Can Decreased Axonal Conduction due to Demyelination be Reversed by Na^+ Channel Clustering at the Demyelinated Sites?

Valentino Wilson
Department of Biomedical Engineering
University of Illinois Chicago
Chicago, Illinois, United States
viwilso2@uic.edu

***Abstract*—Demyelination of neurons leads to improper neural signaling as seen in neurological conditions like Multiple Sclerosis (MS). Currently, there is no cure for MS as treatments are specifically aimed at slowing the progression of the disease and managing symptoms [1]. Neuropathic pain is one such symptom that has historically been treated by MS treatments but has only recently been reported as one of the key symptoms of MS [2]. In this study, we sought to understand and quantify the effects of demyelination on neural signaling with the goal of demonstrating a method for restoring axonal conduction by increasing the voltage-gated Na^+ channel (VGSC) clustering at demyelinated sites. Simulations of active axons were created in MATLAB using in-vivo neuronal conditions and parameters. Voltage-gated channeling was assumed to be the main source of charge distribution across the neuronal phospholipid bilayer. Key results indicated that axonal conduction can be restored by increasing the clustering of VGSCs around demyelinated sites to *20,000x* the concentration of VGSC and voltage-gated K^+ channel (VGPC) accumulation at severely demyelinated sites and *10,000x* the concentration of VGSC and VGPC accumulation at moderately demyelinated sites. Additional results indicated that VGPC accumulation at demyelinated sites can be used as a source for minimizing neuropathic pain induced by damage to the neurons.**

***Keywords*—Multiple Sclerosis, neuropathic pain, demyelination, voltage-gated channels, axonal conduction, neurological conditions**

I. Introduction

The purpose of this study is to understand and quantify the effects of demyelination on neural signaling with the goal of demonstrating a method for restoring axonal conduction by increasing the VGSC clustering at demyelinated sites. Such a method for restoring axonal conduction can be utilized in treatment for neurological diseases like MS.

A. Multiple Sclerosis – A Demyelinating Disease

Multiple Sclerosis is a neurological condition affecting the central nervous system in which the immune system attacks the myelin sheath of neurons, leading to demyelination along segments of the axon [3]. Myelin is an insulating material that serves as a protective covering around the axon and allows neural signals to travel faster through the neuron [4]. Such neural signals are known as action potentials and their propagation down the axon is vital in relaying important information between neurons within the central and peripheral nervous systems. When demyelination occurs, action potential propagation slows and sometimes stops which can then lead to symptoms such as loss of sensation, inability to move, and neuropathic pain [5]. Management of these symptoms is the primary goal of MS treatments, however, there have not been any treatments reported capable of curing the source of the condition.

B. Demyelination and VGSCs

While demyelination is not the source of MS, it can be regarded as the source of its symptoms. Demyelination is a type of neural injury that negatively impacts action potential propagation along the axons of neurons. It has been reported that on the sub-cellular level, an abnormal accumulation of voltage-gated Na^+ channels can be found in regions of neural injury [6]. In MS, this abnormal accumulation occurs at the demyelinated sites. Historically, VGSCs were suspected of causing permanent axonal destruction in cases of MS. Recently, however, it has been reported that these VGSCs may provide an avenue to achieve axonal and neuronal protection against MS [7].

C. Neuropathic Pain and VGPCs

Neuropathic pain is regarded as one of the key symptoms of MS; it can be a major cause of reduced function, decreased sense of well-being, and an important target for treatment [2]. Neuropathic pain has no cure and instead, pain management drugs are used as a treatment to silence neuropathic pain signal firing. It has been reported that small sensory neurons involved with nociception (pain detection) express a large number of VGSCs and VGPCs along their axons [8]. An altered composition and distribution of shaker-type K^+ channels within the nodal complexes of myelinated axons following neural injury have also been observed [9]. This finding indicates that not only are these channels possible tools for protecting neurons against MS, but they can also be tools for managing neuropathic pain symptoms associated with the condition.

II. Methods

All simulations were developed under the assumption of a straight tube modeled as an active axon. Discrete/finite element modeling of Kelvin's continuous cable equation was utilized for the active axon model. The Euler method can be numerically unstable, especially for stiff equations where the numerical solution grows very large when the exact solution does not. Due to this consideration, Runge-Kutta Fehlberg integration with variable step size was used. Within MATLAB, Ordinary

Differential Equation (ODE) solvers were used, specifically *ODE15s()*. All simulations were created without the usage of additional MATLAB add-on toolboxes.

A. Simulation Parameters and Characteristic Properties

Each simulation comprised the same parameters and characteristic properties summarized in Table 1. These values were gathered from various studies including Hodgkin Huxley. The simulation time and number of nodes were arbitrary values that can be modified for subsequent studies. Additional values were calculated through the simulation framework.

TABLE I. PARAMETERS & CHARACTERISTIC PROPERTIES OVERVIEW

Simulation Time	40 µs	**Stimulation Current**	100 pA
Axon Length	70 µm	**Current Pulse Width**	0.2 ms
Number of Nodes	30	**Initial m-Gate**	0.0692
Axon Radius	0.3 µm	**Initial n-Gate**	0.5142
Membrane Capacitance	0.04 pF	**Initial h-Gate**	0.3534
Resting Voltage	-60 mV	**Axonal Conductance**	4.0 nS
Cl^- Nernst Potential	-43 mV	**Cl^- Conductance**	2.9 pS
Na^+ Nernst Potential	0.9 mV	**Na^+ Conductance**	0.9 pS
K^+ Nernst Potential	25 mV	**K^+ Conductance**	25 pS

B. Initial Simulation – Unmyelinated Axon

The initial simulation was developed under the assumption of an unmyelinated active axon. It served as a basis for all subsequent simulations to be built upon. The axon was divided into 30 nodes with each node being equally spaced along the axon's length. A stimulation current was applied to the first node and its induced action potential propagation was observed down the length of the axon. Along the length of the axon, axonal conductance values were accounted for and considered to be constant. At each node, membrane capacitances and voltage-gated channels (Na^+, K^+, and Cl^-) were considered. Voltage-gated channel conductances varied at each node based on the voltage present at that node and the resulting m-, n-, and h-gate activation values. Action potential propagation was plotted and observed on 3-dimensional axes alongside time and node number (Fig. 1).

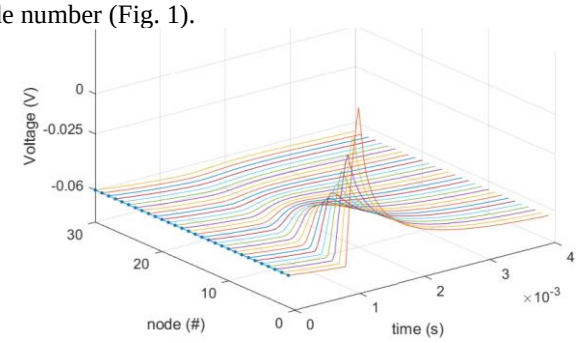

Fig. 1. Unmyelinated Axon. Action potential reached a peak magnitude at node 1 and then proceeded to decrease in magnitude along subsequent nodes until propagation termination at node 17. A 40 µs time delay was recorded between every two nodes when comparing the peak action potential voltage at each node.

C. Subsequent Simulations – Axon Myelination

Subsequent simulations were developed to account for a myelinated axon. Nodes of Ranvier were inserted in the axon at the first node and then were present at every fifth node. This placement created six internode sections that were four nodes in length. At each node of Ranvier, only VGSCs and VGPCs were present. At each internode section, only voltage-gated Cl^- channels were present. Myelination was reflected in the simulation by decreasing the membrane capacitance and increasing the voltage-gated Cl^- channel membrane resistance along the internode sections by a factor of ten. Action potential propagation was plotted and observed on 3-dimensional axes alongside time and node number (Fig. 2).

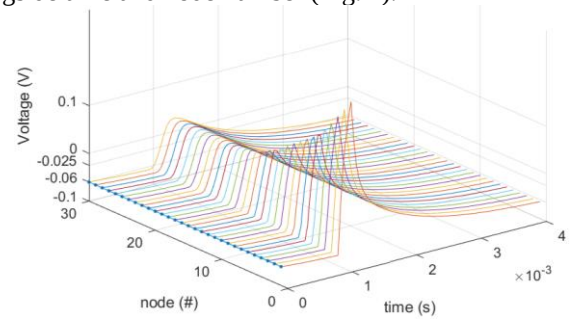

Fig. 2. Myelinated Axon. Action potential propagation reached node 30 with a voltage of 0.027 V. A 40 µs time delay was recorded between every six nodes when comparing the peak action potential voltage at each node.

D. Inducing Neural Injury

Neural injury was reflected in the simulation by inducing demyelination from the sixth through eleventh nodes. Demyelination was taken into consideration by increasing the membrane capacitance and decreasing the voltage-gated Cl^- channel membrane resistance of the demyelinated sections by a factor of 100. Along the length of the demyelinated section, VGSCs and VGPCs were accumulated at *27x* greater than their normal concentration to reflect the abnormal accumulation of these channels around the sites of severe neural injury. Action potential propagation was plotted and observed on 3-dimensional axes alongside time and node number (Fig. 3).

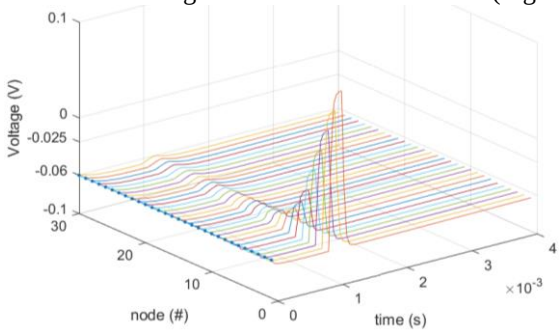

Fig. 3. Severely Damaged Axon. Demyelination at nodes 6-11 led to action potential propagation termination at node 10. Action potential shape was shown to be irregular with a square wave pattern. No significant time delay between peak action potential voltages at each node was recorded.

III. RESULTS

The simulation developed in this study was used as a means for understanding and quantifying the effects of demyelination on axonal conduction and neural signaling. This tool was also used to identify methods for restoring axonal conduction after damage to the myelin has occurred as in MS.

A. Axonal Conduction Restoration

This study primarily indicated that axonal conduction can be restored by increasing the clustering of VGSCs around

demyelinated sites to *20,000x* the concentration of VGSC and VGPC accumulation at severely demyelinated sites and *10,000x* the concentration of VGSC and VGPC accumulation at moderately demyelinated sites. Successful signal restoration was measured as the axon's ability to output the same voltage value at node 30 as was identified in the myelinated axon model (V_{30} = *0.027 V*). Using this metric, it was shown that the restored neural signal was capable of reaching a value of *0.028 V* at node 30. While the voltages at node 30 were identical, the patterns for each signal's action potential propagation differed slightly (Fig. 4). It was observed that the myelinated axon followed a controlled decrease in peak voltage values between nodes 1-20 before leveling off at the node 30 voltage value. Alternatively, in the restored neural signal, the peak voltage values had a sharp decrease between nodes 1-6 before leveling off at the node 30 voltage value. An additional discrepancy between models identified the peak voltage value at node 1 for the myelinated axon to be *0.247 V* while the peak voltage value at node 1 for the restored signal was recorded at *0.170 V*. The combination of these discrepancies in action potential propagation pattern and peak action potential voltage values indicated a possible ulterior function by VGPCs accumulated at sites of neural injuries.

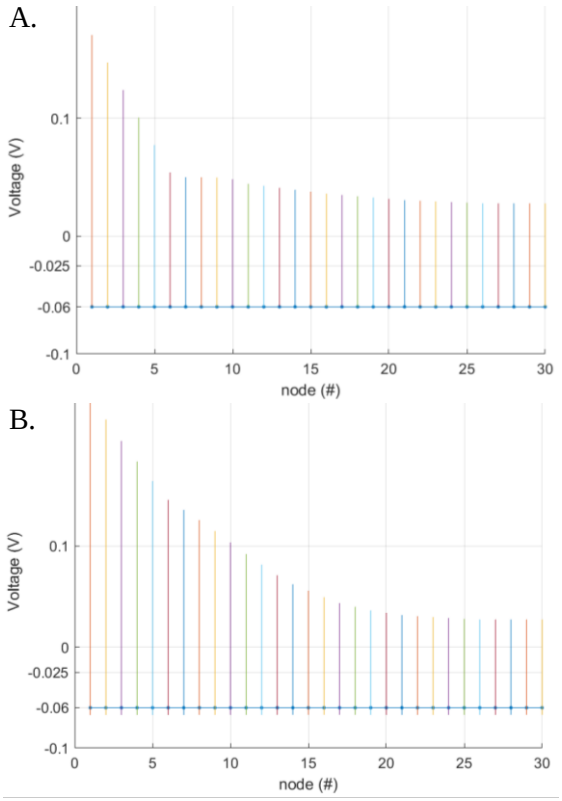

Fig. 4. Restored Neural Signal. (A) Increased accumulation of VGSCs at a ratio of 20,000:1 with VGSC and VGPC accumulation at demyelinated sites, indicated restored neural signaling with action potential propagation reaching node 30 with a voltage of 0.028 V. (B) Myelinated axon control for comparison of the restored neural signal's action potential propagation pattern and peak action potential voltage value at node 1.

B. Neuropathic Pain Symptom Elimination

The function of VGPC activation at sites of neural injuries was investigated following the results of the Na^+ channel clustering signal restoration. VGPC effects were isolated by increasing the K^+ channel accumulation to *20,000x* the concentration of VGSCs and VGPCs accumulated at the severely demyelinated sites. This modification to the model did not result in any significant difference in the action potential propagation. This indicated that K^+ channel activation at sites of neural injuries is not a tool for restoring axonal conduction. Additional efforts to understand the effects of K^+ channel activation included removing the axonal demyelination followed by increasing the concentration of K^+ channels at nodes 6-11. The results from this experiment identified identical action potential propagation patterns to that of the axon with severe demyelination (Fig. 5). This showed that VGPC accumulation at sites of neural injuries can be used as a tool to suppress resulting neuropathic pain signals following neural injury.

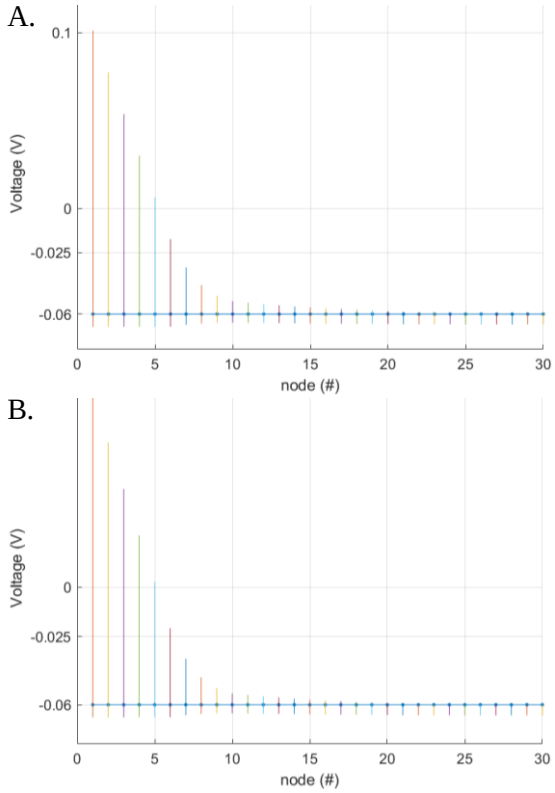

Fig. 5. VGPC Effects on Neural Injuries. (A) Increased accumulation of VGPCs at a ratio of 23:1 with normal VGSC and VGPC accumulation, indicated neural signaling similar to that of the severely damaged axon. (B) Severely damaged axon for comparison.

IV. Discussion

The results presented in this study demonstrated evidence validating and quantifying the observations and hypotheses presented through alternative in-vivo studies. The goal of this study was to initially mathematically represent the neurophysiological systems involved with neural injury, neurological conditions like MS, and neuropathic pain syndromes. The goal was then to make alterations to these

mathematical simulations with the intent of understanding the underlying neurophysiological mechanisms and how they can be manipulated to treat certain neurological conditions.

A. Axon Myelination Mechanics

To account for myelination in the model, two major changes to the unmyelinated simulation were presented; nodes of Ranvier were inserted and myelin was applied to sections of the axon. Nodes of Ranvier are naturally occurring gaps in the myelin sheath that are necessary for action potential propagation along the length of the axon. These nodes function to speed up the propagation of action potentials along the axon via saltatory conduction. Saltatory conduction across each node of Ranvier is made possible by a high concentration of VGSCs and VGPCs that raises the membrane voltage during the creation of an all-or-nothing action potential [10]. The action potential travels across each node of Ranvier and into subsequent myelinated sections. Myelin was taken into consideration within the simulation by modifying the membrane capacitances and resistances within the internode sections (nodes between the nodes of Ranvier). Decreasing the internode membrane capacitance made the axon easier to charge, thus speeding action potential propagation. Increasing the internode membrane resistance, increased the insulation of the axon, thus increasing the electrical space constant and promoting signal transfer from one node of Ranvier to the next [11]. Including the nodes of Ranvier and myelinated sections in the simulation resulted in proper neural signal propagation along the length of the axon. In-vivo, this shows the power that these mechanisms have in allowing proper neural signaling and alternatively, how their damage can hinder neural signaling altogether.

B. VGSC Clustering at Sites of Neural Injuries

Through the evidence presented in this study, the observation of VGSC clustering at sites of neural injury can be defined as a mechanism for axonal conduction restoration. While it was previously reported that Na^+ channel clustering may have been a source of permanent axonal damage in the case of MS, through the results presented in this study, this can be debunked. While the accumulation of VGSCs can restore axonal conduction, the scale of this accumulation may be too large to occur in-vivo naturally. It was undetermined the actual concentrations of VGSCs found at the sites of neural injury, however. If the scale of accumulation is too large for natural interventions, the possibility of external intervention may be an option for treatment. Targeted Na^+ ion injections at the sites of neural injury could be a possible method for increasing the accumulation of Na^+ ions at the site of neural injury. While outside the scope of this study, subsequent work can be taken out to further understand the practicality of this solution. An additional consideration for increasing the concentration of Na^+ ions at the site of neural injuries is the possibility of amplifying the neural pain signals in sensory neurons surrounding the injured area. With this consideration, precise targeting using Na^+ ion injections must be controlled to not reach the nociceptors in the area.

C. K^+ Channel Role in Neuropathic Pain Suppression

Originating from the results presented in the axonal conduction restoration experiment, the role of VGPCs in neural injuries and neuropathic pain detection was called into question. Through the experiments presented in this study, it was identified that VGPCs did not have a role in restoring axonal conduction but rather they reduced neural signaling along the axon. This reduction in neural signaling occurred in the absence of Na^+ and reported similar action potential propagation patterns as the severely demyelinated simulation. These results, in the context of restoring axonal conduction, show that VGPCs are harmful to the neurons. While this may be the case for axonal conduction, this is not the case in the context of neuropathic pain. As was mentioned previously, treatments for neuropathic pain include pain management drugs that aim to silence the neuropathic pain signal firing. VGPCs are capable of accomplishing this same effect by terminating the propagation of pain signal action potentials along the axon. It is unknown if an external intervention exists capable of increasing the concentration of VGPCs in nociceptors and sensory neurons involved with pain signaling. If this intervention can be replicated in-vivo, the result would be a treatment for neuropathic pain, a key symptom of MS.

CONCLUSION

VGSCs can be used to restore axonal conduction, however, in very large concentrations at the sites of neural injury. VGPCs can be a tool used for reducing the effects of neuropathic pain by blocking the propagation of neuropathic pain signals along neuronal axons. While both of these findings are significant in that they solve issues in the medical field that currently do not have solutions, the feasibility of these solutions may be called into question. Assuming each solution can be applied in-vivo and in practice, the result would mean a treatment for restoring neuron function in demyelinated axons as seen in MS and a treatment for neuropathic pain that does not rely on pain management drugs.

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