Modeling Nerve Electro-Stimulation in the Nanosecond Regime

Feng Chen
Old Dominion University

Follow this and additional works at: https://digitalcommons.odu.edu/ece_etds

Part of the Electrical and Electronics Commons, Nanoscience and Nanotechnology Commons, and the Nanotechnology Fabrication Commons

Recommended Citation
https://digitalcommons.odu.edu/ece_etds/307

This Thesis is brought to you for free and open access by the Electrical & Computer Engineering at ODU Digital Commons. It has been accepted for inclusion in Electrical & Computer Engineering Theses & Dissertations by an authorized administrator of ODU Digital Commons. For more information, please contact digitalcommons@odu.edu.
MODELING NERVE ELECTRO-STIMULATION IN THE
NANOSECOND REGIME

by

Feng Chen
B.S. in Microelectronics
University of Electronic Science & Technology of China, Chengdu, P. R. China

A Thesis Submitted to the Faculty of
Old Dominion University in Partial Fulfillment of the
Requirement for the Degree of

MASTER OF SCIENCE
ELECTRICAL ENGINEERING
OLD DOMINION UNIVERSITY
August 2004

Approved by:

Ravindra P. Joshi (Director)

Linda L. Vahala (Member)

Mohsnir Laroussi (Member)
ABSTRACT

MODELING NERVE ELECTRO-STIMULATION IN THE NANOSECOND REGIME

Feng Chen
Old Dominion University, 2004
Director: Dr. Ravindra P. Joshi

Numerical simulations of electrical stimulation of frog gastrocnemius muscles have been carried out for pulse durations in the nanosecond regime. There are a number of potential advantages in using ultra-short pulses for neural stimulation, and no previous electro-stimulation work in the sub-microsecond regime has been reported. A time-dependent, three-dimensional analysis model was developed and implemented for three distinct situations: (i) direct stimulation via electrode contact, (ii) indirect excitation based on electrodes immersed in a saline-filled bath, and (iii) remote electromagnetic stimulation through vacuum. The simulations yielded strength-duration (S-D) curves with pulse durations as short as 5 ns. Good agreement between the model predictions and experimental measurements was obtained. For example, with direct contact a peak current of about 30 A was predicted for the shortest pulse; the measured value was 34 A. The modeling also led to a demonstration of the non-thermal nature of electro-stimulation with nanosecond pulses, even with an applied voltage as high as 5 kV. Calculations of the S-D curves for both direct and indirect stimulation yielded a good match with the available experimental data. The verified model was used to investigate the effects of electrode placement and pulse shape, and a new anode-cathode-anode electrode scheme
was developed for direct stimulation. A time constant of 160 μs was estimated for frog tissue stimulation; this value is indicative of a nerve-based response. Furthermore, it was shown quantitatively that inhomogeneities in the nerve geometry and size can affect the S-D curve. For electrical stimulation, the greatest potential for muscle twitching occurs at boundaries and within regions that have internal non-uniformity of nerve fiber size or potential distribution. For electromagnetic stimulation, the simulations demonstrated that the electromagnetic wave could not penetrate the muscle very effectively. However, non-uniformity of electric field distribution was observed, and this is a desirable pre-requisite for enhancing the activating function for a bio-response.

Co-directors of Advisory Committee:  Dr. Mounir Laroussi  
Dr. Linda L. Vahala
ACKNOWLEDGMENTS

My special appreciation and gratitude go to Dr. Ravindra P. Joshi who has given me this wonderful opportunity to work with him and obtain my master’s degree. His continued support, help and patience made the completion of this thesis possible. His willingness to communicate and offer guidance during my graduate program will never be forgotten. My sincere appreciation also goes to Dr. Mounir Laroussi and Dr. Linda L. Vahala for serving on my thesis advisory committee.

I would like to thank my family for their support and belief in my ability. Their encouragement has always been a constant source of strength during my education.

I am very thankful to my friends Dr. Qin Hu, Dr. Shangping Guo, Dr. Yaqin Li and Feng Wu for the valued discussion and assistance.
# TABLE OF CONTENTS

**LIST OF FIGURES** ........................................................................................................................................................................... vi

**CHAPTER**

I. **INTRODUCTION** ........................................................................................................................................................................... 1  
   NERVE STIMULATION ..................................................................................................................................................... 1  
   ADVANTAGES OF ULTRASHORT PULSES .................................................................................................................... 2  
   OVERVIEW OF THESIS OBJECTIVES .................................................................................................................. 3

II. **BACKGROUND AND LITERATURE** ................................................................................................................................. 6  
    ACTIVATION OF NERVE FIBER .......................................................................................................................... 6  
    MODELS FOR EXCITATION OF MYELINATED NERVE .................................................................................... 10  
    STIMULATION MECHANISMS ...................................................................................................................... 13

III. **SIMULATION MODEL AND APPROACH** ......................................................................................................................... 18  
     INTRODUCTION ............................................................................................................................................... 18  
     NEURAL MODELING IN ................................................................................................................................... 18  
     ELECTRICAL NERVE SIMULATION ............................................................................................................. 23  
     ELECTROMAGNETIC NERVE STIMULATION .............................................................................................. 32  
     VALIDATION & VERIFICATION OF SIMULATION MODEL ........................................................................... 46

IV. **RESULTS AND DISCUSSIONS** .......................................................................................................................... 47  
    INTRODUCTION ............................................................................................................................................... 47  
    RESULTS FOR DIRECT ELECTRODE STIMULATION CASE ........................................................................... 47  
    RESULTS FOR INDIRECT, SALINE-BATH STIMULATION CASE ...... 63  
    RESULTS FOR ELECTROMAGNETIC STIMULATION CASES............................................................................ 68

V. **CONCLUSIONS AND FUTURE WORK** .......................................................................................................................... 77  
    SUMMARIZING CONCLUSIONS ........................................................................................................................... 77  
    SUGGESTIONS FOR POSSIBLE FUTURE WORK ................................................................................................. 80

REFERENCES ........................................................................................................................................................................ 82

VITA ......................................................................................................................................................................................... 89
LIST OF FIGURES

Fig. 2. 1 The major components of a neuron [22]. ................................................................. 7
Fig. 2. 2 A patch of membrane of an excitable cell at rest with part of the surrounding
intracellular and extracellular media [22]............................................................................... 8
Fig. 2. 3 The electrical network equivalent of a myelinated nerve fiber [24].................. 10
Fig. 3. 1 Electrical model of a myelinated nerve fiber.................................................. 20
Fig. 3. 2 The setup used for the direct-contact, electrode-stimulation experiments........ 24
Fig. 3. 3 An example of the fully trimmed body of a frog gastrocnemius muscle. ........ 24
Fig. 3. 4 Schematic of the geometry used for the direct contact simulations................. 26
Fig. 3. 5 Close-up view of a frog gastrocnemius muscle in the bath.................................. 30
Fig. 3. 6 Schematic of the geometry used for the electromagnetic simulations............... 33
Fig. 3. 7 Position of the electric and magnetic field components about a cubic unit cell of
the Yee space lattice [39].................................................................................................. 35
Fig. 3. 8 Upper-right part of a computational domain surrounded by the PML layer..... 41
Fig. 4. 1 Time-evolution of potential across a line parallel to the y-axis (at x = 0.5 cm) on
the z = 0 surface for the 5.8 ns pulse................................................................................. 48
Fig. 4. 2 Time-evolution of potential across a line parallel to the y-axis on the z = 0.081
cm surface for the 5.8 ns pulse........................................................................................ 48
Fig. 4. 3 Snapshot of potential at 0.4 ns across the z = 0 cm surface.......................... 49
Fig. 4. 4 Snapshot of potential at 0.3944 ns across the z = 0.325 cm surface........... 49
Fig. 4. 5 Temperature distribution across at the top surface......................................... 50
Fig. 4. 6 Time-evolution of the "activation function" across line parallel to the y-axis (at
x = 0.5 cm) on the z = 0 surface.................................................................................... 51
Fig. 4. 7 Time-dependent circuit current for the 5 kV pulse............................................. 51

Fig. 4. 8 Comparison between the S-D curve (circles) measured at Brooks City-Base [7] and the calculated S-D line................................................................. 53

Fig. 4. 9 Simulated results for the S-D curves obtained from numerical simulations for muscle stimulation by pulses with different shapes............................................ 55

Fig. 4. 10 Time-evolution of membrane potential along the fiber parallel to the y-axis (at x = 5 mm) on the z = 0.81 mm surface for the 1 ns trapezoidal pulse................................. 55

Fig. 4. 11 Simulated S-D curves for muscle stimulation for different electrode separations...................................................................................................................... 57

Fig. 4. 12 Simulated S-D curves for muscle stimulation for different electrodes positions.................................................................................................................. 57

Fig. 4. 13 Comparison between the potential distribution across z = 0.081 cm surface for Anode-Cathode (AC) scheme and Anode-Cathode-Anode (ACA) scheme........... 59

Fig. 4. 14 Comparison between the time evolution of membrane potential for: (a) the Anode-Cathode scheme, and (b) the Anode-Cathode-Anode scheme......................... 60

Fig. 4. 15 Comparison between the simulated S-D curves for Anode-Cathode (AC) scheme and Anode-Cathode-Anode (ACA) scheme............................................. 61

Fig. 4. 16 Comparison between the simulated S-D curves for Anode-Cathode-Anode schemes with different electrode separation................................................. 62

Fig. 4. 17 Experimental S-D curves for direct (electrode contact) and indirect (bath) excitation................................................................................................................. 64

Fig. 4. 18 Simulated S-D curves obtained from numerical simulations for muscle stimulation in the saline-filled bath................................................................. 65
Fig. 4. 19 Simulated S-D curves with radial non-uniformities for low impedance termination. The data point [7] also is shown................................. 67

Fig. 4. 20 Simulated S-D curves with radial non-uniformities for high impedance termination. The data point [7] also is shown................................. 67

Fig. 4. 21 Electric field at the source point and observation points with different distances from the source. .......................................................... 69

Fig. 4. 22 Snapshot of $E_y$ across the surface $y = 40$ mm at 0.05 ns for vacuum case...... 70

Fig. 4. 23 Snapshot of $E_y$ across the surface $y = 40$ mm at 0.053 ns for vacuum case...... 70

Fig. 4. 24 Snapshot of $E_y$ across the surface $y = 40$ mm at 0.059 ns for vacuum case..... 71

Fig. 4. 25 Snapshot of $E_y$ across the surface $y = 40$ mm at 0.075 ns for vacuum case..... 71

Fig. 4. 26 Electric field at the source point and observation points with different distances from the source. .......................................................... 72

Fig. 4. 27 Snapshot of $E_y$ across the whole surface $z = 42$ mm (a); and snapshot of $E_y$ in the muscle region at 0.96 ns (b) for scattering case................................. 74

Fig. 4. 28 Snapshot of $E_y$ in the muscle region across the surface $z = 42$ mm at a time of 0.19 ns................................................................. 75

Fig. 4. 29 Snapshot of $E_y$ in the muscle region across the surface $z = 42$ mm at time = 0.39 ns................................................................. 75

Fig. 4. 30 Snapshot of $E_y$ in the muscle region across the surface $z = 42$ mm at time = 0.48 ns................................................................. 76
CHAPTER I

INTRODUCTION

1.1 Nerve Stimulation

Nerve excitation, which has been used to stimulate both the central and the peripheral nervous system, has a variety of potential diagnostic and therapeutic applications [1-3]. For example, it is used in implantable devices for neuromuscular stimulation. These devices are designed to control the contraction of paralyzed skeletal muscles, thereby producing functional movements in patients with stroke and spinal cord injuries [4,5]. Electrical excitation is also a useful tool in studying the properties and functions of nerves and muscles. It can provide information on the strength-duration (S-D) characteristics, and quantitative details of the charging time constants. Tissue excitation with ultra-short pulses is also an important issue for health and safety assessment of ultrawideband (UWB) sources, which produce nanosecond pulses. Thus, the military, as well as organizations involved in high-power electrical machinery, have a particular interest in studying and understanding such biological stimulation. This issue is discussed at length in [6], [7].

In general, muscle excitation can be achieved either remotely through the principle of electromagnetic induction [8-10], or directly through electrical contact [11]. In the simplest means of stimulation, two wire electrodes are directly applied on the muscle surface, and pulses of electrical current are passed between the electrodes. Motor

* Model followed: IEEE Transactions on Plasma Sciences
nerve fibers within the muscle are then excited as the result of a potential created within the muscle by the external source. This is called Transcutaneous Electrical Nerve Stimulation (TENS). The requirements for efficient and trouble-free stimulation can be understood on the basis of Ohm’s Law, combined with elementary physiology.

Historically, an important goal of electro-stimulation studies has been to seek a description and an understanding of the S-D curve. This curve plots the threshold voltage (or current) necessary for the onset of muscular “twitching” as a function of the duration of the externally applied pulse. The classic principles of electrical stimulation are (1) “all-or-none”, referring to an inherent threshold effect for twitching, and (2) “graded” response that refers to the principle that once a critical threshold is exceeded, the muscular force produced increases with stimulus magnitude, up to some maximum value. However, the current biological research program, discussed in this thesis, focuses exclusively on determining threshold for tissue twitching; it does not measure the graded aspects of supra-threshold stimulation. Thus, this modeling effort makes no effort to address the complex process excitation, subsequent coupling, and muscular contraction.

1.2 Advantages of Ultrashort Pulses

Formulations for expressing S-D curves have been well developed for a century, starting with the work of Weiss [12], Lapicque [13] and Blair [14]. Historically, pulse durations of 10 μs to 10 ms have been used most frequently for the biological tissue excitation. However, in recent years, with developmental advances in pulsed power engineering, shorter pulses are being examined [15]. It is now possible to generate and apply pulses to biological samples with time durations approaching 1 nanosecond. Such
ultra-short pulsed excitation is a relatively emerging field, and has not been studied in the context of tissue excitation.

The use of ultra-short pulsed excitation can potentially be advantageous for the following reasons [16]: (i) It induces negligible thermal heating, thereby reducing trauma to the body, (ii) it facilitates the creation of large capacitive currents at low energy input levels, (iii) one has the possibility of selecting time scales that are on the order of, or even smaller than, the inherent time constants for nerves, (iv) the ability to fine-tune and optimize the bio-response through pulse width and pulse-shape manipulations, and (v) the ability to penetrate the outer (plasma) membrane, and create large transmembrane potentials across sub-cellular organelles [17]. Thus, for example, triggering of neurotransmitter or calcium release is possible through the use of ultra-short pulses [18]. It is also possible that the use of this new technology to study sub-microsecond pulsed excitations of tissues might reveal new biological phenomena.

1.3 Overview of Thesis Objectives

This thesis focuses on the electro-stimulation of frog muscle tissue. Calculations of the microscopic currents and membrane-level voltage distributions have been carried out, since these electrical parameters provide for the excitation stimulus. Simulations of electrically triggered events at the cellular level are given in other published reports by this group [19-21]. The modeling studies on nerve stimulation described here in the thesis had the following objectives:

(i) Develop a mathematical model to predict S-D curves for electro-stimulation in the sub-microsecond regime.
(ii) Compare the theoretical predictions with available experimentally measured S-D curves

(iii) Determine the roles of pulse shape, electrode position, and electrode separation in electrical nerve simulation. Such information was to be used for developing efficient electrode stimulation schemes.

(iv) Contrast the muscle twitching thresholds observed with direct electrode stimulation with those produced by indirect excitation with the tissue immersed in a saline-filled bath. An additional goal was to determine the role of nerve non-uniformity and inhomogeneity on the S-D curves.

(v) Finally, evaluate the possibility of electromagnetic wave propagation within the muscle bulk for purposes of investigating the possibility of remote electromagnetic bio-stimulation.

In particular, this thesis work on nerve excitation will mainly concentrate on electrical excitation, which has been attracting more attention and appears to be quite promising for non-lethal applications. The nerve model demonstrates that non-uniformities of both the nerve fiber and current distribution can substantially lower the excitation threshold. This is suggestive of preferential locations for maximal excitability responses. It will also be shown that indirect excitation based on applying surface electrodes to a conductive medium containing an immersed muscle preparation can produce a significant bio-response. Details of the S-D curves for such indirect excitation have been probed, and it is demonstrated that the characteristics shift to higher voltages. The role of serial resistance associated with the saline solution, and changes from
relatively sharp contacts to flat, large-area surface electrodes have been investigated through numerical simulations. As an extension, electromagnetic nerve excitation has also been studied.

Chapter 2 provides a literature review of the research work done in the area of electrically triggered, neural excitability. Previous research and published results from experiments and simulations are introduced as the background for this thesis. In chapter 3, details of the theory and numerical simulation, as well as related experimental work are described. This chapter includes a discussion of various important aspects, such as the Neal nerve model, Neumann boundary conditions for zero net current flow, Finite-Difference Time-Domain (FDTD) numerical technique, and other related theoretical issues. Chapter 4 gives the main results obtained for various simulation cases. These include TENS, frog muscles immersed in a saline-filled bath, and remote electromagnetic stimulation. The roles of pulse shape, electrode placement are studied as well, based on which an “Anode-Cathode-Anode (ACA)” electrode scheme is suggested for maximally excitable responses. Finally, a summary of simulation results, followed by suggestions for possible future work, is discussed in Chapter 5.
2.1 Activation of Nerve Fiber

The nerve cell may be divided on the basis of its structure and function into three main parts: (1) the cell body, also called the soma; (2) numerous short processes of the soma, called the dendrites; and (3) the single long nerve fiber, the axon [22]. The structure is shown schematically in Fig. 2.1. The body of a nerve cell is similar to that of all other cells. The cell body generally includes the nucleus, mitochondria, endoplasmic reticulum, ribosomes, and other organelles. The short processes of the cell body, the dendrites, receive impulses from other cells and transfer them to the cell body. For nerve excitation, extensive attention needs to be focused on the axon.

The long nerve fiber, the axon, transfers the signal from the cell body to another nerve or to a muscle cell. Mammalian axons are usually about 1 - 20 µm in diameter. Some axons in larger animals may be several meters in length. The axon may be covered with an insulating layer called the myelin sheath, which is formed by Schwann cells (named for the German physiologist Theodor Schwann, 1810-1882, who first observed the myelin sheath in 1838). The myelin sheath is not continuous but divided into sections, separated at regular intervals by the nodes of Ranvier (named for the French anatomist Louis Antoine Ranvier, 1834-1922, who observed them in 1878).
The cell is enclosed by a cell membrane whose thickness is about 7.5 - 10.0 nm. Fig. 2.2 depicts a small portion of a cell membrane of a nerve cell. The membrane element shown is described as a patch. The significant ions are potassium (K⁺), sodium (Na⁺), and chloride (Cl⁻), but it shall be assumed that the membrane is permeable only to one of them (say, potassium), which is denoted as the $K^+$ ion, to allow later generalization. The ion concentrations on each side of the membrane are also illustrated schematically in Fig. 2.2. At the sides of the figure, the sizes of the symbols are given in proportion to the corresponding ion concentrations. The ions are shown to cross the membrane through channels, as noted above. The number of ions flowing through an open channel may be more than $10^6$ per second.

It turns out that this is a reasonable approximation to actual conditions at rest. The concentration of potassium is normally around 30 - 50 times greater in the intracellular space compared to the extracellular. As a consequence, potassium ions diffuse outward
across the cell membrane, leaving behind an equal number of negative ions (mainly chloride). Because of the strong electrostatic attraction, as the potassium efflux takes place, the potassium ions accumulate on the outside of the membrane. Simultaneously, an equal number of chloride ions (left behind from the KCl) accumulate on the inside of the membrane. In effect, the membrane capacitance is in the process of charging, and an electric field directed inward increasingly develops in proportion to the net potassium efflux.

Fig. 2. A patch of membrane of an excitable cell at rest with part of the surrounding intracellular and extracellular media [22]. (The ions and the membrane not shown in scale.)
The process described above does not continue indefinitely because the increasing electric field produces a force on the permeable potassium ion that is directed inward and, hence, is opposite to the diffusional force. An equilibrium is eventually reached when the two forces become equal in magnitude. The transmembrane potential achieved at equilibrium is called the resting potential [23]. The number of potassium ions required to cross the membrane to bring this about is ordinarily extremely small compared to the number available. Therefore, in the above process, for all practical purposes, one may consider the intracellular and extracellular concentrations of the potassium ion as unchanging throughout the entire transient process.

The concentration of sodium ions (Na⁺) is about 10 times higher outside the membrane than inside, whereas the concentration of the potassium (K⁺) ions is about 30 times higher inside as compared to the outside. When the membrane is stimulated so that the transmembrane potential rises by about 20 mV - that is, when the membrane voltage changes from -70 mV to about -50 mV - and reaches the threshold. The sodium and potassium ionic permeabilities of the membrane change. The sodium ion permeability increases very rapidly at first, allowing sodium ions to flow from outside to inside, making the inside more positive. The inside reaches a potential of about +20 mV. After that, the more slowly increasing potassium ion permeability allows potassium ions to flow from inside to outside, thus returning the intracellular potential to its resting value. The maximum excursion of the membrane voltage during activation is about 100 mV; the duration of the nerve impulse is around 1 ms. While at rest, following activation, the Na-K pump restores the ion concentrations inside and outside the membrane to their original values.
2.2 Models for Excitation of Myelinated Nerve

Many models have been presented in the literature that relate the membrane potential to the transverse membrane current. These also describe the propagation of action potentials along the myelinated fibers. Among them, McNeal’s model [24] was the first efficient model to compute the reaction of an axon stimulated by extracellular electrodes.

In practice, extracellular electrodes and electromagnetic sources produce electrical fields outside the nerve fibers. McNeal’s model (Fig. 2.3) allows one to compute the threshold of a nerve fiber for pulses of finite duration using electrodes that are not in direct contact with the fiber.

Fig. 2.3 The electrical network equivalent of a myelinated nerve fiber [24].

McNeal assumed that the fiber is infinitely long with nodes regularly spaced. Discretization of the axon’s length coordinate allows simulation of the excitation by a
system of differential equations in time and in space. For myelinated fibers, this segmentation is naturally given by the nodes of Ranvier, whereas unmyelinated axons can be segmented arbitrarily. Every segment is represented by an electric circuit. It is assumed that the myelinated sheath is a perfect insulator, and the nodal membrane is modeled by a capacitor $C_m$ and a conductance $G_m$ in parallel. The nodal gap width is considered to be a constant for all fiber diameters as theoretically predicted by Rushton [25] and Dun [26].

In Fig. 2.3 it is assumed that transmembrane current is confined solely to the nodal region. Experimental work, summarized by Chiu and Ritchie [27], has shown that in the mammalian nerve fiber the potassium channels are found in the internodal axolemma. This appears to introduce quantitative but not qualitative differences in the simpler nerve model of McNeal. Here, we shall continue to utilize the latter for its simplicity and qualitatively adequate character.

It may be pointed out that the above model assumes a linear conductance $C_m$ across the membrane, and applies as long as the transmembrane potentials are not too large, e.g., the analysis is certainly applicable in the sub-threshold regime. For larger potentials, the ionic currents would need to be described by complicated differential equations. These are the Hodgkin-Huxley expression [28] for the unmyelinated case and the Frankenhaeuser-Huxley [23] equation for the myelinated case. More sophisticated modifications have also been proposed for myelinated nerves [29], [30]. Here, however, since we are interested in the thresholds as a function of pulse widths, the non-Ohmic aspects have justifiably been ignored.
The concept of a "bi-domain" can be implemented. The external potential $V_{e,n}$ and internal potential $V_{i,n}$ have different amplitudes, but they are at the same spatial point, node n. For a given geometry of the extracellular medium (usually a muscle bulk), the active regions of the axons are determined by purely geometrical considerations that can be extended to inhomogeneous external media [31]. A method based on differential equations discretized in the coordinate along the axon can be used to calculate threshold and superthreshold behavior of myelinated axons. The discretization length $\Delta x$ is given by internodal distance $\lambda$. An axon can also change the extracellular potential by its own activity, but only below 1.0 mV, whereas the intracellular contribution of voltage is much higher [32].

Starting from an unexcited condition, the influence of the externally applied electrical field on each of the segments is given by the activating function $f$ [31], [33], [11]. For equal segments, $f$ is the second spatial difference quotient of the extracellular potential $V_e$ alone the fiber ($f= V_{e,n+1} + V_{e,n-1} - 2V_{e,n})/\Delta x^2$). Ratty showed that the activating function embodies the following points. (1). In general, stimulation by anodic currents needs stronger impulses than that by cathodic currents. (2). Stimulation with strong cathodic signals can lead to a blockade of the action potential (cathodic block) [34].

One significant limitation of the models mentioned above is their restriction to "infinitely long" fibers. In actual simulations, some boundary condition is necessary since no numerical simulation can model an infinitely long fiber. In a numerical simulation of the cochlear implantation, Colombo and Parkins [35] applied physical intuition to the end-condition. "To simulate the end of a neuron, a node is chosen to be the terminal
node. Since all nodes to one side of the terminal node are no longer modeled, their contributions...are deleted from the model’s calculation” [35]. This is essentially an assumption that the end-condition requires the longitudinal intracellular current to be zero. Reilly and Bauer also made this assumption [36]. This end-condition applies well only for a fiber whose length is large relative to the distance separating it from the electrode. In the usual applications of electrical stimulation to regions such as the spiral ganglion or cerebral cortex, this condition does not apply, and it is necessary to consider the termination condition of fibers in the field of a focal electrode.

Axon termination conditions for extracellular stimulation, were investigated by Rubinstein [37]. Instead of assuming a “sealed end”, he took the membrane impedance of termination into consideration. He concluded that effects of the termination impedance of an axon were determined by the termination current, which in turn, was determined by the ratio of the axon’s input impedance to the termination impedance. The larger the ratio, the less effectively was the fiber “sealed” [37]. For a myelinated fiber terminating in a nodal membrane, the unsealed situation appeared to apply. A termination current was found to significantly change the terminal membrane potential, but did not have any significant influence beyond two or three length constants from the terminal.

2.3 Stimulation Mechanisms

Nerve fibers can be stimulated by a number of mechanisms. In the most efficient method, an intracellular microelectrode or whole-cell patch pipette, injects current directly into the cell. However, extracellular stimulation has more significance in the present application and is attracting greater attention. Stimulation with external electrodes
is much less efficient because most of the stimulus current is effectively wasted through flows into the shunt resistance $R_o$. A variety of methods were used to increase the efficiency, primarily by increasing $R_o$. In the specialized grease-gap and sucrose-gap methods, an insulating substance replaced most of the extracellular fluid between the electrodes [17].

For extracellular stimulation, three electrode arrangements may be distinguished: (a) Bipolar: In this case, both the electrodes are close to the nerve. (b) Monopolar: In this case, one electrode (normally the anode), is remote from the nerve. (c) Field stimulation: Here, both electrodes are remote from the nerves. Surface electrodes on the skin, intramuscular electrodes, and cuff electrodes around a nerve are most commonly used in electrical stimulation.

Most of the important principles can be derived from considerations of an arrangement involving two wire electrodes applied to the surface of the extracellular fluid. During the stimulus, a constant current $I$ flows between the electrodes. Complete analysis of such a situation requires a detailed mathematical description of the cable properties of the axon. This has been carried out and explained in detail by Hodgkin and Rushton for a crustacean nerve fiber [38].

Interest in neural excitation using the principle of electromagnetic induction has grown since its utility and potential capabilities have been demonstrated [8], [9], [10]. Since the same nerve model is used for both electromagnetic and electrical stimulation, difference only lies in the methods to calculate the extracellular potential. More precisely, the activating function at each time step is different. Instead of Neumann boundary conditions of zero net current flow used in electrical stimulation, the numerical
technique developed for the analysis of open electromagnetic components is based on the Finite-Difference Time-Domain (FDTD) method and absorbing boundary conditions (ABC). The FDTD algorithm is used for the calculation of electric and magnetic fields inside a pre-defined computational volume, which is divided into cells. Maxwell's equations are solved for every cell at each time step. Near-to-far field transformation modules can be used to obtain the radiated field directly in the time domain [39]. Absorbing boundary conditions were developed to simulate the open free space outside the computational volume, which reduce the numerical wave reflection dramatically [40], [41].

Numerical calculation for full-wave analysis of a structure using the FDTD method could be very time consuming and computationally intensive. Asi and Shafai developed a compact 2D FDTD technique, which calculated the electromagnetic components along two directions numerically, and those on the third direction analytically [42], [43]. However, this technique is difficult to implement for nerve stimulation because it requires the length on one direction to be infinitely long [44]. The full wave analysis is still the preferred route. In 1994, Berenger introduced a perfectly matched layer (PML) to simulate the near-complete absorption of electromagnetic waves [45], and implemented it for a three-dimensional space [46]. This absorbing boundary condition (ABC), called Berenger's PML, has been followed and developed extensively in numerous FDTD implementations [40].

Modeling magnetic stimulation of nerves can be performed in a combination of three steps. The first step involves calculation of the spatial distribution of the induced electric fields produced by a magnetic coil. This is achieved using electromagnetic field
analysis. The second step involves calculations of the temporal distributions of the stimulus fields from a transient analysis of the current sources of the stimulator. The third step is to model the neuronal structures. These three steps are then combined to examine the interaction of the induced fields with neuronal structures [8]. Such models have provided a general framework for understanding and predicting some of the mechanisms of magnetic stimulation. However, the model of Basser and Roth [10] has only analyzed infinitely long unmyelinated and myelinated axons. In such analysis of neuronal structures, an infinite cable is useful for the peripheral nervous system and is justified by the presence of long axons in comparison to the dimensions of the coils. However, in the case of the central nervous system, such analysis would be inappropriate because of the short axon dimensions relative to the coils used, and also because of the bending, branching or termination of axons on boutons or cell bodies. Therefore, finite lengths of the neuronal structures are usually simulated. The effects of both the spatial and temporal distributions of induced fields on finite neuronal structures have been analyzed [47]. The analysis used models of neuronal structures like myelinated axons and cellular dendritic structures, and yielded the following conclusions. First, during magnetic stimulation of finite length neuronal structure, the role of both the field gradient driving function and the boundary field driving function must be considered to predict excitation sites and threshold intensities. Second, spatial localization of the induced electric fields can decrease threshold strengths for long axons of the peripheral nervous system, but would not help during magnetic stimulation of the central nervous system with short axons and cellular dendritic structures. Finally, and most important of all, neuronal structures which
are small compared to the dimensions of the stimulation coil are most likely to be excited at the termination.

In recent years, with developmental advances in pulsed power engineering, shorter pulses are being examined [15]. It is now possible to generate and apply pulses to biological samples with time durations approaching 1 nanosecond. The use of ultra-short pulsed excitation can potentially be advantageous for several reasons [16]. These include the ability to penetrate the outer (plasma) membrane -- without affecting it -- thereby create large trans-membrane potentials across sub-cellular organelles [48]. It is possible that the use of this new technology to study sub-microsecond pulse widths might reveal new biological phenomena [7], [6]. Given the advantages and potential for such ultra-short pulses, a modeling study has been carried out here in this relatively emerging field. The details and related discussions are given in the following chapters.
CHAPTER III

SIMULATION MODEL AND APPROACH

3.1 Introduction

Nerve fibers can be excited by various mechanisms. However, the propagation of neural activities in an axon is eventually a consequence of the electric properties of the membrane. The modeling approach discussed in this chapter can be used to describe the response of the nerve to electric field that arise from charge redistribution (electrical stimulation) and from time-varying electromagnetic fields (EMAG stimulation). In electrical stimulation, time-dependent, three-dimensional analysis was developed and implemented for two cases: (1) electrodes are directly applied onto the skin or muscle surface (2) the tissue is immersed in a saline-bath without electrodes contact. Finally, the water is replaced by vacuum and EMAG simulation is carried out.

3.2 Neural Modeling

Theoretical modeling of nerve stimulation is essential to interpreting and understanding experimental studies of the neural system, and can also provide a quantitative tool for electrode design or parameters measurement, which could be expensive or even impossible in experiments. The stimulation model is developed for a nerve fiber in a bulk of muscle and consists of two main parts. The first part calculates the potentials induced in the muscle region by the externally applied source based on the electrode geometry and configuration. This potential can be obtained analytically only for
simple geometries, but needs numerical computations in general, especially if the temporal dependence is to be included [37]. This potential across the muscle provides the source term for neural excitation. It is assumed that the electrical potential outside the fiber is determined only by the stimulus voltage, tissue outside the nerve fiber and the electrode geometry, and is not distorted by the fiber. The evidence of this assumption will be discussed in details later in this chapter. The second part is to use the excitation potentials within the muscle to determine the response of nerve fibers based on a distributed transmission-line type equation. Since the excitation is a consequence of the electric properties of the membrane, simulation requires adequate membrane models describing the characteristic behavior in the active parts of the fiber, in order to predict the fiber responses to arbitrary applied electrical fields. The nerve fibers can be short or long, straight or curved, and uniform or nonuniform. We begin with the simplest case—the long, straight, uniform peripheral fiber, which is activated by the gradient of the electrical field that is oriented parallel to the fiber axis. The McNeal model for such a fiber, as first discussed by McNeal [24] and then Rattay [31], can be represented by equivalent network shown in Fig. 3.1.

The membrane at a node of Ranvier is approximated by a parallel capacitor $C_m$, and a resistor $R_m$ network, with a voltage source $V_r$ representing the membrane resting potential. The axonal plasma between two nodes is modeled by a resistance $R_i$. And the myelin sheath is regarded as a perfect insulator. $V_{e,n}$ and $V_{i,n}$ are the external and internal potentials at node $n$, respectively. The deviation from $V_r$ of the membrane potential $V_n$, as called transmembrane potential at node $n$, is defined by $V_n = V_{e,n} - V_{i,n} - V_r$, $V_{e,n}$, which is initialized as zero.
Fig. 3. 1 Electrical model of a myelinated nerve fiber.

TABLE I.
Variables and Constants

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_r$</td>
<td>membrane resting potential</td>
</tr>
<tr>
<td>$C_m$</td>
<td>nodal capacitance</td>
</tr>
<tr>
<td>$R_m$</td>
<td>nodal resistance</td>
</tr>
<tr>
<td>$R_i$</td>
<td>axial internodal resistance</td>
</tr>
<tr>
<td>$R_{e,n}$</td>
<td>external potential at node n</td>
</tr>
<tr>
<td>$V_{i,n}$</td>
<td>internal potential at node n</td>
</tr>
<tr>
<td>$V_n$</td>
<td>deviation from $V_r$ of the membrane potential $V_n$</td>
</tr>
<tr>
<td>$V_{\text{thresh}}$</td>
<td>threshold potential for activation of the nodal membrane</td>
</tr>
<tr>
<td>$T$</td>
<td>duration of the stimulus pulses</td>
</tr>
<tr>
<td>$r$</td>
<td>radius of a nerve fiber</td>
</tr>
<tr>
<td>$L$</td>
<td>internodal distance</td>
</tr>
<tr>
<td>$W$</td>
<td>nodal space</td>
</tr>
<tr>
<td>$V_{i,j,k}$</td>
<td>potential at the grid (i, j, k) in a three-dimensional mesh</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>conductivity of the frog gastrocnemius muscle</td>
</tr>
<tr>
<td>$K_r$</td>
<td>relative permittivity of the frog gastrocnemius muscle</td>
</tr>
<tr>
<td>$\sigma'$</td>
<td>conductivity of the ringer solution</td>
</tr>
<tr>
<td>$K_r'$</td>
<td>relative permittivity of the ringer solution</td>
</tr>
</tbody>
</table>
Table I. shows the variables and constants involved in the simulation, which also includes the parameters of the frog gastrocnemius muscle and the Ringer solution in indirect nerve stimulation.

It is assumed that the nodes are regularly spaced with an internodal distance of $L$, and the nodal gap width is considered to be a constant [49]. This model also assumes that the electrical potential outside the fiber is determined solely by the stimulus voltage, tissue outside the nerve fiber and the electrode geometry, and is not distorted by the fiber. This is reasonable because the dimensions of a single fiber are much smaller compared to the muscle, and what’s more, our interest is limited to the period of time prior to excitation (before the internally generated currents becoming significant). The small dimension of the fiber also allows the simplification that the external surface at any point is equipotential, which implies that the variations in the membrane current density over the nodal surface are neglected. With this assumption, the surface of any node is equipotential to $V_{e,n}$, which is defined to be external potential at node $n$, but calculated without consideration to existence of the fiber. There will of course be some variation in potential over the nodal surface due to the finite size of the fiber. This variation is not easy to calculated because of the distortion of the external field in the neighborhood of the fiber; however, the potential over the nodal surface will not differ significantly from $V_{e,n}$, --at least in comparison with the difference in potential between node $n$ and its neighbors since the nodal length is much smaller that the internodal distance $l$. ($<l/100$).

Using $V_n = V_{l,n} - V_{e,n} - V_e$, the following differential equation can be obtained based on the equivalent electrical network shown in Fig.3.1 [11,24,31,50]:

$$
(V_{n-1} + V_{n+1} - 2V_n) + (V_{e,n-1} + V_{e,n+1} - 2V_{e,n}) = R_i C_m \frac{dV_n}{dt} + \frac{R_l}{R_m} V_n.
$$ (3.1)
An analysis of the above equation for a short, rectangular pulse of duration $T$ shows that the change in membrane potential $V_n$ at node $n$ is given by:

$$
\Delta V_n = \frac{T}{RC_m} (V_{e,n+1} + V_{e,n} - 2V_{e,n}).
$$

(3.2)

provided $T < R_i C_m$ and $T < R_m C_m$. Typically, a node is excited when it surpasses a threshold depolarizing shift of $\sim 20$ mV. The values of $R_i$ and $C_m$ are roughly constant for all fibers [24], and so for a given pulse duration $T$, the threshold condition is completely determined by the $V_{e,n+1} + V_{e,n} - 2V_{e,n}$ term. This term is often referred to as the activating function of the fiber [31]. More generally, in a nerve bundle along the $z$-direction in a potential $V(x,y,z,t)$, the activating function $f(x,y,z,l,t)$ of a fiber with node at $(x,y,z)$ and with internodal distance $l$ is given by:

$$
f(x,y,z,t) = V(x,y,z-l,t) + V(x,y,z+l,t) - 2V(x,y,z,t).
$$

(3.3)

Thus, if the excitation function $V_e(x,y,z,t)$ can be determined from an external potential calculation step, then the activation function and the threshold for twitching can be obtained. It may be pointed out that strictly, the above equation assumes a linear conductance $R_m$ across the membrane, and applies as long as the transmembrane potentials are not too large, e.g., the analysis is certainly applicable in the sub-threshold regime. For larger potentials, the ionic currents would need to be described by complicated differential equations, which are the Hodgkin-Huxley expression [27] for the unmyelinated case and the Frankenhaeuser-Huxley [23] equation for the myelinated case.
More sophisticated modifications have also been proposed for myelinated nerves [29]. Here, however, since we are interested in the thresholds as a function of pulse widths, the non-Ohmic aspects have justifiably been ignored.

3.3 Electrical Nerve Simulation

A three-dimensional, time-dependent model has been developed and applied to predict the electro-stimulation in frog muscles under two different situations. Frog muscles were chosen because of the availability of actual experimental data from Brooks City Base for comparison. Here, the S-D curves have been obtained from the model for two cases: (i) one involving direct electrode contact placement on the frog leg, and (ii) a second situation involving indirect excitation with the tissue immersed in a saline-bath.

3.2.1 Case for Simulation Via Direct Electrode Contact

The experimental set up for direct electrode contact on the frog muscle is shown in Fig. 3.2. The geometry and dimensions of the typical frog gastrocnemius muscles used in the experimental work are shown in Fig. 3.3. The shape of the muscle, without tendons, resembles a tapered cylinder (Fig. 3). This gastrocnemius was 35 mm in length. The muscles had a mean length of 32.4 mm (coefficient of variation, CV = 17%) and a mean weight of 0.928 gm (CV = 37%). Additional information on all aspects of experimental methods is given in Rogers et al. [7]. Two wire contacts, 9 mm apart, were placed across the bottom surface.
Fig. 3.2 The setup used for the direct-contact, electrode-stimulation experiments. The gold-plated electrodes are 1 mm in diameter and placed 9 mm apart. The frog gastrocnemius muscle, which was under a standard load of 9.82 gm, rested on top of the electrodes.

Fig. 3.3 An example of the fully trimmed body of a frog gastrocnemius muscle.
The two-step approach discussed above was used to model the tissue response to external electrical stimulation. First, assuming the fiber is not present, the excitation voltage $V_{e,n}(x,y,z,t)$ is calculated within the tissue at each time step. This was based on a finite difference scheme involving the discretization of the entire simulation volume into a distributed array of elemental cubic sub-regions in Cartesian co-ordinates, with a size of $dx*dy*dz$. For flexibility, the grid has nonuniform space increments, i.e. $dx!\neq dy!\neq dz$, even though the muscle is uniformly divided in each direction. This is especially helpful to reduce CPU time and memory space when the property we concern is more sensitive to the distance on a particular direction, because we can make the increment small enough to satisfy the accuracy only on this direction without increasing the size of the whole lattice significantly. Since our interest is focused on the nodes, the active parts equally spaced with a distance of $L$, the potential at each nodes are desired. So on the direction along which the fiber is oriented, the spatial increment should be specified as $l/N$, ($N=1, 2, 3...$). Each element was represented by a parallel resistor-capacitor combination to account for both the conduction and displacement current flows within the bio-system. In essence, a distributed R-C network, inter-connected to six nearest neighbors, was used for the electrical representation of the muscle (or muscle and saline-bath) systems.

For simplicity and computational ease, the geometry was approximated to a homogeneous slab for computing $V_{e,n}(x,y,z,t)$. Since nerves are embedded within the muscle tissue and are activated by electric fields within the bulk, this slight deviation from the actual surface geometry is not expected to be significant. Also, the volume of the nerves relative to the overall tissue is very small, so negligible errors are expected in
assuming a homogeneous muscle medium for purposes of the $V_{e,n}(x,y,z,t)$ calculation. A schematic of a simplified, yet roughly equivalent geometry for the 3D implementation is shown in Figure 3.4. The dimensions are also given. In Fig. 3.4, the x-, y- and z-axis dimensions were: 1.0 cm, 3.4 cm, and 0.65 cm, respectively. The applied voltage was through the two wires placed at the $z = 0$ surface parallel to the x-axis at $y = 1.25$ cm and $y = 2.15$ cm, respectively. It may also be pointed out that since the local electric fields and current densities were calculated at each time step, the simulation procedure allowed for the evaluation of internal power dissipation and local temperature increases within the tissue.

![Schematic diagram](image)

Fig. 3.4 Schematic of the geometry used for the direct contact simulations.
A pair of stripes representing the two wire contacts were imposed across one face to fix the electric boundary condition. These were representative of the electrode geometry used in actual experiments. The applied voltage was taken to be a user specified input parameter for the numerical solution. Neumann boundary conditions of zero net current flow were applied on all other boundary regions that did not contain the electrodes. For simplicity, the passive R-C elements were chosen to be linear, and hence, had voltage and current independent values based simply on the muscle conductivity ($\delta$) and relative permittivity ($Kr$). Based on the available data for frog muscles, $\delta = 1.29 \text{ S/m}$ and $Kr = 80$ were used. Thus Neumann boundary conditions of zero net current flow can be written as:

$$\int_{S}(\delta \star \vec{E} + \zeta \star \frac{d\vec{E}}{dt})d\vec{s} = 0$$  \hspace{1cm} (3.3)

in which $S$ is the surface of cubic element, $\vec{E}$ the electrical field pointing to the element and $\zeta = Kr \star \frac{\zeta}{\rho_0}$.

In a three-dimensional mesh, the potential at the node $(i, j, k)$ is represented as $V_{i, j, k}$. Application of current continuity at the node then resulted in a set of coupled equations for the node voltages. From equation 3.3 we obtain:

\[
\sum_{b \in S} \left[ \frac{V_b - V_{i,j,k}}{R_b} + \frac{[(V_{b}^{t+dt} - V_{i,j,k}^{t+dt}) - (V_{b}^{t} - V_{i,j,k}^{t})]C_b}{dt} \right] = 0
\]

\[
R_b = \frac{d_b}{(A_b \delta)}
\]

\[
C_b = \zeta A_b / d_b
\]
where $S$ includes six adjacent neighbors of node $(i, j, k)$ and $d_b$ and $A_b$ are the distance and cross-sectional area between $(i, j, k)$ and its neighbor $b$, respectively. From above equations, we can eventually get:

$$
[r_{xy}(V_{i-1,j,k} + V_{i+1,j,k} - 2V_{i,j,k}) + (V_{i,j-1,k} + V_{i,j+1,k} - 2V_{i,j,k}) + r_{yz}(V_{i,j,k-1} + V_{i,j,k+1} - 2V_{i,j,k})](1 - \frac{dt}{\tau})
$$

$$
= r_{xy}(V_{i-1,j,k} + V_{i+1,j,k} - 2V_{i,j,k}) + (V_{i,j-1,k} + V_{i,j+1,k} - 2V_{i,j,k}) + r_{yz}(V_{i,j,k-1} + V_{i,j,k+1} - 2V_{i,j,k})
$$

(3.5)

where $r_{xy} = dy^2/dx^2$, $r_{yz} = dy^2/dz^2$ and $\tau = \xi/\delta$. The nodes at the boundary could have less than six neighbors; accordingly, the equation above should be readily modified. For accuracy $dt$ is selected as $\tau/50$.

The voltage source is not ruled by this update equation and its value is fixed by the user specified pulse. With the input pulse, we can update the external potential $V_{i,j,k}$ according to equation (3.5) at each time step. Time dependent values of the potential across each discretized sub-region and current distributions are then directly resulted.

After obtaining the external potential at the fiber nodes as discussed above, we can apply equation (3.1) to calculate the transmembrane potential $V_n$ at each time step. Initially, $V_n = V_{e,n} = 0$ for all $n$. The node, and therefore the corresponding nerve fiber, is excited when $V_n$ surpasses the threshold value $V_{\text{thresh}} (\approx 20mV)$. A twitching of the muscle will be detected when the node gets excited at a time step, e.g. $T$. Change the value of $T$ and calculate the corresponding threshold voltage, the S-D curve can be obtained representing the relationship between the strength $V_{\text{thresh}}$ and the duration $T$.

Equation (3.1) is suitable for pulses with any shapes. However, the stimulation with a short rectangular pulse of duration $T$, imposing the external potential $V_{e,n,T}$ raises
membrane potential at node \( n \) by Equation (3.2). Using the activating function shown in Equation (3.3), the calculation is significantly simplified.

For the direct excitation shown in Fig. 3.2, the contributions of the terminal nodes at the ends are deleted from the McNeal model’s calculation. This is reasonable because with two wire electrodes applied in the middle portion of the fiber, the nonuniformity of the potential distribution is so significant that the excitation always occurs first near the electrodes instead of the terminal. However, the axon termination has to be considered in indirect stimulation through a bath, which will be discussed in details in the following section.

3.2.2 Case for Indirect Excitation Through a Bath

Fig. 3.5 shows actual experimental set-up for the second situation involving indirect excitation with the tissue immersed in a saline-bath. Electrical pulses were applied at the two opposite ends of a rectangular saline-bath system containing a centrally placed frog leg.

The bath electrode consisted of gold-plated electrodes 70 mm apart at each end of a rectangular Plexiglas structure. The interior of the Plexiglas bath measured 21 mm wide by 12 mm deep. The gastrocnemius muscle was suspended at the center of the longitudinal axis, submerged in the Ringer solution. The gastrocnemius muscle has the same conductivity and permittivity as that used in direct stimulation, the Ringer solution as the values \( \sigma^r = 1 \) S/m and \( K^r = 60 \).
Fig. 3. 5 Close-up view of a frog gastrocnemius muscle in the bath. -plated electrodes comprising the ends of the bath are apparent. The Achilles tendon is anchored to a post at the left; the proximal end of the muscle is attached to a wooden shaft going to the force transducer. The muscle is submerged in the Ringer solution.

Again current continuity was used to model and update the node voltages at the boundary. Equation (3.4) is applied in a simulation region that included not just the muscle tissue but also the surrounding saline-filled bath. In the Ringer solution region, $\sigma$ and $K_r$ are replaced by the values of the Ringer solution $\sigma'=1$ S/m and $K_r'=60$. The external potential of the fiber can be resulted. Then the transmembrane potential can be calculated based on McNeal model following similar procedure as direct excitation.

Equation (1) is strictly valid for an infinite medium. In the presence of boundaries and terminations, however, the equation needs to be modified by taking account of a "termination" impedance $Z$ at the ends [37]. This aspect had been ignored in some previous approaches [35,36], wherein all nodes beyond the boundary were deleted from the simulation. This is not physically accurate since in essence, it amounts to an implicit
assumption of zero longitudinal current across the boundary surface. For muscles immersed in a saline-bath, however, the longitudinal currents at the interface between the tissue and the water have to be equal. Here we use current continuity to model and update the node voltages at the boundary. This was made possible by choosing a simulation region that included not just the muscle tissue, but also the surrounding saline-filled bath.

The nerve fiber terminations are expected to be important for initiation of nerve action and subsequent induction of muscle twitching, because the activation function can be expected to undergo much stronger changes at terminations, where the inherent spatial discontinuity is greatest. Predictions of stronger induced fields at the boundaries of finite fibers have been reported [37, 47]. The effect of the terminal is especially important for the indirect excitation (Fig. 3.5), in which the potential distribution over the tissue is very uniform implying a smaller activating function than that in direct excitation (Fig. 3.4).

The results given above apply to straight, uniform fibers. However, in general, nerve fibers can be curved, bent, or non-uniform in cross-section. For example, at the terminus, the nerve fiber radii are the smallest, and increase to a maximum value some distance away from the boundary. Such inhomogeneity is reported to induce electro-stimulation with significantly lower thresholds [51], and is therefore, of interest from a practical standpoint. It also implies that muscle twitching is very likely to be initiated at the boundaries or across other regions where the nerve radii has spatial non-uniformities. Physically, the presence of inhomogeneities alters Equation (3.1) by making the capacitive segments $C_m$ and the resistive elements $R_i$ and $R_m$ spatially dependent functions. As a result, the effective response time constant of the nerve is not fixed, but instead has a distribution about a mean value. Specifically, since the nodes are regularly
spaced and the nodal gap width is considered to be a constant for all axon diameters which implies that the nodal membrane area is proportional to the axon diameter. These electrical parameters depend on the geometry of the fiber and internodal separation $l$ as:

\[ R_l = \frac{\rho l}{\pi r^2}, \quad (3.6a) \]
\[ C_m = c_m 2\pi r W, \quad (3.6b) \]
\[ R_m = \frac{1}{2g_m \pi r W}, \quad (3.6c) \]

where $r$ is the radius of a nerve fiber, $W$ is the nodal space, $\rho$ the axonal resistivity, $c_m$ the capacitance per unit area, and $g_m$ the conductance per unit area of the inter-nodal region. Thus, all parameters are implicitly a function of position along the nerve length. This effectively, makes the electrical parameters of (3.1) vary from segment to segment of the myelinated nerve.

### 3.4 Electromagnetic Nerve Stimulation

In this section, we consider the electromagnetic (EMAG) simulation of nerve excitation, in which the tissue is in free space without electrodes contact (Fig. 3.6). Different from the transition from direct stimulation on the muscle surface to indirect stimulation in bath, current continuity is no longer suitable to analyze potential distribution over the muscle in this case. Instead, we implement Finite-Difference Time-Domain (FDTD) electromagnetic field analysis.
3.4.1 **FDTD solution of Maxwell’ equations: Yee Algorithm**

The FDTD algorithm was introduced by Kane Yee in 1966 [39]. Yee’s algorithm was used to choose a geometric relation for the spatial sample of the vector components of the electric and magnetic fields that robustly represent Maxwell’s curl equations.

*Faraday's Law:*

\[
\frac{\partial \vec{B}}{\partial t} = -\nabla \times \vec{E} - \vec{J}_m
\]  

(3.7)

*Ampere's Law:*

\[
\frac{\partial \vec{D}}{\partial t} = -\nabla \times \vec{H} - \vec{J}_e
\]  

(3.8)
Here $\vec{E} = \vec{E}(x,y,z)$ and $\vec{H} = \vec{H}(x,y,z)$ are the electric and magnetic fields, $\vec{D}$ and $\vec{B}$ are the electric and magnetic flux density vectors, $\vec{J}_e$ and $\vec{J}_m$ are the electric and magnetic conduction current density respectively. In linear, isotropic, nondispersive, lossy materials, these vectors can be related by

$$\vec{B} = \mu \vec{H}$$ \hspace{1cm} (3.9)

$$\vec{D} = \varepsilon \vec{E}$$ \hspace{1cm} (3.10)

$$\vec{J}_m = \sigma^* \vec{H}$$ \hspace{1cm} (3.11)

$$\vec{J}_e = \sigma \vec{E}$$ \hspace{1cm} (3.12)

where $\mu$ and $\varepsilon$ are the magnetic and electric permeability respectively, $\sigma^*$ is an equivalent magnetic resistivity and $\sigma$ is the electric conductivity. Combining the assumptions of (3.9) through (3.12) and substituting into equations (3.8) and (3.9), we obtain

$$\frac{\partial \vec{H}}{\partial t} = -\frac{1}{\mu} \nabla \times \vec{E} - \frac{\sigma^*}{\mu} \vec{H}$$ \hspace{1cm} (3.13)

$$\frac{\partial \vec{E}}{\partial t} = -\frac{1}{\varepsilon} \nabla \times \vec{H} - \frac{\sigma}{\varepsilon} \vec{E}$$ \hspace{1cm} (3.14)

We now write out the vector components of the curl operator in the equations (3.13) and (3.14) to yield the following system of six coupled scalar equations equivalent to Maxwell’s equations in the three-dimensional rectangular coordinate system $(x, y, z)$:

$$\frac{\partial H_x}{\partial t} = \frac{1}{\mu} \left( \frac{\partial E_y}{\partial y} - \frac{\partial E_z}{\partial z} - \sigma^* H_x \right)$$ \hspace{1cm} (3.15a)

$$\frac{\partial H_y}{\partial t} = \frac{1}{\mu} \left( \frac{\partial E_z}{\partial z} - \frac{\partial E_x}{\partial x} - \sigma^* H_y \right)$$ \hspace{1cm} (3.15b)
The system of six coupled differential equations form the basis of the FDTD numerical algorithm for electromagnetic wave interactions with general three-dimensional objects. To implicitly enforce Gauss's Law relations indicating zero free electric and magnetic charge, a Standard unit cell of the Yee space lattice is constructed as Fig. 3.7.

Fig. 3. 7 Position of the electric and magnetic field components about a cubic unit cell of the Yee space lattice [39].
We denote any function $u$ of space and time evaluated at a discrete point in the grid at a
discrete point in time as

$$u(i\Delta x, j\Delta y, k\Delta z, n\Delta t) = u^n_{i,j,k}$$  \hspace{1cm} (3.17)

Here $\Delta x$, $\Delta y$ and $\Delta z$ are, respectively, the lattice space increments in the $x$, $y$ and $z$
directions, and $\Delta t$ the time increments. $i$, $j$, $k$ and $n$ are integers. Using central difference
expressions for the space and time derivatives, the first partial space (in the $x$-direction at
t_{n}=n\Delta t$) and time (at the fixed space point $(i, j, k)$) derivative are:

\[
\frac{\partial u}{\partial x}(i\Delta x, j\Delta y, k\Delta z, n\Delta t) = \frac{u^n_{i+1/2,j,k} - u^n_{i-1/2,j,k}}{\Delta x} + O((\Delta x)^2)
\]  \hspace{1cm} (3.18a)

\[
\frac{\partial u}{\partial t}(i\Delta x, j\Delta y, k\Delta z, n\Delta t) = \frac{u^{n+1/2}_{i,j,k} - u^{n-1/2}_{i,j,k}}{\Delta t} + O((\Delta t)^2)
\]  \hspace{1cm} (3.18b)

For a cubic lattice, $\Delta x=\Delta y=\Delta z=\Delta$. Based on equations (3.15) through (3.18), a set
of finite-difference equations can be obtained as

\[
H_{x}^{n+1/2}|_{i,j,k} = C_{a}(m)H_{x}^{n-1/2}|_{i,j,k} + C_{b}(m)\left(E_{y}^{n}|_{i,j,k+1/2} - E_{y}^{n}|_{i,j,k-1/2} + E_{z}^{n}|_{i,j+1/2,k} - E_{z}^{n}|_{i,j-1/2,k}\right)
\]  \hspace{1cm} (3.19a)

\[
H_{y}^{n+1/2}|_{i,j,k} = C_{a}(m)H_{y}^{n-1/2}|_{i,j,k} + C_{b}(m)\left(E_{x}^{n}|_{i+1/2,j,k} - E_{x}^{n}|_{i-1/2,j,k} + E_{z}^{n}|_{i,j,k+1/2} - E_{z}^{n}|_{i,j,k-1/2}\right)
\]  \hspace{1cm} (3.19b)

\[
H_{z}^{n+1/2}|_{i,j,k} = C_{a}(m)H_{z}^{n-1/2}|_{i,j,k} + C_{b}(m)\left(E_{x}^{n}|_{i+1/2,j,k} - E_{x}^{n}|_{i-1/2,j,k} + E_{y}^{n}|_{i,j,k+1/2} - E_{y}^{n}|_{i,j,k-1/2}\right)
\]  \hspace{1cm} (3.19c)

\[
E_{x}^{n+1}|_{i,j,k} = D_{a}(m)E_{x}^{n}|_{i,j,k} + D_{b}(m)\left(H_{x}^{n+1/2}|_{i,j,k+1/2} - H_{x}^{n+1/2}|_{i,j,k-1/2} + H_{y}^{n+1/2}|_{i,j,k+1/2} - H_{y}^{n+1/2}|_{i,j,k-1/2}\right)
\]  \hspace{1cm} (3.20a)
\[ E_y^{n+1}_{i,j,k} = D_e(m)E_y^n_{i,j,k} + D_b(m) \left( H_x^{n+1/2}_{i,j,k+1/2} - H_x^{n+1/2}_{i,j,k-1/2} + H_z^{n+1/2}_{i+1/2,j,k} - H_z^{n+1/2}_{i-1/2,j,k} \right) \]  
(3.20b)

\[ E_z^{n+1}_{i,j,k} = D_e(m)E_z^n_{i,j,k} + D_b(m) \left( H_y^{n+1/2}_{i+1/2,j,k} - H_y^{n+1/2}_{i-1/2,j,k} + H_x^{n+1/2}_{i,j,k+1/2} - H_x^{n+1/2}_{i,j,k-1/2} \right) \]  
(3.20c)

where the updating coefficients is related to media properties at each point:

\[ C_e(m) = \left(1 - \frac{\sigma_{i,j,k} \Delta t}{2 \xi_{i,j,k}}\right) / \left(1 + \frac{\sigma_{i,j,k} \Delta t}{2 \xi_{i,j,k}}\right) \]  
(3.21a)

\[ C_b(m) = \left(\frac{\Delta t}{\xi_{i,j,k} \Delta}\right) / \left(1 + \frac{\sigma_{i,j,k} \Delta t}{2 \xi_{i,j,k}}\right) \]  
(3.21b)

\[ D_a(m) = \left(1 - \frac{\sigma^*_{i,j,k} \Delta t}{2 \mu_{i,j,k}}\right) / \left(1 + \frac{\sigma^*_{i,j,k} \Delta t}{2 \mu_{i,j,k}}\right) \]  
(3.22a)

\[ D_b(m) = \left(\frac{\Delta t}{\mu_{i,j,k} \Delta}\right) / \left(1 + \frac{\sigma^*_{i,j,k} \Delta t}{2 \mu_{i,j,k}}\right) \]  
(3.22b)

Use equations (3.19) and (3.20), All the $\vec{E}$ components are calculated and stored in memory for a particular time point using $\vec{H}$ data previously stored in the computer memory. Then all the $\vec{H}$ components are calculated and stored in memory using $\vec{E}$ data just computed. The cycle can begin again with the recomputation of the $\vec{E}$ based on the newly obtained $\vec{H}$. The process continues until time stepping is concluded. At each time step, the external voltage $V_e$ along the nerve fiber can be directly calculated using the electric field obtained. Then McNeal model can be used to calculate the membrane voltage $V_m$.

In order to give stable and convergent solutions, the FDTD algorithm must satisfy certain numerical constraints, arising from the choice of the differencing scheme [52].
The stability criterion is a condition imposed on the ratio between the space and the time increments:

\[ \Delta t < \frac{1}{v_{\text{max}} \sqrt{1/\Delta x^2 + 1/\Delta y^2 + 1/\Delta z^2}} = \frac{\Delta}{\sqrt{3}v_{\text{max}}} \]  

(3.23)

\( v_{\text{max}} \) is the maximum velocity of the signal inside the region.

Another typical constraint, known as dispersion limit, arises from the necessity of avoiding numerical dispersion, and relates the maximum mesh-size allowed to the maximum frequency of the signal involved:

\[ \Delta < \frac{1}{20f_{\text{max}} \sqrt{\varepsilon_r}} = \frac{\lambda_{\text{min}}}{20} \]  

(3.24)

### 3.4.2 Perfectly Matched Layer (PML) for Free Space

A basic consideration with FDTD approach to electromagnetic wave interaction problem is that many geometries of interest are defined as "open" regions where the spatial domain of the computed field is unbounded in one or more directions. Since no computer has store unlimited, the computed domain must be limited in size. The computation domain must enclose the structure of interest, and a suitable boundary condition on the outer perimeter of the domain must used to simulate its extension to infinity.

For high accuracy Berenger absorbing boundary condition (ABC), which is called perfectly matched layer (PML), is used to truncate a three-dimensional space grid in free space [45, 46]. This method uses an aggregate of anisotropic absorbing media outside of the computational mesh (muscle and nerve) to absorb outgoing waves and prevent
boundary reflections. The domain is finally ended by perfectly conducting condition. It is a highly effective boundary method with very low reflection coefficient. The cornerstone of Berenger PML medium is the break of the each component into two subcomponents. Then the scalar equations (3.15) and (3.16) are replaced by 12 equations.

\[
\begin{align*}
\frac{\partial H_{xy}}{\partial t} &= \frac{1}{\mu} \left( -\frac{\partial (E_{xz} + E_{yz})}{\partial y} - \sigma_z^* H_{xy} \right) \\
\frac{\partial H_{xz}}{\partial t} &= \frac{1}{\mu} \left( -\frac{\partial (E_{yx} + E_{yz})}{\partial z} - \sigma_z^* H_{xz} \right) \\
\frac{\partial H_{yz}}{\partial t} &= \frac{1}{\mu} \left( -\frac{\partial (E_{yx} + E_{xz})}{\partial z} - \sigma_z^* H_{yz} \right) \\
\frac{\partial H_{yx}}{\partial t} &= \frac{1}{\mu} \left( -\frac{\partial (E_{xz} + E_{yz})}{\partial x} - \sigma_z^* H_{yx} \right) \\
\frac{\partial H_{zx}}{\partial t} &= \frac{1}{\mu} \left( -\frac{\partial (E_{yx} + E_{xz})}{\partial x} - \sigma_z^* H_{zx} \right) \\
\frac{\partial H_{zy}}{\partial t} &= \frac{1}{\mu} \left( -\frac{\partial (E_{yx} + E_{xz})}{\partial y} - \sigma_z^* H_{zy} \right)
\end{align*}
\] (3.25)

\[
\begin{align*}
\frac{\partial E_{xy}}{\partial t} &= \frac{1}{\xi} \left( -\frac{\partial (H_{xz} + H_{yz})}{\partial y} - \sigma_y E_{xy} \right) \\
\frac{\partial E_{xz}}{\partial t} &= \frac{1}{\xi} \left( -\frac{\partial (H_{yx} + H_{yz})}{\partial z} - \sigma_y E_{xz} \right) \\
\frac{\partial E_{yz}}{\partial t} &= \frac{1}{\xi} \left( -\frac{\partial (H_{yx} + H_{xz})}{\partial z} - \sigma_y E_{yz} \right) \\
\frac{\partial E_{yx}}{\partial t} &= \frac{1}{\xi} \left( -\frac{\partial (H_{xz} + H_{yz})}{\partial x} - \sigma_y E_{yx} \right) \\
\frac{\partial E_{zx}}{\partial t} &= \frac{1}{\xi} \left( -\frac{\partial (H_{yx} + H_{xz})}{\partial x} - \sigma_y E_{zx} \right)
\end{align*}
\] (3.26)
where the parameter \((\sigma_x, \sigma_x^*, \sigma_y, \sigma_y^*, \sigma_z, \sigma_z^*)\) are homogeneous to electric and magnetic conductivities. A PML medium \((0,0,\sigma_y, \sigma_y^*, 0,0)\) can absorb a wave \((E_{xy}, E_{yz}, H_{xy}, H_{yz})\) propagating along \(y\), but it does not absorb a wave \((E_{xx}, E_{yx}, E_{zz}, H_{xx}, H_{yy}, H_{zz})\) propagating along any \(x-z\) plane. This is because the case propagation is ruled by equations (3.25a, f) and (3.26a, f), but the second case by (3.25b-e) and (3.26b-e). Moreover, if the matching condition

\[
\frac{\sigma}{\varepsilon_0} = \frac{\sigma^*}{\mu_0}
\]

(3.27)

is satisfied, then the impedance of the medium (3.25-3.26) equals to that of the vacuum and no reflection occurs when a plane wave propagates normally across a vacuum-medium interface [53]. Furthermore, we can have more general properties at an interface between PML media of same \(\varepsilon\) and \(\mu\): there is no reflection from an interface normal to \(y\) lying between two PML media whose transverse conductivities are equal and whose longitudinal conductivities satisfy the matching condition. A vacuum can be regarded as a \((0,0,0,0,0,0)\) PML medium [46]. For instance, provided \(\sigma_y/\varepsilon_0 = \sigma_y^*/\mu_0\), the reflection equals zero from an interface normal to \(y\) located between a vacuum and the PML medium \((0,0,\sigma_y, \sigma_y^*, 0,0)\), whose transverse conductivities \(\sigma_x, \sigma_x^*, \sigma_z, \sigma_z^*\) are equal to those of the vacuum-zero.
Based on the analysis above and the symmetry of the structure, the PML layer is constructed as shown in Fig. 3.8. In the six sides of the domain, the absorbing media are matched PML media of transverse conductivities equal to zero. As a result, outgoing waves from the inner vacuum can penetrate without reflection into these absorbing layers. In the twelve edges, the conductivities are selected in such a way that the transverse conductivities are equal at the interfaces located between edge media and side media. And in the eight corners of the domain, the conductivities are chosen to be equal at the interfaces between edge layers and corner layers. Thus the reflection equals zero from both the side-edge and edge-corner interfaces.

Fig. 3.8 Upper-right part of a computational domain surrounded by the PML layer.
In the PML layer, the conductivity increases from zero at the vacuum-layer interface to a value $\sigma_m$ at the outer side of the layer. Berenger proposed that the magnitude of the wave in the absorbing layer is ruled by:

$$u(\rho) = u(0)e^{-\left(\frac{\sigma \cos(\theta)}{\epsilon_0 \rho}\right)\rho}.$$  \hspace{1cm} (3.28)

where $\rho$ is the distance of any interface, $\theta$ is the incidence angle defined with respect to the interface, $c$ is the wave speed, and $\sigma$ is $\sigma_\infty$, $\sigma_y$ or $\sigma_z$. After crossing the layer, a wave is reflected by the perfectly conducting conditions which end the domain, and then, after a second crossing, it can come back to the vacuum. So, for a layer of thickness $\delta$, an apparent reflection factor can be defined as

$$R(\theta) = e^{-2\left(\frac{\sigma \cos(\theta)}{\epsilon_0 \rho}\right)\delta}.$$  \hspace{1cm} (3.29)

As (3.29), the apparent reflection is a function of the product $\sigma\delta$. For a given layer attenuation, theoretically, the layer thickness $\delta$ can be as thin as intended. In fact, sharp variations of conductivity create numerical reflections [53]. So, in practical computation, the conductivity should change gracefully with depth $\rho$. The profile used for the conductivity in the PML layer is that preferred by most authors in the literature, Equations (3.30).

$$\sigma(\rho) = \sigma_m\left(\frac{\rho}{\delta}\right)^n$$  \hspace{1cm} (3.30)
where \( n \) is the order of the spatial polynomial. For the conductivity \( \sigma (\rho) \), the reflection factor is then

\[
R(\theta) = e^{-2(\cos(\theta)/\varepsilon_0)\int_0^\rho \sigma(\rho)d\rho} = e^{-(2(\varepsilon_0/\varepsilon_r)\cos(\theta))}
\]  \hspace{1cm} (3.31)

\( R(\theta) \) is a theoretical reflection coefficient, which can be chosen according to accuracy requirement. Given \( R(\theta) \), \( \sigma_m \) can be calculated by equation (3.31) as

\[
\sigma_m = \frac{(n+1)\varepsilon_0 c}{2\delta} \ln R(0)
\]  \hspace{1cm} (3.32)

Substituting equation (3.32) into (3.30), The conductivity profile \( \sigma (\rho) \) can be determined for a given \( \delta \).

Up to now, the PML layer is completely constructed. This PML layer has been shown to operate well in most circumstances.

### 3.4.3 Transparent Sources in FDTD Simulation

In the simulation, the source of energy has been embedded within the FDTD grid. A popular source implementation is known as a hard source, which is implemented by specifying the field at a given node with a temporal driving function. Since the update equation does not apply to this source node and its value is fixed solely by the driving function, it scatters any energy incident upon it [54]. In certain applications, scattering from the source node is a spurious artifact of the source implementation that degrades the quality of the simulation. One approach to eliminating source scattering requires the use
of a pulsed driving function that goes to zero after a finite duration. Once the driving function is zero, the value of the source node is set by the update equation. For this approach to succeed, the duration of the driving function must be shorter than the time it takes for energy to travel from the source node to any material discontinuity and back again. However, in many circumstances of the nerve simulation, this requirement is overly restrictive. For example, the applied pulse duration is required to be shorter than 10ns if the distance between the source and the nearest muscle-vacuum interface is 3m, which is already much larger compared to the muscle (34mm long). Even though the driving function could have a longer duration by keeping the source further away from the muscle, it also increases CPU time and memory requirement significantly. Alternatively, a source that radiates the same energy as a hard source, but that does not scatter energy, is used. Such a source is called a transparent field source [55], [56].

A node in an FDTD grid that has the same material properties as its neighbors and that is governed by the standard FDTD update equation does not, per se, scatter energy. Therefore, it appears that one may simply implement a transparent field source by setting the value of the source node equal to the sum of the value returned by the update equation and the value of the driving function. Unfortunately, although this approach yields a node that does not act as a scatterer (and in that sense is transparent), the energy that it couples into the grid may bear little resemblance to that of a hard field node. In fact, a source of energy implemented in this way corresponds physically to a current source rather than a field source. However, it is possible to record a grid impulse response at the source node and then construct a transparent source that couples into the grid the same field as a hard field source.
The impulse response can be used to give the field that will echo back to the source node if the source node is equal to the sum of the update equation and the driving function. Clearly, if a transparent source is to couple the same field into the grid as a hard source, the source node must, in the absence of any reflected field, take on the same values as those of a hard source, i.e., the source node must take on the values of the driving function and the echoed values must all be canceled. The cancellation is realized by subtracting the convolution of the impulse response and the driving function from the source node. In $N$ dimensions, the transparent source $F^n$ corresponding to a driving function $f^n$ is obtained using:

$$F^{n+1}(\tilde{r}_{\text{src}}) = (N - D \text{ update equation}) + f^{n+1} + \sum_{m=0}^{n} I^{n-m+1}_N f^m \quad (3.33)$$

where $I_N$ is the impulse response of the source node in $N$ dimensions.

The impulse response $I_N$ can be measured and recorded at the source node by running an auxiliary simulation. So it is fundamentally different from the time domain Green's function, which itself is an impulse response, but one for which the source and observation points are not collocated. The transparent field source is then realized, in part, by convolving the impulse response with the driving function. Once found, the impulse response can be used for subsequent simulations that have similar geometries.

In three dimensions, the impulse response is infinite in duration. In three dimensions, the impulse response approaches zero and the rate at which it approaches zero depends on a Courant number which is often referred as $c\Delta t/\Delta$, The closer the Courant number is to the limit, the more rapidly the impulse response approaches zero.
(here the rate of fall-off is discussed relative to the number of time steps, not absolute time). Thus, after a sufficient number of time steps, the impulse response can be approximated by zero and the convolution with the source function in (12) does not necessarily have to be done over the entire previous history of the source function. Instead, it only needs to be done over the number of time steps the impulse response is treated as non-zero. Furthermore, in three dimensions the impulse response is independent of the field component, i.e., all six field components have the same impulse response.

3.5 Validation & Verification of Simulation Model

Implementing a time-domain, finite-difference discrimination of difference equations facilitated numerical simulations for both electrical and electromagnetic nerve stimulation. The simulation results obtained are discussed and compared to available experiment data in the next chapter. Temporal independence of the nerve properties was assumed and verified because of the negligible thermal heating by an ultrashort electric pulse. Using Neumann boundary conditions in electric excitation, the current through the cathode and the anode are should to be equal, which is also verified in next chapter. After the duration of the applied pulse, the field also attenuated over time and space as expected. Satisfactory results obtained bode well for the theoretical model and indirectly validates the analytical approach developed.
CHAPTER IV

RESULTS AND DISCUSSIONS

4.1 Introduction

Simulation results for both electrical and EMAG bio-stimulation are discussed in this chapter. The emphasis is on the former given the availability of experiment data for direct comparison, and the possibility for a stronger bio-response in practice. It is shown that the Strength-Duration (S-D) curve for electrical bio-stimulation still holds for pulses as short as 1 nanosecond. It is also shown that remote, electromagnetic (EMAG) stimulation is not very promising, and does not show any advantage over electrical stimulation.

4.2 Results for Direct Electrode Stimulation Case

4.2.1 General Results

The numerical simulation scheme outlined in the previous chapter was used to obtain the time-dependent potentials and currents within the muscle in response to an external electric pulse. Results for a voltage pulse V(t) with a peak magnitude of 5,000 Volts; a rise time of 0.8 ns; a fall-time of 1.0 ns and an ON time of 4.0 ns are discussed first. Figures 4.1 and 4.2 show the time evolution of the potential across a line parallel to the y-axis on the z = 0 and the z = 0.081 cm surfaces, respectively. The presence of two wire electrodes parallel to the x-axis is obvious in Figs. 4.1 and 4.2, with the potential being maintained at 5 kV and 0 V at these sites.
Fig. 4.3 shows a snapshot of the potential distribution at an early time of 0.4 ns across the $z = 0$ surface: Fig. 4.4 is the simulation result with $z = 0.325$ cm. Because of a decrease in potential with depth, the values in Fig. 4.4 are not as large as those of Fig. 4.3.

Fig. 4.1 Time-evolution of potential across a line parallel to the y-axis (at $x = 0.5$ cm) on the $z = 0$ surface for the 5.8 ns pulse.

Fig. 4.2 Time-evolution of potential across a line parallel to the y-axis on the $z = 0.081$ cm surface for the 5.8 ns pulse.
Next, the current and potential distributions within the muscle were used to evaluate the maximum internal heating. Since the applied pulse durations of interest are ultra-short (nanosecond regime), heat outflow effectively is not expected to occur. In this situation, the maximal temperature rise $dT$ produced by the externally applied pulse then can be
estimated as: $dT - Q \frac{dt}{\Delta C_p}$.

Fig. 4.5 Temperature distribution across at the top surface.

The power dissipation was obtained from the potential and current distributions at each time step of the simulation, using a density of $10^3 \text{ kg/m}^3$ for the muscle and $C_p = 4.1 \times 10^3 \text{ m}^2\text{s}^{-2}\text{K}^{-1}$. This produced a profile of the temperature rise (Fig. 4.5) at the end of the applied 5.8 ns voltage pulse. The result shows that minimal heating ($< 0.5$ milli-Kelvin) is predicted.

The time evolution of the activation function $f(x,y,z,t)$ across a line on the $z = 0$ surface shows that the activating function is not symmetric about the cathode and anode: a polarity-dependent effect is predicted (Fig. 4.6). This is in keeping with both some previous reports [1], [33] and with experimental measurements made at the laboratory located at Brooks City-Base [57].
Fig. 4.6 Time-evolution of the "activation function" across line parallel to the y-axis (at $x = 0.5$ cm) on the $z = 0$ surface.

The highest predicted time-dependent circuit current for the 5.8 ns pulse is about 30 A (Fig. 4.7). This was found to be in reasonable agreement with the experimentally measured value of 34 A [7]. This match between theory and experiment bodes well for the theoretical model and indirectly validates the analytical approach developed.

Fig. 4.7 Time-dependent circuit current for the 5 kV pulse.
Based on the activation function, which was calculated at each time instant across the entire, three-dimensional, tissue-simulation volume, the thresholds for muscle twitching were obtained. This involved running simulations for a variety of pulse widths and resulted in the development of S-D curves for the preparation.

The threshold $V_{\text{thresh}}$ for stimulation then is expressed in terms of the maximum value of $f(x,y,z,t)$ as: $V_{\text{thresh}} = f(x,y,z,t)|_{\text{max}} = (V_{\text{dep}} \, \theta_{\text{RC}}) / T_{\text{pulse}}$, with $V_{\text{dep}} = 20 \, \text{mV}$ being the depolarizing potential, $\theta_{\text{RC}}$ the effective RC time constant for nerves, and $T_{\text{pulse}}$ the applied pulse width. In a proto-typical motor neuron, a shift in potential of 20 mV is assumed to result in depolarization and tissue excitation. Typically the resting potential is $\approx -70 \, \text{mV}$ and all-or-none firing occurs at $\approx -50 \, \text{mV}$. Hence, a $V_{\text{dep}}$ value of 20 mV was used here.

As expected, the S-D curve for $V_{\text{thresh}}$ is linear; it also is in good agreement with the experimentally acquired data (Fig. 4.8). The nerve was assumed to be located at the second segment, just below the top surface (i.e. parallel to the z-axis) and perpendicular to the two line electrodes. The solid line corresponds to the model predictions, and circles are the experimental data taken at the Brooks City-Base laboratory [7]. For a good fit, an effective nerve time constant $\theta_{\text{RC}}$ of 160 $\mu$s was adopted. There is good agreement between theory and the actual measurements. This result thus provides validation of the 3D model developed here. Because of both the interest in nanosecond pulses and the need to avoid prohibitively long computational times, the calculations were performed only for pulse durations as long as 1 $\mu$s.
Fig. 4.8 Comparison between the S-D curve (circles) measured at Brooks City-Base [7] and the calculated S-D line.

4.2.2 Effects of Pulse Shape

Based on the verified model, nerve stimulation by different pulses was simulated. Specifically, rectangular, trapezoidal and triangular pulses were applied to the muscle surface via linear electrodes (Fig. 4.9). The following notation has been used here: “t_{rise}” denotes the pulse rise time, “t_{on}” the on-time of the applied pulse, and “t_{fall}” the fall-time. In the present simulations, it is assumed that trapezoidal pulses have characteristics of: $t_{rise} = t_{on} = t_{fall}$, each equal to one-third of the total pulses duration. Triangular pulses, on the other hand, have: $t_{rise} = t_{fall}$, equaling half the total pulses duration. Two conclusions can be obtained from the simulation results. First, rectangular pulses, whose average value is higher than that of the trapezoidal and triangular pulses, have lower voltage thresholds. For pulses other than a rectangular shape, the activating function cannot be
used directly as indicated in equation 3.2. Instead, equation 3.1 needs to be implemented even if the pulses are very short, i.e. $T << R/C$ and $T >> R/C$. In order to understand the stimulation process, however, one can discretize the pulses into smaller pieces over time. If the pieces are small enough so that each piece can be approximated as a short rectangular pulse, one can use equation 3.1 to analyze the effect of each pulse. Obviously, increasing $V_n$ is a cumulative process resulting from a series of small, rectangular pulses. During the rise and fall times, the external voltage is lower than that during the “on time”. This leads to lower activating function values in the case of non-rectangular pulses. Consequently, a higher voltage threshold is required for bio-stimulation by any wave-shape other than a rectangular pulse. Second, since the nerve excitation is the result of a cumulative process during the pulse duration, a sharp rise or fall edge of the pulse does not have any specific advantages. Instead, the average value of applied voltage plays an important role in exciting the fiber. This was verified by carrying out additional simulations.

In order to show the time evolution of the membrane potential, a 1.0 ns trapezoidal pulse with $t_{rise} = t_{on} = t_{fall} = 1/3$ ns was applied, as an example. The applied pulse had a peak amplitude 4548.2 kilovolts, which is required to stimulate the nerve (Fig. 4.9). Just as expected, the membrane potential just exceeded the threshold-depolarizing shift of 20mv at the end of the pulse duration (Fig. 4.10). The maximum value of membrane potential happened just at the cathode, where the activating function had a maximum value. Instead of exciting the nerve directly, the transient amplitude of the pulse just determined how fast the membrane potential was increasing (Fig. 4.6). So the nerve excitation is a result of “integration” of activating function over time.
Fig. 4. 9 Simulated results for the S-D curves obtained from numerical simulations for muscle stimulation by pulses with different shapes. The pulse duration is defined as the sum of rise time, on time and fall time.

Fig. 4. 10 Time-evolution of membrane potential along the fiber parallel to the y-axis (at $x = 5$ mm) on the $z = 0.81$ mm surface for the 1 ns trapezoidal pulse. The threshold voltage was $4.5482 \times 10^4$ Volts.
4.2.3 Effects of Electrodes Placement

The activating function has the maximum value just at the anode (Figs. 4.6 and 4.10). Mathematically, the activating function \( V_{e,n+1} + V_{e,n+1} - 2V_{e,n} \) is proportional to the second-order derivative of external potential \( V_e \) along the fiber. Visually, a deep and sharp "valley" in the snapshot of potential across the \( z = 0.081 \) cm surface will result in a large activating function and consequently a low threshold voltage. By decreasing the distance between anode and cathode, a sharper "valley" in the snapshot will be obtained and the required threshold voltage will be reduced. The simulated S-D curves for different electrode separations are shown in Fig. 4.11. The anode was fixed at \( y = 3 \) mm, but cathode was located at \( y = 13 \) mm, \( y = 23 \) mm and \( y = 33 \) mm, respectively.

On the contrary, Fig. 4.12 shows the simulated S-D curves for fixed electrode separation, but the electrodes are located at different position. Changing electrodes position just changes the peak activating function location, instead of changing the "valley" shape near the cathode. Very little difference was expected and observed in the simulations. Neither theoretical analysis nor numerical simulations shows that electrodes position play any important roll in nerve excitation as long as the electrodes have a distance longer than two or three internodal distance. This also further proves that the shifting of S-D curves in Fig. 4.11 was caused by electrode separation, not the cathode location.
Fig. 4. 11 Simulated S-D curves for muscle stimulation for different electrode separations. Rectangular pulses were applied for each case.

Fig. 4. 12 Simulated S-D curves for muscle stimulation for different electrodes positions. Cathode located at $y = 13$ mm, anode $y = 3$ mm (Position A); Cathode located at $y = 23$ mm, anode at $y = 13$ mm (Position B); and cathode located at $y = 33$ mm, anode at $y = 23$ mm (Position C). Rectangular pulses were applied.
4.2.4 Anode-Cathode-Anode electrode scheme

Based on the observations of the last section, an Anode-Cathode-Anode (ACA) electrode scheme is introduced. The only difference between the ACA scheme and Anode-Cathode (AC) scheme is that two linear anodes are applied to the muscle surface, symmetric to the linear cathode. Cathode is located at $y = 13$ mm, anode at $y = 3$ mm in the AC scheme. For the ACA scheme, the cathode is located at $y = 13$ mm, and the two anodes at $y_1 = 3$ mm and $y_2 = 23$ mm. A 1.0 ns rectangular pulse with amplitude of 10 kilo-Volts was applied in both cases.

Fig. 4.13 (a) and 4.13 (b) show the snapshots of internal potential at 0.994 ns across the $z = 0.081$ cm surface, where the nerve fiber was assumed to be located. Obviously, as seen from the figures, the ACA scheme generates a much deeper and sharper potential "valley" around the anode than does the AC scheme. As discussed in the last section, the activating function: $V_{e,n-1} + V_{e,n+1} - 2V_{e,n}$ is proportional to the second-order derivative of external potential $V_e$ along the fiber, i.e. the $y$-direction in this case. Thus, the ACA scheme can be seen to generate a larger activating function and consequently, a larger membrane potential. This is also verified on the basis of the time-evolving membrane potential for both electrode schemes that is shown in Fig. 4.14 (a) and Fig. 4.14 (b). Although the same pulse was applied, the membrane potential of ACA scheme is seen to increase much faster that for the AC scheme. At the end of the 1-nanosecond rectangular pulse, the maximum membrane potential of ACA scheme is about twice much as that for ACA scheme.
Fig. 4. 13 Comparison between the potential distribution across $z = 0.081$ cm surface for Anode-Cathode (AC) scheme and Anode-Cathode-Anode (ACA) scheme. Cathode is located at $y = 13$ mm, anode at $y = 3$ mm in the AC scheme. For the ACA scheme, the cathode is located at $y = 13$ mm, and the two anodes at $y1 = 3$ mm and $y2 = 23$ mm.
Fig. 4. 14 Comparison between the time evolution of membrane potential for: (a) the Anode-Cathode scheme, and (b) the Anode-Cathode-Anode scheme. For the AC scheme, the cathode was at $y = 13\text{mm}$, and the anode at $y = 3\text{ mm}$. For the ACA scheme, the cathode was located at $y = 13\text{mm}$, and anodes at $y_1 = 3\text{ mm}$ and $y_2 = 23\text{ mm}$. A 1.0 ns rectangular pulse was applied for each case.
Pulses with different durations were applied for both the AC and ACA schemes. Fig. 4.15 shows the S-D curves obtained from the numerical simulations. It can be seen that the ACA scheme requires a lower voltage threshold than the AC scheme, and thus is predicted to have an inherent advantage for nerve stimulation.

Fig. 4. 15 Comparison between the simulated S-D curves for Anode-Cathode (AC) scheme and Anode-Cathode-Anode (ACA) scheme. Cathode is located \( y = 13 \) mm, and anode at \( y = 3 \) mm in the AC scheme. For the ACA scheme, the cathode is at \( y = 13 \) mm, and anodes at \( y_1 = 3 \) mm and \( y_2 = 23 \) mm. Rectangular pulses were applied for each case.

An effect of electrode separation on the activating function as seen for the AC scheme, was also observed through numerical simulations carried out for the ACA scheme (Fig. 4.16). The S-D curves shift downward as the distances between the cathode
and anodes decrease. The optimum Anode-Cathode-Anode separation occurs when both anodes are 1mm away from the cathode, since this 1.0 mm value is the inter-nodal distance \( l \). As compared to the AC scheme shown in Fig. 4.5, the threshold voltage of the optimal ACA scheme is reduced by 75%. Even though the impedance is much smaller as the cathode-to-anode distances decrease to 1.0 mm, it is safe to estimate that minimal heating occurs based on the calculated temperature distribution of Fig. 4.5.

Fig. 4. 16 Comparison between the simulated S-D curves for Anode-Cathode-Anode schemes with different electrode separation. Cathode is located at \( y = 13 \) mm, anodes at \( y_1 = 3 \) mm and \( y_2 = 23 \) mm (solid); Cathode located at \( y = 13 \) mm, anodes at \( y_1 = 8 \) mm and \( y_2 = 18 \) mm (dashdot); Cathode at \( y = 13 \) mm, and anodes at \( y_1 = 12 \) mm and \( y_2 = 14 \) mm (dotted). Rectangular pulses were applied for each case.
4.3 Results for Indirect, Saline-Bath Stimulation Case

Experimental work and simulation analysis were also carried out to examine the response of the frog gastrocnemius muscle preparation when immersed in a water bath containing a conductive physiological saline medium. The experiments were all carried out at an Air Force laboratory in Texas. The intent was to evaluate the stimulation behavior for such indirect stimulation, and ascertain how the S-D properties might be altered.

Given the geometry, one can expect the S-D curves to be shifted to higher voltages. The immersive environment introduces two primary changes. First, there is an additional series resistance provided by the saline solution. Second, there is a change from relatively sharp contacts to flat, large-area surface electrodes. This should work to increase the external voltage required to produce a given bio-response.

4.3.1 Experimental Data

The S-D curves were obtained experimentally by the Texas group. A shift in the S-D characteristic was observed (Fig. 4.17). At the shortest pulse duration examined in the bath study (10 µs), the measured threshold was 20 V. This is about 4-fold higher than the direct-contact case at the same pulse duration.

Voltage readings were made using the automated “high” reading feature of the Tektronix oscilloscope. The error bars are 95% confidence intervals. For the bath stimulation data, the sample size (n) per point is 14. For the contact stimulation data, n varied in the 5 – 7 range. As expected, tissue stimulation thresholds are higher in the absence of direct contact [7].
4.3.2 Effects of Axon Termination Conditions Boundaries

Having obtained satisfactory results for the direct-contact case, the two-step simulation model described above was applied to produce S-D curves with the tissue immersed in the saline bath. In addition, the influence of termination conditions at the boundaries, and the role of nerve inhomogeneity on the stimulation thresholds were assessed. Unfortunately, the boundary impedances are not known precisely, and they cannot be ascertained from the experiments. Only rough estimates can be made, and were used in the simulations.

In the absence of the boundary impedance information, two sets of simulations were carried out. In one set, the terminating impedance was chosen to be very "large", corresponding to an open circuit for current flow from the outside into the nerve fiber.
Thus external flux was effectively sealed off at the nerve endings. In the other set, the terminating impedance was chosen to be very "small" using a boundary condition that allowed free current passage into the nerves at the end points.

A higher threshold was obtained for the small termination impedance case, i.e., with free current flow between the nerve and the solution, in keeping with current continuity (Fig. 4.18). Clearly, allowing for easier current flow lowers the potential; hence, a larger external excitation is required for the nerve to attain the same depolarizing voltage threshold shift. The relevant experimental data point lies at the low-impedance curve. In reality, the termination impedance should have a finite value falling between the high and low extremes. The data point [7] was obtained from Fig. 4.17 for the shortest available pulse width.

![Simulated S-D curves](image)

Fig. 4. 18 Simulated S-D curves obtained from numerical simulations for muscle stimulation in the saline-filled bath. The lower curve is for high impedance; thresholds are higher with low impedance. An available experimental data point is also shown.
4.3.3 Effects of Fiber Inhomogeneities

Next, the role of fiber non-uniformity was studied by allowing for variations in the radius $R$. As given in equation 3.6, this parameter affects the internal time constants by varying the distributed resistances and capacitances. Physically, variations in the radius are expected to occur predominantly near the terminations of nerve fibers. Their values should be roughly uniform over the bulk of the muscle segment. In keeping with this logic, the radius was allowed to vary only over 20 percent of the entire longitudinal span. There is no *a priori* basis for this 20 percent value; it merely provides a condition of partial variation in nerve fiber diameter close to the distal end.

Here the primary goal is to obtain qualitative trends and predicted changes in S-D characteristics in response to parameter variations. Hence, the general predictions are expected to be correct: the exact values might be different, depending on actual data describing variations in the diameter of nerve fibers.

The radius $r$ was taken to be a linear function of the axial distance "$z$", i.e., \( r(z) = r(0) + k \cdot z \), with $r(0)$ being the nerve fiber diameter value at one end of the muscle. Various values of the "$k$" parameter were used, with $k = 0$ signifying complete radial uniformity. The low-impedance termination condition was applied for these simulations. The threshold decreases with increasing $k$ value (Fig. 4.19). Thus, the modeling predicts that it would be easier to produce twitching and stimulation over portions of the muscle that had inherent inhomogeneities. This, typically, can be expected at the extremities.

Increasing inhomogeneity also lowers the excitation signal threshold required for stimulation for the high-impedance termination case (Fig. 4.20). Since some degree of inhomogeneity exists in practice, such shifts towards lower thresholds are predicted.
Fig. 4. 19 Simulated S-D curves with radial non-uniformities for low impedance termination. The data point [7] also is shown.

Fig. 4. 20 Simulated S-D curves with radial non-uniformities for high impedance termination. The data point [7] also is shown.
4.4 Results for Electromagnetic Stimulation Cases

4.4.1 Electromagnetic Wave Propagation in Vacuum Case

Having studied the direct contact and indirect, electrode-based contact cases, attention was next focused on the possibility of remote, electromagnetic nerve stimulation.

In electromagnetic nerve stimulation, the same Neal nerve model can be implemented as that used for the direct electrical stimulation. However, the external potential distribution that is the driving force needs to be obtained by the finite-difference, time-domain (FDTD) method, which was discussed in length in chapter 3. As a validation of the FDTD model, a simple case is studied by locating a point electrical field source in vacuum without any muscle involvement. The calculation domain has a size of 60mm x 60mm x 60mm, surrounded by the PML with a thickness of 10 mm. Spatial increments dx, dy, dz vary corresponding to different accuracy requirements, here 1mm are selected for all three direction. The stability criterion is satisfied by ensuring that the time step “dt” is chosen according to: \[ dt = \frac{dx}{2\sqrt{3}c} \], in which “c” is light speed, and “dx” the smallest spatial mesh size. A point source \( E_y = 0.4\sin(2\pi*3\times10^{10} \cdot t) \) is applied at the center of the calculation domain, and several receivers are placed at different positions. During the calculation, time dependent electric field is recorded as shown in Fig. 4.21. To eliminate noise generated initially, two cycles are executed before recording the E-field.
A sinusoidal signal with the same frequency as the source, as expected by theoretical analysis, is observed at each point. Furthermore, the amplitude of the E-field decreases as it propagates away from the source. Physically the E-field should be proportional to $1/R$, since the total energy is a constant as the wave propagates. Fig. 4.22-4.25 give snapshots of $E_y$ across the x-z plane: $y = 40$ ms at different times. A 10 mm thick, perfectly matched layer (PML) is also included at the boundary to ensure perfectly absorbing conditions for the electromagnetic wave. This sets the values of $E_y$ to be close to zero within the PML.
Fig. 4. 22 Snapshot of E\textsubscript{y} across the surface y = 40 mm at 0.05 ns for vacuum case.

Fig. 4. 23 Snapshot of E\textsubscript{y} across the surface y=40mm at 0.053ns for vacuum case.
Fig. 4.24 Snapshot of E_y across the surface y = 40 mm at 0.059 ns for vacuum case.

Fig. 4.25 Snapshot of E_y across the surface y = 40 mm at 0.075 ns for vacuum case.
4.4.2 Electromagnetic Wave Propagation in Scattering Case

After having obtained satisfactory results for a propagating electromagnetic signal as discussed above, a muscle with a size of \( m_x \times m_y \times m_z = 34 \text{ mm} \times 10 \text{ mm} \times 7 \text{ mm} \) was inserted at the center of the calculation domain. The whole model thus included the muscle, the encompassing PML at the outer boundary, and vacuum in between. The nerve was taken to be 1.0 mm away from the upper surface, oriented along the y direction and centered in the middle. In order to satisfy the dispersion criteria, a sinusoidal source \( E_y \) with a lower frequency of \( f = \frac{c_0}{20 \times \text{dx} \times \sqrt{Kr}} = 1.6759 \text{ GHz} \) was applied. The source \( E_y \) was placed outside the muscle bulk, and aligned with the nerve fiber at a distance of 5 mm from the muscle. Fig. 4.26 gives the evolution of \( E_y \) at the source and two observation points, which were aligned along the y direction. The observation points were chosen to be 1.0 mm and 2.0 mm away from the source, respectively.

![Electric field at the source point and observation points with different distances from the source. The points are aligned along the y-direction.](image)
Snapshots of electric field at the x-y plane cutting across the nerve and source were also obtained, for both the muscle region and the entire modeling space including the PML (Fig. 4.27). The electric field profile shows that the electromagnetic field does not have a strong tendency to propagate into the muscle, and remains at a relatively weak level. Reasons for this weak signal might include: 1) Strong reflections of the electromagnetic signal at the muscle-vacuum interface. This would be caused by the abrupt change in properties of the adjacent media. The reflections effectively make it more difficult for the incoming energy to penetrate through. 2) The muscle with a conductivity of 1.29 S/m is itself a lossy media. Hence, the E-field even without any reflections would decrease during their propagation inside the lossy muscle. 3) Next, the muscle has a relatively large permittivity $K_r$. Consequently, the E-field inside the muscle would become smaller from considerations of continuity for the total displacement vector $D$. Alternatively, looking at this from an energy conservation point of view, the larger permittivity within the muscle forces the electric field to have a smaller value. 4) The muscle is physically located at some distance from the source (5mm) which works to reduce the net E-field due to attenuation and incoherent phase effects. The E-field distribution inside the muscle is seen to be fairly non-uniform (Fig. 4.28-4.30). This should, in effect, help boost the activating function as discussed earlier in this chapter. Selection of an appropriate source frequency and amplitude might enhance this inhomogeneity from the standpoint of enhancing the bio-stimulation.
Fig. 4. 27 Snapshot of $E_y$ across the whole surface $z = 42$ mm (a); and snapshot of $E_y$ in the muscle region (b) at 0.096 ns for scattering case.
Fig. 4. 28 Snapshot of $E_y$ in the muscle region across the surface $z = 42$ mm at a time of 0.19 ns.

Fig. 4. 29 Snapshot of $E_y$ in the muscle region across the surface $z = 42$ mm at time = 0.39ns.
Fig. 4. 30 Snapshot of $E_y$ in the muscle region across the surface $z = 42$ mm at time $= 0.48$ns.
CHAPTER V

CONCLUSIONS AND FUTURE WORK

5.1 Summarizing Conclusions

Numerical computer codes were developed and implemented to simulate the twitching response of tissues to an external sub-microsecond electrical stimulus. The simulations yielded strength-duration (SD) curves down to 5 nanosecond pulse-widths. Such excitation by ultra-short pulses is an important health and safety consideration for personnel working near ultra-wideband sources, since these electronic devices produce nanosecond pulses. Good agreement was obtained between model predictions and experimental measurements for the macroscopic observables, such as, the peak circuit currents and breakdown threshold voltages for a variety of conditions.

For example, with direct electrode-based, electrical stimulation, a peak current of about 30 A was predicted for the shortest (5 ns) pulse; the measured data indicated the threshold current to be 34 A. Similarly, the peak threshold voltage of about 4.6 kV predicted by the model for the shortest pulse was in very close agreement with the 4.5 kV value obtained experimentally [7]. Thus, adequate and successful model validation was achieved.

Calculations of the S-D curve for the direct stimulation case yielded a close match with the available experimental data in the sub-microsecond regime. Use of a time constant of 160 µs produced good comparisons. It is well known there is a large (roughly 10-fold) difference in the time constants of nerves and muscles [2]. Typically, time constants for nerves are around 200 µs, but those for muscles are at about 2 ms. Thus, the
160 μs value that was seen to yield a good match with experimental data, was certainly indicative of a nerve-based response. The experimentally determined time constant averaged 285 μs; this value [7] is also suggestive of nerve stimulation. Presumably motor neurons were excited, thereby inducing the muscle to twitch. This clearly suggests that the muscle contractions seen experimentally are generally elicited by the stimulation of internal nerves.

In addition, the modeling effort led to a clear demonstration of the non-thermal nature of the electro-stimulation process with ultra-short pulses. For example, with an applied voltage 5 kV, a maximum peak temperature rise of about 0.5° milli-Kelvin was predicted.

The role of pulse shape in affecting the bio-response and influencing nerve stimulation was also probed. It was shown that for direct contacted electrical stimulation, a sharp rise or falling edge of the pulse does not contribute significantly to nerve excitation. However, rectangular pulses performed more vigorously in nerve excitation than triangular and trapezoidal ones with the same duration. This was because rectangular pulses, as compared to other shapes, have maximal amplitude for the entire duration, thereby, generating a much larger average activating function.

The present study also showed that inhomogeneities of potential distribution are desirable for nerve stimulation from the standpoint of producing a large activating function. One way of achieving this is through variations in electrode separation for the case of direct stimulation. Based on several simulations of different electrode configurations, an Anode-Cathode-Anode (ACA) scheme was seen to provide the best results. It was shown that the ACA scheme developed was much more efficient than
traditional bipolar electrode arrangements. For example, the threshold voltage is reduced by 50% on using the ACA scheme, instead of a bipolar arrangement for the same 10 mm electrode separation. The most optimal case was seen to result for an electrode separation of 1 mm; with the tissue excitation threshold being reduced by as much as 75%.

The simulations model was shown to be robust and versatile by applying it to indirect bio-stimulation as well, with the tissue immersed in a bath containing physiological saline (a relatively conductive medium). As expected, the S-D concept was seen to hold well in this situation, though the threshold values were somewhat increased. This increase is understandable, given the additional series resistance of the saline that comes into play, and the changes brought about by from using remote electrodes with large surface areas instead of relatively sharp (hence, field-enhancing) contacts. The model predicted that it would be easier to produce nerve stimulation and muscle twitching over portions of the muscle that had inherent inhomogeneities. This typically, can be expected at the extremities of nerve fibers, due to inherent tapering of the geometries.

The possibilities for tissue stimulations based on remote electromagnetic (EMAG) signals, were also probed. This was done by constructing a point electric field source outside of the muscle volume. The simulations showed that the EMAG wave could not penetrate the muscle very efficiently. This was due to a variety of reasons, including: (1) the abruptly changing media and its characteristics across the interface; (2) the relative distance between the muscle and the source which gave rise to signal attenuation and dispersion; and (3) the permittivity and conductivity of the muscle. The induced electric field along the nerve was seen to be much smaller in comparison to the source amplitude.
However, inhomogeneities in the E-field distribution that were predicted seen to bode well, since this could help boost the magnitudes of the activating function for tissue twitching. Detailed analysis of nerve stimulation remains to be carried out for remote electromagnetic scenarios.

5.2 Suggestions for Possible Future Work

Model-based quantitative assessments of the bio-response and twitching reaction of a nerve axon directly stimulated by extra-muscular electrodes have been done for ultra-short (nanosecond) pulses. The results agreed well with experiments, and relative large magnitudes of the activating function were predicted. However, remote electromagnetic bio-stimulation did not appear to be promising, and did not yield significant electrical field penetration. However, the flexibility and portability of electromagnetic stimulation still makes it a useful are of future investigations, and more systematic research studies. Some of the possibilities for future work in this general area include the following.

(i) Possibilities for better, larger magnitude and more focused source development. From the concept of energy conservation, multiple sources such as a plate source or an array of wire transmitters are suggested for producing large extra-cellular electric fields along a nerve fiber. Each of the six EMAG field components (and/or even a combination of these) could be chosen as sources that could then be applied to any direction of the nerve fiber.
(ii) Studies into the effects of pulse shaping and axon termination impedance. Arguably there would be more complex for the case of electromagnetic stimulation. Pulse edge could have more influence and the SD curve would need to be carefully analyzed.

(iii) Rectangular pulses may or may not be good sources for EMAG nerve excitation, regardless of their duration. The predictions for the direct electrode case need to be carefully validated through further simulation and experiments.

(iv) The effects of multiple electrodes can also be assessed. It is possible that strong additive effects might be possible, especially in the context of full-body stimulations.

(v) The role of external conditions, such as water on the tissue, penetration depth of the electrode pins, could be analyzed as well through a systematic parameter variation within the numerical codes.

(vi) Finally, the codes developed could be extended to cover more realistic, three-dimensional (3D) geometries, instead of the simple rectangular ones studied here.
REFERENCES


Feng Chen was born in . He received the B.S. degree in electrical and electronics engineering in 2002 from the University of Electronic Science and Technology of China, Chengdu, P. R. China. Since August 2002, he has been working on his M.S. degree in Electrical Engineering at Old Dominion University, Norfolk, Virginia. He worked as a research assistant for Dr. Ravindra P. Joshi and a teaching assistant for Electrical and Computer Engineering department during his graduate program.