Mathematically modeling action potentials in myelinated neurons to examine the role of myelin, ion channel density, and myelinated lengths on conduction

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ABSTRACT: Since the seminal work of Hodgkin and Huxley, which quantitatively described the propagation of electrical signals through neurons, there has been much investigation into the electrical and geometrical properties of neurons and how they affect conduction velocity along a neuron’s length. To study human neuron behaviors, mathematical models have expanded upon Hodgkin and Huxley’s models to incorporate the effects of neurons that are myelinated by modeling myelinated portions of neurons as passive cables. Here, we present a developed mathematical model that discretizes a myelinated axon length and finely allows for control over a number of important electrical and geometrical properties. Using this model, we present and compare how myelin, inter-node length, and ion channel density affect conduction velocity in two different lengths of axons. We confirm that myelination, internode-length, and ion channel density correlate positively with conduction velocity, and propose potential mechanisms of this effect at lower node length and inter-node length values.

1. Introduction
Neuron cells in our body transmit information via firing action potential, the flow of impulses from the cell body to the axon terminal. The modern understanding of action potential and its properties is largely attributed to the Hodgkin-Huxley (HH) model, a Nobel prize winning study, that used a series of nonlinear differential equations to mathematically describe the molecular basis of an action potential through the idea of an electrical equivalent circuit [1]. The HH model utilizes three major ion channel components: Potassium (K+), Sodium (Na+), and a leak channel, to describe the voltage dependent opening and closings of ion channels, and to calculate the voltage dynamics of an action potential, which matched experimental results, in unmyelinated axons of giant squids.

Unlike giant squid axons, human axons are wrapped in insulated myelin sheaths in both the central and peripheral nervous system. Myelin, partly made of Schwann Cells in the peripheral nervous system and Oligodendroglial cells in the central nervous system, surrounding nerve fibers, increases membrane capacitance and conductance of the axon, thereby serving to enhance the travel speed and efficiency of the electrical impulses down the axon [2]. An action potential involves the canonical fluctuations of membrane potential to reliably and efficiently transmit signals through one neuron and allow for communication with downstream neurons. The process of an action potential involves the precise voltage-regulated opening and closing of different ion channels. In the resting state, the membrane potential of a human brain neuron is typically around -70 to -60 mV [3]. When stimulated with an input voltage or current, the threshold of an action potential needs to be met such that the axon
can depolarize. Thus, a strong enough input will allow for action potential generation in an “all-or-none” manner. During depolarization, Na+ channels rapidly open up to allow sodium ions to enter the membrane, increasing the voltage. Once the Na+ equilibrium potential is reached, potassium channels open up to allow potassium to flow out to restore the voltage back to negative during repolarization [4]. The refractory period that follows allows the neuron to restore its chemical gradient while preventing another action potential from firing. To ensure reliable action potential propagation speed, amounts of myelinated sections of axons are of key importance. In fact, the thickness of myelin has been shown to be a dynamic trait of neuronal axons, whereby neurons can control their action potential propagation speed through activity dependent mechanisms [5,6].

However, when myelin sheaths are depleted or partially damaged in people with diseases such as Multiple Sclerosis and Guillain-Barré syndrome, the transmission of electrical impulses is less efficient, which results in ineffectiveness or inability to control physical actions [7,8]. In recent years, many studies have investigated the role of myelin on action potential conduction velocity [9,10]. But in order to do so, the HH model is not sufficient. While the HH model identified the rate and amplitude of depolarization is proportionally related to the concentration of sodium ions and that sodium and potassium gates as well as their ionic conductances are dependent on time and membrane voltage, it did only examine the action potential in an unmyelinated giant squid axon, but can also be utilized for studying unmyelinated sections of axons. For the purpose of examining the effects of myelin on action potential propagation, a discretized model of the axon using the HH model at unmyelinated nodes and modeling myelinated nodes as passive cables [9,10], would prove fruitful. Using this combination of HH model and wave equation model, scientists investigated the effects of different physical parameters (node of ranvier length, internode length, myelin thickness, axon radius) on conduction velocity. Studies found that conduction velocity has a positive correlation with myelin thickness and axon radius has a negative correlation with node length and internode length. Using a simpler, yet powerful discretized model of the axon, where the axon characteristics and myelination pattern can be easily controlled, this paper examines the effects of a number of physical axon parameters on conduction velocity and compares those effects in two distinct axon lengths.

2. Material and Methods

Expanding upon the classical Hodgkin Huxley model, which examines the unmyelinated giant squid axon, a discretized axonal model was generated, whereby individual nodes of the model could be assigned with myelinated or unmyelinated status, and the corresponding electrical properties for the corresponding section are assigned. Moreover, the two types of sections are modeled as passive cable equations (unmyelinated) and the HH model equations (myelinated). Model parameter values and assumptions for myelin thickness, axon radius, membrane and myelin capacitance, membrane and myelin resistivity, and ionic conductances for Na+, K+, and the leak channel were obtained from literature review [10,11,12]. Tabulated values of model parameters are shown in the appendix. Simulation equations were solved using ode23s solver in MATLAB with resting membrane potential and baseline channel gating parameters as initial conditions. Different myelination patterns were chosen to examine three relationships: 1. The effect of myelinated node percentage on action potential conduction velocity, 2. The effect on inter-node length (length between unmyelinated nodes) on action potential conduction velocity, and 3. The effect of node length (length of unmyelinated nodes) on action potential conduction velocity. To ensure proper conduction, the first and last sectioned node of the model was set to unmyelinated parameters, and the input current stimulus amplitude at the first node was set to an above-threshold value of 0.4 µA to ensure action potential generation in all cases examined. The input current was introduced in the model after 40 ms to ensure stabilization of the model and was kept active for a duration of 40 ms. To determine the conduction velocity, response wave-forms of the voltage at the last section of the axonal model were analyzed and the time of first action potential peak was determined post stimulus. The conduction velocity was calculated using the distance from first to last node of the axon divided by the amount time post-stimulus for the first peak to generate at the end node.
3. Results

3.1. Effect of myelination on conduction velocity in 1 cm axon and 0.25 cm axon
To examine the effect of percent myelin on conduction velocity, an axon was discretized into 13 sections and the node length was set to be a constant length of 1/13 of the axon length. Different internode lengths (myelinated regions of an axon) were constructed by assigning sections of the axon as a myelinated or unmyelinated section. For example, in a 1 cm axon discretized into 13 sections, an inter-node length of 11/13 cm could be constructed by assigning the middle 11 sections as myelinated. For additional myelination patterns, axon myelination patterns were constructed in a uniform pattern, where internode length was conserved for the myelination percentage tested. As shown in Figure 2, conduction velocity increases with increased myelination. For the 1 cm axon, if the percent myelination increase from 46.15% to 84.62%, there is a 76.39% increase in conduction velocity of the neuron. Similarly, when the same percentages of myelin were examined in the 0.25 cm axon, there was a 67.57% increase in conduction velocity of the neuron. Interestingly, this seems to suggest that a decrease in myelination has a more drastic percent change in conduction velocity for larger axons.
Fig. 2 Voltage response of end section of 1 cm axon with different current stimulus

Fig. 3 Voltage response of end section of 0.25 cm axon with different current stimulus

Fig. 4 Voltage response of end section of 0.25 cm axon with different current stimulus

“Zooming in on 1st action potential post stimulus”
3.2. Effect of inter-node length on conduction velocity in 1 cm axon and 0.25 cm axon
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![Fig. 5 The effects of myelination on action potential (AP) propagation. Simulations for different myelination patterns, which conserved node length for each simulation and inter-node length within an axon, were conducted for a 1 cm axon (red) and a 0.25 cm axon (blue). The calculated conduction velocities after a 40ms current pulse of 0.4 µA are shown by each marker.](image)

3.3. Effect of node length on conduction velocity in 1 cm axon and 0.25 cm axon
To examine the effect of inter-node length (INL) on conduction velocity, the node length was again set to a constant of 1/13 of the axon length, while other parameters were kept constant. The axon was separated into 13 sections of equivalent pieces in order to achieve a number of variations of internode length while fixing the node length. It should be indicated that the INL for each stimulation was held constant by generating different myelination patterns on the axon to keep each INL of an axon simulated constant. As shown in Figure 3, as INL is increased from 0.0769 cm to 0.8462 cm in a 1 cm axon, the conduction velocity increased by 76.39%. In a 0.25 cm axon, as the INL is increased from 0.0192 cm to 0.2115 cm, the conduction velocity increased by 67.55%. Both correlations of INL and conduction velocity follow a similar upward and positive trend to the percent myelination; however, as the conduction velocity increased more rapidly with increases in INL, it plateaus the INL approaches axon length. Based on this observation, there could be two possible deeper physical explanations for this trend, beyond a trivial explanation that increased myelination would increase conduction velocity. Interestingly, the results show major increases and higher slopes in conduction velocity at lower INL for both axon lengths. First, increasing INL in the model could confine ion channels of the axon into smaller in number unmyelinated sections of the axon; however, our model assumed a fixed number of ion channels in each unmyelinated section as defined by the electrical properties of the unmyelinated section and the length of each discretized section was held constant. The interesting question about how ion channel density in unmyelinated nodes affects conduction velocity is examined below. In contrast to the previous hypothesis, the higher slopes of conduction velocity at lower INL values examined could be attributed to a critical value of myelination percent or inter-node length, where INL values below this theorized critical value has more drastic effects on conduction velocity. In the lowest INL myelination pattern, an axon of thirteen sections was constructed such that INL was one-
thirteenth of the axon length. Thus, each section of the axon alternated between unmyelinated and myelinated categories and the AP makes twelve jumps from a section of one category to another, with myelinated sections of 1/13 of the axon length. The next INL examined was 2/13 of the axon length. Such axons were constructed by alternating one unmyelinated section followed by two myelinated sections. While the percent myelin increased from approximately 46 to 61% from the previous INL case, the conduction velocity increase by 10.7% for the 1 cm axon and 19.2% for the 0.25 cm axon. This observation would hint that the effect of myelinated lengths along an axon, the INL length, on conduction velocity is not a relative effect of the length of the axon as the INL values examined are equal fractions of the total length.

Fig. 6 Effects of inter-node length on conduction velocity. Simulations for different internode-lengths, which conserved node length and axon length for each simulation, were conducted for a 1 cm axon (red) and a 0.25 cm axon (blue). The calculated conduction velocities after a 40ms current pulse of 0.4 µA are shown by each marker.

3.4. Effect of node length on conduction velocity in 1 cm axon and 0.25 cm axon
To examine the effect of ion channel density on conduction velocity, simulations were conducted to vary node length and calculate the predicted conduction velocity. Given that our model fixes ion channel density indirectly through parameter values of the electrical properties of the myelinated category sections, modulation of node length would allow for perturbations of density. The inter-node length for all simulations was set constant as 8/10 of the axon length. The node length was altered by cutting the axon into different numbers of pieces. As shown in Figure 4, increasing node length (thereby decreasing ion channel density), decreases action potential propagation for both length axons examined. In the 1 cm axon, as the node length increase from 0.01 cm to 0.1 cm, there is a 44.51% decrease in conduction velocity. When the node length increased from 0.0025 to 0.025 cm in the 0.25 cm axon, there was a 41.56% decrease in conduction velocity. Thus, decreasing ion channel density at unmyelinated nodes decreases conduction velocity.

Fig. 7 Effects of node length on conduction velocity. Simulations for different node lengths, while keeping INL constant for each simulation, were conducted for a 1 cm axon (red) and a 0.25 cm axon (blue). The calculated conduction velocities after a 40ms current pulse of 0.4 µA are shown by each marker.
4. Discussion
In an unmyelinated axon, the Na+ channels are distributed uniformly across the length of the axon. But when myelin is introduced, the channels get moved around and gather in the nodes of Ranvier, which increases the conduction velocity because the higher density of ion channels allows signals to travel faster. Our model assumes that electrical properties of each myelinated section and each unmyelinated section are similar based on their category, and that the number of ion channels, represented by the electrical properties of each node are constant. Therefore, as we decrease node lengths, increase INL, or increase percent myelination, the constant number of ion channels are condensed into a smaller space, which allows a more rapid conduction velocity. Thus, by increasing the ion channel density in a unmyelinated node, the conduction velocity can be increased. Oppositely, when we increase node lengths, decrease INL, or decrease percent myelination, the same number of ion channels will be more spread out across the nodes, slowing down the conduction velocity. By looking at a 1cm and a 0.25 cm axon, the effects of different sized axons are investigated. Given the variety of axon lengths that exist in our CNS and PNS, understanding how these correlations can be different in different regions of the nervous system would prove beneficial. From the results, the percent change in conduction velocity of the 0.25 cm axon is smaller compared to the 1 cm axon. This shows that deterioration of myelin in longer neurons in the body may possibly cause more severe symptoms than in shorter neurons. While there are a significant number of axon parameters that can affect conduction velocity, the developed model presents a valuable tool for examining further questions on the effects of myelin patterning, and in particular non-uniform patterning, electrical properties of myelin and nonmyelinated sections, and how different dimensions (length and radii) of axons can perturb conduction velocity.

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