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Mathematical analysis of the relationship between intra- and extracellular potentials from His bundle in rabbit heart

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Rice University, 1993
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Mathematical Analysis of the Relationship between Intra- and Extracellular Potentials from His Bundle in Rabbit Heart

by

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree

Master of Science

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Mathematical Analysis of the Relationship between Intra- and Extracellular Potentials from His Bundle in Rabbit Heart

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Abstract

This study is concerned with the relationship between the intra- and extracellular potentials associated with the His bundle of the rabbit heart. A Hodgkin-Huxley type model of the Purkinje cell is developed and subsequently used to simulate conduction in a cable-model of the His bundle. The simulation results indicate that the field potential waveform can be decomposed and analyzed in terms of the component currents of the His bundle model. A field-theoretic model is also developed to analyze the relationship between the intra- and extracellular potentials of the His bundle. This relationship is treated as an equivalent filtering problem, wherein the extracellular field potential is predicted by specifying the action potential waveform and the equivalent filter characteristic.
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Chapter 1

Introduction

Many studies have been directed toward the measurement and subsequent analysis of the relationship between the intra- and extracellular potential waveforms in an active cardiac cell (see e.g. [10, 14, 27, 35]). Nevertheless, it remains a fundamental problem of importance in electrophysiology. In many cases, this relationship has been studied in vitro in Purkinje strands isolated from the specialized conduction system of mammalian hearts. Although it is currently possible to isolate single cardiac cells of virtually any type (SA or AV node cell, atrial, ventricular, Purkinje) using enzymatic dispersion techniques [2, 11, 22], it is quite difficult to record volume conducted field potentials from these cells due to their small size. Solenoidal action currents from multicellular cardiac preparations such as Purkinje strands, are much larger and result in field potentials that are greater in magnitude and more easily recorded. Comparative anatomical and morphological studies are also available on Purkinje strands [17, 34]. In addition, mathematical models of propagation have been developed in order to study the underlying basis of the conduction process in these strands. Largely, these models are highly-lumped approximations that attempt to characterize the essential electrical and geometrical properties of the strand (see e.g. [19, 32, 36]), rather than provide more detailed descriptions of structural complexities (e.g. regions of nonuniformity and inhomogeneity in the cellular composition of the strand). Although such detailed structural effects may be important, model complexity increases dramatically in any attempt to describe them. As a compromise, investigators often consider either a highly-lumped one-dimensional idealized strand
of individual cells connected end to end via intercalated discs [8, 9, 15, 29, 30, 31], or a lumped equivalent cell model that treats the cardiac strand as a single cylindrical cell much like an unmyelinated axon [19, 32, 36]. Modeling studies on this subject are largely focused on either the fundamental aspects of conduction in a strand of cardiac cells [8, 9, 15, 19, 29, 30, 31, 32, 36] or the relationship between the intracellular action potential and the extracellular field potential of a cardiac strand [10, 14, 27, 35]. Some studies consider both [9, 15, 19, 31, 36], but generally not in detail.

The present study is concerned with a quantitative assessment of the relationship between the intracellular action potential and the volume conducted field potential, which is measured at the outer surface of the His bundle in an isolated in-vitro atrial preparation from rabbit heart. In an attempt to model our experimental results, we first develop a Hodgkin-Huxley (H-H) type model of the isolated Purkinje cell membrane and incorporate it in a segmented distributed network model of the His bundle. We also develop a field-theoretic model of the His bundle for comparison. In this later model, the His bundle is represented in terms of a lumped “equivalent cell” model, which serves as bioelectric source in the volume conductor [10]. This field-theoretic model approach offers the advantage that, given an intracellular action potential as well as certain electrical and geometrical parameters, the field potential in the bathing medium surrounding the His bundle may be calculated accurately and rapidly (see [10]). On the other hand, the distributed network approach to modeling the His bundle, allows the general shape of the field potential waveform to be predicted and subsequently analyzed in terms of the voltage and time-dependent ion channel currents of the H-H type cell membrane model. Specifically, the relative importance of the component cellular membrane currents that are responsible for the production of the extracellular potential waveform can be assessed. The two modeling approaches
are compared and their differences are explained.

**Foreword**

Ahead in Chapter 2, we briefly describe the experimental method utilized to obtain action potential and field potential data, while in Chapter 3, a mathematical model of the rabbit Purkinje cell is developed that includes two major components (the sarcolemmal model and the fluid compartment model). In Chapter 4, we develop an "equivalent single cell" model for an idealized His bundle of finite length. This model incorporates the model of the individual Purkinje cell (chapter 2) into a distributed network in order to better characterize the relationship between potentials and individual ionic currents. A field-theoretic model is developed in Chapter 5 to investigate the relationship between the intra- and extracellular potentials from the viewpoint of filter theory. This is an interesting computationally-efficient approach that employs the principles of both electromagnetic field theory and digital signal processing. The results generated by these models are discussed and compared in Chapter 6.
Chapter 2

Experimental Method

An isolated atrial preparation from rabbit that exposed the Bundle of His (an important component of the specialized conduction system) was utilized to study the relationship between the intracellular action potential and the extracellular field potential in a volume conductor.

2.1 Methodology

We studied in vitro preparations from the hearts of young adult New Zealand white rabbits of either sex, weighting 2.5 - 3.0 kg. Each rabbit was anesthetized with sodium pentobarbital (45mg/kg, intravenously) and anticoagulated with heparin sulfate (100 units/kg, intravenously). The heart was removed quickly from the chest through a midline sternotomy incision and immersed in cool (room temperature), oxygenated Tyrode’s solution containing (mM): NaCl 131.25; KCl 4.0; CaCl₂ 1.3; MgCl₂ 0.5; NaHCO₃ 18.0; NaH₂PO₄ 1.8 and Dextrose (CH₂OH(CHOH)₄CHO)5.5. While immersed, the heart was dissected so as to isolate the AV nodal – His bundle region. The dissection procedure used consists of the following steps:

1. Initially, the inferior third of the ventricular apex is transsected.

2. An incision is made in the anterior right ventricular free wall from the apex to the base of the right ventricle. This incision is made anteriorly, in-line with the right atrial appendage using large dissection scissors. Following this, the vertical incision in the right ventricular free wall is extended obliquely to the right
ventricular outflow tract, across the pulmonary valve, and into the pulmonary artery.

3. The right atrial free wall is similarly exposed using fine dissection scissors, ensuring that the right atrial septal surface is not injured. A vertical incision is then made from the base of the right ventricular free wall (where the incision in the right ventricular free wall has been terminated) to the superior venae cava, anteriorly.

4. The left ventricle and atrium are subsequently removed from the right atrial preparation. This is accomplished by making a vertical incision in the ventricular septum from the apex, superiorly to the left ventricular outflow tract, crossing the aortic valve and extending the incision into the ascending aorta. Residual attachments of the left atrium to the right atrial septum are subsequently trimmed.

5. At this point, the preparation consists of the right atrial and ventricular septum, and a short segment of their respective free wall components. In order to decrease the size of the tissue preparation, and to allow a better, 'flatter' placement of the tissue in the bath, the right ventricular septum is further trimmed to within 7 mm of the AV junction.

The preparation is then transferred to a Lucite chamber, pinned to its bottom and electrically paced with a bipolar electrode. The tissue is superfused at a rate of 35 ml/min with Tyrode's solution, constantly gassed with 95% O₂ – 5% CO₂, and warmed to 37°C. After 30 minutes of recovery, the recordings were started.

2.2 Hydraulic System

The hydraulic system used to superfuse the tissue with the Tyrode's solution at the temperature of 36°C to 37°C is shown in Fig. 2.1. Tyrode solution was constantly
Figure 2.1: Hydraulic System
bubbled with a mixture of 95% \( O_2 \), 5% \( CO_2 \) in a beaker positioned in a warmed water tank (37\(^\circ\)C). The solution was pumped from this beaker to a heat exchanger (Ismatec MV pump system, Ismatec Pumping System Inc., Switzerland, distributed by Cole-Parmer Instruments Co.), and then through a coil within the heat exchanger to the tissue bath in order to superfuse the preparation. The solution was allowed to flow out of the bath via two separate channels, one placed at the bottom of the bath chamber and the other mounted on the top to maintain the level of the solution throughout the experiment. A separate circulating water bath (Haake D3, Haake Inc.) provided heated water to the jackets of both the heat exchanger and the bath chamber.

2.3 Data Acquisition and Stimulation System

The preparation and data acquisition system utilized in this study are shown in Fig. 2.2. The intracellular action potential from a cell within the His bundle was recorded through a standard glass microelectrode filled with 3.0 M KCl (tip resistance 15 - 30 megaohms). The tissue chamber was connected to ground through a 3 M KCl \( Ag/AgCl \) junction. The microelectrode (Fig. 2.2A) was coupled to an electrometer amplifier (model Duo 773, World Precision Instruments (WPI) Inc.) with an input impedance of \( 10^{11}\Omega \) through a \( Ag/AgCl \) junction. The signal was amplified 50 times before digitization (Fig. 2.2B). Surface electrograms were obtained using polyimide-insulated silver unipolar electrodes (ID 50 \( \mu m \), OD 70 \( \mu m \)) placed on the outer surface of the His bundle. The electrogram was amplified 1000 times using a differential amplifier (model DAM 50, WPI). Both the intracellular action potential and the external field potential were digitized (model DT2821, Data Translation Inc.) at the rate of 10 kHz per channel and stored on the hard disc of a PC (AT 286) for further analysis. Stimulation pulses (5 - 10 V amplitude, 2 msec duration) were applied to the prepa-
ration through bipolar electrodes placed on the crista terminalis below the sinoatrial (SA) node (Fig. 2.2A). They were delivered using a WPI 1800 series stimulator and associated isolation unit.

Both the glass microelectrode and the unipolar field potential electrodes were mounted on separate mechanical micromanipulators (model 9708, Narishige Inc., Japan; and model 06-0078, Brinkmann Inc., respectively) for the purpose of obtaining closely separated action potential and field potential recordings. The average distance between the two electrodes was no more than 70 μm. Typical examples of an intracellular action potential and a bathing medium field potential are shown in figures 5.3 and 5.5B, respectively.
Figure 2.2: 

A. Isolated Atrial Preparation (reference and ground are immersed in Tyrode solution); B. Data Acquisition System.
Chapter 3

The Purkinje Cell Model

3.1 Model Development

Our simulation study deals with three distinct models: (a) a model of the isolated Purkinje cell, (b) a distributed "network" model of the His bundle and the surrounding volume conductor, and (c) a field-theoretic model that describes the His bundle as an "equivalent cell" bioelectric source in a volume conductor medium. The development of each of these models is treated in separate chapters. The Purkinje cell model is developed in this chapter, whereas the network model is developed in Chapter 4 and the field-theoretic model of the His bundle is treated in Chapter 5. For clarity, many of the equations and parameters associated with these models are listed in tables located in the Appendices associated with these chapters.

3.1.1 Membrane Model of the Isolated Purkinje Cell

The isolated Purkinje cell from rabbit is modeled as a short cylindrical cell of radius 5 \( \mu m \) [17, 34] and length 125 \( \mu m \). The surface area of the cell membrane is 0.000039 \( cm^2 \). The whole-cell membrane capacitance \( (C_m) \) was set to 50 pF, which using the surface area above, corresponds to a specific membrane capacitance of 1.28 \( \mu F/cm^2 \). Fig. 3.1A below shows a lumped H-H type equivalent circuit model of the sarcolemma which includes the ionic circuits responsible for the fast dynamics of the action potential, as well as ion pumps \( (Na^+/K^+, Ca^{2+} \text{ and } K^+) \) and a \( Na^+\text{-}Ca^{2+} \)
exchanger. Fig. 3.1B shows fluid compartment model of the individual cell inserted into its normal milieu (i.e. a cleft space that is, in turn, surrounded by myocardial tissue).

Under space-clamp conditions, the differential equation describing the changes in membrane potential with time is:

\[
\dot{V} = -\frac{1}{C_m} \left[ I_{Na} + I_t + I_{Ca,T} + I_{Ca,L} + I_K + I_f + I_B + I_{K1} + I_{NaK} + I_{NaCa} + I_{CaP} + I_{KP} - I_{STIM} \right]
\] (3.1)

The fast \(Na^+\) \((I_{Na})\) and transient-outward \(K^+\) \((I_t)\) currents, the T- and L-type \(Ca^{2+}\) currents \((I_{Ca,T})\) and \((I_{Ca,L})\), respectively, the delayed-rectifier \(K^+\) current \((I_K)\) and hyperpolarization-activated current \((I_f)\), are modeled as voltage and time-dependent ionic currents, while the remaining currents are modeled as instantaneous background currents. The linear background current \((I_B)\) depends solely on membrane voltage, while the inwardly rectifying \(K^+\) current \((I_{K1})\) depends on membrane voltage and the \([K^+]\) in the small restricted diffusion (cleft) space just outside the membrane (i.e. \([K^+]_c\)). The \(Na^+-Ca^{2+}\) exchanger current \((I_{NaCa})\) depends on \(V\) and the intracellular concentrations of \(Ca^{2+}\) and \(Na^+\), while the calcium pump current \((I_{CaP})\) is a function of only \([Ca^{2+}]_i\). The \(Na^+/K^+\) pump current \((I_{NaK})\) is a nonlinear function of \([K^+]_c, [Na^+]_i\) and \(V\), while \(I_{KP}\) is a high affinity but small capacity, inwardly-directed \(K^+\) pump that assists the \(Na^+/K^+\) pump in maintaining \(K^+\) homeostasis. \(I_{STIM}\) represents the applied stimulus current.

A full set of equations for the sarcolemmal model are shown in Tables A.1 - A.6 in Appendix A, where the H-H type gating variables \((m, h, dl, fl, dt, ft, pi, pa, y, ra,\)
Figure 3.1: The rabbit Purkinje cell model which consists of the membrane model (A) and fluid compartment model (B).
$s_a$, $s_{\text{react}}$, $rd$ and $sd$) are described as solutions to first order differential equations of the general form:

$$\frac{dz(V,t)}{dt} = \frac{[z(V) - z(V,t)]}{\tau_z(V)} \quad (3.2)$$

where $z(V)$ and $\tau_z(V)$ are the voltage-dependent steady state activation (inactivation) gating variable and time constant functions, respectively, associated with the specific gating variable $z$. The specific equations for the gating variables associated with the membrane currents of the Purkinje cell model are given in Tables A.1 - A.5.

### 3.1.2 Fluid Compartment Model

The complete model also includes a description of the fluid compartments associated with the distribution of $Na^+$, $K^+$ and $Ca^{2+}$ in the intra and extracellular media. Due to the presence of intracellular organelles, and contractile filaments in the intracellular medium, an effective aqueous myoplasmic volume equal to 46.5% of the anatomical volume of the cell is assumed. Material balance equations are written for each of the species ($Na^+$, $K^+$ and $Ca^{2+}$) in both the cleft space and the cell myoplasm. As an example, the material balance equations for these species in the intracellular medium are given below:

$$[\dot{N}a]_i = \sum_j \frac{W_{j,Na} I_{j,Na}}{V_i F} \quad (3.3)$$

$$[\dot{K}]_i = \sum_j \frac{W_{j,K} I_{j,K}}{V_i F} \quad (3.4)$$

$$[\dot{Ca}]_i = \sum_j \frac{W_{j,Ca} I_{j,Ca}}{2V_i F} - \Phi_B \quad (3.5)$$

where the concentrations are given in mM. In these equations, $I_{j,*}$ is particular current (pA) associated with the flow of one of the three ionic species, while $W_{j,*}$ is the ratio
of the net current $I_{j,*}$ expressed in electrostatic units (esu) per second, to the net ionic flow of the particular ion in units of ions/sec. Here $V_1$ is the effective intracellular volume (nl), $F$ is Faraday’s constant and $\dot{\Phi}_B$ is the total flux of $Ca^{2+}$ (milimoles/sec) onto the myoplasmic calcium buffers (calmodulin, troponin C, troponin Mg-C). For a review of the mathematical aspects of intracellular calcium buffering in cardiac cells, see Rasmusson et. al [29, 30].

3.2 Model Implementation

The model has 31 state variables including membrane potential(V), 14 gating variables; 3 intracellular and 3 cleft space concentrations of $Na^+$, $K^+$ and $Ca^{2+}$; 3 buffer occupancies for $Ca^{2+}$ and 1 for $Mg^{2+}$ associated with the three types of intracellular protein buffers. A total of 6 variables (concentrations, occupancies, etc.) are associated with the uptake and release mechanisms of the SR. The model equations used in the simulation are given in Tables A.1 - A.8, while model parameter values and initial conditions are given in Tables A.9 and A.10, respectively. A variable step size Runge-Kutta-Merson numerical integration method (order 4 with relative error bound $0.5 \times 10^{-6}$) was used to solve the system of equations on a Sparc workstation SLC (Sun Microsystems). Typical run time was approximately 6 minutes for 290 ms of simulation. The model parameters were chosen to be consistent with whole-cell voltage clamp data from the literature, but also to yield an acceptable fit to our recorded intracellular action potential data. Fig. 3.2A shows a plot of the recorded and model-generated action potential waveforms. Here we assume that the action potential recorded under conditions of active conduction is similar to that obtained from an individual Purkinje cell (our fundamental model mimics the behavior of a
single cell in its natural milieu).

3.3 Simulation Results of the Isolated Cell Model

An action potential recorded from an isolated myocyte is essentially obtained under space-clamped conditions and is referred to as a "membrane action potential" (MAP). In contrast, an action potential recorded during active conduction in a multicellular cardiac strand is called a "propagated action potential" (PAP). We consider the case of propagation in the His bundle of the rabbit heart in Chapter 4, however, for the present we wish only to achieve a reasonably accurate fit to the recorded action potential data, as is shown in Fig. 3.2A. The remaining panels of Fig. 3.2 show the component ionic membrane currents associated with the action potential. The upstroke of the action potential is attributed to the inward fast sodium current \( I_{Na} \) which is much larger than any of the other currents (23 nA peak). For this reason it is not plotted with the other currents. Fig. 3.2B shows the time course of the transient-outward \( K^+ \) current \( I_t \) and the L-type \( Ca^{2+} \) current \( I_{Ca,L} \). Here \( I_{Ca,L} \) exhibits a spike followed by a maintained 'shoulder' current that lasts throughout the plateau and decays with the onset of final repolarization of the action potential. Fig. 3.2C shows the time course of two additional \( K^+ \) currents, the conventional delayed-rectifier current \( I_K \) and the inward rectifier current \( I_{K1} \), as well as the hyperpolarization-activated inward current \( I_f \). Note from panel C that \( I_K \) is a relatively small current that gradually builds during the plateau to ultimately initiate final repolarization. It is \( I_{K1} \) however, that increases rapidly and strongly to produce the final repolarization phase of the action potential. As membrane potential declines during the final repolarization phase, the inward current \( I_f \) (which is carried by both \( Na^+ \) and \( K^+ \)) is activated at -80 mv. This current increases quite slowly as is shown in Fig. 3.2C. Total mem-
brane current is net inward during the pacemaker potential of phase 4, mainly due to the steadily increasing inward current $I_f$. The slow depolarization produced in phase 4 causes $I_{K1}$ to increase slightly during this phase (Fig. 3.2C). Panel D shows the pump currents ($I_{NaK}$ and $I_{CaP}$) as well as the $Na^+-Ca^{2+}$ exchanger current $I_{NaCa}$. The pump current $I_{KP}$ is not shown since it is very small ($< 4$ pA). The pump currents $I_{NaK}$ and $I_{CaP}$ are simple monophasic outward currents, while $I_{NaCa}$ is a more complex multiphasic current that is mostly inward (panel D). During the upstroke, $I_{NaCa}$ exhibits a short-lived positive spike followed by a small amplitude plateau phase of inward current. During the final repolarization phase $I_{NaCa}$ increases to a negative peak that coincides with the maximum diastolic potential (MDP). During diastolic depolarization $I_{NaCa}$ decreases slowly (Fig. 3.2D).

Fig. 3.3B shows the calculated intracellular calcium transient [$Ca^{2+}$], during the course of the action potential (panel A). Note that the minimum diastolic level of [$Ca^{2+}$] is 80 nM, while the peak value of the transient is 670 nM. The percentage occupancies of the three intracellular buffers are shown in Fig. 3.3C. The greatest amount of cytosolic buffering is due to the competitive $Mg^{2+}-Ca^{2+}$ site on troponin and to a lesser extent by either the calmodulin or $Ca_{2+}$ specific sites on troponin (see Table A.7). The total background current $I_B$ is shown in Fig. 3.3D. $I_B$ is relatively insignificant during most of electrical systole, but increases dramatically during the repolarization to contribute a relatively strong steady current (14 pA) during phase 4, that is comparable to the size of the $I_{NaK}$ and $I_{NaCa}$ currents during the pacemaker potential (see Fig. 3.2D).
Figure 3.2: Simulation results: A. action potential; B. transient outward current $I_t$ and L type calcium current $I_{Ca,L}$; C. delayed rectifier current $I_K$, inward rectifier current $I_{K1}$ and hyperpolarization-activated current $I_f$; D. pump currents $I_{CaP}$, $I_{NaK}$ and exchanger current $I_{NaCa}$.
Figure 3.3: Simulation results: A. action potential; B. intracellular calcium concentration \([Ca]_i\); C. intracellular buffer occupancies; D. background current \(I_B\).
3.4 Summary

Thus, a mathematical Purkinje cell model that consists of two major components (the sarcolemmal model and the fluid compartment model) has been developed. The sarcolemmal model is composed of the membrane capacitance, the ionic channels and background, pump, exchanger currents, while the fluid compartment model describes the balance of the ionic species ($Na^+$, $K^+$ and $Ca^{2+}$), $Ca^{2+}$ buffering and the uptake and release of $Ca^{2+}$ by the sarcoplasmic reticulum (SR). Our simulations indicate that we have achieved a reasonably good fit of the model-generated action potential to the experimental data. In addition, the model predicts reasonable values and waveforms for quantities such as membrane currents (e.g. $I_{Na}$, $I_{Ca,L}$, $I_K$ and $I_{K1}$), as well as intracellular ion concentration (e.g. $[Ca^{2+}]_i$), which are relatively difficult to record during the course of an action potential, or ever impossible in some cases (e.g. $I_{Na}$, $I_{Ca,L}$, $I_K$, $I_{K1}$) given the present state of the art. This single Purkinje cell model will be incorporated into the distributed network model of the His bundle developed in next chapter.
Chapter 4

Distributed Network Model of the His Bundle

In this chapter we investigate the conduction properties of an idealized distributed parameter model of the His Bundle, which is an important element in the specialized conduction system of the rabbit heart. The equations associated with the distributed network are developed and when implemented, produce realistic physiologic simulations of the conduction of electrical activity in the His bundle.

4.1 Description of Model

To simulate the process of conduction in an idealized His bundle of finite length, we have developed an “equivalent single cell” model of this structure. First, we consider what is meant by this term in quotes. Purkinje cells comprising the His bundle are coupled together via intercalated discs and formed into elongated multicellular strands called “trabeculae” that branch. These trabeculae are embedded in a connective tissue matrix where, along with blood vessels, they are bound into small bundles or fasicles. The fasicles are in turn encased in a dense cylindrical connective tissue sheath. Details of the anatomy of the His bundle can be found in [16]. The “equivalent cell” hypothesis considers the His bundle as an equivalent bioelectric current source, wherein the sources of the action current (namely, the cell membranes of the constituent Purkinje cells) are lumped into the membrane of a larger single equivalent cell of cylindrical geometry. This approach to the electrical characterization of multicellular cardiac structures has been taken previously by Ganapathy et. al [10].
Specifically, the intracellular media of the tightly coupled constituent cells are lumped into the myoplasm of the single equivalent cell, which is represented as a uniform, isotropic medium characterized electrically by an average bulk specific conductivity \( \bar{\sigma} \) (S/cm). The average specific conductivity assigned to this medium includes the effect of the axial resistance offered by intercalated discs. We consider disk resistance to be distributed over the length of an individual cell, much as has been done in other modeling studies [15, 18, 19, 20, 31]. Similarly, the interstitial medium of the His bundle (Fig. 4.1A) is assumed to be comprised of extracellular fluid, connective tissue and blood vessels. It is characterized as a uniform, homogeneous medium having an average bulk specific conductivity \( \bar{\sigma}_e \) (S/cm). Further, the bounding sheath of the His bundle (Fig. 4.1A) is characterized as a uniform resistive-capacitative barrier \( (\bar{\sigma}_{sh} \ S/cm^2, \ \bar{C}_{sh} \ \mu F/cm^2) \) to current flow, while the external cylindrical medium bathing the His bundle is assumed to be a purely resistive volume conductor characterized by specific conductivity \( \sigma_o \) (S/cm). Thus, the geometry of the idealized His bundle model is shown in Fig. 4.1A. It consists of a single composite equivalent cell encased in a concentric cylindrical sheath of radius \( b \). The His bundle is in turn surrounded by a finite cylindrical bathing medium, which extends from radius \( b \) to radius \( c \). In this model, the bioelectric source for the production of action current is the membrane of a single equivalent cell representing the electrical properties of the many constituent cells of the His bundle. The intracellular, interstitial and external media are all considered to be purely passive (i.e. they contain no sources or sinks for current flow). As mentioned above, the resistive effects of the intercalated discs that couple the individual cells are considered to be distributed over the length of the cell, and in this manner are incorporated into the general intracellular resistance per unit length \( (r^t) \) of the equivalent cell.
Figure 4.1: Idealized model and equivalent circuit of His bundle. A. geometry of “equivalent cell”; B. circuit diagram.
4.2 Model Development

Fig. 4.1B shows an equivalent network model of the His bundle. The shunting elements (A) in this network model represent membrane patches, and characterized by the Hodgkin-Huxley type model of the Purkinje cell developed in Chapter 3. Kirchhoff's current law is utilized to describe the current flow in the circuit diagram for the intracellular, interstitial and external bathing media, which are represented by the superscripts i, e, and o, respectively. The subscripts j and k are the temporal and spatial indices whose increments are denoted by ∆t and ∆z, respectively. The equations pertinent to each of the three media are developed below.

4.2.1 Intracellular Space

The intracellular medium is modeled as a cylinder of radius a. Applying Kirchhoff's current law to the kth node of the network, where $V_i^k$ is the intracellular potential and $r_i^k$ is the longitudinal resistance per unit length associated with the kth node. Applying Kirchhoff's current law to the kth node, we obtain:

$$\frac{V_i^{k-1} - V_i^k}{r_i^{k-1} \Delta z^2} - \frac{V_i^k - V_i^{k+1}}{r_i^k \Delta z^2} = i_{m,k}$$  \hspace{1cm} (4.1)

where $i_{m,k}$ is the transmembrane current per unit length as a function of time at the kth node which is given as:

$$i_{m,k}(t) = 2\pi a(C_m \frac{\partial(V_i^k(t) - V_o^k(t))}{\partial t} + J_{tot,k}(t))$$  \hspace{1cm} (4.2)

where $C_m$ is the membrane capacitance per unit area. The total transmembrane current density $J_{tot,k}$ is given by:

$$J_{tot,k}(t) = J_{ion,k}(t) - J_{stim}(t)$$  \hspace{1cm} (4.3)

where $J_{ion,k}$ is the total transmembrane ionic current density at node k and $J_{stim}$ is the stimulus current density injected at node k. Using a backward, second-order
finite difference approximation for $\partial V/\partial t$ in equation (4.2) (see e.g., [3, 21]) one may obtain the following second-order implicit finite difference approximation to equation (4.1) where $j$ is the time index:

\[
\frac{V_{j+1,k} - V_{j,k}}{r_i \Delta z^2} - \frac{V_{j+1,k} - V_{j+1,k+1}}{r_i \Delta z^2} = 2\pi a C_m \left( \frac{3}{2\Delta t} \left( (V_{j+1,k}^i - V_{j+1,k}^e) - (V_{j,k}^i - V_{j,k}^e) \right) \right) + J_{tot,j+1,k}
\]

where constant temporal step size $\Delta t$ is assumed. The approximation of the nonlinear function $J_{ion,j+1,k}$ is analogous to that described by Lees [23]:

\[
J_{tot,j+1,k} = J_{tot,j,k} + \Delta J_{tot,j,k}
\]

where

\[
\Delta J_{tot,j,k} = J_{tot,j+1,k} - J_{tot,j,k}
\]

When the temporal step size $\Delta t$ is sufficiently small, $\Delta J_{tot,j,k}$ may be approximated by $\Delta J_{tot,j-1,k}$, i.e.

\[
\Delta J_{tot,j,k} \approx \Delta J_{tot,j-1,k}
\]

Thus, the approximation of $J_{tot,j+1,k}$ may be expressed as:

\[
J_{tot,j+1,k} \approx J_{tot,j,k} + \Delta J_{tot,j-1,k}
\]

\[
= J_{tot,j,k} + J_{tot,j,k} - J_{tot,j-1,k}
\]

\[
= 2J_{tot,j,k} - J_{tot,j-1,k}
\]

From equations (4.4) and (4.8), we obtain the following implicit recurrence equation for the unknown intracellular node potentials:

\[
\Psi_{k-1} i \Psi_{j+1,k-1} - \frac{3}{2} \Lambda e \Psi_{j+1,k} + \frac{3}{2} \Lambda e \Psi_{j+1,k} + \Psi_{j+1,k} = \Phi_{j+1,k}
\]
where

\[
\Psi_{k-1}^i \equiv \frac{1}{r_{k-1}^i} \\
\Psi_k^i \equiv \frac{1}{r_k^i} \\
\Lambda_{cm} \equiv 2\pi a C_m \frac{\Delta z^2}{\Delta t} \\
\Theta_k^i \equiv \Psi_{k-1}^i + \Psi_k^i + \frac{3}{2} \Lambda_{cm} \\
\Phi_k^i \equiv \Lambda_{cm} \left[ \frac{1}{2} (V_{j-1,k}^i - V_{j-1,k}^e) + 2(V_{j,k}^e - V_{j,k}^i) \right] + 2\pi a \Delta z^2 (2 J_{tot,j,k} - J_{tot,j-1,k})
\]

(4.10)  
(4.11)  
(4.12)  
(4.13)  
(4.14)

### 4.2.2 Interstitial Space

The interstitial space is modeled as a small cylindrical region bounded on the inside by the "equivalent cell" membrane, and on the outside by the connective tissue sheath. Based on the morphology study of Sommer and Johnson [34], we assume the cross-sectional area of this cylindrical region to be 10\% of that enclosed by the connective sheath. A lumped resistance \( r_e \) characterizes the longitudinal resistance per unit length in the interstitial space, while a distributed parallel RC network \((r_s, C_s)\) characterizes the impedance to current flow transversely through the outer connective sheath. Applying Kirchhoff's current law to the \( k^{th} \) node in the interstitial space yields the following implicit recurrence equation for the unknown node potentials:

\[
\Psi^e V_{j+1,k-1}^e + \frac{3}{2} \Lambda_{cm} V_{j+k+1}^i - \Theta^e V_{j+1,k}^e + \Gamma V_{j+1,k}^e + \Psi^e V_{j+1,k+1}^e = \Phi_{j+1,k}^e
\]

(4.15)

where

\[
\Psi^e \equiv \frac{1}{r_e}
\]

(4.16)
\[ \Gamma \equiv 2\pi b \frac{\Delta z^2}{r_s} \]  
\[ \Lambda_{cs} \equiv 2\pi b C_s \frac{\Delta z^2}{\Delta t} \]  
\[ \Upsilon \equiv \Gamma + \frac{3}{2} \Lambda_{cs} \]  
\[ \Theta^e \equiv 2\Psi^e + \Upsilon + \frac{3}{2} \Lambda_{cm} \]  
\[ \Phi_k^e \equiv \Lambda_{cm} \left[ \frac{1}{2} (V_{j-1,k}^e - V_{j-1,k}^i) + 2(V_{j,k}^i - V_{j,k}^e) \right] \]  
\[ \Lambda_{cs} \left[ \frac{1}{2} (V_{j-1,k}^e - V_{j-1,k}^o) + 2(V_{j,k}^o - V_{j,k}^e) \right] \]  
\[ -2\pi a \Delta z^3 (2J_{tot,j,k} - J_{tot,j-1,k}) \]  

### 4.2.3 External Volume Conductor

The external volume conductor is modeled as an annular region bounded by the connective sheath and outer volume conductor boundary \((b \leq r \leq c)\). It is characterized electrically by the lumped longitudinal resistance per unit length \(r_o\). Radially-oriented resistances \((r_{ref})\) connect the nodes in the external volume conductor to the reference node. Applying Kirchhoff's current law to the \(k^{th}\) node of the external medium, the following recurrence equation for the unknown node potential can obtained:

\[ \Psi^o V_{j+1,k-1}^o + \Upsilon V_{j+1,k}^e + \Theta^o V_{j+1,k+1}^o + \Psi^o V_{j+1,k}^o = \Phi_{j+1,k}^o \]  

where

\[ \Psi^o \equiv \frac{1}{r_o} \]  
\[ \Pi \equiv 2\pi c \frac{\Delta z^2}{r_{ref}} \]  
\[ \Theta^o \equiv 2\Psi^o + \Upsilon + \Pi \]  
\[ \Phi_k^o \equiv \Lambda_{cs} \left[ \frac{1}{2} (V_{j-1,k}^o - V_{j-1,k}^e) + 2(V_{j,k}^e - V_{j,k}^o) \right] \]
4.3 Matrix Solution for Potentials

Combining the equations (4.9), (4.15) and (4.22), we obtain the matrix equation for the potential at the N nodes of each space:

\[
\begin{bmatrix}
\Phi_{j+1,k-1} \\
\Phi_{j+1,k-1} \\
\Phi_{j+1,k-1} \\
\Phi_{j+1,k} \\
\Phi_{j+1,k} \\
\Phi_{j+1,k+1} \\
\Phi_{j+1,k+1} \\
\end{bmatrix}
= 
\begin{bmatrix}
\Psi_{k-1}^i \\
0 \\
0 \\
0 \\
0 \\
0 \\
0 \\
\end{bmatrix}
\begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
V_{j+1,k-1} \\
V_{j+1,k-1} \\
V_{j+1,k-1} \\
V_{j+1,k} \\
V_{j+1,k} \\
V_{j+1,k+1} \\
V_{j+1,k+1} \\
\end{bmatrix}
\]

\[ (4.27) \]

The left hand side matrix of equation (4.27) for a strand consisting of N segments is a symmetric banded matrix with main diagonal of \(-\Theta\)'s. The ends of the strand are considered to be "sealed", which represents an infinite resistance to longitudinal current flow through either end of the strand. Note that \(\Psi_{k-1}^i \equiv \frac{1}{r_{k-1}}\) from equation (4.10). Thus, the "sealed" end condition may be represented by \(\Psi_{k-1}^i = \Psi_{N-1}^i = 0\).
The same assumption holds for the interstitial and external volume conductor media. For a N segment strand, the order of the left hand matrix is $3N \times 3N$.

4.4 Model Implementation

A His bundle $50 \, \mu m$ in diameter and $0.5 \, cm$ in length was selected for our study. The 40 component cells of the strand are each assumed to have a length of $125 \, \mu m$. Each cell was then further divided into 10 segments ($\Delta z = 12.5 \, \mu m$). Steady-state initial conditions obtained from simulations of single myocyte MAP model were used as the initial conditions for each segment of the strand. The specific resistivity of the lumped myoplasm was chosen as $350 \, \Omega \cdot cm$ in accordance with [7], the specific resistivity of the interstitial medium was chosen as $140 \, \Omega \cdot cm$, while the specific resistivity of bulk medium (modified Tyrode's solution) assumed to be $125 \, \Omega \cdot cm$. The connective tissue sheath is considered to be relatively thick (roughly $10 \, \mu m$ [17]). The specific resistivity of the sheath was assumed to be $10 \, k\Omega \cdot cm^2$, while its specific capacity was assumed to be $0.5 \, \mu F/cm^2$. The nominal parameter values utilized in this study are listed in Table 4.1 below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_i$ ($M\Omega/cm$)</td>
<td>4.5</td>
</tr>
<tr>
<td>$C_m$ ($\mu F/cm^2$)</td>
<td>1.28</td>
</tr>
<tr>
<td>$r_e$ ($M\Omega/cm$)</td>
<td>16</td>
</tr>
<tr>
<td>$r_o$ ($M\Omega/cm$)</td>
<td>50</td>
</tr>
<tr>
<td>$r_s$ ($K\Omega \cdot cm^2$)</td>
<td>10</td>
</tr>
<tr>
<td>$C_s$ ($\mu F/cm^2$)</td>
<td>0.5</td>
</tr>
<tr>
<td>$r_{ref}$ ($M\Omega \cdot cm^2$)</td>
<td>$10^6$</td>
</tr>
</tbody>
</table>

A depolarizing current pulse with amplitude of $40 \, nA$ and duration of $0.2 \, ms$ was applied to the cell on the left end of the strand while the observation point was
located in the segment at the midpoint of the fiber. Temporal and spatial stepsizes of $\Delta t = 2\mu s$ and $\Delta z = 12.5\mu m$ were chosen to achieve good solution accuracy [33]. The distributed network model was implemented in the C computer language on a Sequent Symmetry S81 parallel machine comprised of 20 CPUs. A 250 msec simulation utilizing 10 processors required approximately 120 hours of computing time.

4.5 Simulation Results

Our simulation results include waveshapes of the temporal and spatial distributions of potentials and currents within each medium. We will proceed to calculate the conduction velocity of the propagated action potential (PAP), as well as demonstrate the relationships between the transmembrane currents of the equivalent cell and the external field potential distribution. These items are discussed in the following sections.

4.5.1 Temporal Distributions

A comparison of model-generated and experimentally-recorded action potential data from the rabbit His bundle is shown in Fig. 4.2. The discussion of the currents contributing to the action potential waveform will be divided into two parts based on events occurring during depolarization and events in repolarization.
Depolarization

Fig. 4.3A shows a more detailed comparison of the leading edge of the model-generated action potential with the data. The upstroke velocity of the model-generated action potential is 270 V/sec, while that for the data waveform is 260 V/sec. Overall, the fit achieved is reasonably good. Panel B of Fig. 4.3 shows the transmembrane potential ($V_{te}$), while panel C shows $I_{Na}$ measured at three observation points along the strand (segments 100, 200 and 300, respectively). The calculated time interval between the peaks is 1.5 msec and the length of each segment is 12.5 $\mu$m. The calculated conduction velocity is therefore 83 cm/sec, which agrees quite well with our experimental measurement (88 cm/sec). The second $I_{Na}$ waveform (of the set of three shown in panel C) corresponds to the potentials shown in Figures 4.3A and B.
Figure 4.3: The leading edge of simulated action potentials (observation point $z=0.25$ cm) and sodium current $I_{Na}$. A. comparison of the leading edge of trans-fiber potential $V_{io}$ and the data; B. transmembrane potential $V_{ie}$; C. sodium current measured at an interval of 1.25 mm. The second $I_{Na}$ waveform corresponds to the potential waveforms seen in panels A and B.
Fig. 4.4A shows the longitudinal currents in intracellular ($I_i$), interstitial ($I_e$) and external volume conductor ($I_o$) media. Recall that the longitudinal currents are defined as positive when flowing in the direction of propagation (here from left to the right). Note that $I_i$ flows in the direction of propagation, while the $I_e$ and $I_o$ flow in the opposite direction during the upstroke of the action potential. One may easily demonstrate that the sum of the currents $I_i(z), I_e(z)$ and $I_o(z)$ is zero, when measured in any plane $z = \text{constant}$. Fig. 4.4 B shows that the transmembrane current ($I_m$) at the leading edge of the action potential may be closely approximated by the sum of the capacitative displacement current ($I_d = C_m V_{re}$) and the fast sodium current ($I_{Na}$). The phase difference in the $I_d$ and $I_{Na}$ waveforms indicates that it is $I_d$ that flows first in time. It brings the adjacent "new" membrane ahead of the active region to the threshold level for the sodium current.

Fig. 4.5 shows the relationship of the currents $I_{sr}, I_{sc}$ and $I_s$ to the trans-sheath potential ($V_{eo}$). The trans-sheath potential $V_{eo}$ is initially zero at rest. As the action potential approaches the observation point ($z = 0.25$ cm), the trans-sheath current $I_s$ is at first positive (panel B), and then reverses shortly afterward as inward $Na^+$ current begins to flow through the sheath and into the "cell" beneath the sheath. The corresponding trans-sheath potential $V_{eo}$ first increases in the positive direction and then, as current direction changes from net outward to net inward, $V_{eo}$ decreases, eventually becoming slightly negative during the early phase of the plateau. This slight negativity reflects the small steady net inward flux of current across the sheath and into the cell during the plateau phase.

The resistive ($I_{sr}$) and capacitative ($I_{sc}$) components of total sheath current ($I_s$) are shown in Figs. 4.5C and D. Note that the capacitative current $I_{sc}$ is very much
Figure 4.4: Time courses of longitudinal, displacement and transmembrane currents (observation point z=0.25 cm). A. longitudinal currents in each of the media; B. dispersion, sodium and transmembrane currents associated with the leading edge of the action potential.
Figure 4.5: Trans-sheath potential and related currents (observation point \( z = 0.25 \text{ cm} \)). A. trans-sheath potential \( V_{co} \); B. total trans-sheath current \( (I_s = I_{sr} + I_{sc}) \); C. capacitative component of the trans-sheath current; D. resistive component of the trans-sheath current.
larger than the current flowing through the sheath resistance \( I_{sr} \). Note also that the waveshape of the \( I_s \) during the upstroke of the action potential mainly reflects the dominance of \( I_{sc} \). However during the time period associated with the plateau of the action potential, \( I_{sc} \) is zero, and consequently the relatively small negative component of the \( I_s \) waveform is supplied by \( I_{sr} \). The currents flowing during the plateau phase are indeed small (total transmembrane current \( I_m \) is nearly zero, see Fig. 4.6), but they are very necessary in maintaining depolarization during this phase. These currents enter the cell via either of two pathways: through the interstitial pathway or across the sheath. The particular currents involved in this net current during the early portion of the plateau phase are \( I_{Ca,L} \) and \( I_e \), as can be seen from Fig. 3.2.

Since the total sheath current \( I_s \) is mainly capacitative current, it has a biphasic waveform. This radially-oriented current represents the current flowing into the passive, resistive bathing medium from the His bundle cylinder. Thus, the field potential recorded within the bathing medium will be proportional to the sheath current \( I_s \) flowing into the passive bathing medium. Like \( I_s \) it will be biphasic and its particular waveshape will depend on the phasing of the cell displacement current \( I_d = C_m \dot{V}_{re} \) and the sodium current \( I_{Na} \). It will also have a small negative phase following the biphasic waveform that will be proportional to the relatively steady current flow through the sheath \( I_{sr} \) during the plateau phase.
Repolarization

Events in repolarization are shown in Fig. 4.6. Panel A illustrates the trailing edge of the action potential, while panel B shows the major currents responsible for repolarization. The declining plateau phase of the action potential mainly reflects the competition between the slowly increasing outward current $I_K$, and the slowly decreasing inward currents $I_{Ca,L}$. The final repolarization phase (phase 3) is initiated by relatively strong increases in the outward current $I_{K1}$. Fig. 4.6C shows that the transmembrane current $I_m$ (the sum of $I_d$ and $I_{ion}$) is nearly zero during the final repolarization phase.

Fig. 4.7 shows the longitudinal currents associated with the plateau and final repolarization phases of the action potential. The longitudinal currents change their directions after the upstroke of the action potential (see Fig. 4.4A and Fig. 4.7B). After the peak of the action potential, the longitudinal currents ($I_o$ and $I_e$) at first decrease sharply, but then change more slowly throughout the plateau of the action potential. If spatially-distributed current dipoles were used to represent the bioelectric source, Fig. 4.3 and Fig. 4.7 would suggest that there is a net "activation" dipole associated with the upstroke and a "repolarization" dipole associated with the final repolarization phase of the action potential. The activation dipole has a short spatial extent, but generates very strong current locally. In contrast, the "repolarization" dipole has a wide spatial extent and produces very small currents.

4.5.2 Spatial Distribution

The spatial distribution of the longitudinal currents and the trans-sheath current are shown in Fig. 4.8. The time interval of the recordings is 1 msec (for all the spatial
Figure 4.6: Trailing edge of the action potential major currents during the fast repolarization (observation point \( z = 0.25 \) cm). A. trailing edge of the transmembrane potential; B. major ionic and displacement currents associated with the fast repolarization; C. total ionic current, displacement current and transmembrane current during fast repolarization.
Figure 4.7: Trailing edge of the action potential major currents during the final repolarization (observation point $z=0.25$ cm). A. trailing edge of the transmembrane potential; B. longitudinal currents associated with the plateau and fast repolarization of the action potential; C. panel B in a more sensitive scale.
Figure 4.8: Spatial distribution of longitudinal currents and trans-sheath current. A. spatial distribution of intracellular longitudinal current associated with the leading edge of the action potential; B. spatial distribution of interstitial space longitudinal current; C. spatial distribution of external volume conductor longitudinal current; D. spatial distribution of trans-sheath current associated with the upstroke of the action potential.
waveforms of the potentials and currents). Panel A shows the spatial distribution of intracellular longitudinal current $I_l$. In the active region (during fast depolarization), $I_l$ flows from left to the right, while $I_c$ and $I_o$ flow from right to the left (panels B and C, respectively). Panel D shows the spatial distribution of the trans-sheath current $I_s$. Similar spatial distributions of displacement current $I_d$, fast sodium current $I_{Na}$ and transmembrane current $I_m$ are given in Fig. 4.9.

Fig. 4.10 illustrates the spatial distribution of potential in the intracellular, cleft and external volume conductor spaces. Note the upward shift of the potentials in each medium toward the right end of the strand. This is due to charge accumulation due to the current flow within the bounded medium on the right end of the strand in each of the media.

Fig. 4.11 shows the spatial distributions of the trans-fiber, trans-membrane and trans-sheath potentials. Note that the upward shift in the value of absolute potential (Fig. 4.10) has been removed in taking the respective potential difference.

4.6 Summary

In this chapter, we have developed a distributed network model of the His bundle of rabbit heart to study the relationship between the intra- and extracellular potentials of the His bundle. This network model is capable of explicitly demonstrating the relationship between the propagated potential and its associated currents. The simulation results show that the outward displacement current ($I_d$) and inward sodium current ($I_{Na}$) are the major currents contributing to the field potential associated with the upstroke phase of the action potential, while inward $I_d$ and the instantaneous outward $K^+$ current $I_{K1}$ are the major currents during the fast repolarization phase (phase 3). During final repolarization $I_d$ and $I_{K1}$ are in-phase and nearly equal and opposite. The resultant total transmembrane current is very small. Consequently,
Figure 4.9: Spatial distribution of: A. displacement current; B. sodium current; and C. transmembrane current.
Figure 4.10: Spatial distribution of the potential in each medium. A. spatial distribution of intracellular potential; B. spatial distribution of interstitial potential; C. spatial distribution of outer volume conductor potential.
Figure 4.11: Spatial distribution of: A. trans-fiber potential; B. trans-membrane potential; and C. trans-sheath potential.
the field potential accompanying repolarization is very small relative to the depolarization field potential. In our equivalent network approach, a major assumption is that only axial currents flow in the intracellular, interstitial and external media. Consequently, these conducting media have been represented in a distributed fashion by lumped axial resistors. The resultant model has considerable utility for predicting electrical events within the strand, but in its present form cannot predict the variation encountered in the magnitude of the field potential at arbitrary field points within the external bathing medium. Potential decreases in magnitude with increasing radial distance from the outer surface of the His bundle. If the model were to account for this variation, a resistive ladder network would have to be developed in \( r \) and \( z \) to adequately represent the current flow in the resistive external bathing medium.

In order to further study the problem of elucidating the relationship between the intracellular action potential and the external field potential, we have also developed a field-theoretic model that treats this relationship in terms of an equivalent filter problem. It does not have the limitation discussed above regarding the adequate prediction of the magnitude of the field potential in the bathing medium.
Chapter 5

Field Theoretic Model

5.1 Model Description

A field theoretic model is utilized to analyze the relationship between the intracellular and extracellular potentials. Here the electrical activity of the multicellular His bundle preparation is modeled in terms of the electrical behavior of an "equivalent single cell" model of the bundle (Fig. 5.1). This cell is surrounded by a concentric annular isotropic interstitial medium of average specific conductivity $\sigma_z$ (S/cm), which is bounded by a cylindrical resistive-capacitative sheath ($\bar{\sigma}_{sh} S/cm^2$, $\bar{C}_{sh} \mu F/cm^2$). The His bundle in turn, is immersed in a uniform, isotropic volume conductor of finite extent which is characterized by a specific conductivity $\sigma_o$ (S/cm). Furthermore, the intracellular medium of the "equivalent cell" is considered to be anisotropic, and is characterized by different average specific conductivities $\sigma_{i,z}$ and $\sigma_{i,\theta}$ in the axial ($z$) and tangential ($r, \phi$) directions, respectively. The overall model structure has the same dimensions as the His bundle [16].

5.2 Model Development

The mathematical model utilized in this chapter is based on the solution of Laplace's equation as previously reported by Clark and Plonsey [4, 5, 6]. This model relates the spatial distribution of the extracellular potential in axial distance to the action potential distribution. We will show that with proper boundary conditions, the re-
Figure 5.1: Diagram of the equivalent single cell.
lationship of intra- and extracellular potentials can be represented by an equivalent filter function. The assumptions utilized in this model are as follows:

1. the potential is angular symmetric \( \frac{\partial \Phi}{\partial \phi} = 0 \);
2. the field potential is quasi-static, i.e. the field is established instantaneously at all points in the media of interest;
3. the potential is conducted uniformly along the fiber;
4. the interstitial and extracellular media are purely passive and characterized by specific conductivity parameters \( \sigma_e \) and \( \sigma_o \), respectively;
5. the intracellular medium is purely passive, anisotropic and is characterized by the longitudinal and transverse specific conductivities \( \sigma_{i,x} \) and \( \sigma_{i,\perp} \), respectively;
6. the sources for the field potential lie entirely within the membrane of the “equivalent single cell” which is very thin;
7. the fiber length is large compared to the spatial extent of the field potential spread.

The quasi-static approximation mentioned above has been analyzed by Plonsey [28, chapter 5] and the error in neglecting the propagation effect is considered very small. With the assumptions above, the potential at the arbitrary field point can be obtained by solving the Laplace’s equation in the medium of interest, subject to appropriate boundary conditions. Laplace’s equation in cylindrical coordinates for the problem at hand is given as:

\[
\nabla^2 \Phi = \frac{1}{r} \frac{\partial}{\partial r} \left[ r \frac{\partial \Phi}{\partial r} \right] + \frac{\partial^2 \Phi}{\partial z^2} = 0
\]  

(5.1)

where \( r \) is the radial distance from the axis of the fiber and \( z \) is the axial distance. We begin by defining the following Fourier transform pair associated with the intracellular
potential:

\[ F_{si}(k) \equiv \int_{-\infty}^{\infty} \Phi_{si}(z)e^{jkz}dz \]  \( (5.2) \)

\[ \Phi_{si}(z) \equiv \Phi_{i}(a,z) \equiv \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{si}(k)e^{-jkz}dk \]  \( (5.3) \)

Solving equation (5.1) according to the methods described in [10, 12], one may obtain the following general expressions for potentials within the three media of interest:

\[ \Phi_{i}(r,z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{si}(k) \frac{I_0(\lambda|k|r)}{I_0(\lambda|k|a)} e^{-jkz}dk \quad r \in [0, a] \]  \( (5.4) \)

\[ \Phi_{e}(r,z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} [B(k)I_0(|k|r) + C(k)K_0(|k|r)]e^{-jkz}dk \quad r \in [a, b] \]  \( (5.5) \)

\[ \Phi_{o}(r,z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} [D(k)I_0(|k|r) + E(k)K_0(|k|r)]e^{-jkz}dk \quad r \in [b, c] \]  \( (5.6) \)

where the anisotropy ratio \( \lambda \) is defined as:

\[ \lambda \equiv \left( \frac{\sigma_{i,z}}{\sigma_{i,t}} \right)^\frac{1}{2} \]  \( (5.7) \)

and \( B(k), C(k), D(k) \) and \( E(k) \) are undetermined coefficient functions.

Considering current flow at the cell membrane and sheath boundaries to be continuous in the radial direction:

at \( r = a \)

\[ -\sigma_{i,t} \frac{\partial \Phi_{i}(r,z)}{\partial r} \bigg|_{r=a} = -\sigma_{e} \frac{\partial \Phi_{e}(r,z)}{\partial r} \bigg|_{r=a} \]  \( (5.8) \)

at \( r = b \)

\[ -\sigma_{e} \frac{\partial \Phi_{e}(r,z)}{\partial r} \bigg|_{r=b} = -\sigma_{o} \frac{\partial \Phi_{o}(r,z)}{\partial r} \bigg|_{r=b} = J_{sh}(z) \]  \( (5.9) \)

where \( J_{sh}(z) \) is the trans-sheath current density given as:

\[ J_{sh}(z) = \sigma_{sh} \Phi_{sh}(z) + \theta C_{sh} \frac{\partial \Phi_{sh}(z)}{\partial z} \]  \( (5.10) \)
Here $\Phi_{sh}(z)$ is the trans-sheath potential defined by:

$$
\Phi_{sh}(z) \equiv \Phi_e(b, z) - \Phi_o(b, z)
$$

(5.11)

Upon considering the form of the expressions for potentials $\Phi_e(z)$ and $\Phi_o(z)$ in equations (5.5) and (5.6) as well as their dependence on axial distance $z$, the derivative of the trans-sheath potential with respect to $z$, is given as:

$$
\frac{\partial \Phi_{sh}(z)}{\partial z} = -jk\Phi_{sh}(z)
$$

(5.12)

Using the above expression and defining the equivalent admittance of the sheath $\overline{\eta}_{sh}$ as:

$$
\overline{\eta}_{sh} \equiv \overline{\sigma}_{sh} - jk\overline{C}_{sh}
$$

(5.13)
equation (5.10) may be rewritten as:

$$
J_{sh}(z) = (\overline{\sigma}_{sh} - jk\overline{C}_{sh})\Phi_{sh}(z) = \overline{\eta}_{sh}\Phi_{sh}(z)
$$

(5.14)

where $\overline{\sigma}_{sh}$ and $\overline{C}_{sh}$ are the average bulk specific conductivity and specific capacitance of the sheath, respectively; $\theta$ is the uniform conduction velocity of the action potential along the axial direction $(z)$, while $k$ is the spatial frequency.

The boundary condition at $r = c$ is:

$$
-\sigma_o \frac{\partial \Phi_o(r, z)}{\partial r} \bigg|_{r=c} = 0
$$

(5.15)

After applying the boundary conditions and solving for the unknown coefficient functions in equations (5.5) and (5.6), the solution for potential in the external bathing medium is:

$$
\Phi_o(r, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{\Gamma(k)W(r, k)F_{sh}(k)e^{-jkz}}{\Delta(k)} dk
$$

(5.16)

where

$$
\Gamma(k) \equiv [I_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c)]\Delta(k)
$$

(5.17)
\[
\Delta(k) \equiv \frac{\gamma_h \sigma_a \frac{I_1(\mu|k|a)}{\lambda(ka)} [T_3 K_1(|k|b) - T_1(k) K_0(|k|b)]}{\gamma_h \sigma_a [\frac{2\pi}{\lambda(a)} T_2(k) T_3(k) + T_1(k) T_4(k)] - \sigma_a |k| T_1(k) T_2(k)}
\]

\[
W(r, k) \equiv \frac{I_0(|k|r) K_1(|k|c) + K_0(|k|r) I_1(|k|c)}{I_0(|k|b) K_1(|k|c) + K_0(|k|b) I_1(|k|c)}
\]

\[
T_1(k) \equiv I_1(|k|a) K_1(|k|b) - K_1(|k|a) I_1(|k|b)
\]

\[
T_2(k) \equiv I_1(|k|b) K_1(|k|c) - K_1(|k|b) I_1(|k|c)
\]

\[
T_3(k) \equiv I_1(|k|a) K_0(|k|b) + K_1(|k|a) I_0(|k|b)
\]

\[
T_4(k) \equiv I_0(|k|b) K_1(|k|c) + K_0(|k|b) I_1(|k|c).
\]

Defining the following Fourier transform pairs associated with the extracellular potential \(\Phi_o(r, z)\):

\[
\Phi_o(r, z) \equiv \frac{1}{2\pi} \int_{-\infty}^{\infty} F_o(r, k) e^{-jkz} dk
\]

\[
F_o(r, k) \equiv \int_{-\infty}^{\infty} \Phi_o(r, z) e^{jkz} dz
\]

and

\[
\Phi_{so}(z) \equiv \Phi_o(b, z) \equiv \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{so}(k) e^{-jkz} dk
\]

\[
F_{so}(k) \equiv \int_{-\infty}^{\infty} \Phi_{so}(z) e^{jkz} dz
\]

we obtain the following relationship between the Fourier transforms of the intracellular and extracellular potentials:

\[
F_o(r, k) = \Gamma(k) W(r, k) F_{si}(k)
\]

Here we note that from equation (5.19), when \(r = b\), \(W(r, k) = W(b, k) = 1\). Thus at \(r = b\), we obtain:

\[
F_{so}(k) = \Gamma(k) F_{si}(k)
\]

where \(\Gamma(k)\) functions effectively as a "His bundle filter" while \(W(r,k)\) functions as a "medium filter" representing the external volume conductor. The relationship be-
5.3 Discrete Fourier Method of Solution

The continuous z-domain expression for the intra- and extracellular potentials ($\Phi_{si}(z)$, $\Phi_{so}(z)$ and $\Phi_{o}(z)$) and their respective Fourier transforms ($F_{si}(k)$, $F_{so}(k)$ and $F_{o}(k)$) can be reformulated in the discrete k-domain for implementation on a digital computer by introducing the following Discrete Fourier Transform (DFT) pair (intracellular potential is used as an example):

$$F_{si}(Pq) \equiv \sum_{n=0}^{N-1} \Phi_{si}(Zn)e^{j2\pi Pq/N} \equiv DFT[\Phi_{si}(Zn)] \quad (5.30)$$

$$\Phi_{si}(Zn) \equiv \frac{1}{N} \sum_{q=0}^{N-1} F_{si}(Pq)e^{-j2\pi Pq/N} \equiv IDFT[F_{si}(Pq)] \quad (5.31)$$

where

$$P \equiv \frac{2\pi}{NZ} \quad (5.32)$$

Here, Z and P are the sampling intervals in the z and k domains, respectively, and n and q are integers. The function $\Phi_{si}(z)$ is normally limited in both the z and k domains, i.e. $\Phi_{si}(z)$ is nonzero for a small finite range of z values ($-z_1 \leq z \leq z_2$) and is band-limited in the frequency domain. The sampling interval Z is chosen to be small enough so that no aliasing occurs in the k domain. Specific details of the DFT technique can be found in [25]. Relationships similar in form to the DFT pair of
equations (5.30) and (5.31) exist for $\Phi_{so}(z)$ and $F_{so}(k)$ as well as for $\Phi_s(z)$ and $F_s(k)$. The extracellular potential in the volume conductor may be written as the product of the DFT's. With the intracellular potential specified ($\Phi_{si}(z)$), the DFT of the field potential at a given radius $r$ is:

$$F_o(Pq, r) = \Gamma(Pq) \ W(Pq, r) \ F_{si}(Pq) \quad (5.33)$$

When $r = b$, we obtain the field potential at the outer surface of the sheath as:

$$F_{so}(Pq) = \Gamma(Pq) \ F_{si}(Pq) \quad (5.34)$$

### 5.4 Computational Aspects

The His bundle intracellular potential waveform used in this study is given in Fig. 5.3. Its conduction velocity is assumed to be 83 cm/sec (to be consistent with network model; the experimentally measured velocity is 88 cm/sec). Given the temporal sampling interval $\Delta t$ (0.0001 sec/sample) and conduction velocity $\theta$ (83 cm/sec), the spatial sampling interval $Z$ can be obtained (0.0083 cm/sample). Treating this problem as an equivalent filter problem as in Fig. 5.2, we proceed to identify the proper input and output functions associated with this filter. Fig. 5.4A shows the power spectrum of the measured action potential (input to the filter), while panel B shows the power spectrum of field potential (output of the filter). Panels C and D show the higher frequency components of the panels A and B, respectively, on a more sensitive scale. The intracellular potential data contains 2550 sample points. To compute the spectrum of intracellular potential with FFT algorithm, an additional 1546 sample points are padded to the end of the intracellular potential sequence to make the length of the sequence (N) equal to 4096 ($2^{12}$). Table 5.1 provides a summary of the model parameter values utilized in this simulation study. This field-theoretic model was implemented in both the C and FORTRAN 77 computer languages on a Sparc workstation SLC (Sun Microsystems).
Figure 5.3: Intracellular potential data from His bundle of rabbit heart.

Table 5.1: Nominal parameter values of the field-theoretic model

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a ($\mu$m)</td>
<td>72</td>
</tr>
<tr>
<td>b ($\mu$m)</td>
<td>75.6</td>
</tr>
<tr>
<td>c (cm)</td>
<td>0.5</td>
</tr>
<tr>
<td>$\theta$ (cm/sec)</td>
<td>83</td>
</tr>
<tr>
<td>Z (cm/sample)</td>
<td>0.0083</td>
</tr>
<tr>
<td>N</td>
<td>4096</td>
</tr>
<tr>
<td>$\sigma_{i,z}$ (S/cm)</td>
<td>0.009</td>
</tr>
<tr>
<td>$\sigma_{i,t}$ (S/cm)</td>
<td>0.0009</td>
</tr>
<tr>
<td>$\sigma_e$ (S/cm)</td>
<td>0.0071</td>
</tr>
<tr>
<td>$\sigma_o$ (S/cm)</td>
<td>0.008</td>
</tr>
<tr>
<td>$\sigma_{sh}$ (S/cm$^2$)</td>
<td>0.0001</td>
</tr>
<tr>
<td>$\overline{C}_{sh}$ (µ F/cm$^2$)</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Figure 5.4: Power spectrum of the measured action potential and field potential data. A. power spectrum of the action potential; B. power spectrum of the field potential; C. higher frequency component of action potential on a more sensitive scale; D. higher frequency component of field potential on a more sensitive scale.
5.5 Simulation Results

The simulation results obtained using the field-theoretic model are presented in three parts. First, a comparison of experimentally-recorded and model-generated field potential data is made. Here the nominal parameter values given in Table 5.1 are used for the simulations. Second, the sensitivity of the frequency response of the "His bundle filter" to variations in certain parameter values of the model is demonstrated. Finally, a nonlinear least-squares parameter estimation method (Marquardt [24]) is utilized with the field-theoretic model to obtain very good fits to field potential data. In addition, a parameter sensitivity analysis [1, 26] is performed on a restricted set of model parameters.

At this point, we note that there is an important difference between the absolute potential in each medium of the network model and the potential in the field-theoretic model, i.e. $V^* \neq \Phi$, where * represents the symbol denoting the corresponding medium (i, e or o). In the network model, the longitudinal resistance ($r^o$) and transversal resistance ($r^{rej}$) are made very large in order to satisfy the model constraint that current in the conductive media flows only in an axial direction. Hence in the network model the radial extent of the bathing medium is constrained. No such constraint is required in the field-theoretic model, and any size volume conductor may be utilized. The size of the volume conductor may be adjusted to match either the restrictive axial current constraint of the simple equivalent network model, or the conditions obtained experimentally, where the bathing medium is of essentially infinite extent. The peak to peak value of diphasic field potential and its spatial extent will depend on the resistance offered by the bathing medium to current flow. To a first approximation, the active (cellular) elements of the His bundle will act as a constant current source, delivering the same amount of current to the external medium regard-
less of the resistance offered by this medium. This approximation, however holds only over a physiological range of resistance values. As the extracellular medium becomes very small and is confined to a small annular ring around the bundle, the current waveform from the His bundle will change under these extremely resistive loading conditions. Such conditions occur only in case of severe experimental intervention, and they were not allowed to occur in our in-vitro experiments conducted on the tissue preparations from rabbit heart.

Thus, the field-theoretic model is potentially much more powerful in its descriptive capability than the equivalent network model, particularly with regard to the prediction of changes in the field potential amplitude and waveshape at increasing radial distances from the surface of the His bundle. The network model could be improved in this regard by replacing the simple axial resistance $r_o$ with a two-dimensional radially and axially-oriented resistive ladder-type network, as suggested earlier in Chapter 4. With the network configured as in Fig. 4.1B, the potential $V_o$ recorded at nodes in the external bathing medium is an "average" potential in this medium, which in turn, is assumed to be constant over the annular extent of this medium in order to be consistent with Ohm's law applied to the longitudinal resistance $r_o\Delta z$ (Fig. 4.1B) in this lumped network model. The field-theoretic model has a much better capability for computing the potential at an arbitrary field point in the bathing medium. These same comments extend to the comparisons made between potentials predicted by these models in any other medium of interest (e.g. the intracellular or interstitial media).
5.5.1 Frequency responses of the "equivalent filter" and model-predicted field potential

Fig. 5.5 shows the fit of model-generated field potential to experimental data (panel B). The model-generated field potential has the same general features as the data, particularly a diphasic waveform with a stronger negative phase. The reasonably good agreement of the model-generated potential with the experimental data (regardless of the structural complexity of the His bundle), tends to validate the modeling assumptions stated earlier and offers encouragement that this method may be employed usefully in other contexts to describe the relationship between intra- and extracellular potentials. The particular parameter values used to achieve the fit shown in Fig. 5.5B are given in Table 5.1. We refer to these parameter values as "nominal" values. They do not yield the best fit to data, but they are within the physiological range of values, and are consistent with the parameter values utilized in our simulation studies using the network model.

Fig. 5.6 shows the frequency response of the analytical "His bundle filter" function \( \Gamma(k) \). Panels A and B show the magnitude and phase response of this filter, respectively. In general, \( \Gamma(k) \) is a "high pass" filter function. However, the physiological input to this filter is a band-limited signal (see Fig. 5.4A). The output of the "His bundle filter" is therefore band-limited and the DFT technique can be applied. In order to evaluate the behavior of model-generated filter function \( \Gamma(k) \) in the spatial frequency domain, we derive a representative filter function from experimental data by taking the ratio of \( DFT[\Phi_{si}^{data}] / DFT[\Phi_{so}^{data}] \). Here \( \Phi_{si}^{data}(z) \) is the internal surface potential distribution of the cell, while \( \Phi_{so}^{data}(z) \) is the surface potential distribution on the outer surface of the His bundle. We refer to this input-output filter function formed from recorded data as \( G(k) \). Its real and imaginary parts are shown in Fig. 5.6C and D, respectively, together with plots of the real and imaginary parts of the
Figure 5.5: A. Leading edge of the intracellular potential (data); B. model-generated field potential and the data.
Figure 5.6: Frequency response of the “His bundle filter” function $\Gamma(k)$. A. Magnitude response; B. phase response; Comparison of the filter functions generated by model and data: C. real components; and D. imaginary components.
model filter function $\Gamma(k)$. Note from panel D that the imaginary component of the model filter function fits to the data reasonably well within the bandwidth of the signals (75 rad/cm, see Fig. 5.4), while the real component (panel C) only fits the data at lower frequencies (below 20 rad/cm).

The frequency response of "His bundle filter" function $\Gamma(k)$ may be adjusted by varying the model parameter values. Below we will study the effects of varying certain electrical parameter values of the model, while others are left constant (e.g. the geometrical parameters are assumed to match those of the His bundle reasonably well, and therefore are fixed). This is not to say however, that these geometrical constants (a, b and c) are not sensitive model parameters.

Figs. 5.7 to 5.11 show that the overall frequency response of the filter varies with the electrical parameter values. Specifically, reduction of intracellular anisotropy ratio $\lambda$, leads to the decrease of the specific conductivity of intracellular medium ($\sigma_i = \lambda \sigma_{ii}$). Thus, with the same intracellular potential ($\Phi_{hi}(z)$) distribution, the amplitude of the transmembrane current will decrease, as will the field potential. This effect may be represented by the reduction of the gain of the equivalent filter function as shown in Fig. 5.7.

Fig. 5.8 shows that the increase in specific capacity of the sheath can lead to an increase in the gain of the equivalent filter. This may be explained as follows. An increase in sheath capacitance will effectively increase the admittance of the sheath. This allows more current to pass through the sheath, thus generating a stronger field potential. Fig. 5.9 shows the effect of an increase in specific conductance of the sheath on the frequency response of the equivalent filter. The real component of the filter function increases at all frequency range with more increase in higher frequency range, while the imaginary part decreases at all frequency range. Actually the gain
Figure 5.7: Frequency response of the filter $\Gamma(k)$ for various intracellular anisotropy ratios ($\lambda^2 = \sigma_i^2 / \sigma_i^r$). A. real component; B. imaginary component.
Figure 5.8: Frequency response of the filter $\Gamma(k)$ for various specific capacitances of the sheath ($\mu F/cm^2$). A. real component; B. imaginary component.
Figure 5.9: Frequency response of the filter $\Gamma(k)$ for various specific conductivities of the sheath ($S/cm^2$). A. real component; B. imaginary component.
of the filter function only increases at higher frequency range but decreases at lower frequency range (< 14 rad/cm). Since the dominant power of the action potential is in the lower frequency range (see Fig. 5.4), the increase in $\sigma_{sh}$ will actually reduce the amplitude of the field potential (see Fig. 5.13F).

Fig. 5.10 and Fig. 5.11 illustrate the effects of the specific conductivities of interstitial ($\sigma_i$) and volume conductor ($\sigma_o$) media on the frequency response of the equivalent filter $\Gamma(k)$, respectively. As $\sigma_i$ increases, there is a stronger current flow in the interstitial medium resulting in diminished current flow through the sheath and into the volume conductor. Consequently, the amplitude of the field potential will be smaller. The influence of $\sigma_o$ on the equivalent filter is approximately the same, but occurs via a different mechanism. All the potential measurements are made with respect to the reference potential. When $\sigma_o$ increases, the voltage between the measuring point and the reference decreases. That is, as $\sigma_o$ approaches infinity, the volume conductor is shorted to the reference, and the resultant field potential is zero.

5.5.2 Numerical Method for Parameter Estimation and Sensitivity Analysis

Parameter Estimation

The nominal parameter values used in our field theoretic model are chosen as plausible values in the physiological range. In addition, they are consistent with the values employed in the network model. Overall, they yield a reasonably good fit to the experimental data (see Fig. 5.5B). However, it would be of interest to know how the model parameters could be adjusted to achieve an even better fit to the data using a parameter estimation method. We have chosen the well-known Marquardt nonlinear least squares parameter estimation technique [24] for this study. Our field theoretic
Figure 5.10: Frequency response of the filter $\Gamma(k)$ for various specific conductivities in the interstitial space (S/cm). A. real component; B. imaginary component.
Figure 5.11: Frequency response of the filter $\Gamma(k)$ for various specific conductivities in the external volume conductor space (S/cm). A. real component; B. imaginary component.
model has total of 11 parameters; 5 deal with the geometrical specification of the model and 6 with the electrical properties of either the fiber or the volume conductor. The nominal parameter values can be formed as a $m \times 1$ vector:

$$
\alpha = \begin{bmatrix}
\alpha_1 \\
\alpha_2 \\
\vdots \\
\alpha_m
\end{bmatrix}
$$

(5.35)

A scalar error function is defined as:

$$
e_n(\alpha) \equiv \Phi_{so}(\alpha, Zn) - \Phi_{data}(Zn)
$$

(5.36)

where $\Phi_{so}(\alpha, Zn)$ is the model-generated field potential at the outer surface of the sheath for a given choice of the parameter vector $\alpha$, $Z$ is spatial sampling interval and $n$ is an integer. $e(\alpha, Zn)$ is the error at $n^{th}$ sampling point. Thus we can form a error vector representing the difference between the model-generated field potential and data at each sampling point:

$$
e(\alpha) = \begin{bmatrix}
\Phi_{so}(\alpha, Z) - \Phi_{data}(Z) \\
\Phi_{so}(\alpha, 2Z) - \Phi_{data}(2Z) \\
\vdots \\
\Phi_{so}(\alpha, NZ) - \Phi_{data}(NZ)
\end{bmatrix} = \begin{bmatrix}
e_1(\alpha) \\
e_2(\alpha) \\
\vdots \\
e_N(\alpha)
\end{bmatrix}
$$

(5.37)

The Jacobian matrix is defined as:

$$
J(\alpha) \equiv \left[ \frac{\partial e_i(\alpha)}{\partial \alpha_j} \right]^T ; \quad i=1,2,...,N \\
\quad j=1,2,...,m
$$

(5.38)

Iterative updates of the parameter vector are given by:

$$
\alpha^{new} = \alpha^{old} + \Delta \alpha
$$

(5.39)

where

$$
\alpha \equiv -[JJ^T + \lambda I]^{-1}J(\alpha)e(\alpha)
$$

(5.40)
Here, \( J \) is \( m \times N \) Jacobian matrix, \( \lambda \) is the Levenberg adjustment parameter and \( I \) is a \( m \times m \) identity matrix. As a rule of thumb, the initial value of \( \lambda \) is chosen to be \( 10 \times \) (the maximum diagonal element of \( JJ^T \)) and this parameter is halved at each successive iteration. The \( \frac{\partial e_i(\alpha_j)}{\partial \alpha_j} \) elements of \( J \) are approximated by evaluating the ratio of \( \Delta e_j(\alpha) \) and \( \Delta \alpha_j \) where \( \Delta e_j(\alpha) \) is the error change due to a 1 percent increment in the value of \( \alpha_j \).

Fig. 5.12 displays the model-generated field potential, as well as, the real and imaginary components of the filter function \( \Gamma(k) \) using the parameters estimated by the Marquardt technique. This figure indicates that application of the Marquardt technique improves the fit of the model to data. This is seen by comparing the fits of the nominal and adjusted models to data as in Fig. 5.12A. The adjusted model results also provide closer fits to the real and imaginary parts of the data filter function \( G(k) \) as can be seen in Fig. 5.12B and C. The adjusted model fit extends the range of the good fit to \( G(k) \) achieved at lower frequencies (< 20 rad/cm), and provides a better average fit to the higher frequency behavior of the \( G(k) \) filter. The parameters varied in the Marquardt procedure are given in Table 5.2, which shows the nominal values of the adjusted parameters, as well as those values produced after 12 iterations. Note that changes in parameters \( \bar{\sigma}_{i,z}, \sigma_o, \sigma_e \) and \( \bar{C}_{sh} \) were particularly important in achieving a better fit.

**Sensitivity Analysis of Model Parameters**

Note in equation (5.37) that the \( \Phi_{data}(nZ) \) is not a function of \( \alpha \). Therefore the elements of the Jacobian matrix \( (\partial e_i/\partial \alpha_j) \) are actually the sensitivity coefficients \( (\partial \Phi_{so}(\alpha, nZ)/\partial \alpha_j, \) for \( j=1,2,\ldots,m \)). We define the sensitivity function in relative
Figure 5.12: The improvement of the model-data fit by Marquardt parameter estimation scheme. A. field potential at the outer surface of the sheath. Frequency response of the filter function $\Gamma(k)$: B. real component; C. imaginary component.
Table 5.2: Parameters varied by the Marquardt procedure

<table>
<thead>
<tr>
<th>parameter</th>
<th>nominal value</th>
<th>Marquardt adjusted</th>
<th>% of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_{i,z}$ (S/cm)</td>
<td>0.009</td>
<td>0.00856176</td>
<td>4.87</td>
</tr>
<tr>
<td>$\sigma_{i,t}$ (S/cm)</td>
<td>0.0009</td>
<td>0.00097569</td>
<td>8.41</td>
</tr>
<tr>
<td>$\sigma_c$ (S/cm)</td>
<td>0.0071</td>
<td>0.00636805</td>
<td>10.31</td>
</tr>
<tr>
<td>$\sigma_o$ (S/cm)</td>
<td>0.008</td>
<td>0.00846271</td>
<td>5.78</td>
</tr>
<tr>
<td>$\sigma_{sh}$ (S/cm²)</td>
<td>0.0001</td>
<td>0.00004129</td>
<td>58.71</td>
</tr>
<tr>
<td>$\overline{C}_{sh}$ ($\mu F/cm^2$)</td>
<td>0.5</td>
<td>0.556</td>
<td>11.2</td>
</tr>
</tbody>
</table>

form, as:

$$\xi_j(nZ) \equiv \frac{\alpha_{j0}}{V_0} \frac{\partial \Phi_{so}}{\partial \alpha_j} \quad j = 1, 2, \ldots, m$$ (5.41)

where $\alpha_{j0}$ is the nominal value of the $j^{th}$ model parameter and $V_0$ is the peak to peak voltage of the model-generated field potential at the outer surface of the sheath. We employ sensitivity analysis as an aid in ranking the sensitivity of individual model parameters, that is, the degree to which the model-generated field potential waveform changes in response to a positive 1% change in a single parameter $\alpha_k$.

Figs. 5.13B and C show the relative sensitivities of the field potential to the intracellular longitudinal and transverse specific conductivities, respectively. They indicate that a positive 1% increment in $\sigma_{i,z}$ and $\sigma_{i,t}$ increases both the positive and the negative phase of the diphasic field potential. However, these changes are to different degrees and come about by different mechanisms. Increasing $\sigma_{i,z}$, increases the space constant of the equivalent His bundle cell and more longitudinal current flows ahead of the active zone of the action potential. This increase in $I_L$ also implies an increase in $I_d$ and $I_{Na}$ since current flow is solenoidal. This will bring about a similar change in total membrane current $I_m$ and the trans-sheath current $I_s$, producing an increase in both the positive and the negative phase of the field potential (see Fig. 5.13B).
Figure 5.13: Relative sensitivity function to the specific electrical parameter after 12 iterations. A. adjusted model-generated field potential; B. intracellular longitudinal specific conductivity $\sigma_{l,z}$; C. intracellular transverse specific conductivity $\sigma_{l,t}$; D. specific conductivity of the external volume conductor medium $\sigma_v$; E. specific conductivity of the cleft space medium $\sigma_e$; F. specific conductivity of the sheath $\sigma_{sh}$; and G. specific capacitance of the sheath $C_{sh}$. 
This is in contrast with the results of a 1% increase in $\sigma_{i,t}$. The most noticeable effect in the sensitivity function (Fig. 5.13C) is that this change reduces the spatial extent of the field potential waveform. Here current is allowed to flow to a greater extent in the radial (transverse) direction than under control conditions. As a result, the space constant is reduced and the longitudinal current from the active zone of the action potential is confined to flow across a smaller surface area of the cell membrane. This brings the membrane to threshold more quickly and both $I_d$ and $I_{Na}$ exhibit relatively brisk waveforms. The changes brought about in $I_d$ and $I_{Na}$ are relatively small however, compared with those accompanying changes in $\sigma_{i,z}$. Note the sensitivity function for $\sigma_{i,z}$ is only 10% of that for $\sigma_{i,t}$.

Panel D gives the relative sensitivity of the field potential to the specific conductivity in outer volume conductor space ($\sigma_o$). It demonstrates that an 1% increment in $\sigma_o$ reduces both the positive and the negative phase of the field potential, with a greater effect on the negative phase. Increasing $\sigma_o$ increases current flow in the external volume conductor and hence, due to solenoidal nature of current flow, also increases the trans-sheath current $I_s$. The field potential is proportional to $I_s/\sigma_o$ and therefore the net effect is that 1% change in $\sigma_o$ is greater than $\Delta I_s$.

Panel E shows the relative sensitivity of the field potential to the specific conductivity in cleft space ($\sigma_e$). It shows that a 1% increment in $\sigma_e$ reduces both the positive and the negative phase of the field potential, with a greater effect on the positive phase. Recall from Fig. 4.4A, that the longitudinal currents in the three media of interest have a relationship such that $I_L^e = -(I_L^i + I_L^p)$. Here $I_L^e$ and $I_L^p$ are normally much larger in magnitude than $I_L^i$. Increasing $\sigma_e$ enhances $I_L^i$, as well as the transmembrane current $I_m$ (see Fig. 5.14). However, our simulation results show that this increase in $I_m$ does not enhance trans-sheath current $I_s$. $I_L^i$ takes up the increment in $I_m$ and reduces $I_s$. This reduces the amplitude of the field potential.
Fig. 5.13F and G show the relative sensitivities of the field potential to the specific sheath conductivity $\sigma_{sh}$ and capacitance $C_{sh}$, respectively. The increment in $\sigma_{sh}$ generally reduces the amplitude of the field potential, but it affects the negative phase to a greater extent than the positive phase. Variation in the value of $C_{sh}$ increases both the positive and negative phases of the field potential although it has a stronger effect on the positive phase. An increment in either $C_{sh}$ or $\sigma_{sh}$ will allow a greater amount of current to pass through the sheath and into the outer volume conductor. The sheath current in turn depends upon the amplitude and phase of $I_d$ and $I_{Na}$. We note from Figs. 4.4B and 4.9 that both the temporal and spatial distributions of $I_d$ are greater than those of $I_{Na}$. This indicates that $I_{Na}$ has a higher frequency content than $I_d$. An increment in $C_{sh}$ induces a greater phase
shift ($-\tan^{-1}(\omega C_{sh}/\sigma_{sh})$). Consequently $I_{Na}$ is shifted to a greater extent than $I_d$. This relative phase shift produces the enhancement of the positive phase of the field potential (mainly influenced by $I_d$) to a greater extent than the negative phase (mainly affected by $I_{Na}$). A positive increment in $\sigma_{sh}$ reduces the phase shift which leads to biphasic decrease in the amplitude of the field potential. However, the magnitude of the change in the field potential amplitude is much less than that obtained for the 1% change in $C_{sh}$.

Fig. 5.15B shows the relative sensitivity of the field potential to the radius of the “equivalent single cell” (a). It indicates that a positive 1% increment in radius $a$ increases both the positive and the negative phases of the diphasic field potential with greater effect on the positive phase. Increasing ‘a’ increases the surface area of the “equivalent single cell” membrane, therefore increasing membrane capacitance as well as the total number of sodium channels associated with a membrane segment. Hence, both the $I_{Na}$ and $I_d$ are increased, as well as the amplitude of the field potential. Fig. 5.15C shows the relative sensitivity of the field potential to the radius $b$. A 1% increase in ‘b’ reduces both the positive and negative phases of the field potential with a greater effect on positive phase. Increasing $b$ increases the annular area within the interstitial space, which reduces the resistance of the interstitial space. Therefore a positive change in $b$ has the same effect on the field potential amplitude as that produced by increasing $\sigma_e$ (see Fig. 5.13E). Note that the relative sensitivity of the field potential to variations in the geometrical parameters $a$ and $b$ is at least 10 times greater than that to the electrical parameters ($\sigma_{i,x}$, $\sigma_{i,y}$, $\sigma_o$, $\sigma_z$, $\sigma_{sh}$ and $C_{sh}$).

Fig. 5.15D shows the relative sensitivity of the field potential to a 1% increase in the conduction velocity $\theta$. The relative sensitivity function (panel D) indicates that increasing the conduction velocity of the action potential: (a) increases the spatial extent of the field potential distribution, (b) narrows the ‘shoulder’ of the
Figure 5.15: Relative sensitivity function to the geometrical parameter and conduction velocity after 12 iterations. A. adjusted model-generated field potential; B. radius of “equivalent single cell” a; C. radius of connective tissue sheath b; D. conduction velocity $\theta$. 
positive phase of the field potential and very slightly increases the positive peak, and (c) decreases the negative phase. The net effect of a positive increment in \( \theta \) is a reduction in peak to peak amplitude of the field potential and an increase in its spatial distribution.

5.6 Summary

In this chapter, a field-theoretic model is developed to analyze the relationship between the intra- and extracellular potentials of the His bundle. This model treats the relationship as an equivalent filter problem. The relationship of the intracellular potential and the surface potential on the sheath is represented by a "His bundle filter" function, while the bathing medium is characterized by a "medium filter" function. The model is based on the principles of the electromagnetic field theory applied to the problem of an active His bundle in a volume conductor. The field potential solutions are in the form of a Fourier integral, which are subsequently rewritten as a discrete Fourier series. The discrete Fourier transform (DFT) technique is used (along with the Fast Fourier Transform (FFT) algorithm) for rapid and efficient computation of the field potential. Using a nominal set of parameter values, the model provides a reasonably close least-square fit to experimental field potential data. The fit may be improved however, by employing parameter estimation methods such as the Marquardt method. Application of sensitivity analysis to the parameters of the field-theoretic model, permits the ranking of model parameters according to their relative sensitivity. This can be utilized to provide better fits when used as an adjunct to the Marquardt parameter estimation method.
Chapter 6

Discussion and Future Projection

6.1 Discussion

In this study, two methods are proposed for the characterization of the relationship between the intracellular action potential and the extracellular field potential of a cardiac structure such as the His bundle. These models are called the "equivalent network" and "field-theoretic" models. They are not meant to be comparable in a detailed sense, but are rather presented as two methods of approaching the problem of relating the action potential and the field potential. Each approach has advantages and disadvantages.

6.1.1 Network Model

The "equivalent network" model allows us to study the relationship between the individual branch currents of the cell membrane model and the field potential. As is shown in Fig. 4.4, the diphasic activation complex of the field potential is mainly due to the sum of the displacement current $I_d$ and the fast sodium current $I_{Na}$. During the upstroke of the transmembrane potential, there is a longitudinal current surge in each medium. The inward and outward currents across the membrane are not in phase (Fig. 4.4). During the plateau and final repolarization phases of the action potential, the inward and outward membrane currents are in-phase and net transmembrane current ($I_m$) is very small. Thus, during repolarization there is little noticeable electrical
activity in each medium as shown in Figs. 4.6 and 4.7.

Relatively little is known experimentally about the effect of the connective tissue sheath on the waveshape of the field potential at the outer surface of the His bundle. Our model predicts that since the external bathing medium is a purely passive medium containing no sources or sinks for current flow, the waveshape of the potential recorded in this medium should be strongly related to the waveshape of the transsheath current \( I_s \) that enters the volume conductor from the His bundle. The nature of \( I_s \) in turn depends on the nature of the transmembrane current \( I_m \) emanating from the “equivalent cell” membrane of our model. This later current is determined by the capacitative displacement \( I_d \) and sodium \( I_{Na} \) currents that flow out of phase during the upstroke of the action potential. These monophasic currents sum to produce a diphasic transmembrane current (Figs. 4.4 and 4.9). Consequently, \( I_s \) will also be diphasic as will the external volume conductor potential \( \Phi_o(b, z) \) recorded at the surface of the His bundle. The size and shape of \( I_m \) and \( I_s \) will largely determine the size and shape of \( \Phi_o(b, z) \). During repolarization, the membrane currents \( I_d \) and \( I_{K1} \) largely contribute to \( I_m \). These currents are in phase and largely cancel each other. \( I_m \) is small as is \( I_s \). Consequently, \( \Phi_o(b, z) \) is small as well.

6.1.2 Field-Theoretic Model

In the field-theoretic model, the solution for potential in the volume conductor is formulated as a Fourier integral, which is subsequently re-cast in terms of a Discrete Fourier Transform (DFT). This formulation has the advantage that it permits the boundary value problem to be viewed as an equivalent, linear filtering problem. This DFT formulation of the solution is fast and computationally efficient. Additionally, it
lends itself to the application of some well-known techniques in linear systems theory (e.g., least mean-square filtering for optimal prediction of a signal in random noise in an inverse problem [10, 13]). The simulation results demonstrate that the field theoretic model has certain robustness: it can be applied not only to the nerve trunk [13], but also to the cardiac strand as well.

Cardiac fibers consist of cells connected by the intercalated discs and the cardiac strand consists of several fibers [17]. The individual cells are surrounded by an interstitial medium that contains blood vessels, connective tissue and extracellular fluid. Thus, the lumping of the intracellular and cleft space media is an abstract concept that simplifies the description of the time-varying action current generator located within the His bundle. Thus, in a macroscopic sense, the equivalent cell concept may simplify the description of the cardiac current generator for use in predicting field potentials in the bathing medium, but it does not represent the detailed microscopic field distribution within the His bundle itself. Therefore, even though it is possible with our mathematical formulation of the problem to solve the potentials in the intracellular and cleft spaces, these solutions may not have physiological meaning. The field-theoretic model is therefore clearly intended to provide only predictions of the field potential at an arbitrary field point in the external bathing medium based on intracellular action potential data and estimates of certain geometrical and electrical parameters necessary to initialize the His bundle filter function. On the other hand, the equivalent network model represents a more microscopic approach that attempts to describe the propagation of electrical activity in the equivalent cell of the His bundle and provide a reasonable estimate of the action currents flowing in the interstitial and external bathing media. It represents a better model of the bioelectric source than the source description utilized in the field-theoretic model. At the same time, the
network model uses a more primitive model of the interstitial and external bathing media.

6.2 Future Projection

This study presents models that may be utilized to study the relationship of the intra- and extracellular potentials of the His bundle. The results from these simulations provide insight into the basic electrical activity in a tissue strand. One possible extension of this work is the development of models for two- or three-dimensional propagation in a sheet of tissue or a multicellular strand, respectively. The coupling of different fibers may be implemented via a resistor network, thus producing a distributed network model for the study of uniform and nonuniform conduction in a more realistic cardiac structure.
Bibliography


Appendix A

Purkinje Cell Model Equations

The equations describing the rabbit Purkinje cell model are contained within this Appendix. Expressions for the inward ($I_{Na}, I_{Ca,L}, I_{Ca,T}$) and outward ($I_I, I_K$) transmembrane currents are given in Table A.1, Table A.2, Table A.3 and Table A.4, respectively. The voltage dependent $K^+$ current $I_{K1}$, background current $I_B$, and the hyperpolarization-activated current $I_J$ are shown in Table A.5. The equations in Table A.6 represent the pump and exchanger currents and those in Table A.7 contain the compartmental ion flux equations. The equations in Table A.8 describe the calcium uptake and release mechanism in the sarcoplasmic reticulum. A listing of model parameter values and initial conditions necessary to run the model is provided in Table A.9 and Table A.10.
Table A.1: Sodium Current: $I_{Na}$

$$I_{Na} = P_{Na} m^3 h [Na]_e \frac{F^2}{RT} \frac{\exp((V-E_{Na}+42.434)F/RT)}{\exp(VF/RT)-1}$$

\[ \alpha_m = \frac{-641.87(V+44.4)}{\exp((V+44.4)/-12.673)-1} \]
\[ \tau_m = \frac{1}{\alpha_m + \beta_m} \]
\[ \alpha_h = 144.1 \ e^{(V+68.9)/-5.57} \]
\[ \tau_h = \frac{1}{\alpha_h + \beta_h} \]
\[ \dot{m} = \frac{\bar{m} - m}{\tau_m} \]
\[ P_{Na} = 0.005 mm^3/sec \]

\[ \beta_m = 25674.9 \ e^{(V+44.4)/-12.673} \]
\[ \bar{m}_L = \frac{\alpha_m}{\alpha_m + \beta_m} \]
\[ \beta_h = \frac{4785.16}{1+323.3 \exp((V+96.6)/-12.9)} \]
\[ \bar{h} = \frac{\alpha_h}{\alpha_h + \beta_h} \]
\[ \dot{h} = \frac{\bar{h} - h}{\tau_h} \]
\[ E_{Na} = \frac{RT}{F} \log \frac{[Na]_e}{[Na]_i} \]
Table A.2: Calcium Currents: $I_{Ca,L}$ and $I_{Ca,T}$

$$I_{Ca,L} = g_{Ca,L}(d_L f_L + 0.072d')(V - 46.4)$$

$$I_{Ca,T} = g_{Ca,T}d_T f_T (V - 45.0)$$

$$\alpha_{dL} = \frac{-11.898(V+35)}{\exp((V+35)/-2.5)-1} + \frac{-35.580V}{\exp(-0.208V-1)}$$

$$\beta_{dL} = \frac{3.188(V-5)}{\exp(0.4(V-5))-1}$$

$$d' = \frac{1}{1+\exp((V+5.95)/-6.6)}$$

$$\alpha_{fL} = \frac{7.110(V+28)}{\exp((V+28)/4)-1}$$

$$\beta_{fL} = \frac{56.927}{1+\exp((V+28)/-4)}$$

$$\bar{d}_L = \frac{1}{1+\exp(V+39.8/6.0)}$$

$$\bar{d}_T = \frac{1}{1+\exp((V+26.3)/-6)}$$

$$\bar{d}_T = \frac{1}{1+\exp((V+61.7)/15.38)}$$

$$\bar{f}_T = \frac{1}{1+\exp((V+61.7)/5.6)}$$

$$\alpha_{dT} = 1068 \ e^{(V+26.3)/30}$$

$$\beta_{dT} = 1068 \ e^{(V+26.3)/30}$$

$$\tau_{dT} = \frac{1}{\alpha_{dT} + \beta_{dT}}$$

$$\alpha_{fT} = 15.3 \ e^{(V+61.7)/-83.3}$$

$$\beta_{fT} = 15.3 \ e^{(V+61.7)/-83.3}$$

$$\tau_{fT} = \frac{1}{\alpha_{fT} + \beta_{fT}}$$

$$I_{Ca} = I_{Ca,L} + I_{Ca,T}$$
### Table A.3: Transient Outward Current: \( I_t \)

\[
I_t = I_A + I_D
\]

\[
I_A = g_A r_A s_A s_{react}^4 (V - E_K) \\
\tau_{r_A} = 0.0062273 \\
\tau_{s_A} = 0.0213329 \\
\bar{r}_A = \frac{1}{1 + \exp((V - 3.044697)/-13.715270)} \\
\bar{s}_A = \frac{1}{1 + \exp((V + 49.8)/2)} \\
\tau_{s_{react}} = 1.9659488 \\
\dot{r}_A = \frac{\bar{r}_A - r_A}{\tau_{r_A}} \\
\dot{s}_A = \frac{\bar{s}_A - s_A}{\tau_{s_A}} \\
\dot{s}_{react} = \frac{\bar{s}_{react} - s_{react}}{\tau_{s_{react}}}
\]

\[
I_D = g_D r_D s_D (V - E_K) \\
\tau_D = 0.0241339 \\
\tau_{s_D} = 0.4529619 \\
\bar{r}_D = \frac{1}{1 + \exp((V - 6.584893)/-6.708278)} \\
\bar{s}_D = \frac{1}{1 + \exp((V + 47.3)/8.4)} \\
\tau_{s_{react}} = \frac{0.5}{1 + \exp((V + 71.125730)/0.162638)} + 0.5 \\
\dot{r}_D = \frac{\bar{r}_D - r_D}{\tau_D} \\
\dot{s}_D = \frac{\bar{s}_D - s_D}{\tau_{s_D}}
\]

### Table A.4: \( I_K \): Delayed Rectifier \( K^+ \) Current

\[
I_K = g_K p_a p_i (V - E_K) \\
\bar{p}_a = \frac{1}{1 + \exp(\frac{V + 19}{14})} \\
\tau_{p_a}^{-1} = 17 e^{0.0398V} + 0.211 e^{-0.0510V} \\
E_K = \frac{RT}{F} \log \frac{[K]^4}{[K]^4} \\
\alpha_{p_i} = 100 \ e^{-0.0183V} \\
\beta_{p_i} = 656 \ e^{0.00942V} \\
\dot{p}_a = \frac{(\bar{p}_a - p_a)}{\tau_{p_a}} \\
\dot{p}_i = \alpha_{p_i} (1 - p_i) - \beta_{p_i} p_i
\]
Table A.5: Voltage Dependent $K^+$ ($I_{K1}$), Background ($I_B$) and Hyperpolarization-Activated ($I_f$) currents

$I_{K1}$: Voltage Dependent $K^+$ current

$$I_{K1} = g_{K1} \left( \frac{[K]^3}{[K]^3 + 0.59} \right)^3 \frac{V-E_K}{1+\exp(2.647(V-E_K-24.5)/RT)}$$

Sodium ($I_{B,Na}$) and Calcium ($I_{B,Ca}$) Background Currents

$$I_{B,Na} = g_{B,Na}(V - E_{Na}) \quad I_{B,Ca} = g_{B,Ca}(V - E_{Ca})$$

$$I_B = I_{B,Na} + I_{B,Ca}$$

$I_f$: Hyperpolarization-Activated Current

$$I_f = I_{f,Na} + I_{f,K}$$

$$I_{f,Na} = g_{f,Na}\bar{y}^2(V - E_{Na}) \quad I_{f,K} = g_{f,K}y^2(V - E_K)$$

$$\bar{y} = \frac{1}{1+\exp((V+82.2)/0)} \quad \dot{y} = \frac{(\bar{y} - y)}{\tau_y}$$

$$\tau_y^{-1} = \exp(V+54.06)/24.33 + \frac{14.01055}{0.7 + \exp((V+73)/-5.5)}$$
Table A.6: $\text{Na}^+/\text{K}^+, \text{Ca}^{2+}, \text{K}^+ \text{ Pump and Na}^+/\text{Ca}^{2+} \text{ Exchanger Currents}$

<table>
<thead>
<tr>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{NaK}$: Sodium Potassium Pump current</td>
</tr>
<tr>
<td>$I_{NaK} = \bar{I}<em>{NaK} \left( \frac{[\text{Na}]}{[\text{Na}]+k</em>{mNa}} \right)^3 \left( \frac{[\text{K}]}{[\text{K}]+k_{mK}} \right)^2 \left( \frac{1.6}{1.5+\exp((V+60)/-20)} \right)$</td>
</tr>
<tr>
<td>$I_{CaP}$: Calcium Pump current</td>
</tr>
<tr>
<td>$I_{CaP} = \bar{I}_{CaP} \left( \frac{[\text{Ca}]}{[\text{Ca}]+0.0005} \right)$</td>
</tr>
<tr>
<td>$I_{NaCa}$: Sodium Calcium Exchanger current</td>
</tr>
<tr>
<td>$I_{NaCa} = \frac{k_{NaCa}([\text{Na}]^2[\text{Ca}]+\exp(V\gamma F/RT)-[\text{Na}]^2[\text{Ca}][\exp(V\gamma-1)F/RT])}{1+d_{NaCa}([\text{Ca}][\text{Na}]^2+[\text{Ca}][\text{Na}]_{\text{c}}^2)}$</td>
</tr>
<tr>
<td>$I_{KP}$: Potassium Pump Current</td>
</tr>
<tr>
<td>$I_{KP} = -\bar{I}<em>{KP} \left( \frac{[\text{K}]}{[\text{K}]+k</em>{p}} \right)$</td>
</tr>
</tbody>
</table>
### Table A.7: Compartmental Equations

#### Intracellular Concentrations of Na\(^+\) and K\(^+\)

\[
[Na_i^+] = \frac{-I_{Na} - 3I_{NaK} - 3I_{NaCa} - I_{B,Na} - I_{f,Na}}{FV_i}
\]

\[
[K_i^+] = \frac{-I_I + 2I_{NaK} - I_K - I_{K1} - I_{f,K} + I_KP}{FV_i}
\]

#### Intracellular Calcium Concentration and Buffering

\[
\dot{\Phi}_C = 129000[Ca_i^+] (1 - \Phi_C) - 307\Phi_C
\]

\[
\dot{\Phi}_{TC} = 50568[Ca_i^+] (1 - \Phi_{TC}) - 253\Phi_{TC}
\]

\[
\dot{\Phi}_{TMgC} = 129000[Ca_i^+] (1 - \Phi_{TMgC} - \Phi_{TMgM}) - 4.26\Phi_{TMgC}
\]

\[
\dot{\Phi}_{TMgM} = 1290[Ca_i^+] (1 - \Phi_{TMgC} - \Phi_{TMgM}) - 430\Phi_{TMgM}
\]

\[
\Phi_B = 0.018\Phi_C + 0.032\Phi_{TC} + 0.064\Phi_{TMgC}
\]

\[
[Ca_i^+] = \frac{2I_{NaCa} - I_{Ca} - I_{CaP} - I_{B,Ca} - I_{Ca} + I_{red} - \Phi_B}{2V_i F}
\]

#### Cleft Space Concentrations of Na\(^+\), K\(^+\) and Ca\(^{2+}\)

\[
[Na_c^+] = \frac{I_{Na} + 3I_{NaK} + 3I_{NaCa} + I_{B,Na} + I_{f,Na}}{V_c F} + \frac{[Na_c^+] - [Na_c^+]_{\tau_p}}{\tau_p}
\]

\[
[K_c^+] = \frac{I_{I} - 2I_{NaK} + I_{K1} + I_{f,K} - I_{KP}}{V_c F} + \frac{[K_c^+] - [K_c^+]_{\tau_p}}{\tau_p}
\]

\[
[Ca_c^+] = \frac{-2I_{NaCa} + I_{Ca} + I_{CaP} + I_{B,Ca}}{2V_c F} + \frac{[Ca_c^+] - [Ca_c^+]_{\tau_p}}{\tau_p}
\]
Table A.8: SR Calcium Uptake and Release

\[
\begin{align*}
[\dot{C}a]_{up} &= \frac{I_{up} - I_{tr}}{2V_{up}} \\
[\dot{C}a]_{rel} &= \frac{I_{tr} - I_{rel}}{2V_{rel}} - 11.48\dot{\Phi}_{\text{Calse}} \\
I_{rel} &= \alpha_{rel}\left(\frac{E_3}{E_2 + 0.25}\right)^2[Ca]_{rel} \\
I_{tr} &= ([Ca]_{up} - [Ca]_{rel})\frac{2FV_{up}}{0.00023\text{sec}} \\
\dot{F}_1 &= 0.96F_3 - r_{act}F_1 \\
\dot{F}_2 &= r_{act}F_1 - r_{inact}F_2 \\
\dot{F}_3 &= r_{inact}F_2 - 0.96F_3 \\
\dot{r}_{act} &= 240 \ e^{(V-40)/12.5} + 240\left(\frac{[Ca]_{rel}}{[Ca]_{rel} + k_r}\right)^4 \\
\dot{\Phi}_{\text{Calse}} &= 770[Ca]_{rel}(1 - \Phi_{\text{Calse}}) - 641\Phi_{\text{Calse}} \\
I_{up} &= I_{up} \left(\frac{[Ca]_{rel}/k_{cyca} - k_{kcs}[Ca]_{up}/k_{srcn}}{([Ca]_{rel} + k_{cyca})/k_{cyca} + k_{kcs}([Ca]_{up} + k_{srcn})/k_{srcn}}\right)
\end{align*}
\]
Table A.9: Model Constants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_i$</td>
<td>4.566 picoliters</td>
</tr>
<tr>
<td>$V_{rel}$</td>
<td>$0.0035 V_i = 0.01598$ picoliters</td>
</tr>
<tr>
<td>$V_{sp}$</td>
<td>$0.0315 V_i = 0.14383$ picoliters</td>
</tr>
<tr>
<td>$F$</td>
<td>96487 coul/mole</td>
</tr>
<tr>
<td>$g_{Ca,l}$</td>
<td>13.4 nS</td>
</tr>
<tr>
<td>$g_{D}$</td>
<td>18.1 nS</td>
</tr>
<tr>
<td>$g_{A}$</td>
<td>8.6 nS</td>
</tr>
<tr>
<td>$g_{D}$</td>
<td>0.000733 nS</td>
</tr>
<tr>
<td>$g_{Na,B}$</td>
<td>0.08 nS</td>
</tr>
<tr>
<td>$g_{Ca,B}$</td>
<td>0.006 nS</td>
</tr>
<tr>
<td>$g_{f,K}$</td>
<td>1.9467 nS</td>
</tr>
<tr>
<td>$g_{f,Na}$</td>
<td>2.92 nS</td>
</tr>
<tr>
<td>$g_K$</td>
<td>1.54 nS</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.5</td>
</tr>
<tr>
<td>$\tau_p$</td>
<td>1.45 sec</td>
</tr>
<tr>
<td>$k_{NaCa}$</td>
<td>$0.0224 pA/mM^4$</td>
</tr>
<tr>
<td>$d_{NaCa}$</td>
<td>0.003</td>
</tr>
<tr>
<td>$k_{mNa}$</td>
<td>5.46 mM</td>
</tr>
<tr>
<td>$k_{mK}$</td>
<td>0.621 mM</td>
</tr>
<tr>
<td>$I_{NaK}$</td>
<td>219.8 pA</td>
</tr>
<tr>
<td>$I_{CaP}$</td>
<td>16.8 pA</td>
</tr>
<tr>
<td>$I_{KP}$</td>
<td>7 pA</td>
</tr>
<tr>
<td>$I_{up}$</td>
<td>150 pA</td>
</tr>
<tr>
<td>$[Na^+]_o$</td>
<td>151 mM</td>
</tr>
<tr>
<td>$[K^+]_o$</td>
<td>4.0 mM</td>
</tr>
<tr>
<td>$[Ca^{2+}]_o$</td>
<td>1.3 mM</td>
</tr>
<tr>
<td>$C_m$</td>
<td>50 pF</td>
</tr>
<tr>
<td>$k_{cyc}$</td>
<td>0.0003 mM</td>
</tr>
<tr>
<td>$k_{src}$</td>
<td>0.5 mM</td>
</tr>
<tr>
<td>$k_{xrc}$</td>
<td>0.4</td>
</tr>
<tr>
<td>$k_r$</td>
<td>0.0005 mM</td>
</tr>
<tr>
<td>$\alpha_{rel}$</td>
<td>3000000 pA/mM</td>
</tr>
<tr>
<td>$[Mg^{2+}]_i$</td>
<td>2.5 mM</td>
</tr>
</tbody>
</table>
### Table A.10: Initial Conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$</td>
<td>$-81.595681$ mV</td>
</tr>
<tr>
<td>$h$</td>
<td>0.967891</td>
</tr>
<tr>
<td>$f_L$</td>
<td>0.999967</td>
</tr>
<tr>
<td>$f_T$</td>
<td>0.883271</td>
</tr>
<tr>
<td>$s_A$</td>
<td>0.991731</td>
</tr>
<tr>
<td>$r_D$</td>
<td>0.001256</td>
</tr>
<tr>
<td>$p_a$</td>
<td>0.232209</td>
</tr>
<tr>
<td>$y$</td>
<td>0.270777</td>
</tr>
<tr>
<td>$[K]_i$</td>
<td>96.439367 mM</td>
</tr>
<tr>
<td>$[Ca]_{up}$</td>
<td>0.122255 mM</td>
</tr>
<tr>
<td>$\Phi_G$</td>
<td>0.032846</td>
</tr>
<tr>
<td>$\Phi_{TM2C}$</td>
<td>0.399408</td>
</tr>
<tr>
<td>$\Phi_{Ca,le}$</td>
<td>0.125383</td>
</tr>
<tr>
<td>$F_2$</td>
<td>0.000469</td>
</tr>
<tr>
<td>$[Na]_c$</td>
<td>151.061073 mM</td>
</tr>
<tr>
<td>$[Ca]_c$</td>
<td>1.320975 mM</td>
</tr>
<tr>
<td>$m$</td>
<td>0.002764</td>
</tr>
<tr>
<td>$d_L$</td>
<td>0.000005</td>
</tr>
<tr>
<td>$d_T$</td>
<td>0.000099</td>
</tr>
<tr>
<td>$r_A$</td>
<td>0.002082</td>
</tr>
<tr>
<td>$s_{react}$</td>
<td>0.730177</td>
</tr>
<tr>
<td>$s_D$</td>
<td>0.517830</td>
</tr>
<tr>
<td>$p_i$</td>
<td>0.594288</td>
</tr>
<tr>
<td>$[Na]_i$</td>
<td>8.460251 mM</td>
</tr>
<tr>
<td>$[Ca]_i$</td>
<td>0.00008 mM</td>
</tr>
<tr>
<td>$[Ca]_{rel}$</td>
<td>0.119761 mM</td>
</tr>
<tr>
<td>$\Phi_{TC}$</td>
<td>0.015942</td>
</tr>
<tr>
<td>$\Phi_{TM2M}$</td>
<td>0.529762</td>
</tr>
<tr>
<td>$F_1$</td>
<td>0.135157</td>
</tr>
<tr>
<td>$F_3$</td>
<td>0.766373</td>
</tr>
<tr>
<td>$[K]_c$</td>
<td>3.997897 mM</td>
</tr>
</tbody>
</table>
Appendix B

Derivation of the Expression for the Filter Functions in the Field-Theoretic Model

The filter functions in the field-theoretic model are derived in this appendix. We begin by defining the following Fourier transform pair associated with the intracellular potential:

\[ F_{si}(k) \equiv \int_{-\infty}^{\infty} \Phi_{si}(z)e^{jkz}dz \quad (B.1) \]
\[ \Phi_{si}(z) \equiv \Phi_{i}(a,z) \equiv \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{si}(k)e^{-jkz}dk \quad (B.2) \]

Similarly defining the Fourier transform pairs associated with the extracellular potential:

\[ \Phi_{o}(r,z) \equiv \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{o}(r,k)e^{-jkz}dk \quad (B.3) \]
\[ F_{o}(r,k) \equiv \int_{-\infty}^{\infty} \Phi_{o}(r,z)e^{jkz}dz \quad (B.4) \]
\[ \Phi_{so}(z) \equiv \Phi_{o}(b,z) \equiv \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{so}(k)e^{-jkz}dk \quad (B.5) \]
\[ F_{so}(k) \equiv \int_{-\infty}^{\infty} \Phi_{so}(z)e^{jkz}dz \quad (B.6) \]

For convenience, we rewrite the expressions for the potential distributions in the media of interest and the boundary conditions:

\[ \Phi_{i}(r,z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} F_{si}(k)\frac{I_{0}(\lambda|k|r)}{I_{0}(\lambda|k|a)}e^{-jkz}dk \quad r \in [0,a] \quad (B.7) \]
\[ \Phi_{e}(r,z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} [B(k)I_{0}(|k|r) + C(k)K_{0}(|k|r)]e^{-jkz}dk \quad r \in [a,b] \quad (B.8) \]
\[ \Phi_{o}(r,z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} [D(k)I_{0}(|k|r) + E(k)K_{0}(|k|r)]e^{-jkz}dk \quad r \in [b,c] \quad (B.9) \]
where the anisotropy ratio $\lambda$ is defined as:

\[
\lambda \equiv \left( \frac{\sigma_{i,z}}{\sigma_{i,t}} \right)^{\frac{1}{2}}
\]  

(B.10)

Considering current flow at the cell membrane and sheath boundaries to be continuous in the radial direction, the following boundary conditions are obtained:

at $r = a$

\[-\sigma_{i,t} \frac{\partial \Phi_i(r, z)}{\partial r} \bigg|_{r=a} = -\sigma_e \frac{\partial \Phi_e(r, z)}{\partial r} \bigg|_{r=a}
\]  

(B.11)

at $r = b$

\[-\sigma_e \frac{\partial \Phi_e(r, z)}{\partial r} \bigg|_{r=b} = -\sigma_o \frac{\partial \Phi_o(r, z)}{\partial r} \bigg|_{r=b} = \ldots
\]  

(B.12)

and

\[-\sigma_o \frac{\partial \Phi_o(r, z)}{\partial r} \bigg|_{r=b} = \overline{\gamma}_{sh} \Phi_{sh}(z)
\]  

(B.13)

where $\Phi_{sh}(z)$ is the trans-sheath potential defined by:

\[\Phi_{sh}(z) \equiv \Phi_e(b, z) - \Phi_o(b, z)
\]  

(B.14)

and $\overline{\gamma}_{sh}$ is the equivalent admittance of the sheath defined as:

\[\overline{\gamma}_{sh} \equiv \sigma_{sh} - j k \theta C_{sh}
\]  

(B.15)

at $r = c$:

\[-\sigma_o \frac{\partial \Phi_o(r, z)}{\partial r} \bigg|_{r=c} = 0
\]  

(B.16)

Applying boundary condition at the cell membrane ($r=a$), $C(k)$ may be expressed as a function of $F_{si}(k)$ and $B(k)$:

\[C(k) = \frac{I_1(|k|a)}{K_1(|k|a)} B(k) - \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda|k|a)}{I_0(\lambda|k|a)K_1(|k|a)} F_{si}(k)
\]  

(B.17)

where

\[\sigma_i \equiv \lambda \sigma_{i,t} = \sqrt{\frac{\sigma_{i,z}}{\sigma_{i,t}}} \sigma_{i,t} = \sqrt{\sigma_{i,z} \sigma_{i,t}}
\]  

(B.18)
Applying boundary condition at the sheath \((r=b)\) yields:

\[
\sigma_e |k| [B(k)I_1(|k|b) - C(k)K_1(|k|b)] - \sigma_o |k| [D(k)I_1(|k|b) - E(k)K_1(|k|b)] = 0 \tag{B.19}
\]

and

\[
\bar{r}_{sh} \{[B(k)I_0(|k|b) + C(k)K_0(|k|b)] - [D(k)I_0(|k|b) + E(k)K_0(|k|b)]\}
+ \sigma_e |k| [D(k)I_1(|k|b) - E(k)K_1(|k|b)] = 0 \tag{B.20}
\]

Applying boundary condition at outer boundary of the volume conductor \((r=c)\) gives the relationship between \(D(k)\) and \(E(k)\):

\[
E(k) = \frac{I_1(|k|c)}{K_1(|k|c)} D(k) \tag{B.21}
\]

Upon substitution of equations \((B.17)\) and \((B.21)\) to equations \((B.19), (B.20)\) and collection of terms, the following expressions are obtained:

\[
[I_1(|k|a)K_1(|k|b) - K_1(|k|a)I_1(|k|b)]\frac{B(k)}{K_1(|k|a)} + \frac{\sigma_o}{\sigma_e} [I_1(|k|b)K_1(|k|c) -
K_1(|k|b)I_1(|k|c)]\frac{D(k)}{K_1(|k|c)} = \frac{\sigma_i}{\sigma_e} I_0(\lambda |k|a)K_1(|k|a)F_{si}(k) \tag{B.22}
\]

\[
\bar{r}_{sh}[I_1(|k|a)K_0(|k|b) + K_1(|k|a)I_0(|k|b)]\frac{B(k)}{K_1(|k|a)} + \{\sigma_o |k| [I_1(|k|b)K_1(|k|c) -
K_1(|k|b)I_1(|k|c)] - \bar{r}_{sh}[I_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c)]\}\frac{D(k)}{K_1(|k|c)}
= \frac{\sigma_i}{\sigma_e} I_0(\lambda |k|a)K_1(|k|a)F_{si}(k) \tag{B.23}
\]

Defining \(T_1(k)\) to \(T_4(k)\) as:

\[
T_1(k) \equiv I_1(|k|a)K_1(|k|b) - K_1(|k|a)I_1(|k|b) \tag{B.24}
\]

\[
T_2(k) \equiv I_1(|k|b)K_1(|k|c) - K_1(|k|b)I_1(|k|c) \tag{B.25}
\]

\[
T_3(k) \equiv I_1(|k|a)K_0(|k|b) + K_1(|k|a)I_0(|k|b) \tag{B.26}
\]

\[
T_4(k) \equiv I_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c) \tag{B.27}
\]
Thus, equations (B.22) and (B.23) may be rewritten as:

\[
T_1(k) \frac{D(k)}{K_1(|k|c)} + \frac{\sigma_o T_2(k)}{\sigma_e} = \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda |k|a)K_1(|k|b)}{I_0(\lambda |k|a)K_1(|k|a)F_{si}(k)} \tag{B.28}
\]

\[
\gamma_{sh} T_3(k) \frac{B(k)}{K_1(|k|c)} + \left[\sigma_i |k|T_2(k) - \gamma_{sh} T_4(k)\right] \frac{D(k)}{K_1(|k|c)} = \gamma_{sh} \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda |k|a)K_0(|k|b)}{I_0(\lambda |k|a)K_1(|k|a)F_{si}(k)} \tag{B.29}
\]

Solving equations (B.28) and (B.29), we obtain:

\[
\frac{D(k)}{K_1(|k|c)} = \frac{\gamma_{sh} \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda |k|a)K_1(|k|b)}{I_0(\lambda |k|a)K_1(|k|a)T_3(K_1(|k|b)) - T_1(k)K_0(|k|b)}}{\gamma_{sh} \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda |k|a)K_1(|k|b)}{I_0(\lambda |k|a)K_1(|k|a)T_3(K_1(|k|b)) + T_1(k)T_4(k)} - \sigma_i |k|T_1(k)T_2(k)} F_{si}(k) \tag{B.30}
\]

Defining \(\Delta(k)\) as:

\[
\Delta(k) \equiv \frac{\gamma_{sh} \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda |k|a)K_1(|k|b)}{I_0(\lambda |k|a)K_1(|k|a)T_3(K_1(|k|b)) - T_1(k)K_0(|k|b)}}{\gamma_{sh} \frac{\sigma_i}{\sigma_e} \frac{I_1(\lambda |k|a)K_1(|k|b)}{I_0(\lambda |k|a)K_1(|k|a)T_3(K_1(|k|b)) + T_1(k)T_4(k)} - \sigma_i |k|T_1(k)T_2(k)} \tag{B.31}
\]

it follows that

\[
\frac{D(k)}{K_1(|k|c)} = \Delta(k) F_{si}(k) \tag{B.32}
\]

Upon substitution of equations (B.21) and (B.32) into equation (B.9), the extracellular potential can be rewritten as:

\[
\Phi_o(r, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \left[ D(k)I_0(|k|r) + E(k)K_0(|k|r) \right] e^{-jkz} dk
\]

\[
= \frac{1}{2\pi} \int_{-\infty}^{\infty} \left[ I_0(|k|r)K_1(|k|c) + K_0(|k|r)I_1(|k|c) \right] \frac{D(k)}{K_1(|k|c)} e^{-jkz} dk
\]

\[
= \frac{1}{2\pi} \int_{-\infty}^{\infty} \left[ I_0(|k|r)K_1(|k|c) + K_0(|k|r)I_1(|k|c) \right] \Delta(k) F_{si}(k) e^{-jkz} dk \tag{B.33}
\]

From equations (B.3), (B.5) and equation above, it follows that

\[
F_o(r, k) = \left[ I_0(|k|r)K_1(|k|c) + K_0(|k|r)I_1(|k|c) \right] \Delta(k) F_{si}(k) \tag{B.34}
\]

\[
F_{so}(k) = \left[ I_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c) \right] \Delta(k) F_{si}(k) \tag{B.35}
\]

Thus, from equations (B.34) and (B.35), we have:

\[
F_o(r, k) = \frac{I_0(|k|r)K_1(|k|c) + K_0(|k|r)I_1(|k|c)}{I_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c)} F_{so}(k) \tag{B.36}
\]
defining $\Gamma(k)$ and $W(r,k)$ as:

$$\Gamma(k) \equiv [J_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c)]\Delta(k)$$ (B.37)

$$W(r,k) \equiv \frac{J_0(|k|r)K_1(|k|c) + K_0(|k|r)I_1(|k|c)}{J_0(|k|b)K_1(|k|c) + K_0(|k|b)I_1(|k|c)}$$ (B.38)

Thus, the extracellular potential distribution is given as:

$$\Phi_0(r, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \Gamma(k)W(r, k)F_s(k)e^{-jkz}dk$$ (B.39)