CHARACTERIZING NERVE FIBER ACTIVATION BY VARYING FIBER
DIAMETER AND DEPTH WITHIN A CONDUCTIVE MEDIUM:
A FINITE ELEMENT APPROACH

A Thesis presented to
The Biomedical Engineering Department Faculty Of
California Polytechnic State University, San Luis Obispo

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science in Biomedical Engineering

By
Nathan Daniel Soto

July 2011

© 2011

Nathan Daniel Soto

ALL RIGHTS RESERVED

COMMITTEE MEMBERSHIP

TITLE: Characterizing Nerve Fiber Activation by Varying Fiber
Diameter and Depth within a Conductive Medium:
A Finite Element Approach

AUTHOR : Nathan Daniel Soto

DATE SUBMITTED: August 2011

COMMITTEE CHAIR: Dr. Robert Bruce Szlavik

COMMITTEE MEMBER: Dr. David Clague

COMMITTEE MEMBER: Dr. Scott Hazelwood

ABSTRACT

Characterizing Nerve Fiber Activation by Varying Fiber Diameter and Depth within a Conductive Medium: A Finite Element Approach

Nathan Soto

In some instances neuropathies can be diagnosed through a conduction velocity test. However, not all neuropathies can be classified using this method. Gaining an understanding of how the stimulus level varies for different fiber sizes at different fiber depths within a conductive medium will provide useful information for simulation studies.

Following a two-step approach using COMSOL and MATLAB, a simulation was implemented to investigate the stimulus necessary to activate different sized fibers at different depths. In this two-step approach, COMSOL was used to describe the voltage profile that would be present within a conductive medium after a stimulus was applied. This voltage profile could then be analyzed using a program written in MATLAB to determine if the applied stimulus was sufficient to activate a given fiber. The analysis was performed using a stimulus method using a constant DC source. Two finite element models were also used, one using a homogeneous medium and the other inhomogeneous.

A three dimensional plot was created to describe the effect of both the depth and diameter of a fiber on the required stimulus for fiber activation. From this plot, an equation was fit to the data to represent the activation function of a nerve fiber at various diameters and depths.

Table of Contents

List of Tables	vi
List of Figures	vii
CHAPTER 1 – Introduction.....	1
CHAPTER 2 – Anatomy and Physiology of a Nerve.....	3
2.1 – The Nervous System.....	3
2.2 – Nerve Communication.....	5
2.3 – Nerve Fiber Types.....	8
2.4 Neuropathies	10
CHAPTER 3 – Diagnostic Tools and Methods	11
3.1 Conduction Velocity Test.....	11
3.2 Determining Fiber Size Distribution	13
3.3 Finite Element Analysis	18
3.3.1 COMSOL	21
3.3.2 Finite Element Uses in the Biomedical Field	23
3.3.3 Nerve and Muscle Excitation using COMSOL.....	24
3.4 Similar Work Investigating Fiber Activation	27
CHAPTER 4 – 2D Modeling of Nerve Fibers.....	28
4.1 Model Development	28
4.2 Overall Simulation Setup	40
CHAPTER 5 – 2D Results of Nerve Fiber Activation.....	51
5.1 Initial COMSOL Model Analyses	51
5.2 Initial COMSOL Model Fiber Characterization Results.....	54
5.3 Modified COMSOL Model Analysis	62
CHAPTER 6 – 2D Analysis of Nerve Fiber Activation	68
6.1 Data Analysis: Comparisons	68
6.2 - 3D Data Analysis.....	73
6.3 – Conclusion.....	78
List of References.....	80
Appendix A – MATLAB Program (DC Voltage Source)	82
Appendix B – Flow Chart of Initial Proposed Simulation Method.....	85
Appendix B – Flow Chart of Modified Proposed Simulation Method.....	86
Appendix D – Flow Chart of Modified Proposed Simulation Method Including Fiber Material Characteristics	87

List of Table

Table 2. 1 Conduction Velocites of Various Nerve Fibers [2]	9
Table 4. 1 Material Properties for 2D Model [16] [17]	32
Table 4. 2 Paramater values and formulas used to calculate the equivalent circuit components [16].....	43
Table 4. 3 Voltage Source Values for Myelinated Fiber Model	44
Table 4. 4 PSPICE Simulation Values – DC Source	47
Table 4. 5 MATLAB Program Results – DC Source	50
Table 4. 6 MATLAB vs PSPICE Comparison	50

List of Figures

Figure 2. 1 Nerve fiber bundles within a nerve trunk [1]	3
Figure 2. 2 Ion Transfer within Nerve Fiber [2]	5
Figure 2. 3 Activation of Action Potential [2]	6
Figure 2. 4 Action potential movement across different fibers [3]	8
Figure 3. 1 Nerve Conduction Velocity Test [6]	11
Figure 3. 2 Conceptual Configuration of Proposed Technique by Szlavik [8]	14
Figure 3. 3 Finite Element Model [9]	19
Figure 3. 4 Unsolved FEA Model [11]	23
Figure 3. 5 Solved FEA Model [11]	23
Figure 3. 6 Coupling of two models using COMSOL [12]	25
Figure 3. 7 COMSOL Model Describing Action Potential Location [10]	25
Figure 4. 1 Initial COMSOL model	29
Figure 4. 2 Revised Model using Electrode Model	31
Figure 4. 3 Boundary Condition Setup in COMSOL	32
Figure 4. 4 Subdomain Material Settings in COMSOL	33
Figure 4. 5 Mesh Example	34
Figure 4. 6 Mesh Convergence	35
Figure 4. 7 X-Direction Voltage Profile	37
Figure 4. 8 Y-Direction Model Voltage Profile	38
Figure 4. 9 Simulation Model Setup	39
Figure 4. 10 Simulation Flow Chart	40
Figure 4. 11 Voltage Profile taken at 2mm Deep	41
Figure 4. 12 Equivalent Circuit Model of a Section of Myelinated Axon[16]	42
Figure 4. 13 Five-Node System Setup	44
Figure 4. 14 PSPICE Circuit Diagram Modeling 5 Node System – DC Voltage Source	45
Figure 4. 15 Intracellular Voltage Plot from PSPICE – DC Source	46
Figure 4. 16 Membrane Potential Plot from PSPICE – DC Source	46
Figure 4. 17 MATLAB Simulation: Intracellular Voltage	49
Figure 4. 18 MATLAB Simulation: Membrane Voltage	49
Figure 5. 1 Plot to determine current density necessary to meet 25mV threshold	51
Figure 5. 2 Updated Flow Chart Including Interpolation Function	53
Figure 5. 3 DC Source Model – Depth Correlation	54
Figure 5. 4 16 and 20 Micron Fibers	55
Figure 5. 5 Fit Regression Line – Side-by-Side Comparison	56
Figure 5. 6 Effect of Fiber Diameter on Activation	58
Figure 5. 7: Example Best Fit – Exponential Function	59
Figure 5. 8 Example Best-Fit Power Function	59
Figure 5. 9 FEA Model Including Fiber	63
Figure 5. 10 Modified Flow Chart Including Fiber Material Characteristics	64
Figure 5. 11 DC Case – Fiber Model	65
Figure 5. 12 Individual Plots Relating Stimulus and Depth – Fiber Model	65
Figure 5. 13 Effect of Fiber Diameter – Fiber Model	66

Figure 6. 1 DC Model Comparison – Fiber vs No-Fiber.....	68
Figure 6. 2 Comparing Current Densities Fiber Model vs Omitting Fiber	69
Figure 6. 3 Percent Difference – Fiber Model vs Omitting Fiber	69
Figure 6. 4 Current Density Distribution under two circular electrodes (1) 5 cm radius (2) 2.5 cm radius[18].....	71
Figure 6. 5 3D Plot of Fiber/DC Model.....	73
Figure 6. 6 3D Color Contour Plot	74
Figure 6. 7 3D Plot from Activation Function	75
Figure 6. 8 Contour Plot from Activation Function	76

CHAPTER 1 – Introduction

The biomedical field has changed tremendously throughout the past 20 years. Complicated electrical and mechanical systems are now being implemented into medical devices, which are advancing the field at an extremely high rate. Some of the most significant changes can be seen in the area of neurology and integrating medical devices with the neurological systems of the body. Companies are creating a division to investigate medical devices that address the subject of neuromodulation and neurostimulation.

Understanding the intricacies of the nervous system is very important in developing a device that neuromodulates or neurostimulates correctly. One such example can be seen in devices that target people with chronic back pain. Neurostimulation devices are currently being designed to stimulate specific nerve fiber bundles in an attempt to mask the chronic pain signal. During this stimulation a large group of nerve fibers are usually stimulated because current technology is not capable of controlling the stimulation of individual fibers.

Although this lack of ability to control the stimulation of individual fibers has not hindered these devices from treating their patients, more knowledge of how different fibers are stimulated could offer great benefits to the future of these devices. Neuroprosthetics is one application that would greatly benefit from differentiating the stimulus required to activate various fiber types. Characterizing how individual fibers respond to a given stimulus would allow much finer control of the nerves being targeted in the neuroprosthetic device and could lead to a much more accurate human-computer interface in these devices.

Understanding how different nerve fibers respond to a given stimulus is what inspired the works of this paper. The goal of the simulations in this paper is to explore different sized nerve fibers, at different depths within a conductive medium and develop an equation that will describe the stimulus necessary to activate fibers at different depths and diameters.

CHAPTER 2 – Anatomy and Physiology of a Nerve

2.1 – The Nervous System

Before delving into the technical aspects of this project, it is important to first gain an understanding of the anatomical and physiological systems that will be dealt with. This study focuses on the nervous system, specifically the peripheral nervous system. The peripheral nervous system consists of all the nerves of the human body outside of the brain and spinal cord.

The central nervous system, which consists of the brain and spinal cord, is where all nerve activity is processed and reacted to. Other nerves stemming from the spinal cord and cranial area are thus considered part of the peripheral nervous system. Within these nerves are nerve fibers, which are the contents of the nerves that send and receive information from the central nervous system. Often times a nerve will be referred to as a nerve trunk to prevent any confusion between a nerve trunk and nerve fiber. These nerve fibers are wrapped into bundles within a nerve trunk shown in the figure below.

Figure 2. 1 Nerve fiber bundles within a nerve trunk [1]

In general, fibers classified as afferent fibers, process information from the environment and send this information back to the brain, such as touch or smell. Efferent fibers are the fibers associated with reacting to the information processed by the brain, such as moving your hand away from a hot pan. Often times both of these fibers are present within a given nerve trunk, which classifies the nerve as a mixed nerve[2].

Nerve fibers often have a variety of different sizes, and shapes, which is due to the endless combinations of dendrites and axons that can extend from the body of the neuron. The varying sizes and shapes are based on the type of information that needs to be sent and received. The dendrites receive the information from a neighboring neuron, while the axon transmits the signal across the length of the entire neuron. The body's ability to develop different shaped neurons allows information of different importance to reach different areas of the body at a fast or slow speed.

2.2 – Nerve Communication

The conduction of this information can be described at the physiological level to understand exactly how this information is sent from one neuron to the next and across the length of the nerve. The way in which neurons communicate to each other is through electrical impulses. These electrical signals, called action potentials, are produced within each neuron mostly by three main ions, sodium, potassium and chloride[2]. There are other ions involved in the production of the action potential, but their affect is so small that these three are sufficient to describe the formation of an action potential. When activated within the neuron, these action potentials propagate throughout the neuron as well as along the length of its axon(s).

In order for an action potential to occur, a specialized molecular process has to occur. Figure 2.2 illustrates how these ions move across a nerve fiber.

Figure 2. 2 Ion Transfer within Nerve Fiber [2]

At a resting state, a neuron will have a resting potential of approximately -70 millivolts (mV). The occurrence of an action potential is an all-or-nothing event, and a threshold voltage must be reached for this event to happen. This threshold level is considered to be roughly -55 mV. In order to reach this threshold voltage, specialized molecular processes must occur. Sodium channels open which allow an influx of sodium ions into the membrane causing the first phase of the action potential to occur called depolarization. Once this depolarization causes the internal voltage to reach the threshold of -55 mV, additional sodium ion channels open to allow the action potential to occur and the internal voltage to reach its maximum depolarization level of around +35 mV, as shown in Figure 2.3 [2].

Figure 2. 3 Activation of Action Potential [2]

After the peak is reached, potassium ion channels open and sodium channels that were opened close to cause the repolarization phase, so the neuron can go back to its resting state. The entirety of an action potential occurs on the order of a few milliseconds, which allows the fast transfer of information throughout the body.

2.3 – Nerve Fiber Types

Not all signals move at the same conduction velocities. This is due to the type of fiber that is conducting the signal. Most fibers fall under one of the three different fiber types: A fibers, B fibers, and C fibers. These classifications are based on their diameters, and other physiological characteristics. In general, A fibers are the largest fibers, and are also the fastest conductors. Another factor called myelination also facilitates fast conduction. Myelin is a covering around axons much like a plastic insulator around a wire. However, the myelin is only placed in segments along the entire axon, which results in small areas of the axon being exposed. The electrical properties of myelin are equivalent to a high resistance and low capacitance circuit, allowing it to act much like an insulator. For this reason, myelin causes electrical signals to move quickly because little current flows through the myelin, allowing the signal to “jump” from one exposed area of the axon to the next. These exposed areas are referred to as Nodes of Ranvier.

Figure 2. 4 Action potential movement across different fibers [3]

B fibers also contain this myelination, but are much smaller than A fibers, and have slower conduction velocities. The last types of fibers, C fibers, are the smallest of all the fibers and are unmyelinated, making them far slower than the previous 2 fibers described [2]. Table 2.1 below demonstrates the numerical difference between the conduction velocities of the different fiber types.

Fiber Type	Function	Fiber Diameter (mm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period (ms)
A α	Proprioception; somatic motor	12–20	70–120	0.4–0.5	0.4–1
β	Touch, pressure	5–12	30–70		
γ	Motor to muscle spindles	3–6	15–30		
δ	Pain, temperature, touch	2–5	12–30		
B	Preganglionic autonomic	<3	3–15	1.2	1.2
C dorsal root	Pain, reflex responses	0.4–1.2	0.5–2	2	2
sympathetic	Postganglionic sympathetics	0.3–1.3	0.7–2.3	2	2

Table 2. 1 Conduction Velocites of Various Nerve Fibers [2]

2.4 Neuropathies

Sometimes these fibers do not perform as intended and react at a much slower velocity than expected because of damage that occurs through an injury or from a disease. In either case, the damage that results in a dysfunction of a nerve fiber is known as a neuropathy. Most nerve damage can be associated with physical causes such as cutting your finger with a knife or breaking a bone which can also damage surrounding nerves. These conditions are fairly easy to diagnose and treat because it is known in which area of the body the injury occurs. Neuropathies caused through disease are more complicated. Diabetes is one of the best known examples of how a disease can cause tremendous damage to the nervous system and pin-pointing where this damage is occurring is much more difficult because there are no visual indicators. Often times the damage will be associated with segments of a nerve fiber demyelinating or degeneration of a nerve fiber's axon [4].

The most common classification of diabetic neuropathies is the sensorimotor peripheral neuropathies. Common effects of this nerve damage include prickling or stabbing, and burning or aching pain normally in the lower region of the body, but can also occur in the fingers and hands [4]. Locating where in the body these symptoms are originating from can be extremely difficult because of the larger amount of nerve fibers within each region of the body.

CHAPTER 3 – Diagnostic Tools and Methods

3.1 Conduction Velocity Test

Diagnosing these neuropathies can prove to be very difficult before they develop to the later stages because of the limitation of the diagnostic techniques currently being used. Typically, a nerve conduction velocity test (NCV) is performed on a patient to determine if the patient's nerves are conducting correctly. During a NCV test, a measurement is taken of the speed of conduction of an action potential through a nerve [5]. This measurement is obtained through surface electrode patches. These patches are placed on surface of the skin as shown in figure 3.1 to stimulate a specified nerve.

Figure 3. 1 Nerve Conduction Velocity Test [6]

One of these electrodes acts as the stimulator while the other records when the action potential reaches its position. With this information, it can be determined how fast or slow the nerve is conducting by using the time it takes for the signal to move from the stimulating electrode to the recording electrode and the distance between the two electrodes [5]. As stated before, the conduction velocity of a nerve is strongly dependent on its myelination, and size, so understanding which nerve you intended to stimulate is extremely important. Unfortunately, the NCV test does not provide information regarding the individual fibers within a nerve trunk, because the faster conducting fibers dominate the signal. Faster conducting fibers dominate the signal because the NCV test measures the accumulated signal over time which allows the faster conducting signals to contribute more to the accumulated signal than the slower conducting signals. The measurement found in a NCV test is essentially created from an average of contributions made by all of the individual nerve fibers within a nerve trunk rather than investigating the individual nerve fibers themselves, so a precise diagnosis cannot always be determined solely on this test [7]. In order to address this issue, many studies have been performed to try and investigate the individual contributions of the fibers within a nerve trunk and the effect of these contributions to the overall function of the nerve trunk.

3.2 Determining Fiber Size Distribution

Gaining a better understanding of the nerve fibers within a given nerve trunk have become a recent topic of interest so Szlavik [8] began investigating a technique that could characterize the population of nerve fibers within a nerve trunk in terms of the fiber diameter. Having this information could prove to be very valuable because there would be a better understanding of which fibers, in terms of size, were contributing to the evoked potential. With knowledge of which fiber size is being targeted, a more accurate diagnosis could then be made because in some cases diseases only target specific size fibers. An example of this is in early diabetic peripheral neuropathy, where mainly small diameter fibers are affected.

In this study, Szlavik [8] presents a technique to estimate the size distribution of the nerve fibers which is linearly related to the conduction velocity distribution. The basis of this technique lies on the estimation of the group delay between two sets of recordings electrodes. This group delay is then associated with the individual fibers that contribute to the maximum compound evoked potential [8]. With the group delay information, an estimate of the fibers' diameters is then made and the propagation delay of each individual fiber's potential with respect to the reference electrode is estimated. After the individual evoked potential waveforms are determined, an estimation of the maximum compound evoked potential can then be determined.

The setup for this simulation is very similar to setup shown previously in the conduction velocity tests. Figure 3.2 below demonstrates what the physical setup would look like.

Figure 3.2 Conceptual Configuration of Proposed Technique by Szlavik [8]

One electrode position was used as the stimulator for the system, while the other two electrodes positions were used as the recording sites for the simulation. All values used for the dimensions between these electrodes were arbitrary and were chosen for convenience. Other assumptions that were made for this simulation included the following [8]:

- Each activated nerve fiber would transmit an action potential at the same time from the same site as the stimulus.
- A fixed precise value of stimulus current, dependent on nerve fiber size, is the threshold required to excite a nerve fiber (although it is acknowledged that the threshold required can fluctuate over a small range)
- The conduction velocity distribution (CVD) is invariant along the nerve
- A linear relationship between conduction velocity and fiber diameter is assumed
- Nerve fiber depth will have an influence on activation based on stimulus and tissue anisotropy, but a fixed depth as well as isotropic condition is assumed.

The second and last bullet points are the focus of the work presented in this dissertation.

In conducting the experiment, a random population of nerve fiber diameters were created using a technique used by Szlavik and de Bruin in their previous work [8]. This technique involved using the following equation:

$$p_d(d_k) = \sum_{h=1}^4 \frac{\beta_h}{\sigma_h \sqrt{2}} \exp \left[-\frac{(d_k - \mu_h)^2}{2\sigma_h^2} \right] \quad (1)$$

The result of this equation describes the probability density function with respect to the fiber diameter. After generating a population of nerve fibers using the above distribution, the distribution was exposed to virtual stimulus pulses. These pulses were applied with amplitudes of, Ω and increments of, i giving the value at each increment to be, Ω_i .

The next step was to determine whether or not a nerve fiber had been activated which can be described by the following set of equations. The first of these equations describes the activation function.

$$\xi(d) = \zeta \exp[-\eta d] \quad (2)$$

The diameter of the fiber, d , can vary, but the value for η and ζ are constant, where $\eta = 3.5 \times 10^5 \text{ m}^{-1}$ and $\zeta = 10 \text{ mA}$. The value of this function is then used to determine if a fiber has fired at a given stimulus level or not.

$$\mathbf{\Omega}_i^{(n)}(t) = \sum_{k=1}^m u[\Omega_i - \xi(d_k)] G[v_k \cdot (t - \delta_k^{(n)}, \bar{r})] \quad (3)$$

The above equation describes the compound evoked potential where $n=1,2$ for each recording site, t =time in seconds, G =single fiber action potential waveform, and u =step function. The value of, u , depends on the result from the subtraction operation occurring, $[\Omega_i - \xi(d_k)]$. If the result is found to be zero or positive then the value of the step function is 1. If the result is found to be negative, the value of the step function is 0. This computation determines if a nerve fiber is activated. If the stimulus current, Ω_i , is greater than or equal to the activation function of the specified size fiber, $\xi(d_k)$, then the fiber is considered to be activated. Another noteworthy is the value of $\bar{r}$, which is the fiber depth. In this computation, a constant value of 1mm is used to describe the nerve fiber depth.

The use of the step function within the overall compound evoked potential equation will be investigated in greater detail in this work. The other issue that is going to be addressed is the variation of fiber depth. By investigating how fiber depth and fiber diameter affect the activation of a nerve, a more accurate characterization of fiber size distributions can be made. With these results, the

contents of the step function will be replaced with a more realistic characterization that takes into account depth dependent variation as well as fiber diameter variation.

3.3 Finite Element Analysis

Understanding what the finite element method is as well as its common uses is very important in recognizing why it is the chosen method to be used for this research. In a brief sense, the finite element method is a numerical analysis technique for obtaining approximate solutions to a variety of engineering problems [9]. This type of analysis initially was used solely for airframe structure analysis of stress, but has proved to be applicable to a wide variety of engineering fields. Developing governing equations and boundary conditions for most problems can be done fairly simply, but solving these systems can often be tedious and require a large amount of effort because of the presence of partial differential equations. In some situations, simplifying assumptions or idealizations may be made to decrease the complexity of the problem, at the expense of accuracy. With the finite element method a much more accurate approximation can be made using the constraints of the complex problem and in much less time than traditional methods. The reason the FEM is considered an approximation is because the region being analyzed is broken down into small, interconnected subregions or elements [9]. Each of these elements are normally of different sizes and shapes because the geometry of the models being analyzed are normally fairly complex. The flexibility of element sizes allows the FEM to be an extremely accurate means of approximation because it can adapt to complex geometries. In figure 3.3 below, it can be seen how a model of a turbine blade cross section might be broken down using FEA.

Figure 3. 3 Finite Element Model [9]

With the model broken down into a finite number of elements, the problem can now be solved. Each point that connects the elements and regions are referred to as nodes, which reflect where the value of a solution will lie. In most cases these nodes will be placed along the boundaries of a model as well as areas of connecting elements. These nodes act similarly to points in a data sheet that are used to create a plot. The points within the data sheet are initially unknown values for which a solution can be computed and everything in between is interpolated based on the relationship between the two connecting points. This same concept is the basis for FEA and is where the approximation occurs in the analysis. Each of the nodes is considered an unknown within the model yielding a finite number of unknowns. Once all of these unknowns are determined, interpolation is made based on the determined values of the solution at the nodes. When all of these approximations are made within each region, a result is generated describing the entire system. Essentially, the finite element method breaks down a large complex problem, into multiple simpler problems which are then compiled to describe the entire system.

The accuracy of the solution relies strongly on multiple factors including the size of the elements, shape of the elements, and the interpolation function. As one would guess, as the size of the elements get smaller, the solution of the system will likely become more accurate, but this increase in the number of elements also requires a longer processing time. The shape of the elements also has a strong influence on the result. In most elementary FEM courses, an introduction to using rectangular and triangular shaped elements is discussed. Triangular elements are often used because their ability to flexibly shape to their environment as shown in figure 3.3. Rectangular elements do not have the same flexibility as triangular elements do. Interpolation functions can vary, depending on the element type. Initial uses of the interpolation function often consist of a linear change from one node to the next, but in most situations a linear change will not suffice. In most cases polynomial functions are used because they are easy to integrate and differentiate. The order of the polynomial depends on the number of nodes in each element, number of unknowns at each node and the continuity requirements imposed at the nodes. By using FEM software and running simulations using different element sizes, shapes, and interpolation functions, an optimum solution can be found by comparing these results.

Although the FEM was initially used as a tool for mechanical engineers and civil engineers to analyze structures, applications of FEM have begun to be seen in fluid mechanics, heat transfer, and even electromagnetism [9]. The broader range of applications has allowed projects which deal with electrical systems such as the one investigated in this work to use the FEM in its research.

3.3.1 COMSOL

For this application the finite element software package, COMSOL, was chosen because it contains a pre-programmed module for electrical systems.

COMSOL Multiphysics is a powerful interactive environment for modeling and solving all kinds of scientific and engineering problems based on partial differential equations [10]. Once models are created, it is very easy to add the physical quantities related to the system such as materials properties and/or current sources. Steady-state or time-dependent analysis as well as linear or nonlinear analysis can be performed. This versatility can be of great use because an initial model can be made very simple and then complexities can be added later to more realistically represent the overall system. The reason COMSOL is referred to as a multiphysics program is that it can model a more real world condition where one variable often depends on others. An example of a multiphysics application is a conductor. The electric resistance of a conductor will in many instances vary with temperature [10]. COMSOL allows the relationship between the resistance of a conductor and heat it expels to be modeled within a system.

The module within COMSOL that was chosen for this particular study is called the AC/DC module. This module allows the simulation of AC/DC electromagnetics in 2D and 3D models and can be done under static, quasi-static, transient, or time-harmonic conditions. Material properties can also be changed such as whether the material is inhomogeneous, isotropic, or anisotropic. Some applications for this module include: electrostatics, conductive

media DC, magnetostatics and low-frequency electromagnetics [10]. The simulation type that this study will be using is the conductive media DC because the human body can be considered a conductive media.

Before moving forward, it is important to examine the partial differential equations that are used in solving conductive media models in COMSOL.

At each node from a generated mesh, a partial differential equation is solved to create the contour profile. For this application using a conductive media, the point form of Ohm's Law describing this application can be seen as followed.

$$\mathbf{J} = \sigma \mathbf{E} + \mathbf{J}^e \quad (4)$$

This equation describes the current density with a specific electric conductivity, σ , an electric field, E , and externally generated current density of J^e .

Using the static form of the continuity equation results in the following where, V , describes the electrical potential.

$$\nabla \cdot \mathbf{J} = -\nabla \cdot (\sigma \nabla V - \mathbf{J}^e) = 0 \quad (5)$$

A more generalized equation to include the presence of current sources can then be written by adding Q_j , which is the current source.

$$\nabla \cdot \mathbf{J} = -\nabla \cdot (\sigma \nabla V - \mathbf{J}^e) = Q_j \quad (6)$$

In this case the model has symmetry where the electrical potential varies only in the x and y directions and is constant in the z -direction. With this in mind, COMSOL can then solve the following equation at each node within each subdomain, where d is the thickness in the z -direction.

$$\nabla \cdot \mathbf{J} = -\nabla \cdot d(\sigma \nabla V - \mathbf{J}^e) = dQ_j \quad (7)$$

3.3.2 Finite Element Uses in the Biomedical Field

An example of the finite element method being used for this purpose is in a study investigating the electrode influence on current distribution in the skin. In summary, the investigation wanted to prove that discomfort during surface functional electrical stimulation could be a result of high current density in the skin underneath the electrode [11]. In order to investigate this issue, a finite element model was created to characterize the contents of the body underneath the electrode. Figure 3.4 below demonstrates the setup of the finite element model before the analysis.

Figure 3. 4 Unsolved FEA Model [11]

Figure 3. 5 Solved FEA Model [11]

After dimensioning the model and applying the desired material properties, a solution could then be found. Figure 3.5 above demonstrates the type of results that can be generated from a finite element solver. In this case, a hot-cold visual is used to demonstrate the current-density values throughout the model. With

these model results, an initial conclusion can be made concerning whatever hypothesis is investigated. In this case, it is seen that a large current density occurs between the hydrogel and sweat duct, which verifies their initial hypothesis that high current densities are present underneath the skin.

It is very important to note that using a finite element solver and validating its results requires much more than just creating a model and solving. Validations must be performed such as verifying the boundary conditions are correct, understanding where the mesh convergence occurs, determining mesh sizes, and other factors that will be discussed in more depth later in this work.

3.3.3 Nerve and Muscle Excitation using COMSOL

In another very recent study, an investigation used COMSOL to simulate the Hodgkin-Huxley-like model. The Hodgkin-Huxley model is a mathematical model created to describe the excitation and spike propagation in nerve and muscle fibers using gating mechanisms [12]. In this simulation a coupling of two different models was used to describe the excitation of a muscle fiber within a biological environment.

Figure 3. 6 Coupling of two models using COMSOL [12]

The figure above describes the model created in COMSOL and the plot of the functions used to determine if the fiber was activated. A model of the surrounding tissue was created, as well as a model of the muscle fiber. With these models a square voltage source was used to create a voltage profile in the tissue. The voltage value found at the muscle fiber could then be coupled with a function describing the intracellular activity to this stimulus [12]. This function would then output a solved model such as the one below describing where an action potential would occur.

Figure 3. 7 COMSOL Model Describing Action Potential Location [10]

Models such as these describing the activity of nerve fibers using a finite element solver demonstrate that there is a lot of potential in using this software for biological modeling and is one major reason why the study being performed in this work is using the FEM.

3.4 Similar Work Investigating Fiber Activation

Some work has already been completed regarding the investigation of how nerve fiber depth and diameter affect stimulation of the nerve fiber. In the previous study by Altman and Plonsey, the research focused on using a point source as electrical stimulation along the surface of a nerve bundle [13]. In this case the study hoped to prove how nerve fiber depth and diameter within the constraints of a nerve trunk affected the activation of a nerve fiber. This is different from the study that will be performed in this work because their model constraint is a nerve trunk while the model constraint for this study is the human arm. However, this study will use the same analytical approach as Altman and Plonsey to determine whether a nerve fiber is activated. This approach consists of a two-part process to determine nerve activation. The two-parts consists of computing the potential field through space as a result of electrode stimulation, and applying this potential to a model for myelinated nerve fibers to determine if fiber activation occurs [13]. The model configuration as well as nerve material properties were used from the Altman study, which involved starting with a simple model that is isotropic and homogeneous and then increasing the model complexity. With a multiple model setup, quantitative analysis can be made comparing the effects of changing characteristics within the model.

CHAPTER 4 – 2D Modeling of Nerve Fibers

The first component being investigated in this project will be with a 2-dimensional model. This will allow a baseline set of values that the future models can base their results on.

4.1 Model Development

Determining what needs to be included within the model is very important in the design process. It was decided that this model should follow a similar setup to that used in the simulation proposed by Szlavik concerning fiber size distributions, which can be seen in figure 3.2. In this simulation a stimulating electrode and two recording electrodes are placed along the length of an arm. Creating a theoretical model of a segmented part of the arm as well as the corresponding stimulating electrode are the two most important features that had to be included within this model. The two recording electrodes could be ignored because a finite element solver is being used and the results can be seen along the entire model, so there is no need for a recording electrode. With these ideas in mind, the initial model created is shown below. This model was created to describe a small segment of the arm in which the stimulating electrode would be placed in a conduction velocity test.

Figure 4. 1 Initial COMSOL model

With the model developed, boundary conditions had to be implemented. Based on what was previously stated and the decision to omit the recording electrodes from the model, it was important to set correct boundary conditions. In this case the left and right bound edges of the model were defined to be “ground.” The assumption can be justified when the model is created to a specific size where the voltage profile converges to zero in the x-direction or width of the model. Using the “ground” boundary condition will also result in a smooth voltage profile that decreases to zero as you reach the edges. This is important for the electrical analysis that occurs in the MATLAB portion of this simulation where it is required to have a voltage of essentially zero at the ends. If these boundary conditions were set to an insulating material, the voltage profile would not have

the same smooth decreasing trend and would not reach zero at the boundary edges. The lower bound of the model is to also follow this criterion where the voltage-profile convergence must be found in the y-direction to justify using the ground boundary condition. The only boundary of the model which will not be ground is the upper bound. This boundary can be likened to the skin surface of the human body, and in this case will be considered an insulating material.

In the initial trials using the following model, a point source was used to simulate the stimulation by the electrode with arbitrary material properties. This point source was placed directly under the surface of the skin boundary condition. The results of these initial model simulations were not what were expected, and the reason for the discrepancy was the small size of the point source. The output of this source was too small, and was an incorrect means of modeling an electrode used in a normal NCV test. Electrodes used in an NCV test are normally much larger than a small point. A better application for a point source would be for a subcutaneous needle electrode, which is used in a variety of biomedical applications. With these findings the following model was created, which included a second part to the model to represent the stimulating electrode. Placing the stimulating electrode on the surface of the model creates a more realistic representation of a NCV test and will likely result in more accurate simulation results.

Figure 4. 2 Revised Model using Electrode Model

Using this new model setup, additional boundary conditions had to be applied. The right, left, and lower bound of the model all maintained their previous boundary conditions. The only change applied was at the contact point of the electrode lower edge and skin surface. Initially this was considered electric insulation, but with presence of the electrode model, this contact area could now be considered a current source.

Figure 4. 3 Boundary Condition Setup in COMSOL

The upper, left, and right edge of the electrode followed the same boundary condition as the upper-edge of the skin surface (electric insulation).

Adding the electrode model to the overall system created another variable that had to be investigated. The material properties values used for this model were the same as those used in the study by Sha et al. [11] and Krasteva et al. [14]. Those values are shown in the table below.

	Resistivity (Ωm)
Foil Electrode	1.5×10^{-7}
Skin/Fat	20

Table 4. 1 Material Properties for 2D Model [16] [17]

Along with these material properties, the volume conductor was assumed to be a homogeneous and isotropic material. These assumptions allowed a solid baseline set of values to be created which could be used as a basis of comparison for further results.

Figure 4. 4 Subdomain Material Settings in COMSOL

Figure 4.4 describes how the material properties can be adjusted in the COMSOL interface. Each part of the model, which in this case were the electrode and volume conductor, were considered subdomains. Each of these subdomains could be adjusted to their individual conductivities.

The width of the model was initialized at 10cm, with a depth of 7cm, and an electrode with width of 1cm and height of 2mm. The model width and depth were chosen to describe a segment of the human arm, where 7cm was found to be the average thickness of a human arm [15] and 10cm was chosen as an arbitrary length for a segment of the human arm. It was determined that the height of the model should not be any larger than the size of a normal human forearm, because essentially this model is an idealization of the real volume

conductor. The normal electrode size for NCV tests was found using the BIOPAC website.

Before any of this analysis and verification could be completed, the converging mesh size of the finite element model had to be determined. As stated previously in this paper, a finite element model is used as an approximation, but sometimes this approximation can be made more accurate if the mesh sizes are made smaller. The opposite of the impact on accuracy can also occur if the meshes are not made small enough. It is important to determine which mesh size is necessary for the output values to converge. COMSOL makes it easy to refine mesh sizes and to implement initial mesh sizes through the use of the refine mesh tool that allows you to specify the coarseness or fineness of the initial mesh size. Figure 4.3 below demonstrates how these meshes appear in COMSOL. This mesh is an example of a “fine” mesh setting used in the COMSOL software. A more coarse or more fine setting for these meshes can be implemented if necessary.

Figure 4. 5 Mesh Example

Using these tools allowed the generation of the following three plots.

These plots describe the trend of the voltage output based on the degrees of freedom generated from the mesh size. This voltage value was taken at a depth of 2mm and at the center of the model for each mesh size. This process was followed using a model width of 10cm, 20 cm, and 40cm. There were a few trends that were consistent in all three plots that allowed the determination of a viable mesh size. In all three plots, the voltage values lost consistency after around 50000 degrees of freedom. There also appeared to be a consistent set of values between 10000 and 50000 degrees of freedom (DOF) in all three plots, which led to the conclusion that using a mesh with a DOF value within this range will lead to viable results

Figure 4. 6 Mesh Convergence

In spite of only having a small window of consistent values being generated from various mesh sizes, it is also important to note the scale at which these results are being compared. In the worst case, at a model width of 20 centimeters, the results differed by only around 0.1 mV. Comparing this to the entire scope of the problem, having a variation of only .1 mV will have very little effect on the overall results. However, any error, even if it is small, should be avoided if possible. Allowing small variations in multiple steps throughout the process could cause a significant change in the outcome, which is why it is important to determine which mesh sizes yield the best results.

Verifying the size of the model, as well as the corresponding boundary conditions, could now be investigated by using the following procedure. In the first step, the distance from the top edge to the bottom edge of the model remained constant and a profile of the voltage in the x-direction was taken with the initial width. After the initial profile was found, the width of the model was doubled, keeping the height constant, and another voltage profile was recorded. This procedure to double the width and record the profile continued up to 80cm because, as shown below, in this range the results showed definitive convergence.

Figure 4. 7 X-Direction Voltage Profile

With this graph it was determined a width of 40cm was sufficiently large enough to maintain convergence. It was previously stated that convergence would be also necessary in the y-direction, but when the restriction was applied to not have the depth be any larger than a human forearm, the convergence was no longer necessary. Although the convergence investigation was no longer necessary, a plot was still recorded of the y-direction profile to demonstrate the change that can be seen throughout the depth of the tissue medium as shown in figure 4.8 below.

Figure 4.8 Y-Direction Model Voltage Profile

Figure 4.8 demonstrates the voltage profile that is present using the volume conductor depth of 7cm.

Now that the mesh convergence, x-convergence, and y-profile were demonstrated, the final model shown below could now be subjected to virtual stimulus currents. The model below describes the completed model and its geometries undergoing stimulus from a current source. One attribute to note is the presence of the infinite z-dimension. This creates a plane for the electrode, medium, and fiber that are placed in the model. For the purpose of the following analysis, it was assumed that the fiber plane would act similarly to an individual fiber at the specified depth. A similar method to this was used in a study by Martinek et al. [12].

Figure 4. 9 Simulation Model Setup

4.2 Overall Simulation Setup

Once the model was verified by determining convergence factors the simulation phase of this study was then performed. Before describing this process, it is important to emphasize the goal of this simulation study, which is to develop an equation that specifies the current necessary to stimulate fibers of different diameters at different depths. The flow chart below is a simplified description of the processes necessary in determining if a fiber will be recruited at a specific current. A larger image of this flow chart can be seen in Appendix B.

Figure 4. 10 Simulation Flow Chart

The first four steps necessary for determining the stimulus value can all be performed using COMSOL. The desired mesh size has already been determined, so following the next two steps is fairly simple. Once the voltage profile is obtained it will have a profile similar to the plot shown below. The actual voltage values and the slopes along the profile will vary depending upon how deep the fiber is in the tissue. This voltage profile is necessary for analysis in the next step to determine whether the current stimulus applied was sufficient to activate the fiber.

Figure 4. 11 Voltage Profile taken at 2mm Deep

The following step in the study is where it is necessary to have a circuit theory described model of a nerve fiber to process the effect of this extracellular voltage and determine whether this extracellular voltage profile is enough to activate a nerve fiber. In this case, a cable equivalent circuit was used to model a

myelinated nerve fiber as shown in figure 4.12. This modeling approach is similar to circuits use by Bean, Sweeney et al, and McNeal[16].

Figure 4. 12 Equivalent Circuit Model of a Section of Myelinated Axon[16]

Some notable assumptions that are used for this model are that the conductances of the membrane are linear up until the nerve fiber reaches excitation. In reality, the transmembrane conductance per unit area is a non-linear function of the transmembrane potential and time as stated by Szlavik et al. [16]. When looking at the above circuit, it is important to realize what this circuit is modeling. The exposed areas of a nerve are called the Nodes of Ranvier and in this circuit it is at these nodes where the extracellular voltage sources are placed. The shaded areas between the nodes are considered the Schwann cells covering the nerve which act as insulators and are assumed to have high impedances in relation to the exposed membrane. This assumption for Schwann cells is commonly used in nerve studies.

In using this model, Kirchoff's current law can be applied to determine the transmembrane potential, where the values used for each variable are obtained from table 4.2.

$$\begin{aligned}
C_m \frac{dV_m(n, t)}{dt} + G_m V_m(n, t) + G_c [V_e(n, t) + V_m(n, t)] \\
- G_c [V_e(n - 1, t) + V_m(n - 1, t)] + G_c [V_e(n, t) + V_m(n, t)] \\
- G_c [V_e(n + 1, t) + V_m(n + 1, t)] = 0
\end{aligned} \tag{8}$$

ρ_a	Cytoplasm Resistivity	1.1 (Ωm)
g_m	Membrane Conductance	304 (S/m^2)
c_m	Membrane Capacitance	0.02 (F/m^2)
l	Node of Ranvier Width	2.5 (μm)
D	Fiber Diameter	(m)
d	Axon Diameter	(m)
A	Fiber Radius	(m)
a	Axon Radius	(m)
a/A	Ratio of axon to fiber radius	.7
K	Node of Ranvier spacing	100xD (m)
R_c	Equivalent axoplasm resistance	$(\rho_a K)/(\pi a^2)$ (Ω)
R_m	Equivalent membrane resistance	$(2\pi g_m a l)^{-1}$ (Ω)
C_m	Equivalent membrane capacitance	$(2\pi c_m a l)$ (F)

Table 4. 2 Paramater values and formulas used to calculate the equivalent circuit components [16]

The benefit of using this model is its applicability to nerve fibers that are of varying length and diameter. The model is not amenable to solution by hand because of the amount of calculations that would be necessary to solve much more than a 5 node system. For this reason a MATLAB program had to be created to solve this model for varying fiber diameters and lengths. The code for this program can be seen in Appendix A.

A PSPICE schematic was created and simulated to verify that the results of the MATLAB program were correct. In this comparison, a five node system was used for simplicity. The setup for this system is shown in figure 4.13 below.

Figure 4. 13 Five-Node System Setup

The first case examined utilized DC voltage sources at the nodes of the model. This resulted in an open circuit replacing the capacitors in the model. The voltage source values were taken from a voltage profile obtained from a COMSOL simulation and are shown in the table below.

V_1	25.613386 mV
V_2	26.102502 mV
V_3	26.103662 mV
V_4	25.624722 mV
V_5	24.206055 mV

Table 4. 3 Voltage Source Values for Myelinated Fiber Model

The fiber was assumed to have a diameter of 20 μ m, which led to the following calculations of C_m , R_m , and R_c .

$$C_m = 2\pi c_m a l \quad (9)$$

$$C_m = 2\pi(.02)(.7 * 10e^{-6})(2.5e^{-6}) F \quad (9.1)$$

$$C_m = 2.2e^{-12} F \quad (9.2)$$

$$R_m = (2\pi g_m a l)^{-1} \quad (10)$$

$$R_m = (2\pi(304)(.7 * 10e^{-6})(2.5e^{-6}))^{-1} \Omega \quad (10.1)$$

$$R_m = 2.991e^7 \Omega \quad (10.2)$$

$$R_c = \frac{\rho_a K}{\pi a^2} \Omega \quad (11)$$

$$R_c = \frac{(1.1)(100 * 20e^{-6})}{\pi(.7 * 10e^{-6})^2} \Omega \quad (11.1)$$

$$R_c = 1.4291e^7 \Omega \quad (11.2)$$

With the above known values, a PSPICE model could be generated and simulated, as shown in figure 4.13 to determine the intracellular voltage and transmembrane voltage.

Figure 4. 14 PSPICE Circuit Diagram Modeling 5 Node System – DC Voltage Source

Running the simulation under these conditions resulted in the following two plots. The first plot is the intracellular voltage and the second is the membrane potential.

Figure 4. 15 Intracellular Voltage Plot from PSPICE – DC Source

Figure 4. 16 Membrane Potential Plot from PSPICE – DC Source

The resulting voltages are as followed.

$V_1 = 25.613386$	$V_{i1} = 12.056$	$V_{m1} = 13.557$
$V_2 = 26.102502$	$V_{i2} = 17.636$	$V_{m2} = 8.4665$
$V_3 = 26.103662$	$V_{i3} = 19.171$	$V_{m3} = 6.9323$
$V_4 = 25.624722$	$V_{i4} = 17.395$	$V_{m4} = 8.2296$
$V_5 = 24.206055$	$V_{i5} = 11.688$	$V_{m5} = 12.518$

Table 4. 4 PSPICE Simulation Values – DC Source

With these baseline results obtained from the PSPICE analysis, a conclusion could be made on the credibility of the results found from the MATLAB program that was created to model fibers of varying lengths and diameters.

Using Kirchoff's current law the following equations were created to solve for the system, where V_i = intracellular voltage. This analysis was necessary for the creation of the MATLAB program.

$$\frac{V_{i1}(t) - 0}{R_c} + \frac{V_{i1}(t) - V_1(t)}{R_m} + \frac{V_{i1}(t) - V_{i2}(t)}{R_c} + C_m \frac{dV_{(i1-1)}(t)}{dt} = 0 \quad (12)$$

$$\frac{V_{i2}(t) - V_{i1}(t)}{R_c} + \frac{V_{i2}(t) - V_2(t)}{R_m} + \frac{V_{i2}(t) - V_{i3}(t)}{R_c} + C_m \frac{dV_{(i2-2)}(t)}{dt} = 0 \quad (13)$$

$$\frac{V_{i3}(t) - V_{i2}(t)}{R_c} + \frac{V_{i3}(t) - V_3(t)}{R_m} + \frac{V_{i3}(t) - V_{i4}(t)}{R_c} + C_m \frac{dV_{(i3-3)}(t)}{dt} = 0 \quad (14)$$

$$\frac{V_{i4}(t) - V_{i3}(t)}{R_c} + \frac{V_{i4}(t) - V_4(t)}{R_m} + \frac{V_{i4}(t) - V_{i5}(t)}{R_c} + C_m \frac{dV_{(i4-4)}(t)}{dt} = 0 \quad (15)$$

$$\frac{V_{i5}(t) - 0}{R_c} + \frac{V_{i5}(t) - V_5(t)}{R_m} + \frac{V_{i5}(t) - V_{i4}(t)}{R_c} + C_m \frac{dV_{(i5-5)}(t)}{dt} = 0 \quad (16)$$

With the above development there are 5 equations and 5 unknowns.

However in the DC case, time is not a factor and the capacitor does not affect the

system which allows the capacitive term in this equation to be eliminated.

Implementing these changes to the 5 node system results in the following equations:

$$\frac{V_{i1}}{R_c} + \frac{V_{i1} - V_1}{R_m} + \frac{V_{i1} - V_{i2}}{R_c} = 0 \quad (17)$$

$$\frac{V_{i2} - V_{i1}}{R_c} + \frac{V_{i2} - V_2}{R_m} + \frac{V_{i2} - V_{i3}}{R_c} = 0 \quad (18)$$

$$\frac{V_{i3} - V_{i2}}{R_c} + \frac{V_{i3} - V_3}{R_m} + \frac{V_{i3} - V_{i4}}{R_c} = 0 \quad (19)$$

$$\frac{V_{i4} - V_{i3}}{R_c} + \frac{V_{i4} - V_4}{R_m} + \frac{V_{i4} - V_{i5}}{R_c} = 0 \quad (20)$$

$$\frac{V_{i5} - 0}{R_c} + \frac{V_{i5} - V_5}{R_m} + \frac{V_{i5} - V_{i4}}{R_c} = 0 \quad (21)$$

Using the above method to analyze these equations in the MATLAB program resulted in the following two plots. The first plot describes the intracellular voltage and should output results similar to those seen in figure 4.15. The second plot describes the transmembrane voltage and should output results similar to those seen in figure 4.16.

Figure 4. 17 MATLAB Simulation: Intracellular Voltage

Figure 4. 18 MATLAB Simulation: Membrane Voltage

Analyzing these data points result in the following values.

$V_1 = 25.613386$	$V_{i1} = 12.056$	$V_{m1} = 13.557$
$V_2 = 26.102502$	$V_{i2} = 17.636$	$V_{m2} = 8.4665$
$V_3 = 26.103662$	$V_{i3} = 19.171$	$V_{m3} = 6.9323$
$V_4 = 25.624722$	$V_{i4} = 17.395$	$V_{m4} = 8.2296$
$V_5 = 24.206055$	$V_{i5} = 11.688$	$V_{m5} = 12.518$

Table 4. 5 MATLAB Program Results – DC Source

Comparing these values to those found in the PSPICE simulation can be seen in table 4.6 below.

PSPICE Results	MATLAB Results	Percent Difference
$V_{m1} = 13.557$	$V_{m1} = 13.557$	0%
$V_{m2} = 8.4665$	$V_{m2} = 8.4665$	0%
$V_{m3} = 6.9323$	$V_{m3} = 6.9323$	0%
$V_{m4} = 8.2296$	$V_{m4} = 8.2296$	0%
$V_{m5} = 12.518$	$V_{m5} = 12.518$	0%

Table 4. 6 MATLAB vs PSPICE Comparison

The results from the MATLAB program were found to be identical to the results found in the PSPICE simulations, which are a strong indication that the results found from the MATLAB program are valid. Having no discrepancies between the two models will further validate the results found later in this work.

CHAPTER 5 – 2D Results of Nerve Fiber Activation

5.1 Initial COMSOL Model Analyses

Having each step of the modeling phase developed, the analysis could be performed using the proposed method shown in figure 4.10. Looking at the next step after applying the profile to the stimulus equation, the question may be asked to whether the applied current density results in a membrane voltage of 25mV for the fiber. In most cases it is highly unlikely that the current density applied would result in a transmembrane voltage of exactly 25mV, so another step to the analysis procedure had to be added. This step was added to determine which current density was necessary to stimulate the specified diameter fiber at the specified depth.

In order to explain how the process was implemented, the following graph is shown to provide a reference for the subsequent example.

Figure 5. 1 Plot to determine current density necessary to meet 25mV threshold

A current density of 15 A/m^2 was initially found and labeled point, A on figure 5.1. This stimulus resulted in a membrane voltage of only 13 mV. Following the process of the flowchart in figure 4.10, a larger current density must be applied to attempt to reach the desired transmembrane voltage of 25mV in the fiber. On the second trial, a current density of 17 A/m^2 was used, but again the value fell short. Continuing this process would prove to be long and tedious if the initially proposed method was followed, which is why the following graph was created. It is important to remember that the material properties within the model are homogeneous and isotropic, so a linear change will be seen when changing the current density. The graph shown above is used to plot this linear change and develop an equation to characterize the transmembrane voltage of the fiber based on current density. From this equation, it can then be determined what current density value is necessary to reach the 25mV threshold within the fiber. For example, the calculation below shows how this is done.

The equation obtained from the plot is shown to be as followed, where y = the current density and x = the transmembrane voltage.

$$y = 1.1766x - .0005 \quad (22.1)$$

$$y = 1.1766 * 25 - .0005 \quad (22.2)$$

$$y = \mathbf{29.4145 \text{ A/m}^2} \quad (22.3)$$

Following the flow chart in figure 5.2, it can be seen where the change in the process is made. A larger image of this flow chart can be seen in Appendix C.

Figure 5. 2 Updated Flow Chart Including Interpolation Function

Using this process greatly shortens the overall time to obtain each point for the overall characterization graph and can be repeated for each fiber depth. It is important to note that this equation only holds for the one specific diameter at the one specific depth. If the diameter or depth of the fiber is changed, a new plot and equation must be found to describe the effect of changing the current density.

5.2 Initial COMSOL Model Fiber Characterization Results

The most important set of data which will be investigated shortly will describe how fiber diameter and fiber depth affect the stimulus necessary to excite these fibers. This next set of data will provide a graphical description of how fiber diameter and depth play a factor in stimulating fibers.

The first of these simulations was performed using the DC voltage source model described previously. One notable assumption that was made for this case was that the fiber would have the same conductivity and material properties as the rest of the volume conductor. This assumption was made initially because the diameter of the fiber is extremely small in relation to the rest of the model, so the effects of ignoring the material properties of the fiber should be relatively small. The assumptions results in a homogeneous and isotropic volume conductor.

Following the proposed method in figure 4.10 results in a plot displaying the relationship of depth and stimulus for different diameter fibers.

Figure 5.3 DC Source Model – Depth Correlation

Some observations that stand out are the magnitude of stimulus necessary to activate a fiber of 5 microns and 20 microns at a depth of 22mm because of their large differences. A large increase in required stimulus appears to occur at around 5 microns. The larger diameter fibers do not appear to be as significantly affected by depth as the smaller diameter fibers. From this graph, it appears that there is little variation in current density required to recruit fibers between 16 and 20 microns. In order to relate this difference more clearly, a second plot was made showing only the 16 micron and 20 micron fiber.

Figure 5. 4 16 and 20 Micron Fibers

For these diameter fibers, a difference of only around $10 \frac{A}{m^2}$ was seen at a depth of 22mm. In comparison to the much smaller fibers, these sized fibers

averaged a change of $2.5 \frac{A}{m^2}$ per micron, while the smaller fibers averaged over $80 \frac{A}{m^2}$ per micron.

When comparing the previous two plots to each other, they both appear to follow the same trends. A second-order polynomial was used to represent the data in each of the plots. These plots are shown individually in figure 5.5 to help demonstrate their similarities.

Figure 5. 5 Fit Regression Line – Side-by-Side Comparison

A side-by-side comparison provides a much clearer image of the trend for each set of data. It is expected that all six plots will have a relatively similar trend because they are analyzed using the same model. From these plots a best fit line was generated to describe their trends.

$$4 \text{ Micron Fiber: } y = 1.136x^2 + 2.728x + 25.99 \quad R^2 = 1 \quad (23)$$

$$5 \text{ Micron Fiber: } y = 0.7438x^2 + 1.424x + 18.96 \quad R^2 = .999 \quad (24)$$

$$8 \text{ Micron Fiber: } y = 0.2966x^2 + 0.4276x + 8.787 \quad R^2 = .999 \quad (25)$$

$$10 \text{ Micron Fiber: } y = 0.1913x^2 + 0.2538x + 6.188 \quad R^2 = 1 \quad (26)$$

$$16 \text{ Micron Fiber: } y = 0.07574x^2 + 0.1062x + 3.078 \quad R^2 = 1 \quad (27)$$

$$20 \text{ Micron Fiber: } y = 0.04624x^2 + 0.1359x + 1.981 \quad R^2 = 1 \quad (28)$$

The corresponding r-squared values to each of the six equations validate the accuracy of the equations to correctly describe the data. This statement holds true for all six cases examined, which will make further analysis much easier. If one set of data were to deviate from this second-order polynomial trend, further examination would be necessary to determine where this change occurs. This will provide useful information for more complex modeling because this 2-D representation demonstrates that a similar trend may be used to describe activation of fibers at different depths.

In the previous plot, it was seen how fiber depth affects the required current density for a specific sized fiber. However, it did not provide a clear picture of how fiber diameter affects the required current density for fiber activation. It is important to understand if diameter and depth affect the required stimulus in a similar or different manner, so a second plot was created to demonstrate how different sized fibers affect required stimulus at specific depths.

Figure 5. 6 Effect of Fiber Diameter on Activation

The most notable feature of the graph in figure 5.6 is the trend that the data appears to follow. Focusing mainly on the 22mm depth, the data appears to follow that of an exponential function. As the diameter becomes larger, the stimuli all appear to reach a near zero value. Alternatively, as the diameter becomes smaller, the stimuli appear to move towards an infinite value.

Performing a best-fit analysis of each set of data resulted in plots similar to the following graphs shown in Figures 5.7 and 5.8. Because this data did not follow a typical linear trend, a nonlinear regression analysis was used in Minitab. The initial hypothesis was that an exponential function would properly describe the data, but when comparing the exponential plot to that using a power function expression, it was clear a power function was much more appropriate.

Figure 5. 7: Example Best Fit – Exponential Function

Figure 5. 8 Example Best-Fit Power Function

With the appropriate mathematical function determined for this set of data, a set of equations was found to describe the data. In every case, the power function provided a good fit to the data, which can be seen through the r-squared values. Y describes the current stimulus and x is the diameter of the fiber.

$$2 \text{ mm Depth: } y = 259.813x^{-1.5721} \quad R^2 = .999 \quad (29)$$

$$6 \text{ mm Depth: } y = 1439.65x^{-1.96416} \quad R^2 = .999 \quad (30)$$

$$10 \text{ mm Depth: } y = 2509.02x^{-1.95214} \quad R^2 = .999 \quad (31)$$

$$14 \text{ mm Depth: } y = 4296.43x^{-1.96342} \quad R^2 = .999 \quad (32)$$

$$18 \text{ mm Depth: } y = 6600.12x^{-1.95906} \quad R^2 = .999 \quad (33)$$

$$22 \text{ mm Depth: } y = 9892.81x^{-1.97395} \quad R^2 = .999 \quad (34)$$

Evaluating the data from two different perspectives created a very clear demonstration of the trends of the data. Changing fiber diameter causes a change in which a power function is required to characterize the data, while changing fiber depth can be described using a linear equation of second order polynomials. Having knowledge of their difference in trends will not only be useful for the 3D data characterization, but also provides insight about the effect of changing one of these variable. Decreasing fiber diameter appears to have a much larger effect on the required stimulus than increasing fiber depth.

These data also help verify and clarify some statements made previously about the effect of fiber diameter and fiber depth. At a depth of 2mm there is very little change when fiber diameter is changed. This same trend follows stimulating fibers that are at 20 microns in diameter. Changing the depth has a very little effect on necessary current density at this size fiber in comparison to the other size fibers examined.

With this initial set of data about the effect that fiber diameter and depth have on the current stimulus necessary to activate a fiber, a more complex model can be examined to determine its effects on the results.

5.3 Modified COMSOL Model Analysis

In the previous simulations, one important feature which was dismissed to simplify the simulations was the varying material characteristic of the fiber in the model. This statement does not mean that the fiber ceased from existing in the model, it instead shared material characteristics with the rest of the model. In the ensuing simulations, the fiber will be modeled according to the fiber size being investigated for each case. This fiber will create an inhomogeneous medium, because the fiber will essentially be encompassing an entire plane. The fiber will also inherit conductivity characteristics which were used to characterized extracellular space in the paper by Krasteva et. al. [14]. A resistivity of $6\Omega\text{m}$ for the nerve fiber was used for the following simulations.

Attached is a figure of the proposed model in order to visually be able to differentiate this model, which included the differing fiber characteristics, from the first model which did not.

Figure 5. 9 FEA Model Including Fiber

Notice the black line that moves along the length of the model. This line represents the presence of the nerve fiber in the model and the location of the plane. This change made the system no longer homogeneous, but still isotropic. Adding this change will allow this study to determine the effect of changing the material properties of a plane that is as small as the individual fibers within the medium.

One change that was made to the process of obtaining and analyzing the data was the addition of a step. In order to simulate the fiber being at different depths, the location of the fiber had to be physically changed in the model depending on where the analysis was occurring. If the fiber was being analyzed at 6mm, the model of the fiber had to be moved to 6mm, so the voltage profile could be obtained from the uppermost edge of the nerve fiber. Adding this step

resulted in a change to the flow chart in figure 4.10. The updated flow chart can be seen in figure 5.10 below.

Figure 5. 10 Modified Flow Chart Including Fiber Material Characteristics

The same procedures used in the first model were followed to obtain the results for this second model except for the addition of the step shown before meshing the model. A larger image of the flow chart in figure 5.10 can be seen in Appendix D.

Using the DC model resulted in the following data.

Figure 5.11 DC Case – Fiber Model

The resulting plot demonstrated trends that were very similar to those previously seen and these trends were better visualized with the supplementing graph of each data set individually plotted.

Figure 5.12 Individual Plots Relating Stimulus and Depth – Fiber Model

The corresponding equations for each of these plots followed the expected trend of a second-order polynomial.

$$\text{5 Micron Fiber: } y = 0.7183x^2 + 4.228x + 46.36 \quad R^2 = 1 \quad (35)$$

$$\text{8 Micron Fiber: } y = 0.3278x^2 + 0.5201x + 20.84 \quad R^2 = 1 \quad (36)$$

$$\text{10 Micron Fiber: } y = 0.1853x^2 + 0.9257x + 11.63 \quad R^2 = 1 \quad (37)$$

$$\text{16 Micron Fiber: } y = 0.06630x^2 + 0.5012x + 4.365 \quad R^2 = 1 \quad (38)$$

$$\text{20 Micron Fiber: } y = 0.04753x^2 + 0.2109x + 3.053 \quad R^2 = .999 \quad (39)$$

Because the relationship between stimulus and fiber depth followed a similar trend to those found using the previous COMSOL model, it was expected that the relationship between stimulus and fiber diameter would also follow the same trend.

Figure 5. 13 Effect of Fiber Diameter – Fiber Model

$$2 \text{ mm Fiber Depth:} \quad y = 1394x^{-1.9788} \quad R^2 = 1 \quad (40)$$

$$14 \text{ mm Fiber Depth:} \quad y = 6643.5x^{-2.0744} \quad R^2 = 1 \quad (41)$$

$$18 \text{ mm Fiber Depth:} \quad y = 8929.93x^{-2.00462} \quad R^2 = 1 \quad (42)$$

$$22 \text{ mm Fiber Depth:} \quad y = 12182.7x^{-2.00011} \quad R^2 = 1 \quad (43)$$

Based on figure 5.13 and the corresponding equations, the relationship between fiber diameter and current stimulus are similar in both the model which included the material properties of the fiber and the model that did not include the material properties of the fiber.

CHAPTER 6 – 2D Analysis of Nerve Fiber Activation

6.1 Data Analysis: Comparisons

Compiling the data from the two separate COMSOL models, one including a small plane with the fiber material properties and the other maintaining uniform material properties, a comparison could be made to investigate the effect of adding the fiber plane to the model. The first of these comparisons was done by creating a plot which included the data of the fiber at each depth from both models.

Figure 6. 1 DC Model Comparison – Fiber vs No-Fiber

From this graph, the differences between the small fibers are evident, but the larger fibers are much harder to differentiate from this graph alone. To clarify the differences between the model including the fiber and model excluding the

fiber, a second plot was made showing the difference in required current density for each fiber at each depth.

Figure 6. 2 Comparing Current Densities Fiber Model vs Omitting Fiber

Figure 6. 3 Percent Difference – Fiber Model vs Omitting Fiber

The largest differences occur at the shallower depths, but even the smallest difference at the deepest point is still over 10% change. For these reasons, it is conclusive that assuming the inclusion of a plane containing fiber characteristics will not affect the results is incorrect.

This finding is also important to any future work that involves using these techniques because it was proven that changing even the smallest part of the model resulting in inhomogeneity will yield significant changes.

The final or most realistic model was determined to be the second model, which included the fiber as a separate entity. It was important to compare the data found in this simulation to simulations from other studies. If the values of the current density from this simulation fall into similar ranges to those of simulations from other studies, then the validity of the entire work is much more conclusive. The first of these comparisons was made with the data from the simulations by Sha et al. [11], which were described in detail in the background of this research. The resulting current densities from these simulations ranged from close to zero and in one small instance, 400 mA/mm^2 . Performing a unit conversion on the data from this work to match those seen in the study by Sha et al. [11] a range of $5 \text{ }\mu\text{A/mm}^2$ to $500 \text{ }\mu\text{A/mm}^2$ were found for the current densities. The investigation in the paper by Sha et al. [11] was much different than that used in this work from the perspective of the model setup, but the comparison provided important information about whether the simulation results from this work were reasonable. To further demonstrate the validity of the data, another paper was found which explored a FEA simulation which was more similar to the model used in this

work. In the study by Tungjikusolmun et al. [17], an electrode was modeled as well as the surrounding tissue. The current densities from this case agreed much more closely with what was found in this simulation. Values ranging from 1 – 7 mA/mm², were observed at the electrode surface. These data demonstrate the expected values of current density from an electrode being placed in tissue which are very similar values to those found in the simulations from this work.

The most definitive study which provided the best comparison was that performed by Krasteva and Papazov [18]. In their FEA simulation, estimations were demonstrated concerning the current density under electrodes used for external defibrillation. The results from these analyses are shown in the graph below.

Figure 6. 4 Current Density Distribution under two circular electrodes (1) 5 cm radius (2) 2.5 cm radius[18]

The results from this simulation are the most significant of the three comparisons made because this paper describes properties of a surface electrode. The reason for the larger values of current density can be explained by the application. This electrode is used for defibrillation which requires much larger current densities than those in a NCV test. Other variables, such as electrode

size, and conductivity of the medium were also contributing factors for the difference. The most important piece of knowledge that can be taken from this study is that supports that the data found in this work is within a reasonable range.

6.2 - 3D Data Analysis

Creating an activation function, which includes the effect of fiber depth and diameter, was the overall goal for this work. Fitting the data from the fiber model using the DC source yielded the following graph. This graph clarifies general trends and demonstrates exactly how much the magnitude of the required current density changes as you increase fiber depth and decrease fiber diameter.

Figure 6. 5 3D Plot of Fiber/DC Model

Figure 6. 6 3D Color Contour Plot

Based on the 3D plot and contour plot, the most significant changes appear to occur when the depth reaches around 10mm and when the diameter becomes below 10 microns. This conclusion is based on the magnitude of the colors in the 3D plot and the position of these color changes in the contour plot.

Now with these data a 3D equation was fit to the data by using a MATLAB program available on the Mathworks website.

$$z = 0.2912x^2 - 1.0835xy + 13.5664x + 2.2463y^2 - 56.5306y + 305.3168 \quad (44)$$

$$R^2 = .907$$

Z= the current stimulus in (A/m²), where y= the fiber diameter and x= the fiber depth. The corresponding plot of the equation is shown along with its corresponding contour plot:

Figure 6. 7 3D Plot from Activation Function

Figure 6. 8 Contour Plot from Activation Function

As may be seen from both the contour plot and the 3D plot, the fit is not exact. The goodness of fit can be determined by the r-squared value. The r-squared value is .907, which from an experimental standpoint is considered to be very good. The reason for this difference between the data and the equation can easily be described by the relationship between current density and fiber diameter. The trend found to describe their relationship was a power function, but in the 3D equation, no power function is used. Another notable result from the equation is the effect that is seen once fiber diameter reaches approximately 20 microns. Due to characteristics of the 3D equation, the plot begins to rise which does not correctly describe the data. In this area the current stimulus can also reach values that are negative, which is not realistic. However, when comparing the

rest of the plot, the trend is very similar and based on the r-squared value will provide fairly close results to what was found from the data.

Although an acceptable r-squared value was found for the 3D-equation, it is evident that using the 2D equations will result in much more accurate results because they provide much more accurate descriptions of the data. If necessary, the 2D equations could be used to interpolate or extrapolate values for conditions that were not explored. This 3D equation may not be as accurate as expected, but will still describe the general trend for fibers within the range of values investigated with the simulations, which provides useful information for future work. It is already expected that the current density values will not be 100% accurate for a real-life application because the material properties in the simulation are not completely consistent with a real human arm.

6.3 – Conclusion

From these simulations, some distinct results were found concerning the activation of individual nerve fibers. The first notable results were those describing the effect of fiber diameter and fiber depth on the activation function. Changing the diameter of the fiber had a much different effect on the stimulus than changing the depth. Changing the fiber diameter required a power function to describe the change, while changing the fiber depth required a second-order polynomial to describe its affects. This meant that the size of the fiber had a more significant effect on the current stimulus than the depth.

In regards to the finite element model, it was found that even a very small plane with varying material characteristics in the model can result in significant changes in current density required for nerve activation. This was shown by including the material properties of the fibers themselves to the model. This information could be very useful in determining the effects that could be seen in a 3D model that would include bone, muscles, and other tissues that are likely to cover a plane between the stimulating electrode and nerve fiber. Introducing a small change in the material properties of a small plane caused a very significant difference in the required current density, so it would be expected that introducing a large planar obstruction such as bone or muscle would cause a drastic change in the results.

The FEA model using different fiber properties along with the DC source was used to generate the three dimensional recruitment plots. The three dimensional equation developed from this data did not prove to be 100%

accurate, but was within an acceptable range to describe the general trend of the data.

All of this information is useful for creating a distinction between nerve fibers. The 2D analysis consistently demonstrated similar trends even under different conditions, which provides useful information about the activation of different sized nerve fibers. The data from these simulations provides a solid baseline for future work.

List of References

- [1] Fitzgerald, M. J. T., & Folan-Curran, J. (2001). *Clinical Neuroanatomy and Related Neuroscience* (4th ed., p. 372). Saunders Ltd.
- [2] Waxman, S. G. (2009). *Clinical Neuroanatomy* (26th ed., p. 384). McGraw-Hill Medical.
- [3] *Action Potential: Conduction*. Art. *Encyclopædia Britannica Online*. Web. 23 Mar. 2011. <<http://www.britannica.com/EBchecked/media/66781/Conduction-of-the-action-potential-In-a-myelinated-axon-the>>.
- [4] Tesfaye, S., Boulton, A. J. M., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., et al. (2010). Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. *Diabetes Care*, 33(10), 2285-2293.
- [5] Nerve Conduction Velocity. (2011). . Retrieved from http://www.hopkinsmedicine.org/neurology_neurosurgery/specialty_areas/ionm/types/nerve-conduction-velocity-test.html.
- [6] Nerve Conduction Velocity (NCV) at Jefferson. (2011). . Retrieved from <http://www.jeffersonhospital.org/Tests-and-Treatments/nerve-conduction-velocity.aspx>.
- [7] Farina, D., Fortunato, E., & Merletti, R. (2000). Noninvasive estimation of motor unit conduction velocity distribution using linear electrode arrays. *IEEE Transactions on Bio-Medical Engineering*, 47(3), 380-388.
- [8] Szlavik, R. B., & Turner, G. E. (2008). A novel method for characterization of peripheral nerve fiber size distributions by group delay measurements and simulated annealing optimization. *IEEE Transactions on Bio-Medical Engineering*, 55(12), 5008-5014.
- [9] Huebner, K. H., Dewhurst, D. L., Smith, D. E., & Byrom, T. G. (2001). Meet The Finite Element Method. *The Finite Element Method for Engineers* (4th ed., pp. 3-16). Wiley-Interscience.
- [10] COMSOL Multiphysics: User's Guide. (2007). COMSOL AB.
- [11] Sha, N., Kenney, L. P. J., Heller, B. W., Barker, A. T., Howard, D., & Moatamedi, M. (2008). A Finite Element Model to Identify Electrode Influence on Current Distribution in the Skin. *Artificial organs*, 32(8), 639-43.
- [12] Martinek, J., Stickler, Y., Reichel, M., Mayr, W., & Rattay, F. (2008). A Novel Approach to Simulate Hodgkin-Huxley-like Excitation with COMSOL Multiphysics. *Artificial organs*, 32(8), 614-619.
- [13] Altman, K. W., & Plonsey, R. (1990). Point Source Nerve Bundle Stimulation: Effects of Fiber Diameter and Depth on Simulated Excitation. *IEEE Transactions on Bio-Medical Engineering*, 37(7), 688-98. doi:
- [14] Krasteva, V. T. Z., Papazov, S. P., & Daskalov, I. K. (2003). Peripheral nerve magnetic stimulation: influence of tissue non-homogeneity. *Biomedical Engineering Online*, 2, 1-14.
- [15] Anakwe, R. E., Huntley, J. S., & McEachean, J. E. (2007). Grip Strength and Forearm Circumference in a Healthy Population. *Journal of Hand Surgery*, 32(2), 203-209.

- [16] Szlavik, R. B., & deBruin, H. (2007). The effect of stimulus current pulse width on nerve fiber size recruitment patterns. *Medical Engineering & Physics*, 21(6-7), 507-515.
- [17] Tungjitkusolmun, S., Woo, E. J., Cao, H., Tsai, J. Z., Vorperian, V. R., & Webster, J. G. (2000). Finite element analyses of uniform current density electrodes for radio-frequency cardiac ablation. *IEEE Transactions on Bio-Medical Engineering*, 47(1), 32-40
- [18] Krasteva, V. T., & Papazov, S. P. (2002). Estimation of current density distribution under electrodes for external defibrillation. *Biomedical Engineering Online*, 1, 7.

Appendix A – MATLAB Program (DC Voltage Source)

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
%
% Determination of Membrane Voltage using method similar to that
%
% used by Bean, Sweeney et al. and McNeal. DC Source
%
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

load D22_220A.txt           %Load Data from .txt file created in COMSOL
A = D22_220A;
[extent p] = size(A); %extent = number of data points from COMSOL file

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%Sort data from COMSOL file into single column array

for r = 1:extent

    if r < extent
        data(r) = A(r,2);
    else
        data(r) = 0;
    end

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

[m nmax] = size(data) %nmax = number of data points in sorted
array

D_fiber = 5E-6; %Diameter of nerve fiber
length = .4; %Length of COMSOL model
cm = .02; %Membrane Capacitance
pa = 1.1; %Cytoplasm resistivity
K = length/nmax; %Nodes of Ranvier Spacing
a_fiber = .5*D_fiber; %Radius of nerve fiber
a_axon = .7*a_fiber; %Radius of axon
Gc = (pi*(a_axon^2))/(pa*K); %Equivalent axoplasm conductance
Gm = (2*pi*304*a_axon*(2.5E-6)); %Equivalent membrane conductance
Cm = 2*pi*cm*a_axon*(2.5E-6); %Equivalent membrane capacitance
Rc = 1/Gc; %Equivalent axoplasm resistance
Rm = 1/Gm; %Equivalent membrane resistance

V = data; %Variable name change
Constraint = nmax-2;
```

```

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%Creates an array using Kirchoff's Current Law which analyzes
%intracellular voltages at left-bound ground

x = 1;
for y = 1:1:Constraint
    if y < 2
Vi(x,y) = (1/Rc)+(1/Rc)+(1/Rm);
Vi(x,y+1) = -1/Rc;

        elseif y >= 3
Vi(x,y) = 0;
        end
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%
%Creates an array using Kirchoff's Current Law. In this
%case all three sources have no immediate relationship to
%ground

i=0;
for a = 2:1:Constraint-1
    i = i+1;
    for b = i:1:Constraint
        if b < i+1
Vi(a,b) = -1/Rc;
Vi(a,b+1) = (1/Rc)+ (1/Rc) + (1/Rm);
Vi(a,b+2) = -1/Rc;

                elseif b > i+2
Vi(a,b) = 0;
                end
        end
    end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%Creates an array using Kirchoff's Current Law which analyzes
intracellular
%voltages at the right-bound ground

w = Constraint;

for z=1:1:Constraint

    if z < Constraint-1
Vi(w,z) = 0;

        elseif z >= Constraint
Vi(w,z-1) = -1/Rc;
Vi(w,z) = (1/Rc)+(1/Rc)+(1/Rm);

```

```

end

end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%
%Constant values which are the y components of Ax = y

d=1;
for c= 2:nmax-1
Vf(d,1) = V(c)/Rm;
d = d+1;
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%

V_ex = V(2:nmax-1)';           %Transpose extracellular voltage
array

V_Intra = inv(Vi)*Vf;          %Solves for intracellular array

Vm = V_ex - V_Intra;           %Solves for membrane voltage

V_max = max(Vm)*1000;          %Determines max membrane potential
and                             %returns result in terms of mV

```

Appendix B – Flow Chart of Initial Proposed Simulation Method

Appendix B – Flow Chart of Modified Proposed Simulation

Method

Appendix D – Flow Chart of Modified Proposed Simulation

Method Including Fiber Material Characteristics