express channels that allow an autonomous train of action potentials, while Purkinje fibers represents an efficient conducting system specialized for the fast, uniform excitation of the ventricular myocytes. Ventricular myocytes express the proper proteome to parlay the electrical excitation into force generating elements that ultimately produce the cardiac output and blood delivery to the rest of the body. Even within the ventricle, different models exist for transmural orientation (endocardial cells, middle-myocardial cells (M-cells), and epicardial cells). Models for each type of these cells have been extensively developed and are described in Table 1.1, and the history of these modeling developments is described below.
### Table 1.1. Classical and Modern Models of Various Cardiac Cell Types

<table>
<thead>
<tr>
<th>Classical Models</th>
<th>Type</th>
<th>Novelty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin-Huxley (1952)</td>
<td>Squid Axon</td>
<td>INa, IK</td>
</tr>
<tr>
<td>McCallister, Noble, Tsien (1974)</td>
<td>Purkinje Cell</td>
<td>Iₓ₁, Iₓ₂</td>
</tr>
<tr>
<td>Beeler-Reuter (1977)</td>
<td>Ventricular Cell</td>
<td>Iₛ (slow-inward Iₚₛ)</td>
</tr>
<tr>
<td>Modern Models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiFrancesco-Noble (1985)</td>
<td>Purkinje Cell</td>
<td>INaCa, INaK, Iᵥₛ-L, Iᵥₛ-T</td>
</tr>
<tr>
<td>Luo-Rudy Phase I (1991)</td>
<td>Ventricular Cell</td>
<td>Updated INa, IK</td>
</tr>
<tr>
<td>Luo-Rudy Phase II (1994)</td>
<td>Ventricular Cell</td>
<td>Updated INaCa, INaK, Iᵥₛ-L, Iᵥₛ-T; Ca-buffering</td>
</tr>
<tr>
<td>Zhang et al. (2000)</td>
<td>Sinoatrial Nodal cells</td>
<td>Updated Ca handling</td>
</tr>
</tbody>
</table>

1.1.2.1 Classical models of the cardiac action potential

In 1975, McCallister, Noble and Tsien introduced a prototype numeric model for the rhythmic “pacemaker activity” of cardiac Purkinje cells by using the voltage-clamp method to study an outward potassium current, Iₓ₂ (McAllister et al. 1975). After repolarization of the action potential, the deactivation of outward Iₓ₂ current allows a net inward current to produce a diastolic slow wave of depolarization in between action potentials (Figure 1.5). As this slow wave of depolarization brings membrane potential towards threshold, Iₓ₂ is a prominent current in producing the automaticity of pacemaker cells. Additionally, the McCallister, Noble and Tsien (M-N-T) model reconstructed the entire action potential, using a modified Hodgkin-Huxley sodium conductance for the rapid upstroke phases, while using voltage-clamp methods to describe an Iₓ₁, a generalized plateau and repolarization current. Thus, this landmark model was able to simultaneously describe characteristic pacemaker activity and rapid conduction velocities associated with Purkinje cells.

However, given the vast diversity of cardiac cell types, the M-N-T model could not describe the characteristics of ventricular action potentials—namely, the prominent plateau phase that is crucial for forceful contraction. To this end, Beeler and Reuter developed a numerical model (the B-R model) for the ventricular myocyte in 1977 (Beeler and Reuter 1976). This model incorporates an Iᵥₛ component, a slow inward calcium current that is responsible for the slow depolarization and the prominent plateau phase. This Iᵥₛ current follows Hodgkin-Huxley formalism, in that state variables d (activation) and f (inactivation) describe time-varying conductances of the slow inward current. However, unlike other Hodgkin-Huxley ions, the initial low level of intracellular calcium, [Ca²⁺]ᵢ does not remain constant with the arrival of the transmembrane Iᵥₛ current. In fact, the range of [Ca²⁺]ᵢ can range from 1 to 10⁻⁷ M, widely altering the Nernst potential, Eᵥₛ. Thus, Beeler and Reuter modeled the intracellular handling of calcium by assuming it flows into the cell and accumulates while being exponentially reduced by an uptake mechanism (in the sarcoplasmic reticulum). At any given state, the flux of [Ca²⁺]ᵢ can be described by:

\[
\frac{d[Ca]_i}{dt} = -10^{-7} \cdot I_v + 0.07(10^{-7} - [Ca]_i) \tag{1.12}
\]

En toto, the model incorporated four major components: the familiar INa current, the Iᵥₛ calcium current, the time-activated outward Iₓ₁ current and Iₓ₁, a time-independent...
outward potassium current. With this model, Beeler and Reuter began to predict pathological phenomena, including determinants of action potential duration, and oscillatory behavior in ventricular cells.

1.1.2.2 Modern models of cardiac action potentials

While modern models utilize many of the concepts introduced in the classical models described above, current models now incorporate a larger repertoire of ion channels,
a richer history of experimentation, and complex intracellular and sarcoplasmic calcium handling. In addition, improved computational power and numerical techniques can solve hefty systems of differential equations, allowing a more precise description of cellular electrophysiology (one-cell) and the interaction of many cells (network models). As a result, the focus of modeling has shifted from describing normal behavior of myocytes to describing pathological phenomena.

In 1985, DiFrancesco and Noble described an improved model of the Purkinje action potential (D-N model) (DiFrancesco and Noble 1985), that included the traditional ion channel formulation, along with improved assumptions on calcium channels (L-type and T-Type) and intracellular calcium handling. Nevertheless, the experimental recording technique at the time was rather limited, and could not account for important arrhythmogenic phenomena. In 1991, Luo and Rudy published an updated version of the D-N model that included more recent experimental data for the sodium and potassium currents, but omitted the B-R formation of the inward calcium current ($I_{Ca,L}$), citing a lack of single-channel and one-cell experimental history (Luo and Rudy 1991). But in 1994, Luo and Rudy published an updated model which comprehensively updated the D-N description of the sarcolemma L-type Calcium channel ($I_{Ca,L}$), the sarcolemma Na$^+$/Ca$^{2+}$ exchanger, the sarcolemma Na/K pump, the sarcoplasmic Ca-ATPase, and Ca$^{2+}$-induced Ca$^{2+}$ release. Processes not described in the D-N model were also added, such as the buffering of Ca$^{2+}$ in the myoplasm, and a non-specific Calcium current (Luo and Rudy 1994). The model consists of three compartments—the myoplasm, network sarcoplasmic reticulum, and the junctional sarcoplasmic reticulum. This enhanced model has provided a breakthrough in simulations of excitation-contraction (E-C) coupling and reentrant mechanisms of arrhythmogenesis. In 1998, the Luo-Rudy model was updated by substituting animal data in favor of recent human data (Priebe and Beuckelmann 1998).

While the Luo-Rudy model describes ventricular action potentials, several other models exist for other cardiac tissues. Recently, Zhang et al. have incorporated recent sinoatrial data to formulate a modern model of various sinoatrial nodal cells (central nodal and peripheral nodal cells) (Zhang et al. 2000). Lindblad et al. have used existing biophysical data to simulate a family of action potentials recorded in rabbit atria (Lindblad et al. 1996).

### 1.1.3 MODELING PATHOLOGIC ACTION POTENTIALS

Currently, there is a comprehensive understanding of basic ionic mechanisms and their behavior in normal cardiac cells. The various cardiac models listed in Table 1.1 have widely contributed to this theoretical understanding. However, less is accepted about how impairments of these ionic mechanisms ultimately predict or provoke gross events, such as infarction and/or arrhythmogenesis. Among many others, two areas of cardiac pathology, myocardial ischemia and long-QT syndromes (LQTS), are now the focus of intense modeling research. These studies have contributed not only to a theoretical understanding of the diseases, but also to electrocardiographic detection and appropriate pharmaceutical intervention. Though both myocardial ischemia and long-QT syndromes can lead to fatal arrhythmias (Wit and Janse 1993; El-Sherif et al. 1996), myocardial ischemia does so by shortening the action potential duration (APD) while LQTS induces arrhythmias by lengthening the APD.
To study impaired cells, one must modify existing models of normal behavior. These modifications may be achieved by: (1) adding novel channels to the existing repertoire of known membrane channels; (2) altering the quantitative dynamics of known channels—for example by altering ionic concentrations or pH; or (3) a combination of new channels and altered channel dynamics. Figure 1.6 summarizes the various cellular phenomena associated with myocyte ion channels.

1.1.3.1 Myocardial ischemia

Myocardial ischemia results from a withdrawal of oxygen from myocardial tissue (due to inefficient or absent perfusion), resulting in disturbances to aerobic respiration and ATP production. Alterations in intracellular ATP ([ATP]i), can alter the activity of membrane pumps, and thus the distribution of critical ions (Na+ and K+) that are largely responsible for the electrophysiological characteristics of myocardium and proper action potential propagation. Thus, ischemia develops at the cellular level, when the amount of oxygen (P_{O2}) in...
the vicinity of the mitochondria fails to meet the demand of rephosphorylation in the Kreb’s cycle (Factor and Bache 1998). Myocardial ischemia has at least four cellular sequellae: (1) hyperkalemia, or an increase in extracellular potassium \([K^+]_o\); (2) acidosis, or a decrease in cell-medium pH (intracellular) or interstitial space pH (extracellular); (3) anoxia, or oxygen withdrawal that results in a decrease in \([ATP]\); and (4) decoupling of cells. The effects of these individual manifestations on excitability have been widely reported, experimentally (Kagiyama et al. 1982; Kodama et al. 1984; Kleber et al. 1986; Weiss et al. 1992; Yan et al. 1993) and theoretically (Ferrero et al. 1996; Shaw and Rudy 1997; Shaw and Rudy 1997).

**Hyperkalemia**

As the intracellular stores of ATP diminish due to reduced aerobic respiration, Na\(^+\)/K\(^+\) pumps responsible for ion distribution also demonstrate reduced activity. Though normally this pump acts to relocate sodium out of the cell and potassium into the cell, a lethargic pump performs this process inefficiently. Thus, there is an extracellular accumulation of potassium, referred to as “hyperkalemia”. The electrophysiological consequences of hyperkalemia are two-fold. First, the upstroke velocity (\(dV/dt_{\text{max}}\)) of the action potential can be diminished. With the increased extracellular potassium, the resting membrane potential (RMP) becomes more positive, increasing sodium channel inactivation and reducing the inward sodium current (Weidmann 1955; Morena et al. 1980). This dominating effect is somewhat mitigated by the increased RMP being closer to the action potential threshold. Thus, moderate increases (5.4 mmol to 7.5 mmol) in potassium (>7.5 mmol) may actually increase upstroke velocity (this is termed “superconduction”), while large increases in extracellular potassium begin to inactivate the sodium current and decrease upstroke velocity. Even larger increases can prevent the upstroke entirely and produce conduction block (Wit and Janse 1993; Cascio et al. 1995). Hyperkalemia can also significantly decrease the APD. This effect is due to exaggerated outward potassium current late in the action potential that is able to overcome the inward calcium current relatively earlier, reducing the APD (Figure 1.7). Both effects of hyperkalemia, APD shortening and conduction depression, have been successfully modeled by Shaw and Rudy (Shaw and Rudy 1997; Shaw and Rudy 1997).

**FIGURE 1.7.** Action potential simulations with varying degrees of \([K^+]_o\). Increasing extracellular potassium (hyperkalemia) results in decreasing APD. (From Shaw and Rudy 1997; used by permission)
Acidosis

In the absence of aerobic respiration, alternate pathways that attempt to maintain energy production result in the formation of acidic species, thus initially creating intracellular acidosis. An increase in the intracellular proton concentration leads to proton extrusion into the extracellular space—resulting in extracellular acidosis. Changes in acidity can subtly change three-dimensional protein structures, including ion channels embedded in the sarcolemma. Most notably, the sodium channel experiences a decrease in maximum conductance \( (g_{Na}) \) with extracellular acidosis. Intracellular acidosis reduces the availability of the L-type calcium channel (described below). These changes considerably affect upstroke velocity (Shaw and Rudy 1997).

Hypoxia

The accumulation of intracellular ADP (at the expense of intracellular ATP) activates a special K-ATP channel in the sarcolemma, described by the following equation:

\[
I_{K-ATP} = \bar{g}_{K-ATP} f_{ATP}(V_m - E_K)
\]  

(1.13)

where \( f_{ATP} \) is represented by:

\[
f_{ATP} = \frac{1}{1 + \left( \frac{[ATP]_i}{35.8 + 17.9[ADP]_i^{256}} \right)^H}
\]  

(1.14)

where \( H \) is the Hill coefficient that decreases exponentially with \([ADP]_i\). From Eq. (14), a decrease in the \([ATP]/[ADP]_i \) leads to an increase in the \( f_{ATP} \) coefficient and the outward \( I_{K-ATP} \). This outward potassium current supplements the normal potassium current, enhancing the total outward current and drastically reducing the APD (Ferrero et al. 1996) (Figure 1.8).

Incidentally, the power of computer modeling was used to settle the controversy surrounding APD shortening and the role of the K-ATP channel. Because experiments showed

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**FIGURE 1.8.** AP simulations with varying degrees of \( f_{ATP} \). An increase in the fraction of open K-ATP channels results in profound APD shortening. (From Ferrero et al. 1996; used by permission)
FIGURE 1.9. Classifications of afterdepolarizations: (A) Plateau EAD - an oscillation during the Phase 2 plateau; (B) Phase 3 EAD; and (C) DAD - an oscillation after complete repolarization.

that anoxia induced a 40–60% shortening of the APD while K-ATP channels demonstrated only a 1% activation, many investigators felt that the K-ATP channel was not a major conducive factor to APD shortening. However, several investigators (Ferrero et al. 1996; Shaw and Rudy 1997) were able to quantitatively model the K-ATP channel with conductance $f_{ATP}$, being dependent on the amount of intracellular ATP. By adding this individual channel to the model, they were able to show that even a .4% channel activation can actually shorten the APD by 50%. Thus, this channel has been implicated as the major factor in APD shortening and thus may be a crucial factor in arrhythmogenesis.

1.1.3.2 Early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs)

Early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) (Figure 1.9) are single-cell arrhythmogenic triggering events, typically depending on Ca$^{2+}$ alterations and the interactions between the intracellular and sarcoplasmic compartments within the myocyte (Marban et al. 1986; Priori and Corr 1990). Because of the dependence on intracellular calcium, which can accumulate or depreciate from beat-to-beat, multiple beat models (paced at a basic cycle length) are required to reach a steady state. Simply stated,
afterdepolarizations are notches of depolarization that occur after the typical action potential upstroke. By definition, the EADs occur before the completion of repolarization, whereas DADs occur after the completion of repolarization.

EADs may occur during the plateau-phase (Figure 1.9a) of the action potential (plateau EADs) (Marban et al. 1986; Priori and Corr 1990) or during the phase-3 repolarization downstroke of the action potential (phase-3 EADs, Figure 1.9b). The plateau EAD is highly dependent on the L-type Ca\(^{2+}\) current (also involved in acidosis) (January and Riddle 1989), which is a non-specific cation channel permeable to Ca\(^{2+}\), Na\(^{+}\), and K\(^{+}\). Briefly, the formation of this current is the sum of ICa, ICa,K, ICa,Na, each of which are modulated by a [Ca\(^{2+}\)]-dependent factor (Luo and Rudy 1994; Luo and Rudy 1994):

\[
\frac{1}{f_{ca}} = \frac{1}{1 + \left[ \frac{[Ca^{2+}]_{i}}{K_{m,ca}} \right]^{2}} \tag{1.15}
\]

where \(K_{m,ca}\) is a half-maximal constant, equivalent to .6 \(\mu\)mol/L. As the intracellular calcium concentration increases, \(f_{ca}\) and the L-type current decrease monotonically. Additionally, the channel is controlled by voltage dependent f-gate. During the plateau phase, when intracellular Ca\(^{2+}\) is elevated, the L-type Ca\(^{2+}\) channel is relatively inactive due to a low \(f_{ca}\). However, due to rapid intracellular Ca\(^{2+}\) recovery (a phenomenon associated with long-duration action potentials), \(f_{ca}\) and inward ICa are elevated, resulting in a net depolarization during an otherwise repolarizing phase.

Unlike the plateau EAD, phase-3 EADs and DADs (Figure 1.9c) are dependent on Na\(^{+}\)-Ca\(^{2+}\) exchanger and In(Ca), the non-specific calcium current. Like the ICa(L) current, the In(Ca) is permeable to K\(^{+}\) and Na\(^{+}\)—however, an increase in [Ca\(^{2+}\)]\(_{i}\) increases the In(Ca). Thus, spontaneous Ca\(^{2+}\) release by the SR into the intracellular compartment further increases the inward current, producing either DADs or EADs (Stern et al. 1988).

Both EADs and DADs produce links between cellular conditions and arrhythmogenesis. For example, simulation studies have reproduced experimental studies demonstrating that EADs can generate ectopic activity (Saiz et al. 1996). In addition to one-cell studies, afterdepolarizations are studied in the context of linear networks (see Section 1.2) EADs have also been implicated in the long-QT syndrome, as the triggering event to a specific type of polymorphic reentrant tachycardia, or Torsades de Pointes (TdP) (El-Sherif and Turitto 1999; Viswanathan and Rudy 1999).

### 1.1.3.3 Long-QT syndrome

While myocardial ischemia results in APD shortening, other myocardial pathologies such as Long-QT syndrome may result in APD lengthening. The etiologies of LQTS are diverse, ranging from various genetic deficiencies at distinct loci, to acquired and iatrogenic causes. Long-QT syndrome is characterized by a prolongation of the QT-interval in the ECG, presumably due to structurally-deformed potassium and sodium channels. Impaired outward potassium flow would tend to delay the repolarization phase (Phase 3) and increase the duration of the action potential. Ultimately, this predisposes the patient to fatal cardiac arrhythmias and the unfortunate sequel—sudden cardiac death, even at early ages.

Currently, investigations of LQTS are a prototype for blending human genomics with advanced cardiac modeling. In the early 1990’s, a considerable flurry of molecular genetics
studies linked LQTS populations to mutations in three putative genes located on chromosomes 3, 6 and 11 (LQT1, LQT2, LQT3). The LQT1 and LQT2 genes represent an $I_{Kr}$ current (potassium delayed rectifier) and $I_{Ks}$ current (potassium slow delayed rectifier), respectively (Barhanin et al. 1996; Wang et al. 1996). The LQT3 gene represents an enhanced (incomplete inactivation) late sodium current. From these ground-breaking bench discoveries, several modeling studies were able to place molecular genetics in the context of comprehensive myocyte electrophysiology. For example, Viswanathan and Rudy were able to show that different myocardial cells (epicardial, mid-myocardium (M-cell), and endocardial cells) respond to LQT gene defects with differing amounts of APD lengthening, producing a transmural heterogeneity ripe for the formation of EADs (Figure 1.10) (Viswanathan and Rudy 1999; Viswanathan and Rudy 2000). They modeled LQT1 and LQT2 by reducing the density of $I_{Ks}$ and $I_{Kr}$ channels (thereby reducing the maximal channel conductance per
cell). LQT3 was simulated by a right shift in the steady-state inactivation curve, such that the $h$ and $j$ gates demonstrated incomplete inactivation, resulting in a late sodium current.

Truly, long-QT syndromes are demonstrating the cutting-edge interaction between molecular genetics and advanced computer modeling. While the molecular techniques have been instrumental in identifying the particular channelopathy, computer models have been successful in placing the channelopathy in the context of other channels and the whole cell, producing a quantitative understanding of the disease.

1.2 NETWORK MODELS

1.2.1 CELL-CELL COUPLING AND LINEAR CABLE THEORY

While the previous section treats the cardiac myocyte as an isolated element, it actually exists in a densely interconnected network with other myocytes. This brings up the issue of how current spreads from one excitable myocyte to a neighboring myocyte. The predominant model of current spread among excitable elements is termed cable theory (Miller and Geselowitz 1978; Spach et al. 1981; Plonsey and Barr 1986; Malmivuo and Plonsey 1995). Cable theory provides the crucial link from one-cell to many cells. In its simplest form, it presents a set of myocytes lined up next to each other and connected by gap junctions—forming a linear “cable” of excitable elements (Figure 1.11).

Cable theory assumes the existence of two compartments, subdivided into differential compartments, $dx$. Each differential compartment is connected to its adjacent compartment by resistances. Each transmembrane resistance, $r_m$, represents a pathway for transmembrane current, either passive or active (action potential producing elements like ion channels). In the extracellular space, $r_e$ represents the resistance between two extracellular differential elements. The monodomain model assumes that this resistance is negligibly small ($=0$), whereas bidomain models assume $r_e$ to be non-zero. Likewise, $r_i$ represents the resistance between two differential intracellular elements. In bulk, $r_i$ accounts for both the inherent cytoplasmic resistance and the cell-to-cell resistance (gap junctions).

![FIGURE 1.11. A one-dimensional cable representing intracellular resistances, transmembrane resistances, and extracellular resistances. The transmembrane resistance can be replaced with an active component, such as a voltage-sensitive ion channel.](image-url)