EQUIVALENT CIRCUIT IMPLEMENTATION OF DEMYELINATED HUMAN
NEURON IN SPICE

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NEURON IN SPICE

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ABSTRACT

EQUIVALENT CIRCUIT IMPLEMENTATION OF DEMYELINATED HUMAN NEURON IN SPICE

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This work focuses on modeling a demyelinated Hodgkin and Huxley (HH) neuron with Simulated Program with Integrated Circuit Emphasis (SPICE) platform.

Demyelinating disorders affect over 350,000 people in the U.S and understanding the demyelination process at the cellular level is necessary to find safe ways to treat the diseases [9]. Utilizing a previous SPICE model of an electrically small cell neuron developed by Szlavik [32], an extended core conductor myelinated neuron was produced in this work. The myelinated neuron developed has seven active Nodes of Ranvier (nodes) separated by a myelin sheath. The myelin sheath can be successfully modeled with a resistive and capacitive network known as internodes. Both the Nodes of Ranvier and internode equivalent circuits were implemented in P-SPICE sub-circuit library files. Properties of the neuron can be changed in the library files to simulate neurons of different electrical or geometric properties. Using the P-SPICE code developed in this work, a myelinated neuron's action potential was simulated and the action potential at each node was recorded. The action potential at each node was uniform in amplitude and pulse width. The conduction velocity of the action potential was calculated to be 57.15 m/s.

Demyelination can be modeled by decreasing the capacitance and increasing the resistance of the myelin [34]. Two demyelinated neuron models were simulated in this work. The first model had one internode segment demyelinated, and the second model

was of three consecutive internode segments. The resulting conduction velocity was calculated for both simulations. For one and three internode segment demyelinated the conduction velocity was slowed to 44.15 m/s, and 27.15 m/s respectively. This model successfully showed that an HH neuron implemented in SPICE could show the effects of demyelination on conduction velocity

The goal of this work is to develop a demyelinated neuron so that treatments for Multiple Sclerosis (MS) and other demyelinated neurons could be simulated to test various treatments' effectiveness. A current treatment for MS is ion channel blockers. Future work would be to use this model to test current ion channel blocker therapy and to validate if such therapies alleviate conduction slowing.

Keywords: Myelinated neuron model, Demyelination simulation, Equivalent circuit neuron model

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I Introduction

This work focuses on modeling a myelinated/demyelinated Hodgkin and Huxley (HH) neuron using Simulated Program with Integrated Circuit Emphasis (SPICE) platform. Understanding the electrical properties of myelinated neurons is the key to treating diseases such as Multiple Sclerosis, in which the myelinated neuron begins to demyelinate. Demyelinating disorders affect over 350,000 people in the U.S [9]. Understanding the demyelination process at the cellular level is critical to find safe ways to treat these diseases. Modeling neurons with a SPICE platform may allow inserting individual neurons into circuit designs to facilitate the design of neuro-electronic interface devices. Potassium and sodium ion channels are the main contributor to propagation of neural signals. By modifying the ion channel behavior, the symptoms of demyelination, such as conduction slowing or blockage, may be alleviated. The HH neuron model describes the behavior of the ion channels in neurons and is an acceptable model to study diseases that affect action potential propagation. Simulating neurons demonstrating aberrant function have been successful in ischemia [5, 6] and demyelination [24, 26, 30, 36]; therefore, it is possible to extend equivalent circuit HH models to successfully model a disease process. Unmyelinated HH neuron models have been developed for SPICE [23, 32]; however, no such model exists for myelinated neurons. One advantage of using SPICE to model neurons is that SPICE does not require the differential equation to be put in a specific form to be solved. Other methods to implement a neuron model include MATLAB, but MATLAB requires the differential equation to be put in a specific form before the equation can be solved.

In this work, an unmyelinated HH neuron model will be extended to model myelinated neurons and the demyelinating disease process. Presented in the following sections is an overview of neuron physiology and anatomy, ion channel and action potential mechanics, all of which are important to understanding neuron modeling. Previous neuron models and demyelinating neuro-degenerative diseases will then be discussed.

1.1 Neuron Anatomy

Neurons are the fundamental unit of the nervous system and act as the communication and control network for an organism. Neurons are interconnected in what are known as neural circuits and communicate information using pulse frequency modulation of action potentials [34]. A 4-6 nm lipid bilayer surrounds a neuron which is partially hydrophobic and does not allow ions to freely enter the cell [21]. Water can diffuse through specific membrane transport proteins, known as aquaporins, by means of osmosis. Water is a dipolar molecule with a partial positive on the hydrogen and a partial negative on the oxygen. Electrostatic forces cause positively charged ions (cations) to be attracted to the oxygen in water and the negatively charged ions (anions) to be attracted to the hydrogen. For an ion to break away from water and pass through the membrane of a neuron, it would require a large amount of energy. Due to the lipid bilayer's chemical composition, it is impenetrable to the ions surrounded by water molecules. Neuron membranes contain gated ion channels which regulate the ions entering and exiting the cell (gated ion channels are discussed further in Chapter 1.2) [22].

Mammalian peripheral neurons have several main components, which include the soma and axon (Figure 1).

Figure 1: Functional anatomy of a peripheral motor neuron.

The soma is the main processing and production center for the neuron and it produces enzymes, proteins, and other essential cell chemicals [22]. Extending from the soma are the dendrites, which receive both excitatory and inhibitory synaptic inputs from presynaptic terminals. An excitatory synaptic input increases the membrane potential, bringing it closer to the threshold membrane potential. An inhibitory synaptic input lowers the membrane potential, driving it farther away from the threshold membrane potential. If the potential across the neuron membrane is equal to the threshold potential, an action potential will result. A single presynaptic cell does not possess a sufficient electrical response to elicit an action potential in a postsynaptic neuron. The integration of many excitatory postsynaptic potentials (EPSPs), however, can result in an action potential [21]. For example, in a post synaptic motor neuron, it may take 50-100 EPSPs to reach the threshold membrane potential, which then would result in an action potential. EPSPs and IPSPs are summed spatially and temporally, and the combined inputs determine whether an action potential will occur. Spatial summation causes EPSPs and

IPSPs that occur closer to the axon hillock to produce a more drastic depolarization or hyperpolarization of the membrane compared to EPSPs and IPSPs farther from the hillock. The axon hillock has the largest concentration of voltage gated ion channels and therefore has the lowest membrane threshold potential [21].

Temporal summation is the process where EPSP are close in time, thus having an additive effect on the membrane potential. If many EPSPs occur in a short amount of time, the individual effects will be summed together and an action potential is more likely. Temporal and spatial inputs are integrated at the axon hillock to generate action potentials that propagate down the axon to the terminal buttons [17]. The action potential generated at the axon hillock passively decays as it conducts down segments of myelinated axon and would only conduct down small lengths of the axon if it were not for the Nodes of Ranvier [35]. There is no myelin sheath in non-myelinated neurons, such as a squid axon, therefore, the action potential does not decay in a non-myelinated neuron. Without a myelin sheath the conduction velocity down a length of axon is much slower. The dendrites collect presynaptic inputs but do not generate a local action potential due to a low concentration of ion channels [33]. Recent studies show that the single dendrite may perform some preprocessing of the synaptic input [7].

Myelin is made up of Oligodendrocytes and Schwann cells in the central and peripheral nervous system, respectively. Oligodendrocytes and Schwann cells form a tightly wrapped multilamellar structure around the axon [21]. The myelin structure has a high electrical resistance, which increases conduction efficiency and velocity [15]. The myelin sheath does not allow the regeneration of the action potential because it isolates the inside of the neuron from the excitatory extracellular fluid [16]. The conduction of the

electrical signal down an axon covered by a myelin sheath passively decays. The action potential would attenuate to 50% of its peak value in about 20mm of axonal length if it were not for the Nodes of Ranvier [34]. The Nodes of Ranvier are uniformly spaced at 1-2 mm and are not encased in a myelin sheath; this exposes the axon directly to the extracellular fluid, which contains ions necessary to regenerate an action potential [13]. The Nodes of Ranvier have a large concentration of sodium channels that can be excited once the action potential reaches them. Due to the combination of the myelin sheath and the Nodes of Ranvier, the propagation of an action potential in a myelinated neuron looks as though the electrical signal is leaping from node to node [28]. The leaping of the action potential from node to node is called saltatory conduction. A high rate of attenuation of the action potential would occur rapidly if it were not for the increased conduction efficiency resulting from the myelin sheath. In disease processes, such as demyelination, a neural action potential may be slowed and completely attenuate before it reaches a Node of Ranvier to be regenerated. During a demyelination disease process, the Nodes of Ranvier may become non-uniformly located on an axon. The relocation of Nodes of Ranvier may allow for an action potential to propagate to the end of the axon. The pulse frequency of the action potentials will not be as consistent as a non-demyelinated neuron though, due to the non-uniform spaced Nodes of Ranvier.

1.2 Ion Channels

The plasma membrane of all cells, including neurons, is made up of a lipid membrane and proteins. Proteins can form complex structures, such as ion channels, which conduct ions across the plasma membrane. The ion channels of particular

importance to neuron modeling have the main characteristics of selectivity, voltage controlled, and passive conductance.

An ion channel is selective such that only a specific ion can travel through the channel [10]. A large portion of the selectivity of an ion channel is determined by the size of the ion it is meant to conduct. Smaller ions have a more localized charge and thus a stronger electric field; the opposite is true of larger ions, due to decreased charge density [21]. Water is attracted to ions due to electrostatic interactions; therefore smaller ions can attract more water molecules than larger ions. The process of water surrounding an ion is known as hydration [22]. The hydration of an ion depends upon its size; the more hydrated an ion, the larger the radius of the hydrated shell. As an ion travels through a selective ion channel, it is dehydrated at the narrowest part of the channel known as the selectivity filter. The selectivity filter contains negatively polarized amino acids in a specific geometry optimized to dehydrate a specific ion, which allows the ion to travel across the membrane [21]. The proteins that make up potassium and sodium channels will be discussed further in section (1.2.1 and 1.2.2)

Although there are many types of ion channels, such as stretch responsive, ligand gated, and phosphorylation activated, the voltage gated ion channels are the most relevant with respect to neuron modeling [10,11]. As discussed above, ion channels are made up of membrane proteins. Membrane proteins that make up ion channels may undergo a conformational change to alter the state of an ion channel. Voltage gated potassium ion channels can exist in one of two states: open or closed [21]. Voltage gated sodium ion channels can exist in one of three states: open, closed, or inactive [21]. The energy required to change states for voltage gated ion channels comes from the difference in

voltage across the cell membrane. The conformational rearrangement of the ion channel proteins has been visualized with electron microscopy [35]. The conformational changes allow a specific ion to travel through the channel by increasing the lumen size as well as positioning polar amino acids to optimize ion conductance through the channel.

The final common feature of neural ion channels important to neuron modeling is that the conductance through the channel is passive. As discussed in section 1.1, the lipid bilayer isolates the inside and outside of the cell; therefore, a difference in osmotic and electrostatic forces is present across the cell membrane (see section 1.3). When an ion channel is open, the ions located inside and outside of the cell will travel down electrical and/or osmotic gradients to reach a lower energy state (see section 1.4). An ion traveling down a concentration gradient does not use additional energy (such as ATP) to travel through the channel, making the conductance passive.

The ion channels that were first studied in neurons were sodium and potassium channels using voltage clamp experiments [18]. Cole and Marmont developed the voltage clamp technique, which uses two electrodes. The electrodes are placed on the inside and outside of the neuron membrane, respectively, to set a predetermined transmembrane potential [33]. Although the membrane potential may be fixed at certain levels, the voltage gated ion channels will still conduct ions. The voltage clamps maintain the transmembrane potential by either sourcing or drawing current from the membrane (Figure 2) [21].

Figure 2: Voltage clamp block diagram of a circuit used to determine the voltage gating dynamics of ion channels. A voltage clamp circuit is a current generator that keeps the membrane potential constant by drawing or sourcing current to the membrane.

A feedback loop can be set up to measure the current that is sourced or drawn from the neuron by using an ammeter. Hodgkin and Huxley applied the voltage clamp technique to describe the conductance of ion channels to changes in membrane potential [18,19] The voltage clamp technique allows the conductance across the membrane to be calculated using Ohm's law ($V=IR$; $V=I/G$). The conductance being measured is the summation of the bulk ion channel conductance in the cell membrane. To record individual ion channel

conductance, channel blocker drugs are applied to the neuron to block specific ion channels [22]. The first potassium and sodium channel drugs used to test for individual ion channel conductance were tetraethyl ammonium and tetrodotoxin, respectively [21]. The calculation of the conductance of an individual channel is accomplished by using an equivalent circuit model and applying Ohm's law. The current $I_{[X]}$, where $[X]$ is the conducting ion, measured in the feedback loop is a function of the membrane conductance $g_{[X]}$, the voltage V_M being applied to the membrane, and the battery potential $E_{[X]}$ (see section 1.3 for explanation of battery potential).

$$I_K = g_k(V_M - E_k) \quad (1)$$

$$g_k = \frac{I_k}{(V_M - E_k)} \quad (2)$$

$$I_{Na} = g_{Na}(V_M - E_{Na}) \quad (3)$$

$$g_{Na} = \frac{I_{Na}}{(V_M - E_{Na})} \quad (4)$$

To experimentally determine E_{Na} and E_k the voltage clamp can be varied until I_{Na} and I_K reverse polarity, which is known as the reversal potential [18]. For example, if potassium channels are blocked using tetraethylammonium, the membrane potential could be varied until $I_{Na} = 0A$. The sodium battery potential E_{Na} is the membrane potential when $I_{Na} = 0A$. Once the battery potentials have been determined, all quantities in (1 – 4) are known except for the ion channel conductance. Hodgkin and Huxley varied the command voltage and measured the resulting current. With both the voltage and current known, the membrane conductance for sodium and potassium was calculated as a function of membrane potential. Hodgkin and Huxley then fit the data to a set of

empirical equations to model the individual ion channels as a function of membrane potential [34].

1.2.1 Voltage gated Potassium Channel

Voltage gated potassium channels are made up of integral membrane proteins with six membrane spanning alpha helical regions. In-between the fifth and sixth alpha helical is the ion selectivity filter, which allows only potassium ions to conduct. The fourth alpha helical is thought to be a voltage sensor due to its positively charged amino acid [20].

Voltage dependent ion channels can be activated or deactivated as a result of structural rearrangement of the channels under the influence of electrical fields. Hodgkin and Huxley fitted the ionic conductance determined from voltage clamp experiments with power variables satisfying first order kinetic equations [34]. Conductance of potassium depended on the maximum potassium conductance $\overline{G_K}$, and a gating variable n .

$$G_k = \overline{G_K} n^4 \quad (5)$$

In the above equation, $\overline{G_K}$ is a measured constant. The first order kinetic equation defines the n gating variable, which represents the closing and opening of the channel (Figure 3). The variable n is bounded between zero and one. The potassium channel conductance is equal to the maximum potassium channel conductance when n is equal to one. An n value of zero indicates no potassium channel conductance.

Closed Voltage dependent Potassium Channel

Open Voltage dependent Potassium Channel

Figure 3: Function diagram of voltage gated potassium channel and its states. First state is open and the second state is closed.

The gating variable's dependence on voltage and time can be put into two forms. One such form is dependent on the rate constants α_n and β_n .

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (6)$$

The other form is written in terms of a time constant τ_n and the final value n_∞ .

$$\tau_n \frac{dn}{dt} + n = n_\infty \quad (7)$$

$$\text{With, } n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \quad (8)$$

The time and rate constants for the potassium channel n gate, τ_n , α_n and β_n are all functions of the membrane potential V_m . Hodgkin and Huxley characterize the rate and time constants empirically using data collected from voltage clamp experiments.

$$\alpha_n = \frac{-0.01(V_m+50)}{e^{-0.1(V_m+50)}-1} \quad (9)$$

$$\beta_n = 0.125e^{-0.0125(V_m+60)} \quad (10)$$

$$\tau_n = \frac{1}{\alpha_n + \beta_n} \quad (11)$$

The membrane potential V_m , is expressed in mV, and the α and β quantities are expressed in ms^{-1} . Some neuron models have further separated the potassium ion channel into a slow and fast acting ion channel [28]. The gating variable relationship to voltage for fast and slow acting potassium channels would look similar to (5), but the gating variables may be to different powers, and the rate constants equations would differ.

1.2.2 Voltage Gated Sodium Channel

Sodium channel conductance is dependent on the maximum sodium conductance $\overline{G_{Na}}$, as well as the activation and inactivation gate, m and h respectively [34].

$$G_{Na} = \overline{G_{Na}}m^3h \quad (12)$$

Unlike the potassium ion conductance, the conductance equation for sodium is more complicated and requires two gating variables. $\overline{G_{Na}}$ is a measured constant, and the m and h gating variables are both described using a first order differential equation. The gating variables n , m and h are all bounded between zero and one. Consequently, the product of m and h is also bounded between zero and one. The sodium conductance is dependent on two gating variables, each of which need to be nonzero for sodium conduction to occur.

Due to the dependence of sodium on two separate gating variables, sodium ion channels have 3 states (Figure 4).

Figure 4: Function diagram of voltage gated sodium channel and its states. First state is open, second state is closed and third state is inactive

In the above diagram the open and closed states are determined by the m gating variable. The h gate is known as the inactivation gate and is represented by the ball and tail in the above diagram. The gating variables dependence on voltage and time can be expressed in two forms.

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad (13)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad (14)$$

The other form uses a time constant τ_m, τ_h and the final values m_∞ and h_∞ .

$$\tau_m \frac{dm}{dt} + m = m_\infty \quad (15)$$

$$\tau_h \frac{dh}{dt} + h = h_\infty \quad (16)$$

$$\text{With, } m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \quad (17)$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h} \quad (18)$$

The rate and time constants in (13)-(16), $\tau_m, \alpha_m, \tau_h, \alpha_h, \beta_m$ and β_h , are all functions of membrane potential. Hodgkin and Huxley characterize the rate and time constants empirically using data collected from voltage clamp measurements.

$$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1} \quad (19)$$

$$\beta_m = 4e^{-\frac{0.0125(V_m + 60)}{18}} \quad (20)$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m} \quad (21)$$

$$\alpha_h = 0.07e^{-0.05(V_m + 60)} \quad (22)$$

$$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}} \quad (23)$$

$$\tau_h = \frac{1}{\alpha_h + \beta_h} \quad (24)$$

As the membrane potential increases, the m gate increases conduction and the h gate decreases conduction. Therefore, the m gate is an activation factor and the h gate is an inactivation factor [34]. Similar to potassium channels, sodium channels in some neuron models have been separated into fast and slow acting channels [4, 24, 25, 28].

Other ion channels besides sodium and potassium have been used in neuron models. Two examples are the inward rectifying channel and a leakage current [1,4]. A study by Baker shows that in myelinated nerve fibers, there are up to three inward rectifying channels [1]. The inward rectifying, or repolarizing channel, channels limit hyperpolarization of an action potential by fully conducting once the membrane potential begins to hyperpolarize. For example, a potassium inward rectifying channel would not be conducting until the membrane potential passed a certain threshold. Once the membrane potential has passed a certain threshold, the inward rectifying channel starts to conduct potassium out of the neuron, bringing the membrane potential closer to the potassium battery potential. The potassium inward rectifying channel will have a different rate equation and constants than the Hodgkin and Huxley potassium rate equation. The inward rectifying ion channels are diverse and conduct many different ions, the majority being potassium and calcium [1]. The leakage channel in a neuron model represents other conducting ions not represented by the potassium or sodium channels. A table below is included with a summary of ion channel characteristics.

Table 1: Comparison between ion channels and their effect on membrane potential.

Property	Voltage dependent sodium channels	Voltage Dependent Potassium Channels	Inward Rectifying channels	Leakage channels
Ions conducted	Na ⁺	K ⁺	Mostly K ⁺ , and other ions	Mixture
Effect on membrane potential	Depolarize/Hyperpolarize Cell	Repolarize Cell	Used for repolarizing of the neuron used to limit hyper polarization	Constant leak depolarize cell
Number of gates	3 states for gates: closed, open, inactive	2 states for gates: open/closed	2 states open and closed	1: always open

1.3 Resting Membrane Potential

The resting membrane potential is the cell's steady state with regards to diffusion and electrical gradients. If a cell cannot maintain osmotic equilibrium the cell volume will become unstable. The cell must maintain a constant particle concentration on either side of the membrane to maintain a stable volume. Additionally to maintaining osmotic equilibrium, the neuron must also maintain electrical equilibrium, or charge neutrality. Charge neutrality dictates that for the regions external and internal to the cell, the aggregate concentration of positively charged particles must equal the aggregated concentration of negative charged particles. The lipid bilayer is only semi-permeable to ions; ions are therefore prevented from freely traveling across the membrane. Ions can only cross the cell membrane through regulated ion channels. Due to the regulation of ions and other particles across the neuron membrane, a concentration gradient develops of ionic species across the cell membrane. The electrostatic and osmotic gradients put

opposing movement factors on the ions. For example, if ions travel down a diffusion gradient due to osmotic drift, an electrostatic gradient develops. The resulting electrostatic gradient causes an equal number of ions to drift in the opposite direction. The process described above allows the neuron to maintain electrostatic and osmotic equilibrium.

Each ionic species has an equilibrium potential, known as the battery potential, due to the diffusion and electrostatic gradient in a neuron. Consider the case of only sodium and potassium ions. Each ion would have its own battery potential, denoted as E_{Na} and E_K , respectively. For a cell only permeable to potassium ions, the battery potential E_K would be the resting membrane potential. In the case of multiple membrane permeable ions, the battery potentials act as boundary values for the membrane potential. The membrane potential must lie in-between the battery potentials for the membrane permeable ions. The battery potential for a specific ion may be calculated using the Nernst equation. The Nernst equation requires knowledge of the ionic species inside and outside the membrane denoted as $[X]_i$ and $[X]_o$, where X is the concentration of ionic species in moles per cubic centimeter. In the Nernst equation, T is temperature of the environment in kelvin, and z is the valence of the ion. The constants in the equation are the gas constant R (in joules per kelvin per mole) and Faraday's constant F (in coulombs per mole).

$$E_x = \frac{RT}{zF} \ln\left(\frac{c_x^o}{c_x^i}\right) \quad (25)$$

The battery potential, or Nernst potential E_x , takes into account both diffusion and electrostatic gradients for an ionic species. Potassium and sodium ions are not in equal

concentration on either side of the cell membrane. As a result, sodium and potassium have different Nernst potentials. The resting membrane potential will not equal the Nernst potential for sodium or potassium. For example, if the battery potential for sodium is the potential across the membrane, the sodium ions would be in electrochemical and osmotic balance, and would no longer conduct across the membrane. The battery potentials contribute to the membrane permeability, and thus to the ion channel conductivity.

To calculate the resting membrane potential, the Goldman equation may be used. The Goldman equation takes into account all ionic species to which the membrane is permeable. To write the Goldman equation for a neuron membrane permeable to only potassium and sodium, the intracellular and extracellular concentrations of the ions are required, as well the relative permeability of sodium to potassium, b .

$$V_r = \frac{RT}{F} \log \left(\frac{c_K^o + bc_{Na}^o}{c_K^i + bc_{Na}^i} \right) \quad (26)$$

The relative permeability of sodium to potassium is a measure of the importance of the sodium battery potential as compared to the potassium battery potential on the resting membrane potential. The Goldman equation can be expanded to account for any number of membrane permeable ions. Common values used to calculate the resting membrane potentials are shown in table 2.

Table 2: Common parameters used in the Goldman equation

Parameter	Value
c_K^o (mmol/L)	20.11
c_K^i (mmol/L)	400
c_{Na}^o (mmol/L)	491
c_{Na}^i (mmol/L)	50
b	0.2
Temperature ($^{\circ}\text{C}$)	6.3

1.4 Action Potential Propagation

Neurons have receptors that can be stimulated to generate synaptic or action potentials. Some examples are photoreceptors in neurons in the eye, which respond to light, or mechanical stretch receptors in muscles that respond to deformation of the cytoskeleton [34]. Other receptors include chemoreceptors, nociceptors and thermoreceptors [35]. A common mechanism for the receptors to initiate an action potential is the opening of sodium channels. The opening of the sodium channels causes an influx of sodium into the neuron, which begins membrane depolarization towards the sodium battery potential [34]. The large influx in sodium causes the rising edge of an action potential. The falling edge of the action potential is caused by two factors: The first factor is a decrease in sodium conductance due to its dependence on membrane potential and time. The second factor is caused by a change in potassium channel permeability, increasing channel conductance. When the potassium channels are conducting, they are allowing potassium to travel down their electrochemical gradient,

out of the neuron, causing the membrane to repolarize once again. After an action potential has been generated, there is an absolute refractory time until another action potential can be generated again [11, 24].

Neurons communicate information with pulse frequency modulation of action potentials in networks by means of electrical or chemical synapsis. Electrical synapses are fast acting small junctions between cells, i.e. neurons and glial cells, which are found in large concentration in the brain [35]. An electrical synapse is the fastest cell to cell communication and is formed with direct, low resistance connections of ion channels from one cell to the next [21]. The direct connection of ion channels between cells is called a pore. The communication in an electrical synapse is bidirectional, meaning that current generated in either cell can influence the other cell [22].

At chemical synapses there is no direct communication between the two cells because the cell membranes are separate by a gap known as the synaptic cleft [33]. Communication in chemical synapses is accomplished with neurotransmitters. Unlike the electrical synapses, chemical synapses are generally unidirectional, and thus one can refer to a pre and post synaptic element [22]. A brief summary of synaptic transmission at chemical synapses is described in the following: Once an action potential reaches a presynaptic terminal, the terminal is depolarized, which causes calcium channels to open, allowing calcium to enter the cell. The intracellular rise in calcium triggers fusion of vesicles containing neurotransmitter with the plasma membrane. The transmitter is then released from the presynaptic cell, allowing it to diffuse across the synaptic cleft to bind to specific postsynaptic element receptors on the postsynaptic cell's plasma membrane. The binding of the postsynaptic receptors and neurotransmitter causes a change in the

conductance of the postsynaptic membrane, which alters the excitability of the cell. An example of a chemical synapse is the neuro-muscular junction between neurons and muscle fibers. The primary neurotransmitter that communicates between the neuro-muscular junctions is acetylcholine [22].

Once an action potential has been initiated in a post synaptic element, the action potential will propagate down the length of the axon to the terminal buttons. The speed at which the action potential travels down the axon is known as the conduction velocity [33]. Many factors can affect the conduction velocity of a neuron. Two primary factors that have been studied extensively with modeling are fiber diameter and myelination [2, 12, 19]. As fiber diameter increases, the longitudinal resistance decreases with the square of the diameter, and the membrane resistance increases linearly [12]. The overall effect is that there is less resistance to conduction and therefore, the action potential will travel faster longitudinally down the neuron. Myelin insulates the neuron, thus reducing leakage of ions that are conducting the action potential. Another main effect is that myelin increases the separation of charge present across the neuron membrane, thus decreasing the capacitance. Capacitance is the ability of a body to hold charge. The capacitance of a body depends on the electric constant ϵ , the separation of charge d , and the surface area A .

$$C = \epsilon \frac{A}{d} \quad (27)$$

The separation of charge may not be a constant for a neuron membrane, but the trend that increasing the charge separation, decreases the membrane capacitance is still valid. By decreasing the membrane capacitance, the membrane is less able to hold a charge

separation. Thus, the membrane will depolarize quicker, allowing increased action potential conduction velocity down an axon. The higher capacitance requires more charge, or ions, to maintain a certain voltage. The insulation and decreased capacitance of a neuron membrane is caused by the myelin sheath, which is wrapped in more than 100 layers around the axon. Due to the myelin insulating the axon of the neuron from the extracellular fluid, action potentials can only begin at the Nodes of Ranvier. In myelinated neurons, the action potential amplitude and width is uniform at each node of ranvier.

1.5 Neuron Models

Modeling neural action potentials started in the 1950's with Hodgkin and Huxley's modeling the action potential of a giant squid axon using equations (5) and (12) [18, 19]. The Goldman equation (26) is insufficient for modeling an action potential because it cannot determine how rapidly the membrane potential changes in response to a change in membrane permeability [34]. The transient response of the membrane potential in response to changes in membrane permeability can be determined from an equivalent circuit model of a neuron [34]. In an equivalent circuit model of a neuron, all of the important functional properties are represented by a circuit consisting of resistors (for ion channel permeability), batteries (for the Nernst potential of a specific ion), and capacitors (to represent the membranes ability to hold charge). All of the ion channels for any specific ion can be lumped into a single equivalent electric structure composed of a battery and a variable resistor or conductor ($\text{resistance} = 1/\text{conductance}$) in series. A variable resistor is necessary to model voltage gated ion channels because the permeability of the channel is not constant. Several battery-resistor structures can be put

in parallel to describe differing ion channel's effect on the membrane potential. The first HH neuron described the dynamic behavior of voltage gated sodium and potassium ion channels (Figure 5).

Figure 5: Hodgkin and Huxley equivalent circuit model of an electrically small neuron with an external pulse applied to the inside of the neuron.

The HH model above is an accurate representation of an electrically small cell. In an electrically small cell the membrane potential is the same everywhere in the neuron at any given time. The HH membrane potential can be found using Kickoff's Current Law (KCL) at the unknown node potentials. In the above HH neuron the membrane potential is dependent on the conductance of potassium G_K , the potassium battery potential E_K , the conductance of sodium G_{Na} , the sodium battery potential E_{Na} , membrane potential C_m , and the current applied to the membrane I_{pulse} . Figure 5 has only one unknown voltage and therefore, the neuron describes membrane potential as a function of time but not space. A neuron in which the potential across the membrane is not the same everywhere

at any given instant of time is an electrically large cell, and must be modeled with a core conductor model [34].

1.6 Core conductor model and the Cable equation

In modeling electrically large cells, it is necessary to show changes in membrane potential as both a function of time and space [34]. To model a large neuron successfully, a core conductor model can be used (Figure 6). The core conductor model has parameters of both electrical and geometric properties.

The core conductor model makes the following assumptions.

- 1) The cell membrane is a cylindrical boundary that separates two conductors of electrical current, the intracellular and extracellular solutions. These conductors are assumed to be homogenous and ohmic.
- 2) All electrical variables have cylindrical symmetry.
- 3) Ohms law of voltage and current is sufficient to describe the system therefore electromagnetic effects are considered negligible.
- 4) Current in the inner and outer conductors flow in the longitudinal directions only and current through the membrane is through the radial direction only
- 5) At a given longitudinal position the inner and outer conductors are equipotential. Therefore, the only change in membrane potential is in the longitudinal direction.

Variables for cylindrical cell core conductor:

- $I_o(z,t)$: Total longitudinal current flowing in the positive z direction in the outer conductor (A)
- $I_i(z,t)$: Total longitudinal current flowing in the positive z direction in the inner conductor (A)
- $J_m(z,t)$: Membrane current density flowing from the inner conductor to the outer conductor (A/m^2)
- $K_m(z,t)$: The membrane current per unit length flowing from the inner conductor to the outer conductor (A/m)
- $K_e(z,t)$: Current per unit length of external source applied cylindrically (A/m)
- $V_m(z,t)$: The membrane potential which is a positive quantity when the inner conductor has a positive potential with respect to the outer conductor (V).
- $V_i(z,t)$: Potential in the inner conductor (V).
- $V_o(z,t)$: Potential in the outer conductor (V).
- r_o : Resistance per unit length of the outer conductor (Ω/m).
- r_i : Resistance per unit length of the inner conductor (Ω/m).
- a : Radius of the cylindrical cell.

Figure 6: Core conductor model

The core conductor model can effectively model current traveling down the inner and outer conductors. Using KCL, The current going into and out of the conductor can be defined as following

$$I_i(z + \Delta z, t) - I_i(z, t) = -K_m(z, t) \Delta z \quad (28)$$

$$I_o(z + \Delta z, t) - I_o(z, t) = K_m(z, t) \Delta z - K_e(z, t) \Delta z \quad (29)$$

Next, the potential on the inside and outside the conductor can be written using a similar relationship.

$$V_i(z + \Delta z, t) - V_i(z, t) = -r_i I_i(z + \Delta z, t) \Delta z \quad (30)$$

$$V_o(z + \Delta z, t) - V_o(z, t) = -r_o I_o(z + \Delta z, t) \Delta z \quad (31)$$

By dividing by Δz and taking the limit as z approaches zero, (28)- (32) are in the form of the definition of a derivative and can be written to relate the currents and voltages in the core conduction model.

$$\frac{\partial I_i(z,t)}{\partial z} = -K_m(z,t) \quad (32)$$

$$\frac{\partial I_o(z,t)}{\partial z} = K_m(z,t) - K_e(z,t) \quad (33)$$

$$\frac{\partial V_i(z,t)}{\partial z} = -r_i I_i(z,t) \quad (34)$$

$$\frac{\partial V_o(z,t)}{\partial z} = -r_o I_o(z,t) \quad (35)$$

The voltage across the membrane can then be written as the inner subtracted from the outer conductor potential.

$$V_m(z,t) = V_i(z,t) - V_o(z,t) \quad (36)$$

By taking the derivative of (36) with respect to z , (34) and (35) can be substituted in, relating the membrane potential to the currents in the inner and outer conductors.

$$\frac{\partial V_m(z,t)}{\partial z} = -r_i I_i(z,t) + r_o I_o(z,t) \quad (37)$$

Taking a further derivative of (37),

$$\frac{\partial^2 V_m(z,t)}{\partial z^2} = r_o \frac{\partial I_o(z,t)}{\partial z} - r_i \frac{\partial I_i(z,t)}{\partial z} \quad (38)$$

A further substitution of (30) and (31) into (38) results in the following equation.

$$\frac{\partial^2 V_m(z,t)}{\partial z^2} = r_o + r_i K_m(z,t) - r_o K_e(z,t) \quad (39)$$

Equation (40) is known as the core conductor equation. The core conductor equation is valid independent of the properties of the membrane, which for neuron models is nonlinear. To extend the core conductor model to neurons, the membrane potential can be described by the HH neuron (Figure 7).

Figure 7: Core conductor model with Hodgkin and Huxley neuron model. The HH neuron model is placed in-between the inner and outer conductor.

The model above can have repeated segments in series to show variation of membrane potential as a function of space. To further extend the core conductor equation to myelinated neurons, a cable model can be derived in which the membrane potential of the core conductor is described with a resistor and capacitor in parallel.

Figure 8: Equivalent circuit model of myelin sheath

The model in figure 8 can be used to represent myelin and separate the HH active membranes [11]. The capacitance C_m is the ability of the myelin to hold charge, the battery V_m is the resting membrane potential of the neuron, and the conductor G_m is the permeability of the myelin sheath. Below is a table summarizing values used to model a frog myelinated neuron using the core conductor model with the HH neuron to describe the membrane potential.

Table 3: A summary of the electrical and geometric characteristics of the nodes and internodes of a frog myelinated nerve fiber. Table values obtained from [31]

	Characteristic	Value
Fiber geometry	Fiber Diameter (D)	14 μm
	Thickness of myelin ($(D-d)/2$)	2 μm
	Distance between nodes (l)	2 mm
	Area of nodal membrane (πdl)	22 μm^2
Node parameters	Capacity of node ($\pi dl C_{mn}$)	0.6-1.5 pF
	Capacity per unit area of nodal membrane (C_{mn})	3-7 $\mu\text{f}/\text{cm}^2$
	Resistance of resting node ($R_{mn}/\pi dl$)	40-80 $\text{M}\Omega$
	Space constant of node	0.2 mm
	Time Constant of node	30-140 μs
Internode parameters	Resistance per unit length of axis cylinder (r_i)	140 $\text{M}\Omega$
	Resistivity of axoplasm	110 $\Omega \text{ cm}$
	Capacity per unit length of myelin sheath (C_m/l)	10-16 pF/cm
	Capacity per unit area of myelin sheath (C_m/A)	0.0025-0.005 $\mu\text{F}/\text{cm}^2$
	Dielectric constant of myelin sheath	5-10
	Resistance of unit area of myelin sheath (R_m)	0.1-0.16 $\text{M}\Omega$
	Resistivity of myelin sheath	500-800 $\text{M}\Omega \text{ cm}$
	Space constant of internode	4.4 – 5.6 mm
	Time constant of internode	250-800 μs
Potential characteristics	Action potential peak voltage	116 mV
	Resting potential	-71 mV
	Peak inward current density	20mA/cm ²
	Conduction velocity	23 m/s

1.7 Methods for Solving Neuron Models

All of the neuron models require solving nonlinear differential equations due to properties of neural ion channel permeability, which were discussed in section 1.2.

Circuit simulators have classical been used to describe nonlinear differential equations, and have been successful to describe the behavior of the HH neuron [23, 32]. Differential equation solvers, such as those found in MATLAB, require the first derivatives of the equation isolated. This can lead to much algebraic manipulation which will be prone to

error. Circuit simulators are a viable option to describe the behavior of differential equations because they do not require the isolation of first derivative terms. Capacitors and inductors can be used to model differential equation behavior in combination with Kickoff's current or voltage laws. Additionally, once a circuit model has been made, parameters can be changed much simpler, therefore the model becomes more modular than traditional differential equation solvers. The SPICE platform presents a good platform for modeling differential equations using primitive circuit elements. SPICE can define an equation for a node in a circuit using voltage and current dependent voltage sources. SPICE's ability to solve the transient response of circuits can be used to describe membrane potential of a neuron.

1.8 Neurodegenerative diseases

Demyelination is a symptom of many demyelinating diseases such as Multiple Sclerosis (MS). Multiple sclerosis is the leading cause of disability for young adults, therefore studying its cure is of benefit [9, 31]. Demyelination is caused by the immune system attacking the myelination surrounding the axon, which causes inflammation and leads to further auto immune attack [20]. Multiple Sclerosis is a disease of the central nervous system. A pathologic criterion of demyelinating is

- Destruction of myelin sheath around nerve fibers
- A relative sparing of other nervous tissue
- Infiltration of inflammatory cells
- A distribution of lesions primarily in the white matter.

Classic features of this disease include motor weakness, paralysis, vision impairment, tremors and others, many of which are caused by slowed action potential conduction velocity [33]. All of the symptoms of demyelination are difficult to model, and not possible with an equivalent circuit model. The causality of these symptoms, however, is the reduction of axonal myelination, and thus demyelination can be effectively modeled with an equivalent circuit model [24, 26, 31]. Some studies show that positive symptoms may also be present in Multiple Sclerosis due to either hyper excitability of injured axon, or persistent reflection of action potentials, which causes epileptic activity [36].

Treatments for demyelinating diseases have traditionally included immune modifying medications or exchange modification or plasma exchange. Plasma exchange is invasive and many patients relapse after such treatment [33]. More recently potassium channel blocking medications have been used to improve electrical conduction through demyelinated axons. Modification to the immune system has shown the most improvement of symptoms, but is not a permanent solution. Animal models have been used to determine the effectiveness of ion channel blockers on demyelinated neurons. The animal studies concluded that by applying 4-aminopyridine (4AP) and tetraethylammonium (TEA) to demyelinated neurons, normal conduction velocity can return [3, 20, 27]. Potassium channels blockers increase amplitude and duration of an action potential by binding to the cytoplasmic side of ion channels [20]. Most potassium channel blockers that have been tested have an affinity for slow acting or delayed rectifying channels [20]. Channel blocker treatment is limited though due to the narrow toxic to therapeutic ratios.

Blocking specific ion channels may not only reduce symptoms of demyelination by altering ion channel gating dynamics, but may weaken the cytokine activation which attacks the neurons. Some studies suggest that specific potassium channels may have feedback loops with cytokine and other immune system response mechanisms, therefore by suppressing these channels, the cell may not face autoimmune attack [3]. Other studies suggest that potassium channel blockers may enhance CNS motor evoke brain activation to improve symptoms of demyelination, but have no effect on motor conduction [20]. A goal of this work is to develop a SPICE simulated demyelinated neuron that later could be extended test (MS) therapies. The SPICE neuron models the gating dynamics of a neuron and does not take into account cytokine activation or other feedback loops. The model presented in this work would not be robust enough to model the benefit of potassium channel blockers due to feedback loops.

II Methods

The presented model extends the previous electrically small cell model by Hodgkin and Huxley [18] into a myelinated neuron. A myelinated neuron can be simulated with an equivalent circuit model of an electrically large cell. An equivalent circuit model can account for the geometric and electrical properties of the Nodes of Ranvier (nodes), as well as the myelinated axon (internodes). A connection of nodes with internodes allows for the simulation of any length of myelinated neuron. P-SPICE was used to implement the myelinated neuron using netlist coding. Referencing a circuit component and specifying its value can be implemented with a netlist code in P-SPICE. Connections of the circuit component must then be specified. For example, to simulate a battery and resistor in series the following netlist could be used.

Circuit Component	Node 1	Node 2	value
V	0	1	20
R	1	0	10

In the above netlist, V is the battery with a value of 20 volts and it is placed between nodes zero and one. Node zero is the ground node. The resistor of 10 ohms is set between nodes one and zero (ground), completing the circuit. The netlist code above would implement a circuit diagram as shown below:

Figure 9: Circuit model of a battery resistor network for netlist code.

The above circuit diagram is simple, but by extending the number of nodes, P-SPICE can simulate more complex circuits.

In the following chapters, the approach to simulate a demyelinated neuron will be presented, starting with the electrically large cell model. The properties of the nodes will then be presented, followed by the properties of the internodes. Concluding the methods section will be the implementation and connection of the discrete neuron sections.

2.1 Electrically large Cell model

By utilizing a previous SPICE model of an electrically small cell neuron, an extended core conductor myelinated neuron was developed. The electrically small cell is not sufficient to model a myelinated neuron because it does not account for spatial variation of membrane potential. A spatial variation in membrane potential is observed

in a myelinated neuron, because the action potential travels down a nerve fiber. To model a myelinated neuron, the membrane potential must change as a function of space and time. The simplest way of extending a model of an electrically small cell to a large cell is to connect a series of nodes separated by resistors. The nodes represent the excitable Nodes of Ranvier. Nodes separated by resistors, however, do not account for a myelin sheath. The myelin sheath can be successfully modeled with a resistive and capacitive network known as internodes [31]. The nodes and internodes are separated by resistors on the inner and outer conductor, which represent length of the axon (Figure 6).

2.2 Circuit Model of Node

The nodes in this work are based off a SPICE simulation developed by Szlavik [32]. In this neuron model, the potassium and sodium channels are modeled using the Hodgkin Huxley rate equations (5) and (12). The gating variables nonlinear differential equation are implemented in a sub-circuit using voltage controlled current and voltage sources in conjunction with capacitors (Figure 10).

Figure 10: Neuron model of the Node of Ranvier

The neuron model above has battery potentials, E_{Na} and E_K . The capacitance of the membrane is modeled with a capacitor, C_m . Current controlled current sources, FNA and FK, generate current for the sodium and potassium channels which are described in the gating circuit. The current controlled current sources supply the current through a variable resistor, representing the varying ion channel permeability.

A voltage controlled voltage source, ENAK, senses the voltage across the neuron membrane [32]. The HH rate equations, (9) (10) (19) (20) (22) and (23), are implemented in voltage controlled voltage sources EAx and EBx, where x signifies the n,m, and h gates. The alpha rate constant is outputted from EAx and the beta rate constant is outputted from EBx. Sources EAx and EBx, require the membrane potential as an input to determine the rate constant output. The alpha and beta terms in the rate equation are outputted from GAx and GBx. For GAx and GBx to describe the alpha and beta terms correctly, a feedback loop is required (see below for more detail). The value of a gating variable is determined by writing KCL at the GAx and GBx. The gating variable can easily be taken to any power with the POLY function in SPICE. The sodium and potassium battery potentials subtracted from the membrane potential are EMK and EMNA respectively. The sodium and potassium battery potentials subtracted from the membrane potential are then multiplied by the channel conductance and the gating variables to yield the ion channel current with (5) and (12). Each ionic current is sensed by VINA and VIK, and supplied to the circuit through current controlled current sources FNA, and FK respectively. Descriptions of the variables used to model the potassium and sodium channel using SPICE are summarized in tables 4 and 5.

Voltage Controlled Voltage Source

Voltage Controlled Current Source

Figure 11: Gating sub-circuit schematic for m, h and n gates.

Table 4: Potassium ion channel values used in SPICE neuron model

Potassium channel variable	Description	Quantity
V_m	Measured potential across membrane	$V_{\text{outside}} - V_{\text{inside}}$
ENAK: voltage controlled voltage source	Potential across membrane	$V_m = V_{\text{outside}} - V_{\text{inside}}$
EAN: voltage controlled voltage source	α_n voltage relationship	$\alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m + 50)} - 1}$
EBN: voltage controlled voltage source	β_n voltage relationship	$\beta_n = 0.125e^{-0.0125(V_m + 60)}$
GAN: voltage controlled current source	α_n rate equation term	$\alpha_n(1 - n)$
GBN: voltage controlled current source	β_n rate equation term	$-\beta_n n$
CN: capacitor	Time derivative for n gate, and temperature constant ϕ	$C_n = -(1/\phi) \frac{dn}{dt}$
EN4: voltage controlled current source	n gating variable to the fourth power	n^4
E_K : Constant voltage source	Battery potential for potassium	$E_K = \frac{RT}{F} \ln\left(\frac{c_K^o}{c_K^i}\right)$
EMK	Difference of battery and membrane potential	$V_m - E_K$
I_K : Voltage controlled Current Source	Current through potassium channel	$G_k = \bar{G}_K n^4 (V_m - E_K)$
VIK: Voltage controlled Voltage source	Potassium ionic current	I_K

Table 5: Sodium ion channel values used in SPICE neuron model

Sodium channel variable	Description	Quantity
V_m	Measured potential across membrane	$V_{\text{outside}} - V_{\text{inside}}$
ENAK: voltage controlled voltage source	Potential across membrane	$V_m = V_{\text{outside}} - V_{\text{inside}}$
EAM: voltage controlled voltage source	α_m voltage relationship	$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1}$
EBM: voltage controlled voltage source	β_m voltage relationship	$\beta_m = 4e^{-0.0125(V_m + 60)/18}$
GAM: voltage controlled current source	α_m rate equation term	$\alpha_m(1 - m)$
GBM: voltage controlled current source	β_m rate equation term	$-\beta_m m$
EAH: voltage controlled voltage source	α_h voltage relationship	$\alpha_h = 0.07e^{-0.05(V_m + 60)}$
EBH: voltage controlled voltage source	β_h voltage relationship	$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}}$
GAH: voltage controlled current source	α_h rate equation term	$\alpha_h(1 - h)$
GBH: voltage controlled current source	β_h rate equation term	$-\beta_h h$
CM: capacitor	Time derivative for m gate, and temperature constant ϕ	$C_m = -(1/\phi) \frac{dm}{dt}$
CH: capacitor	Time derivative for h gate, and temperature constant ϕ	$C_h = -(1/\phi) \frac{dh}{dt}$

EM3: voltage controlled current source	n gating variable to the fourth power	m^3
E_{Na} : Constant voltage source	Battery potential for potassium	$E_{Na} = \frac{RT}{F} \ln(\frac{c_{Na}^o}{c_{Na}^i})$
EMNA	Difference of battery and membrane potential	$V_m - E_{Na}$
I_{Na} : Voltage controlled Current Source	Current through potassium channel	$G_{Na} = \overline{G_{Na}} m^3 h (V_m - E_{Na})$
VINA: Voltage controlled Voltage source	Sodium ionic current	I_{Na}

Each node in Figure 11 represents a part of the Hodgkin and Huxley equivalent circuit model. For example, KCL can be applied at the n node in the diagram shown below.

By applying KCL at the n node, one can see that

$$i_1 + i_2 + i_3 = 0 \quad (41)$$

The current through the capacitor, $i_{capacitor}$ (which also equals i_I), is the product of the inverse of the capacitance and the differential of the voltage across the capacitor,

$i_{capacitor} = C \frac{dV}{dt}$. The other currents, i_2 and i_3 , are defined by voltage controlled current sources. The voltage controlled current sources, GAN and GBN require two inputs to output the alpha and beta terms in the rate equation. One input is the rate constant, alpha (9) or beta (10), shown as EAn and EBn. The other input is a feedback loop of the voltage at the n node. The current outputted by the capacitor (42), GAN (43) and GBN (44) are therefore defined as following:

$$i_1 = \frac{dn}{dt} \quad (42)$$

$$i_2 = \alpha_n(1 - n) \quad (43)$$

$$i_3 = -\beta_n n \quad (44)$$

By substituting in (42) (43) and (44) into (41) following equation can be written.

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (45)$$

Equation (45) is the same as the n gate rate equation (6) for the potassium channel. A similar equation can be used to define the m and h gate of a sodium channel.

The quantities in the sub-circuit that needed defining were the initial conditions to the gating variables, the concentration of potassium inside and outside the cell, the

temperature, the cell capacitance, as well as the conductance of the potassium and sodium channels. All of these parameters have been previously published and are presented in Table 6 [29] [32] [34].

Table 6: Parameters for myelinated neuron node of ranvier

Parameter	Value
m_o	0.0393
h_o	0.6798
n_o	0.2803
Temperature	6.3 °C
c_{Na}^o	491.0 mm/L
c_{Na}^i	50.0 mm/L
c_K^o	20.11 mm/L
c_K^i	400.0 mm/L
$\overline{G_{Na}}$	120.0 mS
$\overline{G_K}$	36.0 mS
CE	1.0 pF

With the concentration of ions defined in Table 6, the battery potentials for sodium and potassium are 55 and -72 mV respectively. With the parameters defined in this section a netlist PSPICE code was developed by Szlavik, and modified in this work (See Appendix A).

2.4 Circuit Model of Internode

The internode was developed with a resistive capacitive (RC) network to describe the membrane potential of the core conductor model (Figure 6). The resistor values for the inner and outer conductors, R_i and R_o , corresponded to an internode segment of approximately 0.285 mm in axon length. Seven internode segments were required to model the 2mm separation of nodes seen in human physiology. The resistor values for connecting the internodes were obtained from a simulation of a myelinated neuron by Stephanova [30]. Part of the internode networks contains a battery set to the resting membrane potential, V_m . The battery is put in series with the myelin sheath's conductance, G_m . A conductor and battery in series models the conductance of ions across the myelin. The battery value, representing the resting membrane potential, was obtained from using the Goldman equation (26). The value for the conductance of the myelin sheath was obtained from simulations by Weiss, Stephanova and Halter [14] [28] [34]. The myelin sheath has an ability to store charge represented by a capacitor, C_m . the value for the myelin sheath capacitance was obtained from Halter and Stephanova [14] [28]. The battery and conductor series network is put in parallel with the capacitor to model the properties of the myelin sheath's permeability. The internode parameter values are summarized in Table 7.

Table 7: Parameters for internode

Parameter	Value
G_m	250 M Ω
C_m	1.5 pF
R_o	8 M Ω
R_i	8 $\mu\Omega$
V_m	-62.5 mV

2.5 Connection and stimulation

P-SPICE allows the creation of sub-circuit library files. A sub-circuit is a predesigned circuit network saved into a library (.LIB file). The sub-circuit can interact with an overall circuit design at specific nodes, which are defined in the sub-circuit library file. Sub-circuits are useful when a specific sub-network will be used many times in a circuit design.

The node of the myelinated neuron was implemented as a sub-circuit node.LIB (Figure12). The internode was implemented as a sub-circuit Internode.LIB (Figure 13). Seven internode connections were implement as a sub-circuit internode_seg.LIB. The connection of nodes and internode segments simulates a myelinated neuron (Figure 14).

Figure 12: Node sub-circuit model for myelinated neuron.

Figure 13: Internode Segment sub-circuit.

The node and internodes both have an input and output to the inner conductor, as well as the outer conductor. The inner conductor represents the inside of the neuron, and the outer conductor represented the extra cellular fluid, outside the neuron. The resistance of the inner conductor, R_i , of each internode segment is set to $8 \text{ M}\Omega$ to model a 2 mm

separation of nodes. The total inner conductor resistance between nodes is therefore 64 M Ω . The inner conductor resistance in library file Internode.LIB is set to 4 M Ω , half of the 8 M Ω . The inner conductor resistance is set to half the required resistance because when two resistors are connected in series the resistances are additive. The outer conductor resistances are set to 1⁻²² Ω to act as dummy resistor connectors, in order to simulate connecting wires with no resistance. Below shows a schematic of the connections of the sub-circuits (Figure 14).

Figure 14: Myelinated neuron segment. Nodes are connected by seven internode segments.

Seven internode segments were connected in series and saved into library file Internode_seg.LIB. The PSPICE sub-circuit libraries allow for quick modification of the

any parameter of the model presented in this work. Multiple embedded library files were found necessary to quickly change parameters for differing simulations. Additionally, the library files allow for the modeling of any size neuron with ease. A neuron length can be modified by adding more nodes connected by seven internode segments. If library files were not made for the internode segments, it would require six times more lines of code to simulate an equal length neuron. The code length greatly increases if the ion channel gating dynamics are not implemented in a library file. See text below for a myelinated neuron with seven nodes.

```
I 0 2 pulse(0 6E-9 10E-3 100.0E-9 100.0E-9 .1E-3 0)
R2 1 0 1E100
```

```
*node1
```

```
xsub1 1 2 3 4    NODE
xsub2 3 4 5 6    INTERNODE_seg
```

```
*node2
```

```
xsub3 5 6 7 8    NODE
xsub4 7 8 9 10   INTERNODE_seg
```

```
*node3
```

```
xsub5 9 10 11 12  NODE
xsub6 11 12 13 14  DMINTERNODE_seg
```

*node4

xsub7 13 14 15 16 NODE

xsub8 15 16 17 18 INTERNODE_seg

*node5

xsub9 17 18 19 20 NODE

xsub10 19 20 21 22 INTERNODE_seg

*node6

xsub11 21 22 23 24 NODE

xsub12 23 24 25 26 INTERNODE_seg

*node7

xsub11 25 26 27 28 NODE

R3 27 0 1E100

R4 28 0 1E100

To stimulate the neuron, a current pulse of six nA was sufficient. The current pulse was applied to the inner conductor, which was sufficient for propagation of an action potential down the axon fiber. Most simulations assume an open circuit at the end of the last node for a simulation; therefore, terminal resistances, R3 and R4, were set to high resistance values, $10^{100} \Omega$, to mimic this condition. The membrane potential for each node, ENAK, was plotted versus time. To limit an overflow error received in OrCad PSPICE A/D it is necessary to modify the Pspice.config in the P-SPICE file by adding

the following line, MathExceptions=OFF. Turning the math exceptions off caused the system to be more robust for dividing by small numbers.

2.6 Modeling demyelination

Modified versions of the INTERNODE_seg.LIB were designed to simulate demyelinated cases, and were implemented in a library file, DMINTERNODE_seg.LIB. The myelin resistance in DMINTERNODE_seg.lib was reduced from 250 M Ω to 10 M Ω . The capacitance was also increased from 1.5pF to 37.5pF to represent demyelination. Decreasing the capacitance and increasing the resistances represent a decreasing of the thickness of the myelin sheath. The values of the demyelinated resistance and capacitance were obtained from Stephanova [29].

Two demyelination simulations were performed. The first simulation modeled one internode segment being demyelinated, the second modeled three consecutive internode segments being demyelinated. The conduction velocities between the myelinated and demyelinated simulations were compared. Conduction velocity was measured from the peak of the second and seventh node.

III Results

The results of the PSPICE myelinated and demyelinated neuron presented below. First the action potential of a single node is shown and compared to a MATLAB simulation to verify that PSPICE can successfully simulate the Hodgkin and Huxley equations. The action potential of a seven node myelinated and a demyelinated neuron are then shown. The simulations took approximately 20 minutes to complete on a Intel® Core(TM)2 Duo CPU @ 3.00 GHz.

3.1 Node Simulation

The node in the myelinated neuron represents the active Node of Ranvier. The Node of Ranvier is the excitable membrane that generates an action potential by opening and closing the m, h, and n gates. Shown below in figure 15 is the action potential of a node modeled in P-SPICE.

Figure 15: SPICE Hodgkin and Huxley model of a neuron. A square pulse was applied to the inner conductor and the transient response of the membrane potential is observed.

The action potential in figure 15 has the characteristics and shape of a neural action potential. The peak amplitude is approximately 52 mV. The gating variables activation for the action potential were also plotted (Figure 16).

Figure 16: P-SPICE simulation of HH neuron node showing m,h, and n gate activation. The yellow line is the m gating variable, the red line is the h gate activation variable, and the blue line is the n gate activation.

The yellow plot is the m gate and the red plot is the h gate of the sodium ion channel. The green line is the n gate of the potassium ion channel. When an action potential is initiated, the m gating variable goes to one, opening the m gate. The opening of the m gate causes sodium to move into the neuron resulting in the potential to increase towards the sodium battery potential. As the potential increases both the n and h gating variables begin to change. The h gating variable decreases, lowering the sodium conductance. The n gating variable increases, and potassium moves out of the neuron restoring the potential to the resting membrane potential. All of the gating variables are between zero and one and therefore the plots are bounded correctly as dictated by the HH neuron model.

The PSPICE model can be compared to a MATLAB neuron model of an action potential using MATLAB's ordinary differential equation solver. An action potential

generated by the model implemented in MATLAB is shown in figure 17 (see appendix B for MATLAB code).

Figure 17: MATLAB Hodgkin and Huxley model of a neuron. A square pulse was applied to the inner conductor and the transient response of the membrane potential is observed.

The PSPICE and MATLAB models show the same shape, same peak amplitude and roughly same pulse width. Figure 18 shows the gating variables activation.

Figure 18: MATLAB simulation of HH neuron node showing m, h, and n gate activation in response to a square pulse applied to the inner conductor. The green line is the n gate, the blue line is the m gate, and the red line is the h gate.

Similar to the PSPICE model, the MATLAB gating variables are bounded between zero and one. The gating variables show the same rising and falling behavior in both the MATLAB and PSPICE models. Both MATLAB and PSPICE solved the HH neuron equation yielding a similar solution, which validates the methodology presented in this work.

3.2 Myelinated neuron model simulation

The myelinated neuron has multiple Nodes of Ranvier along its axon that allows for regeneration of the action potential. The conduction velocity was calculated by measuring the distance between the second and seventh node, and dividing this quantity

by the time it takes the action potential to travel between the nodes. In human physiology the distance between two nodes is 2mm [34]. An action potential of a seven segment PSPICE myelinated neuron is shown in figure 19.

Figure 19: SPICE Myelinated neuron action potential propagation for seven node neuron. A square pulse was applied to the center of the first node in the inner conductor of the neuron. The transient response of the membrane potential in response to the pulse is the observed.

The membrane potential is shown at the Nodes of Ranvier. The action potential is equivalent in amplitude and pulse width from node to node. The conduction velocity measured from the first to last action potential was found to be 57.14 m/s. Median sized myelinated human neurons, such as the one simulated, can have conduction velocities from 36-72 m/s [21]. The action potentials show slight hyperpolarization which is normal.

3.3 Demyelination neuron model simulation

A seven node P-SPICE neuron was simulated with one and three consecutive demyelinated internode segments. The conduction velocities were calculated and compared for both the normal and the disease model cases (Table 8).

Figure 20: One internode segment with demyelination, action potential propagation for a seven node neuron. A square pulse was applied to the center of the first node in the inner conductor of the neuron. The transient response of the membrane potential in response to the pulse is the observed.

The amplitude of the node directly after the demyelinated internode segment had a 10mV reduced amplitude from normal and the conduction velocity was reduced from 57.15 m/s to 44.44 m/s. The pulse width remained uniform with the non-diseased human neuron.

Figure 21: Three internode segments with demyelination, action potential propagation for seven node neuron. A square pulse was applied to the center of the first node in the inner conductor of the neuron. The transient response of the membrane potential in response to the pulse is the observed.

Conduction velocity for three node demyelinated was 27.02 m/s with a decrease in amplitude of 15 mV at the internodes that were demyelinated.

Decreased resistance and increased capacitance are two main effects that can be effectively modeled using a Hodgkin Huxley neuron. Both capacitance and resistance were examined separately in the three internode demyelinated neuron. The resulting conduction velocities were calculated to determine which component of demyelination affected conduction velocity more. By decreasing the resistance to 10 M Ω from 250 M Ω , the conduction velocity was decreased to 40 m/s from 57.15 m/s. By increasing the capacitance to 37.5 pF from 1.5 pF, the conduction velocity was decreased to 27.2 m/s. In table 8 the conduction velocities of the myelinated and demyelinated simulations are shown.

Table 8: Comparison of conduction velocity under different demyelination conditions

Simulation type	Conduction Velocity (m/s)
Human Physiological Normal neuron $R_{\text{myelin}} = 250 \text{ M}\Omega$ $C_{\text{myelin}} = 1.5 \text{ pF}$	57.15
14.3% axon length demyelinated $R_{\text{demyelinated}} = 10 \text{ M}\Omega$ $C_{\text{myelin}} = 37.5 \text{ pF}$	44.44
42.9% axon length demyelinated $R_{\text{demyelinated}} = 10 \text{ M}\Omega$ $C_{\text{myelin}} = 37.5 \text{ pF}$	27.02
42.9% axon length demyelinated $R_{\text{demyelinated}} = 10 \text{ M}\Omega$	40.00
42.9% axon length demyelinated $C_{\text{myelin}} = 37.5 \text{ pF}$	27.2

IV Discussion

The SPICE HH neuron model presented in the methods and results is successful in modeling the action potential of a myelinated and demyelinated neuron. The SPICE model was validated against a mathematical model using MATLAB. The mathematical model and the circuit model both showed a similar solution to the Hodgkin and Huxley equations. Once the neuron models in MATLAB and SPICE were shown to produce similar results, the action potential of a seven node myelinated neuron was simulated. The action potential response of a myelinated neuron is uniform in amplitude, pulse width, and distance between nodal activation (Figure 19).

4.1 Gating Variables

The implementation of the HH gating variables were physiologically accurate (Figure 16). The sodium channel m gate has a cubic activation going from rapidly from zero to one. The m gate is the activation gate. The characteristic spike of an action potential towards the sodium battery potential is a result of an increase of the m gating variable from value zero to one. As the m gating variable approaches one, sodium conductance increases. The increase in sodium conductance causes sodium ions to move across the membrane into the neuron. The h gating variable steady state value is approximately 0.68 and while the m gate is increasing, the h gate value decreases to less than 0.1. The potassium channel n gating variable has a steady state of about 0.3. The n gate activation, limits the hyperpolarization of an action potential by bringing the potential towards the potassium battery potential. The gating variables m, h, and n limit ion channel conductance between zero and the maximum channel conductance, as shown

in (2) and (4). The conductance of ion channels and the Nernst potential determine the membrane potential of a cell. The sodium battery potential of 55mV is never achieved across the neuron membrane because the sodium channel conductance depends on the m and h gating variables, as well as the potassium ion channel conductance. For example, if the membrane potential was the sodium battery potential, both the m and h gate would need to be fully open and the potassium channel n gate would need to be fully closed, or a value of zero. The gating variable's values are never the required values to allow the membrane potential to be at either the sodium or potassium battery potential. The ion channel activations are the same as the Hodgkin and Huxley neuron model, and therefore produce an accurate simulated action potential.

4.2 The Effect of Demyelination on Conduction Velocity

A major goal of this work was to model a demyelinating neuron to simulate diseases such as Multiple Sclerosis. Two primary effects of demyelination that can be modeled with the HH neuron are a decreased resistance and an increased capacitance. Demyelination was examined with one (14.3% total axon length demyelinated) and three (42.9% total axon length demyelinated) internode segments being demyelinated. By comparing the values in table 8, it is clear that the neuron without demyelination has the fastest conduction velocity. Table 8 also shows that the higher the percentage of fiber length that is demyelinated, the slower the conduction velocity. Values for demyelination were obtained from a simulation by Stephanova where she modeled demyelination using a differential equation solver [29]. The P-SPICE demyelinated neuron shows how the effects of demyelination, reduced myelin resistance and increased capacitance, will

decrease conduction velocity. A decrease in conduction velocity has many negative physiological effects that were described in chapter 1.8.

To gain greater insight on demyelination's effect on conduction velocity, both capacitance and resistance were examined separately. For a three internode segment just the resistance was decreased to the demyelinated value. As expected the conduction velocity decreased, but only to 44.4 m/s. The capacitance was then increased to demyelinated value which results in a lowered conduction velocity of 27.2 m/s. The capacitance accounts for nearly all of the decrease in conduction velocity seen in demyelination. The myelin capacitance is the ability of the myelin to store electrical energy. At the segments of demyelinated axon, the neuron's ability to store energy increases. The capacitance, C , can be related to a voltage across an insulator V , as well as the charge on either side of the insulator q .

$$C = \frac{q}{V} \quad (45)$$

Equation (45) shows that if the myelin sheath has an increased capacitance, that more charge, or ions, will be required to maintain a certain voltage across the membrane. The time for the myelin to conduct an action potential, therefore, increases due to the increased capacitance.

The demonstration found in this work that myelin capacitance has a more significant effect on conduction velocity than myelin conductance was also found in other myelinated neuron model [34]. Examining the capacitance and resistance separately does not have physiological basis because both values depend on the thickness of myelination. It is not physiologically accurate, therefore, to drastically change the capacitance of

myelin without any change in resistance. A speculation of this simulation is that therapies for demyelination targeting myelin conductance would not be very successful in increasing conduction velocity.

4.3 Limitations

Several limitations to this work are presented. The assumption of the core conductor model, which the HH myelinated neuron, makes many simplifying assumptions that were discussed in chapter 1.5. Another limitation is how the demyelination is modeled. The Nodes of Ranvier are not uniformly placed for chronic demyelination because in the disease of demyelination either the disease itself or the neuron's reaction to the disease results in non-uniformly spaced Nodes of Ranvier [26]. The demyelination model presented, therefore, is more valid for recently demyelinated neurons. Even though there are many simplifying assumptions in this work, the neuron model presented can show trends of the effects of demyelination on conduction velocity. Due to the assumptions made in this work, the results of the neuron simulations will not exactly match the impact of the disease process in an *in vivo* human motor neuron.

4.4 Future Directions

The goal of this work was to develop a model for a human demyelinated neuron. A computation demyelinated model is useful because it allows studying certain properties of neurons without requiring a real neuron. Ion channel blockers are becoming a common treatment for Multiple Sclerosis, and other neural diseases [3]. If the effects of a therapy on myelin capacitance, conductance or ion channel permeability are known, the model

presented can quickly be modified to test whether the therapy could alleviate symptoms of slowed conduction velocity.

Future work could be done to test several channel blockers and to see the effect on the shape of the action potential, and the conduction velocity. To accurately test channel blocker therapies, it may be necessary to break the potassium and sodium channels into smaller sub channel categories. G. Reid's work shows that there are at least five types of voltage dependent potassium channels [25]. This work models the lumped response of all potassium channels into a single variable resistor and battery network. Potassium channel blockers in particular have a higher affinity towards specific potassium channels therefore it may be required to stop conduction on a sub potassium channel, instead of the all potassium channels [3]. An improvement to this work would be to extend the single lumped potassium channel response into several potassium channels. Each potassium channel would have a differing rate equation. Developing a gating equation modeling each specific potassium channel's conductance would be required to develop sub potassium channels.

Appendices

Appendix A: P-SPICE Node netlist

.SUBCKT NODE 100 99 101 102

*

*

* coNa = 491.0E-3 Extracellular sodium concentration (mol/L)

* ciNa = 50.0E-3 Intracellular sodium concentration (mol/L)

* coK = 20.11E-3 Extracellular potassium concentration
(mol/L)

* ciK = 400.0E-3 Intracellular potassium concentration
(mol/L)

*

* GNaMax=120.0E-3

* GKMax =36.0E-3

*

* V_r = -62.5E-3 Resting Membrane Potential (V)

*

* Temp = 6.3 Temperature (Degrees Celsius)

*

* b = 0.02 Relative permeability of sodium to
potassium

* R = 8.314 Reiberg gas constant
(joules/(mole*kelvin))

* Z = 1.0 Sodium and potassium ionic
valence

* F = 9.648E4 Faraday's constant (coulombs/mole)

*

*

.PARAM MO=0.0393

.PARAM HO=0.6798

.PARAM NO=0.2803

.PARAM VNA=55.0E-3

.PARAM VK=-72.0E-3

Rax1 99 31 4E6

Rax 31 102 4E6

Ri1 100 103 1E-22

Ri 103 101 1E-22

Rnode 103 30 30E-6

FNA 31 27 VINA 1

FK 31 28 VIK 1

VNk 28 30 {VK}

VNNa 27 30 {VNA}

ENAK 26 0 31 30 1

CE 31 30 {1E-12} IC=-62.5E-3

*Sodium current current pathway

*M variable

CM 2 0 0.26E-3 IC={MO}

RM 2 0 1E10

GAM 0 2 POLY(2) 2 0 5 0 0 0 1 0 -1

GBM 0 2 POLY(2) 2 0 6 0 0 0 0 0 -1

EAM 5 0 value= $\{-0.1*(v(26)*1E3+35)/(exp(-0.1*(v(26)*1E3+35))-1)\}$

RAM 5 0 1E10

EBM 6 0 value= $\{4*exp(-(v(26)*1E3+60)/18)\}$

RBM 6 0 1E10

* Sodium current current pathway

* H Variable

CH 3 0 0.26E-3 IC={HO}

RH 3 0 1E10

GAH 0 3 POLY(2) 3 0 7 0 0 0 1 0 -1

GBH 0 3 POLY(2) 3 0 8 0 0 0 0 0 -1

EAH 7 0 value= $\{0.07*exp(-0.05*(v(26)*1E3+60))\}$

RAH 7 0 1E10

EBH 8 0 value= $\{1/(1+exp(-0.1*(v(26)*1E3+30)))\}$

RBH 8 0 1E10

*Potassium current current pathway

* K parameters

CN 4 0 0.26E-3 IC={NO}

RN 4 0 1E10

GAN 0 4 POLY(2) 4 0 9 0 0 0 1 0 -1

GBN 0 4 POLY(2) 4 0 10 0 0 0 0 0 -1

EAN 9 0 value= $\{-0.01*(v(26)*1E3+50)/(exp(-0.1*(v(26)*1E3+50))-1)\}$

RAN 9 0 1E10

EBN 10 0 value= $\{0.125*exp(-0.0125*(v(26)*1E3+60))\}$

RBN 10 0 1E10

EMNA 15 0 26 11 1

RMNA 15 0 1E10
EM3 53 0 POLY(1) 2 0 0 0 0 1
EM3H 16 0 POLY(2) 53 0 3 0 0 0 0 0 1
RM3H 16 0 1E10
GNA 0 20 POLY(2) 15 0 16 0 0 0 0 0 6.7858E-006
VINA 20 0 0
VNA 11 0 {VNA}
RNA 11 0 1E10
VK 12 0 {VK}
RK 12 0 1E10
EMK 17 0 26 12 1
RMK 17 0 1E10
EN4 18 0 poly(1) 4 0 0 0 0 0 1
RN4 18 0 1E10
GK 0 21 POLY(2) 17 0 18 0 0 0 0 0 2.0358E-006
VIK 21 0 0
.ENDS

Appendix B: P-SPICE Internode and Demyelinated Internode netlist

```
.SUBCKT INTERNODE 99 101 100 1
```

```
Rax 99 103 4E6
```

```
Rax2 103 100 4E6
```

```
RMY 103 30 250E6
```

```
CMY 103 31 1.5E-12
```

```
Rout 101 31 4E-6
```

```
Rout2 31 102 4E-6
```

```
VNAK 31 30 -63E-3
```

```
.ENDS
```

```
.SUBCKT DMINTERNODE 99 101 100 102
```

```
Rfake 99 103 4E6
```

```
Rfake2 103 100 4E6
```

```
RMY 103 30 10E6
```

```
CMY 103 31 37.5E-12
```

```
Rax 101 31 4E-6
```

```
Rax2 31 102 4E-6
```

```
VNAK 31 30 -62E-3
```

```
.ENDS
```


Appendix C: P-SPICE Internode Segment & Demyelinated Internode Segment

```
.SUBCKT INTERNODE_seg 3 4 17 18
```

```
xsub2 3 4 5 6    INTERNODE  
xsub3 5 6 7 8    INTERNODE  
xsub4 7 8 9 10   INTERNODE  
xsub5 9 10 11 12  INTERNODE  
xsub6 11 12 13 14 INTERNODE  
xsub7 13 14 15 16 INTERNODE  
xsub8 15 16 17 18 INTERNODE
```

```
.ENDS
```

```
.SUBCKT DMINTERNODE_seg 3 4 17 18
```

```
xsub2 3 4 5 6    DMINTERNODE  
xsub3 5 6 7 8    DMINTERNODE  
xsub4 7 8 9 10   DMINTERNODE  
xsub5 9 10 11 12  DMINTERNODE  
xsub6 11 12 13 14 DMINTERNODE  
xsub7 13 14 15 16 DMINTERNODE  
xsub8 15 16 17 18 DMINTERNODE
```

```
.ENDS
```

Appendix D: MATLAB Hodgkin and Huxley Neuron Model

```
clc
clear
%% Program: Main_Program
% Revision Date: 05/28/10
% Author: Nathan Angel
%
% Current clamped electrically small cell solution.
%
% USES FUNCTIONS: odefun
% V_Na
% V_K
% V_r
% m_bound
% h_bound
% n_bound
% ode45
%
% Internal: a = Cell radius (m)
% d = Cell diameter (m)
% L = Cell length (m)
% temp = Temperature (deg. C)
% gmax_Na = Maximum sodium conductance per unit area
% (S/m^2)
% gmax_K = Maximum potassium conductance per unit area
% (S/m^2)
% co_Na = Extracellular Na concentration (M/L)
% ci_Na = Intracellular Na concentration (M/L)
% co_K = Extracellular K concentration (M/L)
% ci_K = Intracellular K concentration (M/L)
% C_m = Membrane capacitance per unit area (F/m^2)
% b = Relative sodium to potassium conductance
% delta_t = Time step (s)
% max_time = Maximum time (s)
% pulse_width = Stimulus pulse width (s)
% pulse_amp = Stimulus pulse amplitude (A)
% Area = Cell surface area (m^2)
% C = Cell capacitance (F)
% maxcond_Na = Maximum sodium conductance (S)
% maxcond_K = Maximum potassium conductance (S)
% Na_Battery = Sodium Nernst potential (V)
% K_Battery = Potassium Nernst potential (V)
% V_rest = Resting membrane potential (V)
% m_o = m gating variable initial value
% h_o = h gating variable initial value
% n_o = n gating variable initial value
% t = Vector of time points (s)
% y0 = Vector of initial conditions
% options = default solver options data structure
%% Variable declarations
a = 20E-6; % Cell radius (m)
d = 2*a; % Cell diameter (m)
L = 40.0E-6; % Cell length (m)
```

```

temp = 6.3; % Temperature (deg. C)
gmax_Na = (120E-3)*100^2; % Maximum sodium conductance per unit area (S/m^2)
gmax_K = (36E-3)*100^2; % Maximum potassium conductance per unit area (S/m^2)
co_Na = 491E-3; % Extracellular Na concentration (M/L)
ci_Na = 50E-3; % Intracellular Na concentration (M/L)
co_K = 20.11E-3; % Extracellular K concentration (M/L)
ci_K = 400E-3; % Intracellular K concentration (M/L)
C_m = (1.0E-6)*100^2; % Membrane capacitance per unit area (F/m^2)
b = 0.02; % Relative sodium to potassium conductance
delta_t = 1.0E-6; % Time step (s)
max_time = 20.0E-3; % Maximum time (s)
pulse_width = 10E-6; % Stimulus pulse width (s)
pulse_amp = 59E-9; % Stimulus pulse amplitude (A)

%% Compute cell parameter values
Area = 2*(pi*a^2) + 2*pi*a*L; %area in m^2
C = Area*C_m;
maxcond_Na = Area*gmax_Na;
maxcond_K = Area*gmax_K;
Na_Battery = V_Na(co_Na, ci_Na, temp);
K_Battery = V_K(co_K, ci_K, temp);
V_rest = V_r(co_Na, ci_Na, co_K, ci_K, temp, b);
m_o = m_bound(V_rest);
n_o = n_bound(V_rest);
h_o = h_bound(V_rest);

%% Set up the time vector
t = zeros(floor(max_time/delta_t),1);

for i = 1:floor(max_time/delta_t)
    t(i) = (i-1)*delta_t;
end

%% Specify the initial conditions vector
y0 = [V_rest, m_o, h_o, n_o];
options = odeset();

%% Invoke the solver
[T,Y] = ode45(@odefun, t, y0, options, C, maxcond_Na, maxcond_K, Na_Battery, K_Battery, pulse_width, pulse_amp);

%% Plot the solution
figure(1)
plot(T,(Y(:,1)*10^3))
grid
xlabel('Time(s)')
ylabel('Transmembrane Potential(mV)')
title('Action Potential')

figure(2)
plot(T,Y(:,2))
hold on
plot(T,Y(:,3),'r')

```

```

hold on
plot(T,Y(:,4),'g')
grid
xlabel('Time(s)')
ylabel('Gating Variable')
title('Gating Variable dynamics')

%%
% Function: alpha_h
% Revision Date: 15/28/10
% Author: Nathan Angel
% Computes the value of the alpha rate constant for the h gating
% variable.
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: ah = Returns the alpha rate constant for the h
% gating variable (1/ms)
%
%%
function ah = alpha_h(Vm)
Vm = Vm/1.0E-3;
ah = 0.07*exp(-0.05*(Vm+60));

%%
%
% Function: alpha_m
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the value of the alpha rate constant for the m gating
% variable. The function error traps for the denominator singularity
% condition.
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: am = Returns the alpha rate constant for the m
% gating variable (1/ms)
%
%%
function am = alpha_m(Vm)
Vm = Vm/1.0E-3;
if Vm ~= -35
am = -0.1*(Vm+35)/(exp(-0.1*(Vm+35))-1);
end
if Vm == -35
up = Vm + 1.0E-4;
down = Vm - 1.0E-4;
am = (-0.1*(up+35)/(exp(-0.1*(up+35))-1)+(-0.1)*(down+35)/(exp(-0.1*(down+35))-1))/2;
end

%%

```

```

% Function: alpha_n
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the value of the alpha rate constant for the n gating
% variable. The function error traps for the denominator singularity
% condition.
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: an = Returns the alpha rate constant for the n
% gating variable (1/ms)
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function an = alpha_n(Vm)
Vm = Vm/1.0E-3;
if Vm ~= -50
an = -0.01*(Vm+50)/(exp(-0.1*(Vm+50))-1);
end
if Vm == -50
up = Vm + 1.0E-4;
down = Vm - 1.0E-4;
an = (-0.01*(up+50)/(exp(-0.1*(up+50))-1) + -0.01*(down+50)/(exp(-0.1*(down+50))-1))/2;
end

```

```

%%
% Function: beta_h
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the value of the beta rate constant for the h gating
% variable.
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: bh = Returns the alpha rate constant for the h
% gating variable (1/ms)
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function bh = beta_h(Vm)
Vm = Vm/1.0E-3;
bh = 1/(1+exp(-0.1*(Vm+30)));

```

```

%%
% Function: beta_m
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the value of the beta rate constant for the m gating
% variable.

```

```

%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: bm = Returns the beta rate constant for the m
% gating variable (1/ms)
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function bm = beta_m(Vm)
Vm = Vm/1.0E-3;
bm = 4.0*exp(-(Vm+60)/18);

```

```

%%
% Function: beta_n
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the value of the beta rate constant for the n gating
% variable.
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: bn = Returns the beta rate constant for the n
% gating variable (1/ms)
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function bn = beta_n(Vm)
Vm = Vm/1.0E-3;
bn = 0.125*exp(-0.0125*(Vm+60));

```

```

%%
% Function: Current
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the value of the beta rate constant for the m gating
% variable.
%
% Inputs: t = Time in (s)
% pw = Stimulus pulse width in (s)
% amp = Stimulus current pulse amplitude in (A)
%
% Returns: I = Returns the stimulus current value in (A)
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function I = Current(t,pw,amp)
if t >= 0.0 & t <= pw
I = amp;

```

```

else
I = 0.0;
end

%%%
%
% Function: h_bound
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the final value of the m gating variable given a step
% excitation.
%
% USES FUNCTIONS: alpha_h
% beta_h
%
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: hb = Final value of h gating variable given a step
% excitation
%%%
function hb = h_bound(Vm)
hb = alpha_h(Vm)/(alpha_h(Vm)+beta_h(Vm));

```

```

%%%
%
% Function: m_bound
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the final value of the m gating variable given a step
% excitation.
%
% USES FUNCTIONS: alpha_m
% beta_m
%
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: mb = Final value of m gating variable given a step
% excitation
%
%%%
function mb = m_bound(Vm)
mb = alpha_m(Vm)/(alpha_m(Vm)+beta_m(Vm));

```

```

%%%
%
```

```

% Function: n_bound
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the final value of the n gating variable given a step
% excitation.
%
% USES FUNCTIONS: alpha_n
% beta_n
%
% Inputs: Vm = Membrane Potential (V)
%
% Returns: nb = Final value of n gating variable given a step
% excitation
%
%%
function nb = n_bound(Vm)
nb = alpha_n(Vm)/(alpha_n(Vm)+beta_n(Vm));

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
% Function: odefun
% Revision Date: 5/28/10
% Author: Nathan Angel
%
% Implement the system of nonlinear ordinary differential equations
% associated with the problem presented in Section 6.1.
%
% USES FUNCTIONS: m_bound
% h_bound
% n_bound
% tau_m
% tau_h
% tau_n
% Current
%
% Inputs: t = current time point being evaluated in (s)
% y = previous value of the ODE variables, VECTOR
% Cm = membrane capacitance in (F)
% GNa_max = maximum sodium conductance in (S)
% GK_max = maximum potassium conductance in (S)
% VNa = sodium Nernst potential in (V)
% VK = potassium Nernst potential in (V)
% pw = stimulus pulse width in (s)
% amp = stimulus pulse amplitude in (A)
%
% Returns: dy = first derivative value of ODE variables
%
% Internal: mf = step bounded value of m gating variable
% hf = step bounded value of h gating variable
% nf = step founded value of n gating variable
% taum = step rise time value of m gating variable

```



```

% tauh = step rise time value of h gating variable
% taun = step rise time value of n gating variable
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

```

```

function dy = odefun(t, y, Cm, GNa_max, GK_max, VNa, VK, pw, amp);
mf = m_bound(y(1));
hf = h_bound(y(1));
nf = n_bound(y(1));
taum = tau_m(y(1));
tauh = tau_h(y(1));
taun = tau_n(y(1));
dy = [-(GK_max/Cm)*(y(4)^4)*(y(1)-VK)-(GNa_max/Cm)*(y(2)^3)*y(3)*(y(1)-
VNa)+Current(t,pw,amp)/Cm;
(mf-y(2))/taum;
(hf-y(3))/tauh;
(nf-y(4))/taun];

```

```

%%
% Function: tau_h
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the the step rise value of the h gating
%
%
% Inputs: y0 = (Vrest, m_o, h_o, n_o)
%
% Returns: th, the step rise in seconds
%
%%
function th = tau_h(Vm)
th = 1/((alpha_h(Vm)+beta_h(Vm)))*(1/1000);

```

```

%%
% Function: tau_m
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the the step rise value of the m gating
%
%
% Inputs: y0 = (Vrest, m_o, h_o, n_o)
%
% Returns: tm, the step rise in seconds
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function tm = tau_m(Vm)

```

```
tm = (1/(alpha_m(Vm)+beta_m(Vm)))*(1/1000);
```

```
%%
% Function: tau_n
% Revision Date: 15/28/10
% Author: Nathan Angel
%
% Computes the the step rise value of the n gating
%
%
% Inputs: y0 = (Vrest, m_o, h_o, n_o)
%
% Returns: tn, the step rise in seconds
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function tn = tau_n(Vm)
tn = (1/(alpha_n(Vm)+beta_n(Vm)))*(1/1000);
```

```
%%
% Function: V_K
% Revision Date: 5/28/10
% Author: Nathan Angel
%
% Find the resting membrane potential for sodium and potassium using
% the Goldman Equation.
%
% Inputs: coK = Extracellular K concentration in
% (moles/liter)
% ciK = Intracellular K concentration in
% (moles/liter)
% T = Temperature in degrees (Celsius)
%
% Returns: V_K = Resting transmembrane potential of sodium in (V)
%
% Internal: R = Reiberg Gas Constant in (joules/(mole*kelvin))
% F = Faraday's Constant in (coulombs/mole)
% Z = Sodium and potassium ionic valence
% TKelvin = Temperature in degrees (Kelvin)
%
%%
```

```
function VK = V_K(co_K, ci_K, temp)
R = 8.314; % Reiberg gas constant (joules/(mole*kelvin)).
F = 9.648E4; % Faraday's constant (coulombs/mole).
Z = 1; % Sodium and potassium ionic valence.
TKelvin = 273.15 + temp;
VK = ((R*TKelvin)/(Z*F))*log((co_K)/(ci_K));
```

```

%%
% Function: V_Na
% Revision Date: 5/28/10
% Author: Nathan Angel
%
% Find the resting membrane potential for sodium and potassium using
% the Goldman Equation.
%
% Inputs: coNa = Extracellular sodium concentration in
% (moles/liter)
% ciNa = Intracellular sodium concentration in
% (moles/liter)
% T = Temperature in degrees (Celsius)
%
% Returns: V_Na = Resting transmembrane potential of sodium in (V)
%
% Internal: R = Reiberg Gas Constant in (joules/(mole*kelvin))
% F = Faraday's Constant in (coulombs/mole)
% Z = Sodium and potassium ionic valence
% TKelvin = Temperature in degrees (Kelvin)
%
%%

```

```

function VNa = V_Na(co_Na, ci_Na, temp)
R = 8.314; % Reiberg gas constant (joules/(mole*kelvin)).
F = 9.648E4; % Faraday's constant (coulombs/mole).
Z = 1; % Sodium and potassium ionic valence.
TKelvin = 273.15 + temp;
VNa = ((R*TKelvin)/(Z*F))*log((co_Na)/(ci_Na));

```

```

%%
% Function: V_r
% Revision Date: 5/28/10
% Author: Nathan Angel
%
% Find the resting membrane potential for sodium and potassium using
% the Goldman Equation.
%
% Inputs: coNa = Extracellular sodium concentration in
% (moles/liter)
% ciNa = Intracellular sodium concentration in
% (moles/liter)
% coK = Extracellular potassium concentration in
% (moles/liter)
% ciK = Intracellular potassium concentration in
% moles/liter
% T = Temperature in degrees (Celsius)
% b = Relative permeability of sodium to potassium
%
% Returns: Vr = Resting transmembrane potential in (V)
%
% Internal: R = Reiberg Gas Constant in (joules/(mole*kelvin))
% F = Faraday's Constant in (coulombs/mole)

```

```

% Z = Sodium and potassium ionic valence
% TKelvin = Temperature in degrees (Kelvin)
%
%%

function Vr = V_r(coNa,ciNa,coK,ciK,T,b)
R = 8.314; % Reiberg gas constant (joules/(mole*kelvin)).
F = 9.648E4; % Faraday's constant (coulombs/mole).
Z = 1; % Sodium and potassium ionic valence.
TKelvin = 273.15 + T;
Vr = ((R*TKelvin)/(Z*F))*log((coK + b*coNa)/(ciK + b*ciNa));

```

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