Mathematical Modeling of the Evolution and Development of Myelin

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Abstract

Nerve impulses exhibit an increased conduction velocity in axons that are wrapped with myelin. Although unmyelinated and myelinated axons are well studied, the process of myelination that allow the formation of myelin on previously unmyelinated axons is not well understood. In this paper we develop a mathematical model of myelination. By varying a parameter that represents the tightness of myelin, this model was made to describe the unmyelinated axon, the fully myelinated axon, and the transitional states in between. As myelin tightens, a slowdown in conduction velocity occurs in the transitional states before a speedup. Varying other geometric parameters such as the thickness and length of myelin shows that some sequences of geometric changes are more optimal than others.
Acknowledgments

I am thankful for ton of people! You especially! *Gotta finish this*....
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1 Introduction to neuroscience

Overview of axons and myelin

To function as a complex organism, nearly all animals must have a means of communication. This includes both a communication within the organism and between the organism and its environment. The nervous system is a network of specialized cells called neurons and glial cells that allow this communication in most animals.

The neurons that make up the most fundamental components of the nervous system are responsible for creating and transmitting signals throughout the body. This is possible due to the long tubular projections called axons that extend out from the neuron (figure 1.1a). The membrane of the axon, called the axolemma, creates an uneven separation of ions between its inside and outside. Ions are charged particles with electrical potential energy so the separation gives the axon a voltage (difference in electrical potential energy) across the axolemma. The axolemma also has voltage-gated ion channels which are passages in the membrane that open or close depending on the voltage of the membrane. By default, these channels are closed but if the voltage of the axon is changed, then these channels may open and allow ions to shuffle in and out of the axon. This shuffling of ions results in a spike in voltage called an action potential. The action potential is the signal that propagates down the axon as a traveling wave and allows for communication (figure 1.2a).

Figure 1.1: Neurons with (a) unmyelinated and (b) myelinated axons. To emphasize morphological details, the figures are not drawn to scale. The boxes on the right are cross sections of the nerve fibers.
Figure 1.2: Action potential propagation in an (a) unmyelinated and (b) myelinated axon. Each line color denotes a different time $t = n\Delta t$ where $\Delta t = 1.7$ and $n \in \{0, 1, \ldots, 5\}$. For the green line, $n = 0$ and $n$ increases for each subsequent color until $n = 5$ for the blue line. The gray background in (b) represents the location of the myelinated internodes.

Glial cells are a large class of cells in the nervous system. They have a myriad of functions that primarily but not exclusively assist neurons. In this paper, we are only concerned about the glial cells that are responsible for myelination. Myelination is the process of wrapping axons with many tight layers of cell membranes (figure 1.1b). Note in figure 1b, that myelin does not form on the entire length of the axon. Instead, myelin forms in segments separated by relatively short segments of exposed axon. The myelinated segments are called internodes and the exposed unmyelinated segments are called nodes. In the internodes, myelin changes the electrical properties of the axon. This results in a change in the action potential propagation. Action potentials do not propagate continuously down the myelinated axons, but instead hop and skip on the exposed nodes in an accelerated form of conduction called saltatory conduction.

The mechanisms of both continuous conduction in the unmyelinated, and saltatory conduction in the myelinated axon will be discussed in later sections. When needed, the term nerve fiber will be used to collectively describe both the unmyelinated and myelinated axon.

Evolution and development of myelin

Throughout evolutionary history there are several examples of animals with myelin, but lacking a common myelinated ancestor. This implies that myelin was not originally developed in a single species that later
passed this trait onto all myelinated descendants. Instead, several species must have independently evolved myelin as an adaptation (source: Hartline). A similar transition from unmyelinated to myelinated axons also occur in normal development of myelinated species. In early fetal development, unmyelinated axons are initially formed. Later in development, a portion of these axons are myelinated by glial cells. Some axons undergo myelination well into the juvenile stages of the organism’s life, while other axons are never myelinated at all (source).

The speedup in conduction velocity of myelinated axons is an important and well studied advantage in many animals. However the effect of myelin on action potential propagation in the transitional stages during myelination is not clear. In this study, we aim to derive a mathematical model that describes the unmyelinated axon, the fully myelinated axon, and the possible transitional states between these two extreme states. With the versatility of this model we hope to explore the evolution and development of myelin further.
2 Formulation of model

Overview

Nerve fibers function a lot like an electrical circuit, by shuffling charged particles around in a concerted way. As such, the study of axons involve the use of circuit equations and laws of electromagnetism. A brief overview of fundamental electromagnetism topics is discussed in Appendix 1. The main difference between the circuitry of a phone (for example) and the circuitry of a nerve fiber is that the moving particles in a phone are primarily electrons while ions move in a nerve fiber. Thus, movement in a nerve fiber circuit is not only driven by differences in electrical potential energy, but also by chemical concentration gradients. The combination of electrical and chemical differences is called an electrochemical gradient.

We model our nerve fiber as two concentric cylinders, where the inner cylinder represents the axolemma and the outer cylinder represents the myelin in internodes, or the lack of myelin in nodes. The difference between the nodal and internodal segments of the outer cylinder is that we assign negligible electrical properties to the nodal sections. We begin the formulation of our model by discussing the electrochemical behavior of ions moving radially through a ∆x length of axolemma. We assume that ∆x is small enough such that all electrical components are approximately constant with respect to x. Then we discuss the behavior of ions moving radially through a ∆x length of myelin. Note that these sections will utilize per-length units such as “current per unit length.” Finally, we discuss the axial activity in the regions partitioned by the two cylinders. Units in the axial direction are absolute and not “per-length.” In the end, we will have a system of partial differential equations that describe the electrochemical behavior of our model in both the radial and axial directions.

Axon structure and models

Most physiologically accurate axon models are constructed by examining the structure and electrical properties of the axolemma and considering its equivalent circuit components (figure 2.1). As previously mentioned, the axolemma has a voltage which is the electrical potential of the intracellular space minus that of the extracellular space. The sodium and potassium ions also have particular voltages associated with them called the reversal potentials, $E_{Na}$ and $E_{K}$. Even at rest, ions are constantly moving through the axolemma by passive leaking along or active pumping against their electrochemical gradients. The reversal potentials are the voltages required to maintain a net zero flux of their respective ions across the axolemma. These quantities are important because it is not the membrane voltage, V, that drives a particular ion, but its difference from the reversal potential $V - E_{ion}$ (where ion is Na or K).

The cell membrane itself is made up of two parallel sheets of phospholipid molecules approximately 10 nm across (source?). This thin separation of conductive intercellular and extracellular space means that the
axolemma has a capacitance. Ions are capable of moving across the axolemma through channels called voltage-gated ion channels. At most voltages, these channels are closed and give the axolemma a high resistance. At particular voltages, the channels open and the resistance of the axolemma drops. Finally, the axolemma also has various channels that constantly leak a relatively small amount of ions, proteins, and other small molecules. If $V$ is the voltage of the membrane, and $c_A$ is the capacitance per unit length, then the per-length capacitative current of the axon is given by $c_A \frac{dV}{dt}$ (Appendix 1). The per-length resistive current of the ions Na and K is given by $g_{ion}(V)(V - E_{ion})$ where $ion$ is Na or K and $g_{ion}$ is the voltage dependent per-length conductance (1/resistance) of the particular ion (Appendix 1). The per-length leak current is given by $g_L(V - E_L)$ where $g_L$ is the constant per-length conductance and $E_L$ is the reversal potential of the leaking molecules.

![Diagram of axolemma](image)

**Figure 2.1**: Structure and equivalent circuit of axolemma.

As the name suggests, voltage-gated ion channels are channels in the membrane that have voltage dependent gates that are either closed and obstruct or opened and allow the passage of ions. Sodium channels have four gates: three “activation” and one “inactivation” gate. Potassium channels have four “activation” gates. If all the gates are forced open, the sodium and potassium channels exhibit a maximum conductance of $g_{Na}$ and $g_{K}$ respectively. If we let $m$, $h$, and $n$ be the proportion of opened sodium activation, sodium inactivation, and potassium activation gates, respectively, then $g_{Na} = g_{Na0}m^3h$ and $g_{K} = g_{K0}n^4$. Let $\alpha_i(V)$ and $\beta_i(V)$ for $i = m, h, n$ be the experimentally determined opening and closing rates respectively for $m$, $h$, and $n$. The gates are defined by a differential equation that basically states the following: the change in the proportion of open gates is equal to the opening of closed gates minus the closing of opened gates. By applying Kirchhoff’s Current Law (Appendix 1) we obtain with a system of differential equations that
accurately describes the circuitry of the axolemma. This mathematical model is called the Hodgkin-Huxley Model (equations 2.1-2.4) (citation and significance). Here we have $I$ representing the total positive current leaving the axon.

$$I = c_A \frac{dV}{dt} + I_{Na} + I_K + I_L$$

(Kirchhoff’s Current Law)

$$= c_A \frac{dV}{dt} + \overline{g}_{Na} m^3 h (V - E_{Na}) + \overline{g}_K n^4 (V - E_K) + g_L (V - E_L)$$

The Hodgkin-Huxley equations are

$$c_A \frac{dV}{dt} = I - \overline{g}_{Na} m^3 h (V - E_{Na}) - \overline{g}_K n^4 (V - E_K) - g_L (V - E_L) \quad [\text{Eq } 2.1]$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m \quad [\text{Eq } 2.2]$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h \quad [\text{Eq } 2.3]$$

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n. \quad [\text{Eq } 2.4]$$

The current through the axolemma can be experimentally controlled to express several important phenomena that allow proper axon function. Computationally, this applied currents can be represented by the variable $I$ in the Hodkin-Huxley model to accurately reproduce many of the same phenomena. Applied currents often occur as current injections. By a “current injection” we mean a brief (1 ms) stepping of $I = 0$ up to the value of $I_0$, i.e. $I(t) = I_0 (1 - H(t - 1))$ where $H(t)$ is the Heaviside step function. In the absence of current injections, ($I_0 = 0$ (units?)) the voltage $V$ remains at a constant level (figure 2.2). This voltage is called the resting potential. Small positive current injections change the voltage slightly before returning to the resting potential. Slightly larger current injections result in the voltage hanging at some constant value before dropping and settling to the resting potential. At some still larger current, the voltage spikes rapidly up and then falls back down towards the resting potential. This spike in voltage is the action potential. The lowest voltage at which action potentials generate is called the threshold. Larger current injections do not alter the resulting shape of the action potential. Instead the action potential occurs sooner.
The response of the Hodgkin-Huxley model to current injections. When $I_0 = 0$ (green line), the membrane voltage remains at the resting potential of $-60\text{mV}$. When $I_0 = 0.035$ (dark green), the voltage increases slightly before returning to the resting potential. When $I_0 = 0.0703$ (black), voltage rises and hangs around threshold before returning to the resting potential. $I_0 = 0.0704$ (dark blue) results in the generation of an action potential. The action potential generates sooner with $I_0 = 0.15$ (blue). Need to discuss parameter values used. Appendix 2?

The mechanism for an action potential is as follows. When the voltage is at threshold, the sodium activation gates $m$ quickly open, significantly increasing the sodium conductance (figure 2.3). Sodium ions are concentrated on the outside of the axon so these ions now rush in, making the voltage more positive (remember that membrane voltage is defined as the inside potential minus the outside potential). At an elevated voltage and after a slight delay, the sodium inactivation gates shut and the potassium activation gates open. Potassium conductance now starts to increase while sodium conductance starts to decrease. Thus, the potassium ions concentrated on the inside of the axon start to flow out and the sodium ions on the outside stop coming in. What results is the voltage becoming less positive. At a lower voltage, sodium activation gates now close and the membrane voltage continues to decrease until the potassium activation gates close.

Although the Hodgkin-Huxley Model accurately describes the axolemma, its high-dimensionality and many parameters make it difficult to analyze. The Fitzhugh-Nagumo model is a simplification of the Hodgkin-Huxley model (two dependent variables versus the Hodgkin-Huxley’s four) and describes the qualitative behavior of action potential rather than the detailed electrical properties of the axolemma (figure 2.4). Prac-
tically speaking, the Hodgkin-Huxley model is more physiologically valid, but the Fitzhugh-Nagumo model is relatively easier to analyze and less computationally demanding to numerically integrate.

Following a current injection and prior to the recovery of an action potential (if one occurs), the membrane voltage tends towards either the resting potential, \( V_{\text{rest}} \), or the peak of the action potential \( V_{\text{peak}} \). Between \( V_{\text{rest}} \) and \( V_{\text{peak}} \) is the threshold voltage, \( V_{\text{thresh}} \), which voltages tend away from in this time frame. If the voltage is normalized so that \( V_{\text{rest}} = 0 \), \( V_{\text{thresh}} = \alpha \in (0, 1) \), and \( V_{\text{peak}} = 1 \), then a simple way to represent this behavior is with the differential equation

\[
\frac{dV}{dt} = -V(V - \alpha)(V - 1)
\]

since \( V = 0 \) and \( V = 1 \) are its stable equilibria and \( V = \alpha \) is its unstable equilibrium.

After an action potential is initiated (\( V \) approaches \( V_{\text{peak}} \)), the voltage behavior changes. The action potential begins its recovery by decreasing through \( V_{\text{rest}} \) and dipping to some lower voltage \( V_{\text{dip}} \). So \( \frac{dV}{dt} \) now has one stable equilibrium at \( V_{\text{dip}} \). A simple way to represent this is by subtracting from the previous differential equation, a recovery variable \( W \). The recovery variable, \( W \) must become large and positive so that \( V_{\text{thresh}} \) and \( V_{\text{peak}} \) annihilate one another via saddle node bifurcation and \( V_{\text{rest}} \) drops from 0 to \( V_{\text{dip}} \). We have that the system is changed by \( W \) only when \( V \) is large (near \( V_{\text{peak}} \)) so \( W \) changes proportionally with \( V \). After \( W \) becomes large enough to change our system and recover the voltage, the system returns to its original state. Hence the change in \( W \) is also inversely proportional to \( W \), so \( \frac{dW}{dt} = V - \gamma W \), where \( \gamma \geq 0 \). Finally, the change in \( W \) is slow compared to the change in \( V \), otherwise the recovery of \( V \) may interfere with its firing. So \( \frac{dW}{dt} \) is scaled by a small constant.

The Fitzhugh-Nagumo equations are

\[
\begin{align*}
c_A \frac{dV}{dt} &= I - (V(V - \alpha)(V - 1) + W) \quad \text{[Eq 2.5]} \\
\frac{dW}{dt} &= \epsilon (V - \gamma W) \quad \text{[Eq 2.6]}
\end{align*}
\]

where \( I \) is the total positive current leaving the axolemma, \( \alpha, \epsilon \in (0, 1) \), and \( \gamma \geq 0 \). \( c_A \) represents the per-length capacitance of the Fitzhugh-Nagumo “axon,” and is added for consistency with other models and are not necessarily present in all formulations of the Fitzhugh-Nagumo equations. Since the \( V \) variable changes on a faster time scale than \( W \), it is sometimes interpreted as a voltage-like or sodium activation-like variable. This is because, as shown in the Hodgkin-Huxley model, \( V \) and \( m \) change more readily than \( h \) and \( n \).
**Figure 2.4:** The response of the Fitzhugh-Nagumo model to current injections. When $I_0 = 0$ (green line), the voltage-like variable $V$ is at the “resting potential” of $V = 0$. When $I_0 = 0.085$ (dark green), the $V$ increases slightly before returning to the resting potential. When $I_0 = 0.168$ (black), voltage rises and hangs before returning to the resting potential. $I_0 = 0.169$ (dark blue) results in the generation of an action potential. The action potential generates sooner with $I_0 = 0.4$ (blue). *Need to discuss parameter values used. Appendix 2?*

In both models, we have a total outward current $I$ consisting of a capacitative current and an ionic/resistive current, which has no driving force when $V = V_{rest}$. If we let $g_A(V)$ be the conductance of the axolemma, defined by Ohms law as the ratio of the ionic current to $V - V_{rest}$, then we can represent the axolemma generically as figure 2.5.

\[ I = c_A \frac{dv}{dt} + g_A(V)(V - V_{rest}) \quad \text{[Eq 2.7]} \]

where the positive outward ionic current $g_A(V)(V - V_{rest})$ is $g_{Na} m^3 h (V - E_{Na}) + g_{K} n^4 (V - E_{K}) + g_L (V - E_L)$ in the case of Hodgkin-Huxley or $V(V - \alpha)(V - 1) + W$ in Fitzhugh-Nagumo.
Myelin structure and model

In the absence of myelin, there are two regions where ions exist, the intracellular space within the axon and the extracellular space outside. The addition of myelin creates a third region, the submyelin space between the myelin and the axon. Myelin itself consists of many compact layers of phospholipid cell membranes. This separation of the conductive submyelin and extracellular spaces gives the myelin a voltage and a capacitance (figure 2.6). The myelin obstructs the movement of ions between the extracellular and submyelin space so the myelin has a resistance as well. Each layer of myelin adds a resistor and capacitor in series. So if $r'_M$ and $c'_M$ are the per-length resistance and capacitance for a single layer and $nl$ is the number of layers, then the per-length resistance and capacitance of the myelin are $r_M = r'_M (nl)$ and $c_M = \frac{c'_M}{nl}$, respectively (figure 2.7 and equation 2.8). A single myelin layer can be thought of as an axolemma without ion channels. So a myelin layer has the same capacitance, but smaller conductance than that of an axolemma. Hence $c'_M = c_A$ and $\frac{1}{r_M} \in (0, g_A(V_{rest}))$.

![Diagram of myelin structure and equivalent circuit](image)

**Figure 2.6**: Structure and equivalent circuit of myelin.
If $I$ is the total positive current leaving the myelin then myelin equation for $nl$ layers is

$$c_M \frac{dV}{dt} = I - \frac{1}{r_M} V \quad [\text{Eq 2.8}].$$

To model the nodes, where the axon lacks myelin, we simply adjust $r'_M$ and $c'_M$ to that of a “layer” of extracellular space. This space has zero capacitance so $c'_M = 0$. If $r_e$ is the per-length axial resistance of the extracellular space, as discussed in the next section, then the magnitude of $r'_M$ is about a millionth of the magnitude of $r_e$. This is because $r_e$ is conventionally calculated as the resistance in 1 cm of material however the thickness of a myelin layer is about $1 \times 10^{-6}$ cm. The resistance $r_e$ is very small ($0 < r_e \ll 1$) so $r'_M \approx 0$.

Let $r'_{M,1}$ and $c'_{M,1}$ be the axial per-layer resistance and capacitance of the internodal myelin. Let $r'_{M,N}$ and $c'_{M,N}$ be the axial per-layer resistance and capacitance of the nodal extracellular space. Let $L_N$ and $L_I$ be the node and internode lengths. Without loss of generality let $x = 0$ be the left edge of the first node. So the $n$th node is the interval $X_{N,n} = [(n-1)(L_N + L_I), (n-1)(L_N + L_I) + L_N]$ for $n = 1, 2, \ldots$. Similarly, the $n$th internode is $X_{I,n} = [(n-1)(L_N + L_I) + L_N, n(L_N + L_I)]$. Then we can represent $r_M$ and $c_M$ as functions that are periodic with respect to $x$ (equations 2.9 and 2.10).

$$r_M(x) = \begin{cases} r'_{M,N,nl} & \text{if } x \in \bigcup_{n=1,2,\ldots} X_{N,n} \\ r'_{M,1,nl} & \text{if } x \in \bigcup_{n=1,2,\ldots} X_{I,n} \end{cases} \quad [\text{Eq 2.9}]$$

$$c_M(x) = \begin{cases} c'_{M,N,n} \frac{1}{n} & \text{if } x \in \bigcup_{n\in\mathbb{N}} X_{N,n} \\ c'_{M,1,n} \frac{1}{n} & \text{if } x \in \bigcup_{n\in\mathbb{N}} X_{I,n} \end{cases} \quad [\text{Eq 2.10}]$$

During numerical integration, discontinuities often result in errors. So it is helpful to approximate $r_M(x)$ and $c_M(x)$ with continuous functions. For example a Fourier sine series could be used. As discussed in a later
section on numerical integration, we used a simpler, continuous, piecewise linear function in our computer simulations.

### Axial currents and final equations

Now that we have equations for the electrical circuits of the axolemma and the myelin, we shall relate them together through the environment that they share. We’ll begin with a discretized diagram of our model. Next we’ll derive a few identities and link the voltages with the currents. Finally, we’ll formulate the final equations.

To avoid confusion, lowercase subscripts are used to denote components that act in the axial direction, while uppercase subscripts denote components that act in the radial direction. Furthermore, $V$ is no longer used to represent the membrane voltage. Instead, $V_A$ and $V_M$ are used to clearly distinguish the voltages across the axolemma and the myelin, respectively.

### Potentials and Potential Differences:

<table>
<thead>
<tr>
<th>Axial</th>
<th>Currents:</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta V_i = V_i(x + \Delta x) - V_i(x)$</td>
<td>$I_i$ Internal</td>
</tr>
<tr>
<td>$\Delta V_s = V_s(x + \Delta x) - V_s(x)$</td>
<td>$I_s$ Submyelin</td>
</tr>
<tr>
<td>$\Delta V_e = V_e(x + \Delta x) - V_e(x)$</td>
<td>$I_e$ External</td>
</tr>
</tbody>
</table>

### Radial

| $V_A(x) = V_i(x) - V_s(x)$ | $I_A$ Axolemma |
| $V_M(x) = V_s(x) - V_e(x)$ | $I_M$ Myelin |
As before, $\Delta x$ is assumed to be small enough such that all electrical components are approximately constant between each point. In figure 2.8, “Myelin” and “Axolemma” denote the circuitry of the myelin sheath and axolemma, respectively, in the radial direction. The details of these circuits were described in the previous sections. In the same figure, three new circuit components are introduced: $r_i$, $r_s$, and $r_e$. These represent the per-length axial resistances of the internal, submyelin, and external spaces, respectively. Geometrically, our nerve fiber is modeled as two concentric cylinders so $r_i$, $r_s$, and $r_e$ correlate to the tightness of the spaces partitioned by these cylinders. Furthermore, we assume that the tightness is uniform along the length of the nerve fiber. So $r_i$, $r_s$, and $r_e$ are constant with respect to $x$.

In figure 2.9, the arrows denote the direction of positive current. The radial currents were described in previous sections and axial currents are described with Ohm’s Law. Note that current moves from high potential to low potential. So a positive current to the right occurs when there is a negative change in potential from left to right. Let’s first consider $I_i$.

\[
V_i(x + \Delta x) - V_i(x) = -I_i(x)r_i\Delta x \quad \text{(Ohm’s Law)}
\]

\[
I_i(x) = -\frac{1}{r_i}\frac{V_i(x + \Delta x) - V_i(x)}{\Delta x}
\]

\[
I_i(x) = -\frac{1}{r_i}\frac{\Delta V_i}{\Delta x}
\]
Taking the limit as $\Delta x \to 0$ gives equation 2.11.

\[ I_i = -\frac{1}{r_i} \frac{\partial V}{\partial x} \quad [\text{Eq 2.11}] \]

Similarly we have

\[ I_s = -\frac{1}{r_s} \frac{\partial V}{\partial x} \quad [\text{Eq 2.12}] \]
\[ I_e = -\frac{1}{r_e} \frac{\partial V}{\partial x} \quad [\text{Eq 2.13}] \]

Now let’s apply Kirchhoff’s Current Law to the three intersecting nodes of figure 2.9. We’ll begin with the bottom node (where $I_i$ and $I_A$ intersect), then the top (where $I_e$ and $I_M$ intersect), and finish with the middle (where $I_s$, $I_A$, and $I_M$ intersect).

Bottom node:

\[ 0 = I_i(x) + (-I_i(x + \Delta x)) + (-I_A(x)\Delta x) \quad \text{(Kirchhoff’s Current Law)} \]
\[ \frac{I_i(x+\Delta x)-I_i(x)}{\Delta x} = -I_A(x) \]
\[ \frac{\Delta I_i}{\Delta x} = -I_A(x) \]

Top node:

\[ 0 = I_e(x) + (-I_e(x + \Delta x)) + I_M(x)\Delta x \quad \text{(Kirchhoff’s Current Law)} \]
\[ \frac{I_e(x+\Delta x)-I_e(x)}{\Delta x} = I_M(x) \]
\[ \frac{\Delta I_e}{\Delta x} = I_M(x) \]

Middle node:

\[ 0 = I_s(x) + (-I_s(x + \Delta x)) + I_A(x)\Delta x + (-I_M(x)\Delta x) \quad \text{(Kirchhoff’s Current Law)} \]
\[ \frac{I_s(x+\Delta x)-I_s(x)}{\Delta x} = I_A(x) - I_M(x) \]
\[ \frac{\Delta I_s}{\Delta x} = I_A(x) - I_M(x) \]

Taking the limits as $\Delta x \to 0$ gives us equations 2.14-2.16.

\[ \frac{\partial I_i}{\partial x} = -I_A \quad [\text{Eq 2.14}] \]
\[ \frac{\partial I_e}{\partial x} = I_M \quad [\text{Eq 2.15}] \]
\[ \frac{\partial I_s}{\partial x} = I_A - I_M \quad [\text{Eq 2.16}] \]
Now we apply Kirchhoff’s Voltage Law to loops in figure 2.8. First we’ll consider the smaller lower loop from $V_i(x)$ to $V_i(x + \Delta x)$ to $V_s(x + \Delta x)$ to $V_s(x)$. Then we’ll consider the smaller upper loop from $V_s(x)$ to $V_s(x + \Delta x)$ to $V_e(x + \Delta x)$ to $V_e(x)$. A third larger loop from $V_i(x)$ to $V_i(x + \Delta x)$ to $V_e(x + \Delta x)$ to $V_e(x)$ is possible, but does not give a relevant result.

Small lower loop:

\[
0 = (V_i(x + \Delta x) - V_i(x)) + (V_s(x + \Delta x) - V_i(x + \Delta x)) + (V_e(x) - V_s(x + \Delta x)) + (V_e(x + \Delta x) - V_e(x)) \quad \text{(Kirchhoff’s Voltage Law)}
\]

\[
= \Delta V_i - V_A(x + \Delta x) - \Delta V_s + V_A(x)
\]

\[
= -I_i(x)r_i \Delta x - V_A(x + \Delta x) + I_s(x)r_s \Delta x + V_A(x) \quad \text{(Ohm’s Law)}
\]

\[
V_A(x + \Delta x) - V_A(x) = -I_i(x)r_i \Delta x + I_s(x)r_s \Delta x
\]

\[
\Delta V_A = -I_i(x)r_i \Delta x + I_s(x)r_s \Delta x
\]

\[
\frac{\Delta V_A}{\Delta x} = -I_i(x)r_i + I_s(x)r_s
\]

Taking the limit as $\Delta x \to 0$ gives

\[
\frac{\partial V_A}{\partial x} = r_s I_s - r_i I_i
\]

Taking the partial derivative with respect to $x$ gives us the following.

\[
\frac{\partial^2 V_A}{\partial x^2} = \frac{\partial}{\partial x} (r_s I_s - r_i I_i)
\]

\[
= r_s \frac{\partial I_s}{\partial x} - r_i \frac{\partial I_i}{\partial x}
\]

\[
= r_s (I_A - I_M) - r_i (-I_A) \quad \text{(by Eq 2.14, 2.16)}
\]

\[
\frac{\partial^2 V_A}{\partial x^2} = (r_i + r_s) I_A - r_s I_M \quad \text{[Eq 2.17]}
\]

Small upper loop:

\[
0 = (V_s(x + \Delta x) - V_s(x)) + (V_e(x + \Delta x) - V_s(x + \Delta x)) + (V_e(x) - V_e(x + \Delta x)) + (V_e(x + \Delta x) - V_e(x)) \quad \text{(Kirchhoff’s Voltage Law)}
\]

\[
= \Delta V_s - V_M(x + \Delta x) - \Delta V_e + V_M(x)
\]

\[
= -I_s(x)r_s \Delta x - V_M(x + \Delta x) + I_e(x)r_e \Delta x + V_M(x) \quad \text{(Ohm’s Law)}
\]

\[
V_M(x + \Delta x) - V_M(x) = -I_s(x)r_s \Delta x + I_e(x)r_e \Delta x
\]

\[
\Delta V_M = -I_s(x)r_s \Delta x + I_e(x)r_e \Delta x
\]

\[
\frac{\Delta V_M}{\Delta x} = -I_s(x)r_s + I_e(x)r_e
\]
Taking the limit as $\Delta x \to 0$ gives
\[ \frac{\partial V_M}{\partial x} = r_e I_e - r_s I_s \]

Taking the partial derivative with respect to $x$ gives us the following.
\[ \frac{\partial^2 V_M}{\partial x^2} = \frac{\partial}{\partial x} \left( r_e I_e - r_s I_s \right) \]
\[ = r_e \frac{\partial I_e}{\partial x} - r_s \frac{\partial I_s}{\partial x} \]  
(by Eq 2.15, 2.16)
\[ = r_e (I_M) - r_s (I_A - I_M) \]  
[Eq 2.18]

We will now modify equations 2.17 and 2.18 by isolating and uncoupling the time derivative terms within the radial currents $I_A$ and $I_M$. $I_A$ is the total current through the axolemma given by $I$ from equation 2.7, and $I_M$ is the total current through the myelin given by $I$ from equation 2.8. These currents are the sums of positive outward capacitative and ionic currents.

\[ I_A = c_A \frac{\partial I_A}{\partial t} + g_A(V_A)(V_A - V_{rest}) \]  
[Eq 2.19]
\[ I_M = c_M \frac{\partial I_M}{\partial t} + \frac{1}{r_M} V_M \]  
[Eq 2.20]

where $g_A(V_A)(V_A - V_{rest})$ is the ionic current from the Hodgkin-Huxley (equation 2.21) or Fitzhugh-Nagumo (equation 2.22) models:

\[ g_A(V_A)(V_A - V_{rest}) = \frac{1}{g_{Na}} m^3 h (V_A - E_{Na}) + \frac{1}{g_K} n^4 (V_A - E_K) + g_L (V_A - E_L) \]  
[Eq 2.21]

or
\[ g_A(V_A)(V_A - V_{rest}) = V_A(V_A - \alpha)(V_A - 1) + W \]  
[Eq 2.22].

Substitution of equations 2.19 and 2.20 into 2.17 and 2.18 gives the following.
\[ \frac{\partial^2 V_A}{\partial x^2} = (r_1 + r_s) \left( c_A \frac{\partial V_A}{\partial t} + g_A(V_A)(V_A - V_{rest}) \right) - r_s \left( c_M \frac{\partial V_M}{\partial t} + \frac{1}{r_M} V_M \right) \]
\[ \frac{\partial^2 V_M}{\partial x^2} = (r_s + r_e) \left( c_M \frac{\partial V_M}{\partial t} + \frac{1}{r_M} V_M \right) - r_e \left( c_A \frac{\partial V_A}{\partial t} + g_A(V_A)(V_A - V_{rest}) \right) \]
Algebraic manipulations were used to decouple and isolate the time derivatives. This leads us to equations 2.23 and 2.24 our model equations.

\[
\begin{align*}
\frac{c_A}{r_{i_r+r_{i_r}+r_{i_e}+r_{i_e}}} & = \frac{1}{r_{i_r+r_{i_r}+r_{i_e}+r_{i_e}}} \left( (r_s + r_e) \frac{\partial^2 V_A}{\partial x^2} + r_s \frac{\partial^2 V_M}{\partial x^2} \right) - g_A(V_A)(V_A - V_{rest}) \quad \text{[Eq 2.23]} \\
\frac{c_M}{r_{i_r+r_{i_r}+r_{i_e}+r_{i_e}}} & = \frac{1}{r_{i_r+r_{i_r}+r_{i_e}+r_{i_e}}} \left( (r_s + r_e) \frac{\partial^2 V_A}{\partial x^2} + (r_s + r_e) \frac{\partial^2 V_M}{\partial x^2} \right) - \frac{1}{r_{i_M}} V_M \quad \text{[Eq 2.24]}
\end{align*}
\]

Note that at the nodes, \(c_M = 0\) and \(r_M \approx 0\). Hence, equation 2.25 approximates 2.23 and equation 2.27 approximates 2.24 at the nodes.

\[
\begin{align*}
V_A(x, 0) & = V_{rest} \quad \text{[Eq 2.28]} \\
V_M(x, 0) & = 0 \quad \text{[Eq 2.29]}
\end{align*}
\]

**Boundary conditions**

For our system of partial differential equations to be a well-posed problem, we need well-behaved boundary and initial conditions. We are interested in the effects of myelination on the conduction velocity, so we want to minimize the effects of boundary conditions on the propagating action potential. In particular, we ideally want a semi-infinite axon where a stimulus is applied to \(x = 0\) and the axon is at rest as \(x \to \infty\). Hence if \(V_{rest}\) is the resting potential of the axolemma, and \(ST(t)\) is a stimulus, then the following initial and boundary conditions are desirable.

\[
\begin{align*}
V_A(0, t) & = ST(t) \quad \text{[Eq 2.30]} \\
V_M(0, t) & = 0 \quad \text{[Eq 2.31]} \\
\lim_{x \to \infty} V_A(x, t) & = V_{rest} \quad \text{[Eq 2.32]} \\
\lim_{x \to \infty} V_M(x, t) & = 0 \quad \text{[Eq 2.33]}
\end{align*}
\]
For our stimulus $ST(t)$, we use a step function although other functions are also acceptable.

$$ST(t) = V_{rest} + V_0 (H(t - t_0) - H(t - t_1))$$

where $H(t)$ is the Heaviside function, $0 < t_0 < t_1$, $V_0 > 0$, and $V_{rest} + V_0$ is above the threshold of the axolemma.
3 Model summary and geometric considerations

In summary, by modeling a nerve fiber as two concentric cylinders representing the axolemma and myelin, we obtain a system of partial differential equations.

\[ c_A \frac{\partial V_A}{\partial t} = \frac{1}{r_i r_s + r_i r_e + r_s r_e} \left( r_s \frac{\partial^2 V_A}{\partial x^2} + r_e \frac{\partial^2 V_M}{\partial x^2} \right) - g_A(V_A)(V_A - V_{rest}) \]  \[ \text{[Eq 3.1]} \]

\[ c_M \frac{\partial V_M}{\partial t} = \frac{1}{r_i r_s + r_i r_e + r_s r_e} \left( r_s \frac{\partial^2 V_A}{\partial x^2} + (r_i + r_s) \frac{\partial^2 V_M}{\partial x^2} \right) - \frac{1}{r_M} V_M \]  \[ \text{[Eq 3.2]} \]

The variable \( V_A \) is the voltage across the inner cylinder, which is the axolemma. The parameter \( c_A \) is the per-length capacitance of the axolemma so \( c_A \frac{\partial V_A}{\partial t} \) is the outward capacitative (radial) current. The outward ionic current is represented as \( g_A(V_A)(V_A - V_{rest}) \). If the axon is modeled with the Hodgkin-Huxley equations, then \( g_A(V_A)(V_A - V_{rest}) \) is as follows:

\[ g_A(V_A)(V_A - V_{rest}) = \frac{g_{Na} n^3 h}{V_A} (V_A - E_{Na}) + g_K n^4 (V_A - E_K) + g_L (V_A - E_L) \]  \[ \text{[Eq 3.3]} \]

\[ \frac{dm}{dt} = \alpha_m(V_A)(1 - m) - \beta_m(V_A)m \]  \[ \text{[Eq 3.4]} \]

\[ \frac{dh}{dt} = \alpha_h(V_A)(1 - h) - \beta_h(V_A)h \]  \[ \text{[Eq 3.5]} \]

\[ \frac{dn}{dt} = \alpha_n(V_A)(1 - n) - \beta_n(V_A)n \]  \[ \text{[Eq 3.6]} \]

If the axon is modeled with the Fitzhugh-Nagumo equations, then \( g_A(V_A)(V_A - V_{rest}) \) is as follows:

\[ g_A(V_A)(V_A - V_{rest}) = V_A(V_A - \alpha)(V_A - 1) + W \]  \[ \text{[Eq 3.7]} \]

\[ \frac{dW}{dt} = \epsilon (V_A - \gamma W) \]  \[ \text{[Eq 3.8]} \]

The variable \( V_M \) is the voltage across the outer cylinder representing the myelin (or lack of myelin in nodes), and \( c_M \) is the per-length capacitance of the axolemma so \( c_M \frac{\partial V_M}{\partial t} \) is the outward capacitative (radial) current. The outward ionic current is represented as \( \frac{1}{r_M} V_M \), where \( r_M \) is the per-length resistance of the myelin.

Along the length of a myelinated axon, nodes and internodes alternate. So the nodal and internodal values of \( c_M \) and \( r_M \) also alternate along \( x \). Let \( c'_{M,I} \) and \( r'_{M,I} \) be the per-length capacitance and resistance of a single myelin layer, respectively, and let \( c'_{M,N} \) and \( r'_{M,N} \) be the per-length capacitance and resistance of a single “layer” of external space. Then for a myelin sheath that is \( nl \) layers thick,

\[ r_M(x) = \begin{cases} r'_{M,N}nl & \text{if } x \text{ is in a node} \\ r'_{M,I}nl & \text{if } x \text{ is in an internode} \end{cases} \]  \[ \text{[Eq 3.9]} \]
\[ c_M(x) = \begin{cases} 
\frac{1}{\pi d} & \text{if } x \text{ is in a node} \\
\frac{1}{\pi d} & \text{if } x \text{ is in an internode} 
\end{cases} \quad [\text{Eq } 3.10] 
\]

Without loss of generality, let \( x = 0 \) be the left edge of the first node. Let \( L_N \) be the node length and \( L_I \) be the internode length, then a position \( x \) is considered to be in a node, if \( x \in [(n-1)(L_N+L_I), (n-1)(L_N+L_I)+L_N) \) for some \( n = 1, 2, \ldots \). Similarly, \( x \) is in an internode, if \( x \in [(n-1)(L_N + L_I) + L_N, n(L_N + L_I)] \) for some \( n = 1, 2, \ldots \).

Since \( r_{M,N}' \approx 0 \) and \( c'_{M,N} = 0 \), the model equations at the node can be approximated as

\[
\begin{align*}
&c_A \frac{\partial V_A}{\partial t} = \frac{r_s + r_e}{r_i r_s + r_i r_e + r_s r_e} \frac{\partial^2 V_A}{\partial x^2} - g_A(V_A - V_{rest}) \quad [\text{Eq } 3.11] \\
&V_M = 0 \quad [\text{Eq } 3.12]
\end{align*}
\]

\( r_i, r_s, \) and \( r_e \) are the per-length axial resistances of the internal, submyelin, and external spaces. These variables are directly related to the “tightness” of their respective spaces. The external space is considered to be “infinitely loose” so \( r_e \) is very small. Realistically, the external space of axons is not superconducting with zero resistance, so we have that \( 0 < r_e << 1 \). If \( r_e \) represents the resistance of an infinitely loose space, then it is a lower bound for \( r_i \) and \( r_s \). The “tightness” of the internal space is inversely related to the cross sectional area of the axon. Axons always have a finite and nonzero diameter, so \( r_e < r_i < \infty \). In our model, the myelin sheath is allowed to shrink until its diameter approaches that of the axon it surrounds, or stretched until its diameter is infinitely large. Hence the submyelin space can be infinitely loose or tight, so \( r_s \in [r_e, \infty) \).
Our system of equations were numerically integrated with MATLAB’s \texttt{pdepe} algorithm, which solves systems of partial differential equations (PDEs) in time $t$ and one spatial variable $x$. Parabolic and elliptical PDEs of the following form are acceptable.

\[ C(x,t,V, \frac{\partial V}{\partial x}) \frac{\partial V}{\partial t} = x^{-m} \frac{\partial}{\partial x} \left( x^m F(x,t,V, \frac{\partial V}{\partial x}) \right) + S(x,t,V, \frac{\partial V}{\partial x}) \]

For a system of $n$ equations, $V$ is a $n \times 1$ vector, $C$ is a $n \times n$ diagonal matrix not identically zero, $F$ is the $n \times 1$ flux vector, $S$ is the $n \times 1$ source vector, and $m = 0, 1, \text{ or } 2$.

Our system consist of at least two equations, so expressing our system into its most basic form results in the following:

\[
\begin{align*}
m &= 0 \\
V &= \begin{bmatrix} V_A \\ V_M \end{bmatrix} \\
C &= \begin{bmatrix} 1 & 0 \\ 0 & \frac{1}{c_M(x)} \end{bmatrix} \\
F &= \frac{1}{r_i r_s + r_s r_e + r_i r_e} \begin{bmatrix} (r_s + r_e) \frac{\partial V_A}{\partial x} + r_e \frac{\partial V_M}{\partial x} \\ r_s \frac{\partial V_A}{\partial x} + (r_i + r_s) \frac{\partial V_M}{\partial x} \end{bmatrix} \\
S &= \begin{bmatrix} -g_A(V_A)(V_A - V_{rest}) \\ -\frac{1}{r_M(x)} V_M \end{bmatrix}
\end{align*}
\]

Note that in practice, there may be additional equations ($n > 2$). For example, there are three additional equations for the gates $m, h, n$ in the Hodgkin-Huxley model and one additional equation for the $W$ variable in the Fitzhugh-Nagumo model.

Numerical errors often occur when there are discontinuities such as those present in $r_M(x)$ and $c_M(x)$ (equations 3.9 and 3.10) when $x$ is at the border of a node and an internode. To deal with these discontinuities, we define a paranodal region of length $L_P$ between every node and internode. The resistance and capacitance of nodes and internodes are defined as before. However, at the paranodes, we connect the electrical properties of adjacent nodes and internodes with a linear function. Without loss of generality, we let $x = 0$ be the left edge of the first node. For $n = 1, 2, \ldots$, let the $X_{N,n}$ and $X_{I,n}$ be the $n$th node and internode respectively.
Let $X_{NP,n}$ and $X_{IP,n}$ be the paranodes that immediately follow the $n$th node and internode, respectively. Then we have the following nodal, internodal, and paranodal regions and associated functions

\[
X_{N,n} = [(n-1)(L_N + 2L_P + L_I), (n-1)(L_N + 2L_P + L_I) + L_N)
\]
\[
X_{NP,n} = [(n-1)(L_N + 2L_P + L_I) + L_N, (n-1)(L_N + 2L_P + L_I) + L_N + L_P)
\]
\[
X_{I,n} = [(n-1)(L_N + 2L_P + L_I) + L_N + L_P, (n-1)(L_N + 2L_P + L_I) + L_N + L_P + L_I)
\]
\[
X_{IP,n} = [(n-1)(L_N + 2L_P + L_I) + L_N + L_P + L_I, n(L_N + 2L_P + L_I))
\]

\[
\begin{align*}
    r_M(x) &= \begin{cases} 
    r_{M,N}^{n} & \text{if } x \in X_{N,n} \text{ for some } n \in \mathbb{N} \setminus \{0\} \\
    \left(\frac{r_{M,1}^{r_{M,N}}}{L_P} \right)(x - \inf X_{NP,n}) + r_{M,N}^{n} & \text{if } x \in X_{NP,n} \text{ for some } n \in \mathbb{N} \setminus \{0\} \\
    r_{M,1}^{n} & \text{if } x \in X_{I,n} \text{ for some } n \in \mathbb{N} \setminus \{0\} \\
    \left(\frac{r_{M,N}^{r_{M,1}}}{L_P} \right)(x - \inf X_{IP,n}) + r_{M,1}^{n} & \text{if } x \in X_{IP,n} \text{ for some } n \in \mathbb{N} \setminus \{0\}
    \end{cases}
\end{align*}
\]

\[
\begin{align*}
    c_M(x) &= \begin{cases} 
    c_{M,N}^{1} & \text{if } x \in X_{N,n} \text{ for some } n \in \mathbb{N} \setminus \{0\} \\
    \left(\frac{c_{M,1}^{c_{M,N}}}{L_P} \right)(x - \inf X_{NP,n}) + c_{M,N}^{1} & \text{if } x \in X_{NP,n} \text{ for some } n \in \mathbb{N} \setminus \{0\} \\
    c_{M,1}^{1} & \text{if } x \in X_{I,n} \text{ for some } n \in \mathbb{N} \setminus \{0\} \\
    \left(\frac{c_{M,N}^{c_{M,1}}}{L_P} \right)(x - \inf X_{IP,n}) + c_{M,1}^{1} & \text{if } x \in X_{IP,n} \text{ for some } n \in \mathbb{N} \setminus \{0\}
    \end{cases}
\end{align*}
\]

For a solution, MATLAB needs well-behaved initial and boundary conditions. Initial conditions are in the form of $n \times 1$ vector $V_0(x) = V(x, t = t_0)$.

\[
\begin{align*}
    t_0 &= 0 \\
    V_0 &= \begin{bmatrix} V_{\text{rest}} \\ 0 \end{bmatrix}
\end{align*}
\]

MATLAB's `pdepe` requires the spatial domain to be of finite length, so the boundary conditions given in equations 2.32 and 2.33 must be modified. If $x \in [a, b]$, then MATLAB syntax requires that the boundary conditions be of the following form.

For $x = a$ or $x = b$,

\[
P(x, t, V) + Q(x, t)F(x, t, V, \frac{\partial V}{\partial x}) = 0
\]

Without loss of generality, we set $a = 0$ and $b = L$, where $0 < L < \infty$. Typically, axons of finite length have one of two boundary conditions: one that represents a cut (open) end, and one that represents a sealed
In the open axon, all the potentials—$V_i$, $V_s$, and $V_e$—are equivalent to the external space. Since $V_i(L, t) = V_s(L, t) = V_e(L, t)$, $V_A = V_i - V_s$, and $V_M = V_s - V_e$, we have that $V_A(L, t) = V_M(L, t) = 0$ are the boundary conditions of an open axon. For our computer simulations, we will use the closed axon. In a closed axon, there are no axial currents at $x = L$. So $I_i = I_s = I_e = 0$. By equations 2.11-2.13, we have that $\frac{\partial V_i}{\partial x} = \frac{\partial V_s}{\partial x} = \frac{\partial V_e}{\partial x} = 0$. So $\frac{\partial V_A}{\partial x} = \frac{\partial V_M}{\partial x} = 0$ is an appropriate boundary condition at $x = L$. In MATLAB syntax, boundary conditions must be written in terms of $((r_s + r_e) \frac{\partial V_A}{\partial x} + r_s \frac{\partial V_M}{\partial x})$ and $(r_s \frac{\partial V_A}{\partial x} + (r_i + r_s) \frac{\partial V_M}{\partial x})$. Both of these terms are equivalently zero so equations 4.1 and 4.2 are appropriate boundary conditions along with equations 2.28 and 2.29.

\[
\begin{align*}
(r_s + r_e) \frac{\partial V_A}{\partial x}(L, t) + r_s \frac{\partial V_M}{\partial x}(L, t) &= 0 \quad \text{[Eq 4.1]} \\
r_s \frac{\partial V_A}{\partial x}(L, t) + (r_i + r_s) \frac{\partial V_M}{\partial x}(L, t) &= 0 \quad \text{[Eq 4.2]}
\end{align*}
\]

Equations 2.28, 2.29, 4.1, and 4.2 give the following.

\[
\begin{align*}
P(0, t, V) &= \begin{bmatrix} V_A(0, t) - ST(t) \\ V_M(0, t) \end{bmatrix} \quad Q(0, t) = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \\
P(L, t, V) &= \begin{bmatrix} 0 \\ 0 \end{bmatrix} \quad Q(L, t) = \begin{bmatrix} 1 \\ 1 \end{bmatrix}
\end{align*}
\]

\texttt{pdepe} solves partial differential equations by first replacing the spatial derivatives with finite difference approximations. Discretization of the spacial dimension and a system of ordinary differential equations results. After spatial discretization, time integration is done with MATLAB’s \texttt{ode15s}. \textbf{Finish this part! talk about xmesh}
5 Myelination

Fully unmyelinated and myelinated axon

To validate our model, we must show that by changing some of its parameters, it can accurately describe fully unmyelinated and myelinated axons. Both of these types of nerve fibers have existing standard models, which we will discuss and compare. Let $V_F$ be the trans-fiber voltage, that is the potential difference between the intracellular and extracellular space. Equivalently $V_F$ is the sum of the trans-axolemma and trans-membrane voltages.

$$V_F = V_i - V_e$$
$$= V_i - V_s + V_s - V_e$$
$$= V_A + V_M$$

Standard unmyelinated axon models consist of a single cylinder with axolemma properties (figure 5.1). There is no external cylinder representing myelin and thus, no submyelin space.

<table>
<thead>
<tr>
<th>Potentials and Potential Differences:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td></td>
</tr>
<tr>
<td>$\Delta V_i = V_i(x + \Delta x) - V_i(x)$</td>
<td>Internal</td>
</tr>
<tr>
<td>$\Delta V_e = V_e(x + \Delta x) - V_e(x)$</td>
<td>External</td>
</tr>
<tr>
<td>Radial</td>
<td></td>
</tr>
<tr>
<td>$V_F(x) = V_i(x) - V_e(x)$</td>
<td>Fiber (trans-fiber)</td>
</tr>
</tbody>
</table>

Figure 5.1: Unmyelinated axon and equivalent circuit.

As usual, we let $g_A(V_F)(V_F - V_{rest})$ and $c_A \frac{\partial V_F}{\partial t}$ be the outward ionic and capacitative currents through the axolemma, respectively. These currents can follow either the Hodgkin-Huxley or Fitzhugh-Nagumo equations. Similar to the derivation of equations 3.1 and 3.2, the application of Kirchhoff’s and Ohm’s Laws
result in the following equation.

\[ c_A \frac{\partial V_F}{\partial t} = \frac{1}{r_1 + r_2} \frac{\partial^2 V_F}{\partial x^2} - g_A(V_F)(V_F - V_{rest}) \]  

[Eq 5.1]

This type of partial differential equation is called a reaction-diffusion equation, where \(-g_A(V_F)(V_F - V_{rest})\) is the reaction term that generates an action potential at a position and time for which \(V_F\) is greater than threshold. The action potential diffuses along \(x\) in agreement with the diffusion term \(\frac{1}{r_1 + r_2} \frac{\partial^2 V_F}{\partial x^2}\). Due to the continuity of voltage with respect to \(x\), the voltage of regions adjacent to an action potential will increase until an action potential is generated. This cascade of reaction and diffusion creates a traveling wave, more specifically a propagating action potential (figure 5.2). *(Discuss briefly what a traveling wave is and cite the proofs that they occur in both HH and FN.)*

![Figure 5.2: Propagating action potential in an unmyelinated Fitzhugh-Nagumo axon. Each line color denotes a different time \(t = n\Delta t\) where \(\Delta t = 1.7\) and \(n \in \{0, 1, \ldots, 5\}\). For the green line, \(n = 0\) and \(n\) increases for each subsequent color until \(n = 5\) for the blue line.]*

We claim that our model can be made to represent unmyelinated axons by “loosening” the myelin. As discussed in section 3, the tightness of the myelin is directly related to \(r_s\), the per-length axial resistance of the submyelin space; so as myelin loosens, \(r_s\) approaches its lower bound \(r_c\), the resistance of the external space.

**Lemma 1**

If \(r_s = r_c\), where \(0 < r_c << 1\), then our model equations

\[ c_A \frac{\partial V_A}{\partial t} = \frac{1}{r_1 r_s + r_2 r_c + r_s r_c} \left( (r_s + r_c) \frac{\partial^2 V_A}{\partial x^2} + r_s \frac{\partial^2 V_M}{\partial x^2} \right) - g_A(V_A)(V_A - V_{rest}) \]  

[Eq 3.1]

\[ c_M \frac{\partial V_M}{\partial t} = \frac{1}{r_1 r_s + r_2 r_c + r_s r_c} \left( r_s \frac{\partial^2 V_A}{\partial x^2} + (r_1 + r_s) \frac{\partial^2 V_M}{\partial x^2} \right) - \frac{1}{r_M} V_M \]  

[Eq 3.2]
become the standard unmyelinated axon model

$$c_A \frac{\partial V_F}{\partial t} = \frac{1}{r_1 + r_2} \frac{\partial^2 V_F}{\partial x^2} - g_A(V_F)(V_F - V_{rest}) \quad [\text{Eq 5.1}]$$

Setting $r_s = r_e$ in our model equations 3.1 and 3.2 yield the following equations.

$$c_A \frac{\partial V_A}{\partial t} = \frac{1}{2r_i + r_e} \left( \frac{\partial^2 V_A}{\partial x^2} + \frac{\partial^2 V_M}{\partial x^2} \right) - g_A(V_A)(V_A - V_{rest}) \quad [\text{Eq 5.2}]$$

$$r_e c_M \frac{\partial V_M}{\partial t} = \frac{r_e}{2r_i + r_e} \frac{\partial^2 V_A}{\partial x^2} + \frac{r_i + r_e}{2r_i + r_e} \frac{\partial^2 V_M}{\partial x^2} - \frac{V_e}{r_M} V_M \quad [\text{Eq 5.3}]$$

As discussed in section 3, the per-length axial resistance of the external space is assumed to be very small ($0 < r_e << 1$). This reduces equation 5.3 into the following approximate equation.

$$0 = 0 + \frac{r_i + r_e}{2r_i + r_e} \frac{\partial^2 V_M}{\partial x^2} + 0 \quad [\text{Eq 5.4}]$$

Substitution of equation 5.4 into 5.2 yields the following equation.

$$c_A \frac{\partial V_A}{\partial t} = \frac{2}{2r_i + r_e} \frac{\partial^2 V_A}{\partial x^2} - g_A(V_A)(V_A - V_{rest}) \quad [\text{Eq 5.5}]$$

Without loss of generality, assume that an internode is of length $L_I$ with left and right ends at $x = 0$ and $x = L_I$. Integrating equation 5.4 twice with respect to $x$ gives equation 5.6.

$$V_M(x,t) = A(t)x + B(t) \quad [\text{Eq 5.6}]$$

$V_M(0,t)$ and $V_M(L_I,t)$ are connected to nodes so by the continuity of voltage and by the result of equation 3.12 for a node, $V_M(0,t) = V_M(L_I,t) = 0$. Applying these boundary conditions to equation 5.6 gives us $V_M = 0$ for all internodes as well as nodes. Hence $V_M = 0$ for all $x$ and all $t$ when myelin is loose, and $V_A = V_F$. If we let $r_i = r_1$ and $r_e = 2r_2$, then equation 5.5 from our model is identical to the standard unmyelinated axon model, equation 5.1. □

Most myelinated axon models make the following assumptions. First, the myelin is assumed to be attached to the axolemma so there is no submyelin space. Second, the myelin resistance, $r_M$ is assumed to be very high. Third, the myelin capacitance, $c_M$ is very low. Finally, it is assumed that the circuitry of the axolemma...
is present in the nodes, but absent in the internodes. A schematic diagram and equivalent circuit for the myelinated axon is in figure 5.3.

**Figure 5.3**: Myelinated axon model and equivalent circuit.

Once again, Kirchhoff’s and Ohm’s Laws are used to obtain the equations for the standard myelinated axon model. Equation 5.7 represents the nodes while equation 5.8 represents the internode.

\[
\begin{align*}
\frac{c_A}{\tau} \frac{\partial V_F}{\partial t} &= \frac{1}{r_1 + r_2} \frac{\partial^2 V_F}{\partial x^2} - g_A(V_F)(V_F - V_{rest}) \quad \text{[Eq 5.7]} \\
\frac{c_M}{\tau} \frac{\partial V_F}{\partial t} &= \frac{1}{r_1 + r_2} \frac{\partial^2 V_F}{\partial x^2} - \frac{1}{r_M} V_F \quad \text{[Eq 5.8]}
\end{align*}
\]

Action potential propagation in a myelinated axon differs from that in an unmyelinated axon. Due to low capacitance of myelin, the voltage of internodes readily increase in response to a neighboring action potential. Due to the high resistance of myelin, the increased voltages of internodes exhibit minimal decay. This means that an action potential in one node can easily generate an action potential in a succeeding node. This apparent skipping of action potential from node to node is called saltatory conduction and the main benefit of this is an acceleration in conduction velocity (figure 5.4).
Figure 5.4: Propagating action potential in a myelinated Fitzhugh-Nagumo axon. Each line color denotes a different time $t = n\Delta t$ where $\Delta t = 1.7$ and $n \in \{0, 1, \ldots, 5\}$. For the green line, $n = 0$ and $n$ increases for each subsequent color until $n = 5$ for the blue line.

We claim that our model can be made to represent the myelinated axon by “tightening” a thick myelin. As before, $r_s$ is directly related to the tightness of the myelin. For an infinitely tight myelin, we let $r_s \to \infty$. For a thick myelin, we let $nl$ be large.

Lemma 2

For large $nl$, as $r_s \to \infty$, our model equations

\[
\begin{align*}
    c_A \frac{\partial V_A}{\partial t} &= \frac{1}{r_1 r_s + r_1 r_s + r_s r_e} \left( (r_s + r_e) \frac{\partial^2 V_A}{\partial x^2} + r_s \frac{\partial^2 V_M}{\partial x^2} \right) - g_A(V_A)(V_A - V_{rest}) \quad [\text{Eq 3.1}] \\
    c_M \frac{\partial V_M}{\partial t} &= \frac{1}{r_1 r_s + r_1 r_s + r_s r_e} \left( r_s \frac{\partial^2 V_A}{\partial x^2} + (r_i + r_s) \frac{\partial^2 V_M}{\partial x^2} \right) - \frac{1}{r_M} V_M \quad [\text{Eq 3.2}]
\end{align*}
\]

become the standard myelinated axon model

\[
\begin{align*}
    c_A \frac{\partial V_A}{\partial t} &= \frac{1}{r_1 + r_2} \frac{\partial^2 V_A}{\partial x^2} - g_A(V_F)(V_F - V_{rest}) \quad [\text{Eq 5.7}]
\end{align*}
\]

in nodes and

\[
\begin{align*}
    c_M \frac{\partial V_M}{\partial t} &= \frac{1}{r_1 + r_2} \frac{\partial^2 V_M}{\partial x^2} - \frac{1}{r_M} V_F \quad [\text{Eq 5.8}]
\end{align*}
\]

in internodes.

Let’s first consider the node. At the node, our equations 3.1 and 3.2 are approximated by equations 3.12 and 3.13. Taking the limit as $r_s \to \infty$ of equation 3.12 yields equation 5.9.

\[
\begin{align*}
    \lim_{r_s \to \infty} \left( c_A \frac{\partial V_A}{\partial t} \right) &= \lim_{r_s \to \infty} \left( \frac{r_s + r_e}{r_1 r_s + r_1 r_s + r_s r_e} \frac{\partial^2 V_A}{\partial x^2} - g_A(V_A)(V_A - V_{rest}) \right) \quad \text{(from Eq 3.12)} \\
    c_A \frac{\partial V_A}{\partial t} &= \frac{1}{r_1 + r_e} \frac{\partial^2 V_A}{\partial x^2} - \frac{1}{r_M} V_A \quad [\text{Eq 5.9}]
\end{align*}
\]

Equation 3.13 tells us $V_M = 0$ so $V_A = V_F$. This substitution makes our model equation 5.9 into the standard
myelinated axon model at the node, equation 5.7, where \( r_1 = r_i \) and \( r_2 = r_e \).

Now let’s consider the internode equations. As \( r_s \to \infty \), \( I_s = \frac{1}{r_s} \frac{\partial V_s}{\partial x} = 0 \) (equation 2.12). So the circuit for our model can be represented as figure 5.5 for some internodal position \( x \).

![Figure 5.5: Circuit of our model when the myelin is tight \((r_s \to \infty)\) for some position \( x \) in an internode.](image)

In this special case of our model, we have that the radial trans-axolemma current \( I_A \) is equivalent to the radial trans-myelin current \( I_M \). Since the radial current does not change as it moves from the internal to the external space, we can easily compare the relative voltage drops across the axolemma and myelin. Note that in general, when \( r_s < \infty \), we cannot easily compare the voltage drops since some of the outward radial current through the axolemma will move axially along the submyelin space. This was expressed in equation 2.16. Recall from figure 2.6 that the myelin sheath consists of \( nl \) myelin circuits in series. If we let \( V'_M \) be the voltage drop across a single layer of myelin, then the drop across the sheath of \( nl \) layers is \( V_M = (nl)V'_M \). So as \( nl \) is increased, the following proportional voltage drops are obtained.
\[ \lim_{n_l \to \infty} \frac{V_A}{V_F} = \lim_{n_l \to \infty} \frac{V_A}{V_A + V_M} = \lim_{n_l \to \infty} \frac{V_A}{V_A + n_lV_M} = 0 \]

\[ \lim_{n_l \to \infty} \frac{V_M}{V_F} = \lim_{n_l \to \infty} \frac{V_M}{V_A + V_M} = \lim_{n_l \to \infty} \frac{n_lV_M^U}{V_A + n_lV_M} = 1 \]

So for large \( n_l \), as in a thick myelin sheath, we have

\[ V_A \approx 0 \]
\[ V_M \approx V_F \quad [\text{Eq 5.10}] \]

For a tight sheath, our model equation 3.2 becomes equation 5.11.

\[
\lim_{r_s \to \infty} \left( c_M \frac{\partial V_M}{\partial t} \right) = \lim_{r_s \to \infty} \left( \frac{1}{r_i r_s + r_i r_s + r_s r_e} \left( r_s \frac{\partial^2 V_A}{\partial x^2} + (r_i + r_s) \frac{\partial^2 V_M}{\partial x^2} \right) - \frac{1}{r_M V_M} \right) \quad [\text{Eq 5.11}]
\]

Apply the result of equation 5.10 to equation 5.11 and setting \( r_i = r_1 \) and \( r_e = r_2 \), gives us the standard myelinated axon model at an internode, equation 5.8. □

**Transition from unmyelinated to myelinated**

For \( r_e > 0 \), we have that the model is unmyelinated for \( r_s = r_e \) and myelinated as \( r_s \to \infty \). Note that only the coefficients of the diffusion terms are dependent on \( r_s \). Rewriting these coefficients as functions of \( r_s \) gives us the following.

\[
\begin{align*}
 c_A \frac{\partial V_A}{\partial t} &= A(r_s) \frac{\partial^2 V_A}{\partial x^2} + B(r_s) \frac{\partial^2 V_M}{\partial x^2} + \frac{1}{r_A} f(V_A) \\
 c_M \frac{\partial V_M}{\partial t} &= B(r_s) \frac{\partial^2 V_A}{\partial x^2} + C(r_s) \frac{\partial^2 V_M}{\partial x^2} + \frac{1}{r_M} g(V_M)
\end{align*}
\]

where

\[
\begin{align*}
 A(r_s) &= \frac{r_s + r_e}{r_i r_s + r_i r_e + r_s r_e} \\
 B(r_s) &= \frac{r_i + r_s}{r_i r_s + r_i r_e + r_s r_e} \\
 C(r_s) &= \frac{r_i + r_s}{r_i r_s + r_i r_e + r_s r_e}
\end{align*}
\]
These coefficients are rational functions so they are continuous for all \( r_s \) except when \( r_i r_e + r_s r_e + r_s r_e = 0 \). This occurs when \( r_s = \frac{-r_i r_e}{r_i + r_e} \). Since \( r_i, r_e > 0 \) and \( r_s \in [r_e, \infty) \), we have that \( \frac{r_i r_e}{r_i + r_e} < 0 < r_s \). Hence the coefficients are continuous with respect to \( r_s \). Furthermore, for all \( r_s \in [r_e, \infty) \),

\[
\begin{align*}
\frac{dA}{dr_s} &= \frac{-r_i^2}{(r_i r_s + r_i r_e + r_s r_e)^2} < 0 \\
\frac{dB}{dr_s} &= \frac{r_i r_e}{(r_i r_s + r_i r_e + r_s r_e)^2} > 0 \\
\frac{dC}{dr_s} &= \frac{-r_i^2}{(r_i r_s + r_i r_e + r_s r_e)^2} < 0.
\end{align*}
\]

Over its domain, the coefficients are continuous and changes strictly monotonically between the extrema attained when \( r_s = r_e \) and \( r_s \to \infty \). These extrema are positive and finite.

\[
\begin{align*}
A(r_e) &= \frac{2}{2r_i + r_e} \\
\lim_{r_s \to \infty} A(r_s) &= \frac{1}{r_i + r_e} \\
B(r_e) &= \frac{1}{2r_i + r_e} \\
\lim_{r_s \to \infty} B(r_s) &= \frac{1}{r_i + r_e} \\
C(r_e) &= \frac{r_i + r_e}{(2r_i + r_e)r_e} \\
\lim_{r_s \to \infty} C(r_s) &= \frac{1}{r_i + r_e}.
\end{align*}
\]

Hence, by changing \( r_s \), our equations model an unmyelinated axon, a myelinated axon, and gradual transitions between the two in a well-behaved way.

Let’s examine what happens as \( r_s \) changes to modify the model from an unmyelinated to a myelinated axon. When \( r_s = r_e \), the action potential propagates continuously (figure 5.6a). As \( r_s \) increases, the action potential slows down significantly (figure 5.6b). Further tightening of \( r_s \) results in the onset of saltatory conduction, show as nodes peaking differently from internodes in figure 5.6c. Finally, when \( r_s \) is very large, saltatory conduction becomes more prevalent, and the speed of action potential propagation is significantly increased (figure 5.6d).
Figure 5.6: Change in action potential propagation of the FitzHugh-Nagumo model as the tightness of the myelin, $r_s$, changes. Each line color denotes a different time $t = n\Delta t$ where $\Delta t = 1.7$ and $n \in \{0, 1, \ldots, 5\}$. For the green line, $n = 0$ and $n$ increases for each subsequent color until $n = 5$ for the blue line. The gray background represents the location of the myelinated internodes. Each plot represents a different $r_s$. (a) When the myelin is loose, $r_s = r_\epsilon = 1 \times 10^{-6}$, the model is essentially unmyelinated. (b) The action potential slows down as the myelin is tightened to $r_s = 1$. (c) The onset of saltatory conduction occurs with further tightening to $r_s = 5$. (d) When the myelin is tight, $r_s = 500$, the model is essentially myelinated and the action potential is significantly faster than that of the unmyelinated axon.
The presence of saltation and accelerated conduction velocity is a well known characteristic of myelination but, the slowdown in the intermediate tightnesses is not well documented in healthy neurological development. On the other hand, in studies of neurological disorders and diseases, the slowdown is well documented. In a study on vibrational damage to nerve tissue, source vibrated the tails of rats and inspected the resulting physiology and anatomy of the tail nerves. They found that prolonged vibration resulted in irreversible loosening of myelin and an associated significant decrease in conduction velocity.

**Geometry and evolution**

The theory of evolution by natural selection offers an explanation to why a slowdown is not observed in healthy neurological development. Several groups of animals have evolved myelin independently from one another. This suggests that myelin provides a significant improvement in evolutionary fitness. It is agreed that the most significant advantage of myelination is in the improved conduction velocity of action potential propagation. This is in agreement with the observation that the fastest axons in many animals are the ones directly responsible for survival. For example, copepods, a marine plankton animal have myelinated axons along its antennae, uses its antennae to detect and swim away from predators. Shrimps escape predation by firing the rapid neurons along its tail muscles and flipping away with a tail swipe. Squids do not have myelin, but their fastest axons are the giant axons that control their siphon, an organ that gives them the propulsion they need to move quickly. If the fastest axons of these animals were to experience a significant slowdown, then they would be at risk of being selected against. In other words, figure 5.6 showed a pronounced slowdown as a thick myelin sheath is tightened. If this slowdown is significant enough to negatively affect survivability then natural selection suggests that it is more likely to be killed and less likely to be seen in healthy development.

If the speedup is the benefit of the evolution and development of myelin, then the slowdown is the most obvious cost. If this benefit and cost directly affects evolutionary fitness, then natural select likely favors processes of myelination that minimizes slowdown while maximizes speedup. Young et al (2013) showed in the NEURON simulation environment, that different sequences of geometric changes from the unmyelinated to the myelinated axon results in very different slowdowns and speedups experienced. Their work suggests that tightening thick myelin results in significant slowdown followed by a large speedup. Their work also suggests that slowdown can be reduced by tightening short thin myelin then thicken and lengthening the internode once myelin is tight. We illustrate this result with our model (figure 5.7).
Figure 5.7: Change in action potential propagation of the Fitzhugh-Nagumo model as thin, short myelin is tightened then thickened and lengthened. Each line color denotes a different time $t = n\Delta t$ where $\Delta t = 1.7$ and $n \in \{0, 1, \ldots, 5\}$. For the green line, $n = 0$ and $n$ increases for each subsequent
color until \( n = 5 \) for the blue line. The gray background in represents the location of the myelinated internodes. (a)-(e) Short (internode lengths \( L_I = 1 \)) thin \( (nl = 2) \) myelin is tighten. The tightnesses increases through these plots with \( r_s = 10^m \) for \( m \in \{-3, -2, -1, 0, 1\} \). (f)-(j) Tight myelin continues to tighten while lengthening and thickening. For these plots, \( r_s = 10^{m+1}, L_I = 2m, nl = 20m, \) for \( m \in \{1, 2, 3, 4, 5\} \).

Implications and future work

Appendix 1: Overview of basic electromagnetism topics

Voltage
Current
Capacitors in series
Capacitative current
Resistors in series
Resistors in parallel
Conductance of resistors in series
Resistive current (Ohm’s law)
Kirchoff current law
Kirchoff voltage law

Appendix 2: Programming

References