Chapter 4

Effective Nerve Signal Transmission through an Axon without Information Loss in Extracellular Space

This chapter examines the similarities in the neuronal signal for a myelinated nerve fiber across two distinct axon locations under the influence of the ECS. An action potential is first generated at a Node of Ranvier which is propagated along a myelinated segment towards the next Node. The similarity of the initially generated signal and the signal when it reaches the next Node of Ranvier is then compared for nerve fiber of different lengths. Understanding the importance of fiber length in maintaining the information content of the signal under the influence of the ECS would be better understood through this chapter.

4.1 Introduction

A nerve signal goes through a number of influences as it travels through a nerve fiber, these processes include attenuation due to the axial resistance and leakage channels of the nerve fiber, attenuation due to the influence of the ECS etc. It is essential to maintain the information content of the signal as the signal needs to reach its destination with the maximum amount of information retained. Moreover, fiber anatomy also plays a crucial role in retaining the information content of the signal as the strength of the signal is maintained for a myelinated fiber than a non-myelinated or unmyelinated fiber, also the impulse velocity is higher for a myelinated fiber than a non-myelinated fiber [88], [111], [112], [122]. Similarly, in the case of a fiber with larger diameter, the velocity of conduction is higher than for a fiber with smaller diameter [81], [89], [104], [105], [106], [107]. This is because a fiber with larger diameter offers less axial resistance to the forward movement of the signal thus increasing its speed of conduction. The effect of ECS is also significant in maintaining the information content of the signal as a fiber which is surrounded by a larger ECS results in more attenuation of the signal in comparison to a fiber which is surrounded by a smaller ECS. This is because a larger ECS offers less resistance to the outward movement of the ions, thus the mobile ions get easily dissipated towards the external media through the leakage channels [64].

The length of the fiber also plays a crucial role in retaining the overall information content of the signal. A longer fiber corresponds to a larger or increased axial resistance within

the axon which eventually causes the impulse velocity to reduce; this is comparable to the increased resistance found in a longer electrical cable; this process is known as decremental conduction of neuronal impulse [159], [160]. Moreover, there are also an increased number of open channels through which leakage of ions increases resulting in the decrease in the signal strength. For a shorter fiber, the chances of decremental conduction are less because the effect of the axial resistance is less and also there are a smaller number of open channels (leakage channels) to facilitate leakage of ions towards the external media.

For a myelinated nerve fiber, the exchange of ions take place only at specific location along the fiber which is known as Node of Ranvier [161]. These nodes, which are small spaces between the segments of the myelin sheath, are produced by oligodendrocytes in the central nervous system or Schwann cells in the peripheral nervous system. The axonal membrane is exposed to the extracellular environment at the Node of Ranvier, and this exposure is essential for the quick propagation of action potentials via a process known as saltatory conduction [33], [34], [36]. Here, the action potential or neuronal impulse jumps from one node to the next rather than moving continuously along the axon, significantly accelerating neuronal transmission. The Voltage-gated sodium channels, which are necessary for the production and spread of the action potential, are abundant in the nodes [32]. Thus, for a myelinated axon, the speed of neuronal signal propagation is significantly greater than that for an unmyelinated axon which enables quick reflexes and the intricate coordination of movements in multicellular animals by facilitating effective and quick communication within the neural system. Ford et.al, in their work [162], found out that myelinated axons with shorter internodal lengths transmit nerve signals more effectively because they increase sodium current at synaptic terminals, which speeds up conduction velocities. On the other hand, thicker axons with longer internodal lengths are better able to optimize energy efficiency and modify action potential arrival times. Moreover, Arancibia-Carcamo et.al, in their work [163] suggested that the conduction speed may be increased by shorter internodal lengths because of more effective depolarization spread, whereas conduction speed may be decreased by longer internodal lengths as efficiency declines. Their work, however, did not consider the fundamental parameters pertaining to the ECS. These works relating to the fiber length suggests that the length of the fiber plays a key role in effecting the neuronal signal.

Thus, keeping all these factors under consideration, it is essential to understand how length of the fiber affects neuronal signal under the influence of the ECS, and how much of the original signal is retained with changing length of the fiber. In this regard, a robust

mathematical framework is essential to comprehend the above-mentioned conditions which would be mathematically and computationally less complex and also which can mimic the real nerve scenarios. The current work focuses on this aspect of neuronal signal transmission.

4.1.1 Node of Ranvier

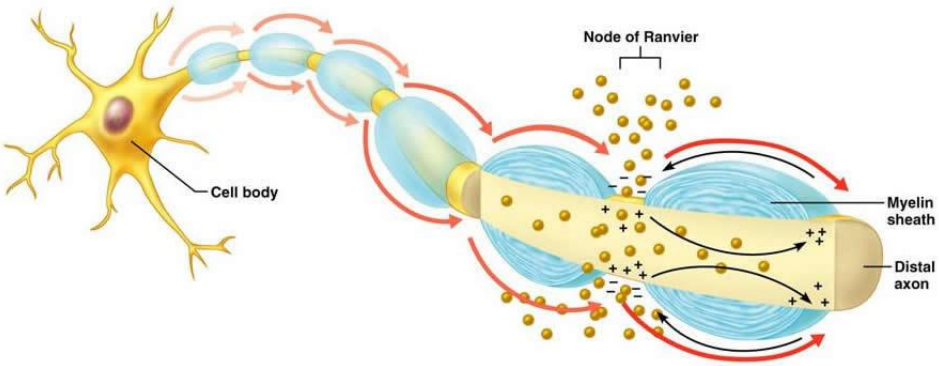

Fig.4.1 Myelinated Neve fiber with Node of Ranvier at distinct locations

Nerve fiber or axons transmits information in the form of electrical signal or action potential. Myelin, which is formed by Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS), frequently wraps axons along their whole length except for certain locations called the Node of Ranvier [161]. Myelin preserves ionic charge when the axolemma depolarizes during action potential propagation by raising membrane resistance and lowering membrane capacitance. High concentrations of voltage-gated sodium ion (Nav) channels are present at the axon initial segment (AIS), a myelin-free section that is roughly 20–40 mm long and located next to the cell soma which is essential for the generation of an action potential [164]. Moreover, Potassium channel accumulation is found at comparatively late developmental stages, following the formation of the Node of Ranvier [32], [39]. Due to the availability of the Nav channels, the nerve signal or action potential gets regenerated at the Node of Ranvier which then propagates forward to carry the information towards its intended target. Thus, the Node of Ranvier can be considered as a repeater to regenerate the neuronal signals so that the information content of the signal is not lost along the course of propagation [36] [35]. The Node of Ranvier are surrounded by paranodal areas, which are composed of septate-like junctions connecting glial loops that are helicoidally wrapped to the axonal membrane [31]. Moreover, distinct cell adhesion molecules (CAMs), cytoskeletal scaffolding, and extracellular matrix (ECM) components make up the Node of Ranvier and the paranodal junctions that surround them. The involvement of distinct nodal as well as paranodal components in neurological illnesses serves as more evidence of the

Node of Ranvier's significance to the normal operation of the nervous system. Thus, it is evident that the Node of Ranvier are very much essential for the generation and propagation of an action potential which is important to retain the information content of the signal.

4.1.2 Saltatory Conduction

The process through which neuronal signal regeneration and propagation in a myelinated nerve fiber is known as the saltatory conduction [33], [34], [36]. This process takes place at the Node of Ranvier, which are tiny openings in the sheath that surrounds and insulates the axon. Action potentials are exclusively produced in the Node of Ranvier of myelinated axons. Here, sodium ions rush into the axon during the generation of an action potential causing a local depolarization. After that, the depolarisation process passively proceeds to the subsequent node via the myelinated internodes, where it initiates a new action potential or refreshes the signal. Thus, saltatory conduction makes it possible for electrical nerve signals to travel great distances quickly and without signal deterioration. The action potential appears to jump along the axon, but in reality, this phenomenon is only the signal conduction occurring rapidly within the myelinated part of the axon. Signal deterioration would occur if an axon's whole surface were insulated because action potentials could not be reproduced along the axon. Compared to the slower conduction speeds of unmyelinated fibers, which vary from 0.5 to 10 meters per second, this so called "jumping" from node to node allows for substantially quicker transmission speeds up to 150 meters per second [35]. In addition to being quicker, saltatory conduction uses less energy as well. As less ions are needed to be exchanged across the membrane, the myelin sheath reduces the requirement for sodium and potassium pumps to restore the resting membrane potential following an action potential. When myelin sheath degradation or loss occurs, as in the case of multiple sclerosis (MS), saltatory conduction efficiency is significantly reduced. Nerve impulses travel more slowly when myelin is lost, and in extreme situations, action potentials may not even begin to propagate at all. This results in the multiple sclerosis that include loss of coordination, muscle weakness, and reduced sensory abilities [165]. Thus, understanding saltatory conduction and its influencing factors contribute significantly to the understanding of fundamental neurophysiology as well as the mechanisms underlying a wide range of neurological illnesses.

4.2 Contribution

In this work, the similarities in the neuronal signal between two different axon location for a myelinated nerve fiber under the effect of the ECS. An action potential is first generated at a

Node of Ranvier which is propagated along a myelinated segment towards the next Node. The similarity of the initially generated signal and the signal when it reaches the next Node of Ranvier is then compared for nerve fiber of different lengths. This work would aid towards understanding the significance of fiber length in preserving the information content of the signal under the effect of the ECS. The result obtained from this work shows that for myelinated fibers, there exists a critical length at which point the information content of the signal is preserved without alteration. To carry out the work, the cable model of nerve is used to model and simulate the environment. The parameters pertaining to the ECS has been incorporated into the cable model to provide a robust framework in understanding nerve signal transmission in a detailed manner. This approach provides results that are mathematically and computationally less complex and could replicate an actual nerve fiber.

4.3 Proposed Methodology

The foundation for the proposed myelinated nerve model is based on the equivalent cable model suggested by Wilfrid Rall [91], which shows the nerve fiber as an equivalent electrical cable. Here, the parameters pertaining to the ECS have been incorporated into the model which is inspired from Holt and Koch's work [75]. Initially, an action potential or nerve impulse is generated at a Node of Ranvier. This action potential is then propagated through a myelinated segment to the next Node of Ranvier. The similarity between the original signal and the signal when it reaches the next Node of Ranvier is compared to observe whether the originality of the signal is maintained or not for a fiber of different lengths.

Fig.4.2 shows the representation of the proposed model and Fig.4.3 shows the electrical equivalent cable representation of the proposed model. Moreover, the ECS related parameters have been incorporated to the cable model so that a holistic approach in understanding nerve signal transmission could be obtained that would be robust and would be able to replicate a real nerve. Here, the similarity between the signals at the initial Node of Ranvier and the subsequent Node of Ranvier shows the amount of modulation or the amount of the actual signal has been modified as it passes from one Node to the other along the nerve fiber.

Observing Fig.4.2, it can be seen that an action potential or nerve signal is generated at the first node of Ranvier, it is then propagated along the myelinated segment on to the next

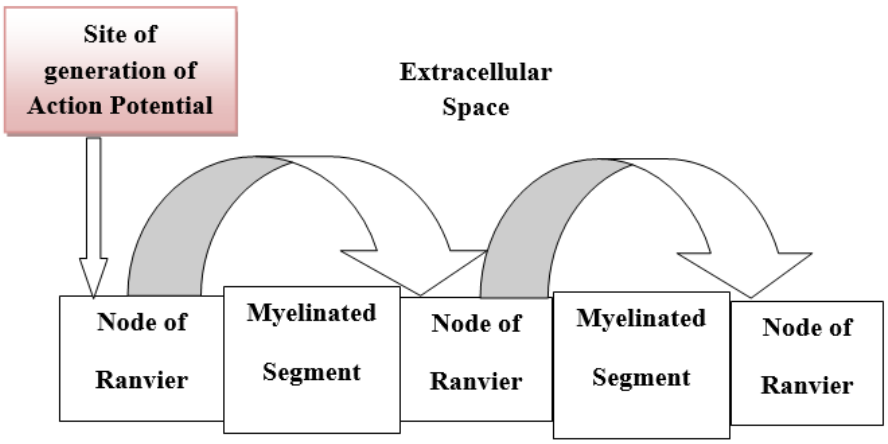

Fig.4.2 Representation of the Proposed Model

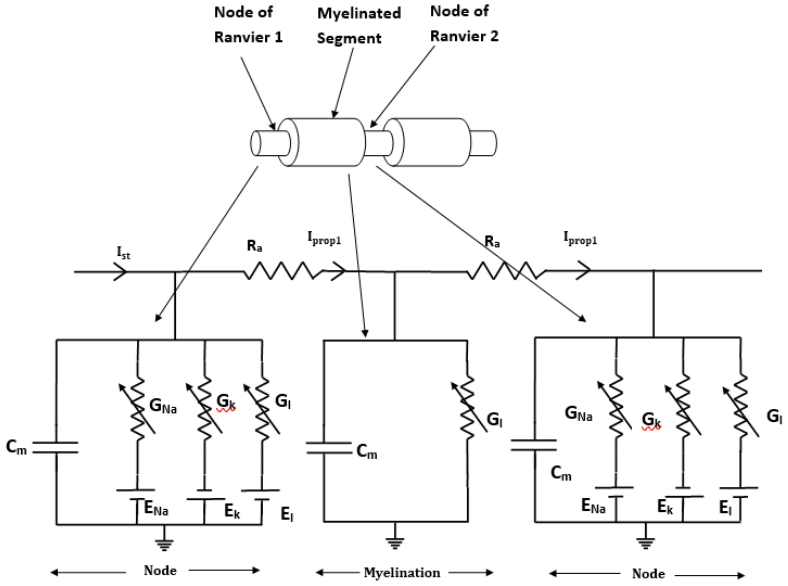

Fig.4.3 Electrical equivalent cable representation of the proposed model

Node of Ranvier. The first Node produces an action potential, which causes a local depolarization that opens voltage-gated sodium channels. The membrane potential at the node quickly changes as a result of sodium ion inflow. The electrical signal can move swiftly as a local current in the myelinated segment between the two Nodes because the insulating myelin layer prevents the leakage of ions. In the next Node, the action potential will be regenerated due to Saltatory conduction which ensures that the depolarization will take place effectively. For a myelinated fiber, exchange of ions viz sodium and potassium ions take place at the Node of Ranvier only, thus this segment can be viewed as an active segment or an active nerve fiber. In the myelinated segment, the exchange of ions is negligible thus this segment can be viewed as a passive fiber where exchange of ions does not take place and only the forward propagation

of electrical signal occurs. Therefore, in Fig.4.3 the Node of Ranvier is depicted as an active Hodgkin-Huxley (H-H) nerve fiber and the myelinated segment is shown as a passive nerve fiber. At the next Node of Ranvier, the active ion channels generate a response based on the amount of current delivered to the node after accounting for propagation losses.

At the first node of Ranvier, spike train with a duration of 1 mSec to 8 mSec and 15 mSec to 22 mSec is given as an input. Given that the first Node of Ranvier is an active fiber, the Hodgkin and Huxley (H-H) equation can be used to get its mathematical expression which is,

$$I_{st} = C_m \frac{dV_m}{dt} + G_{Na}(Vm - E_{Na}) + G_k(Vm - E_K) + G_l(Vm - E_l) \qquad (4.1)$$

Here, G_{Na}, G_K, and G_l are the sodium, potassium and leakage conductances which can be further expressed as $G_{Na}= \overline{g_{Na}}\, m^3h$, $G_k= \overline{g_k} n^4$, and $G_l= \overline{g_l}$ and m^3, h are the activation variable for sodium ions and n^4 is the activation variable for potassium ions respectively. E_{Na}, E_k, E_l, are the equilibrium potential of sodium, potassium and leakage ions. From H-H model, the rate of change of gating variables over time can be shown that,

$$\frac{dn}{dt} = \propto_n (V_m)(1 - n) - \beta_n(V_m)n$$
$$\frac{dm}{dt} = \propto_m (V_m)(1 - m) - \beta_m(V_m)m$$
$$\frac{dh}{dt} = \propto_h (V_m)(1 - h) - \beta_h(V_m)h$$

Here, n, m, and h are dimensionless quantities between 0 and 1 that are associated with potassium channel activation, sodium channel activation, and sodium channel inactivation, respectively. These quantities are represented by Boltzmann equations as functions of the membrane potential. $\propto_i$ and β_i are rate constants for the i-th ion channel that depend on voltage but not time. Now, the functions $\propto$ and β can be expressed as,

$$\propto_n (V_m) = \frac{0.01(V_m+50)}{1-\exp\left(\frac{V_m+50}{-10}\right)}, \quad \propto_m (V_m) = \frac{0.1(V_m+35)}{1-\exp\left(\frac{V_m+35}{-10}\right)}, \propto_h (V_m) = 0.07\exp\left(\frac{V_m+60}{-20}\right),$$

$$\beta_n(V_m) = 0.125\exp\left(\frac{V_m+60}{-80}\right), \ \beta_m(V_m) = 4\exp\left(\frac{V_m+60}{-18}\right), \ \beta_h(V_m) = \frac{1}{1+\exp\left(\frac{V_m+30}{-10}\right)}$$

These empirical equations, which represent the physical model of a gate travelling within a channel to open and close, are based on the equations describing the motion of a charged particle in an electric field. Now, using Eq.4.1,

$$\frac{dV_{mnode1}}{dt} = -\frac{1}{C_m}[(G_{Na}(V_{mnode1} - E_{Na}) + G_K(V_{mnode1} - E_k) + G_l(V_{mnode1} - E_l) + I_{st})] \qquad (4.2)$$

Here, V_{mnode1} is the membrane potential of the initial Node of Ranvier. The adjacent myelinated region receives the current that leaves the initial Node of Ranvier, this current can be expressed as,

$$I_{prop1} = \frac{V_{mnode1} - V_{mnodemye1}}{R_a} + \text{Leakage current} \quad (4.3)$$

Since the leakage current for a myelinated segment is negligible, it can be considered as zero. Therefore Eq.4.3 can be rewritten as,

$$I_{prop1} = \frac{V_{mnode1} - V_{mnodemye1}}{R_a} \quad (4.4)$$

The current that traverses from the Node of Ranvier to the adjacent myelinated segment is I_{prop1} and the two input and output nodes between which the current is calculated are V_{mnode1} and V_{mnode2} respectively. V_m is the resting membrane potential, C_m is the volumetric membrane capacitance which can be further expressed as $C_m = c_m \pi D_i l$. Here, c_m is the characteristic membrane potential, D_i is the internal diameter of the nerve fiber and l is the length of the fiber under consideration. The axial resistance or the longitudinal resistance is R_a which can be expressed as,

$$R_a = R_i + R_e \quad (4.5)$$

R_i and R_e are the volumetric internal resistance of the nerve fiber and the extracellular resistance respectively which can be further expressed as, $R_i = \frac{4r_i}{\pi {D_i}^2} \Delta x$ and $R_e = \frac{4r_e}{\pi {D_e}^2} \Delta x$ [97] where r_i and r_e are the characteristic internal resistance of the nerve fiber and the characteristic external resistance and D_e is the diameter of the ECS respectively. The mathematical equation governing the myelinated segment can be expressed as,

$$\frac{V_{out} - V_{in}}{R_a} + C_m \frac{dV_{out}}{dt} + \frac{V_{out} - E_l}{R_l} + I_{prop1} = 0 \quad (4.6)$$

Therefore, rearranging Eq.4.6,

$$dV_{out} = \left(\frac{V_{in} - V_{out}}{R_a} + \frac{E_l - V_{out}}{R_l} - I_{prop1} \right) \frac{dt}{C_m} \quad (4.7)$$

Now, the current expression that leaves the myelinated segment can be given as,

$$I_{prop2} = C_m \frac{dV_{mnode2}}{dt} + G_{Na}(V_{mnode2} - E_{Na}) + G_k(V_{mnode2} - E_K) + G_l(V_{mnode2} - E_l) \quad (4.8)$$

Rearranging Eq.4.8, the membrane potential expression of the next node of Ranvier can be obtained which is,

$$\frac{dV_{mnode2}}{dt} = -\frac{1}{C_m}\left[\left(G_{Na}(V_{mnode2} - E_{Na}) + G_k(V_{mnode2} - E_k) + G_l(V_{mnode2} - E_l)\right) + I_{prop2}\right] \tag{4.9}$$

To compute the similarity between the signal at the first Ranvier node and the signal at the second node, $d_{Vmnode1}$ and $d_{Vmnode2}$ is compared for two fibers of different lengths. Initially, the experimentation is conducted for a fiber with length 80 μm and then in the second case the length of the fiber considered is of 50 μm and a spike train of duration 1 to 8 mSec and 15 to 22 mSec is considered an input signal.

4.4 Simulation Considerations

The simulation parameters used for the experiment are as follows: Characteristic membrane capacitance (cm) is 1 μF/cm^2, the resting membrane potential is -65 mV; these values are considered from H-H model [17]. The length of the fiber under consideration are 80 μF and 50 μF respectively. These lengths are so considered because it strikes a balance between computing efficiency, biological realism, and accurate signal propagation dynamics modelling. Small axons, and fine neuronal branches typically fall within this range, which guarantees that the model can faithfully capture physiological behaviour while also being computationally viable [147], [148]. The internal diameter of the fiber (Di) considered for this work is 5 μm, and the ECS diameter (De) considered is 50 nm as the value aligns with the conventional width of the ECS suggested by [60]. The equilibrium potentials for sodium ion (E_{Na}), potassium ion (E_K), and leakage (E_l) ions are 55 mV, -72 mV, and -50 mV, respectively. The conductance values of sodium ions (g_{Na}), potassium ions (g_K) and leakage ions (g_l) are 120 Siemens/ cm^2, 36 Siemens/ cm^2, and 0.0003 Siemens/cm^2 respectively which are considered from H-H experiment [17].

4.5 Results and Discussions

Spike train of duration 1 to 8 mSec and 15 to 22 mSec initiates the first node which then travels via a myelinated section of the fiber to the subsequent Node of Ranvier. To find out how much information of the originally generated signal is retained, the similarity between the signal at the first Ranvier node and the subsequent node is computed.

Initially a fiber of length 80 μm is considered for the purpose of computation. For a fiber of length 80 μm, Fig.4.4 shows the initial spike train generated at the first Node of Ranvier, which then passes to the adjacent myelinated segment. The spike train at the myelinated segment is given in Fig.4.5. Fig.4.6 shows the regenerated spike train at the next Node of Ranvier and Fig.4.7 shows the overlaying plot of the initial spike train and the spike train at the next Node of Ranvier. It is observed that attenuation of the signal occurs as the spike train moves from the first Node of Ranvier to the passive (myelinated) region with the information content of the signal remaining intact. This attenuation of the signal amplitude is because of the decremental conduction of nerve signal that takes place due to the longitudinal resistance present along the fiber's length. Since the myelinated segment has negligible leakage channels to facilitate losses, the axial resistance of the intracellular media contributes to the decremental conduction of nerve fiber. Because of the nerve fiber's passive membrane

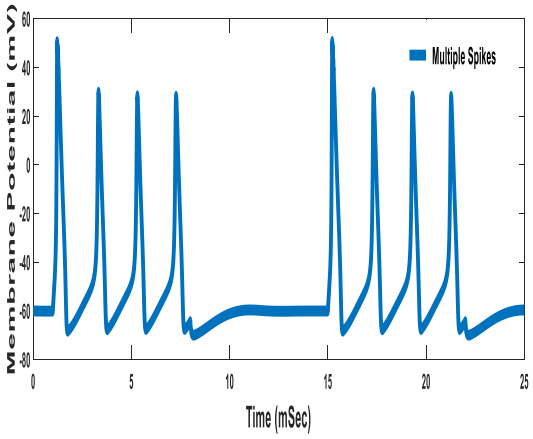

Fig.4.4 Initial Spike train

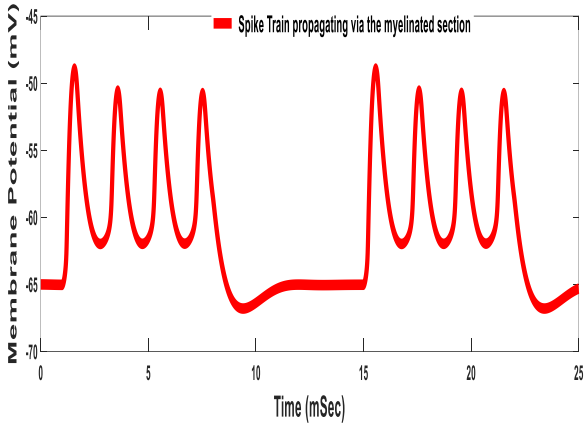

Fig.4.5 Spike train at the myelinated segment

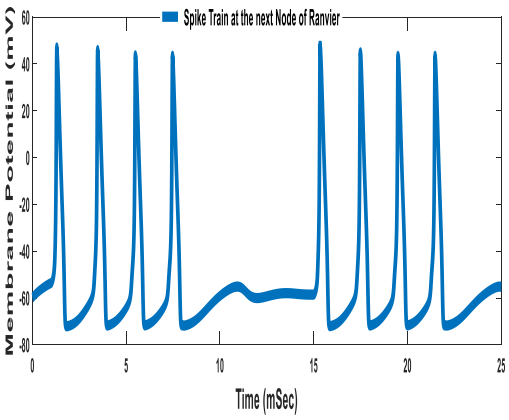

Fig.4.6 Spike train at the next Node of Ranvier

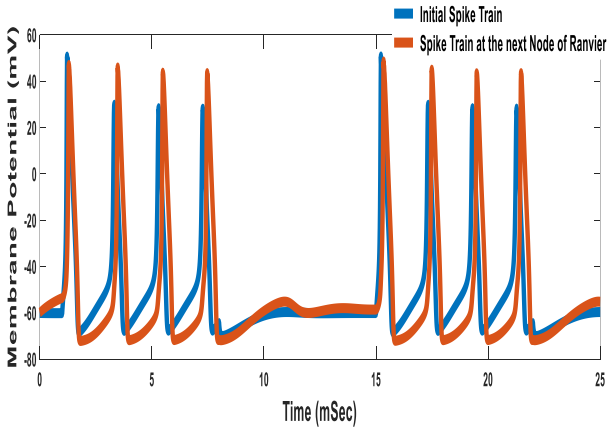

Fig.4.7 Overlaying plots of initial Spike train and Spike train at the next Node of Ranvier

characteristics, which are mostly caused by its capacitive characteristics, a tiny amount of DC shift is also seen in the passive region.

From Fig.4.6, it can be observed that the propagating signal regenerates again at the next Node of Ranvier due to Saltatory conduction. Moreover, much of the information content of the signal is retained with a small amount of information loss taking place. This can be also observed from the overlaying plot given in Fig.4.7.

Now, the simulation is repeated considering a shorter fiber of length 50 μm. Similar to the above scenario, a spike train is generated at a Node of Ranvier which is shown in Fig.4.8 which then moves to the adjacent myelinated segment shown in Fig.4.9 and then the signal regenerates at the next Node of Ranvier as shown in Fig.4.10. The similarities between the initially generated spike train and the spike train when it reaches the next Node of Ranvier is then observed which is shown in the overlaying plot shown in Fig.4.11.

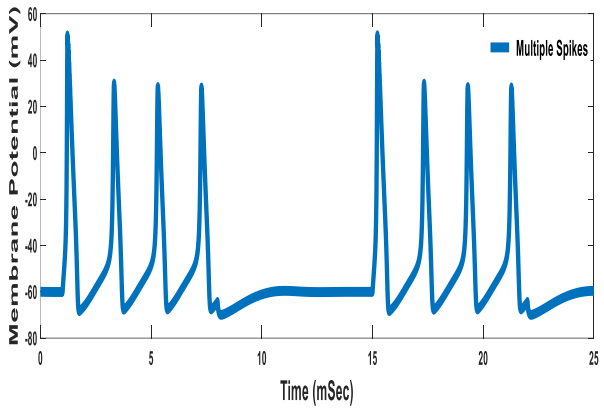

Fig.4.8 Initial Spike train

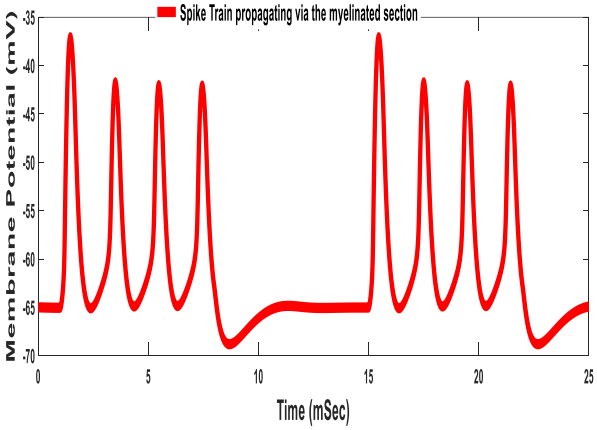

Fig.4.9 Spike train at the myelinated segment

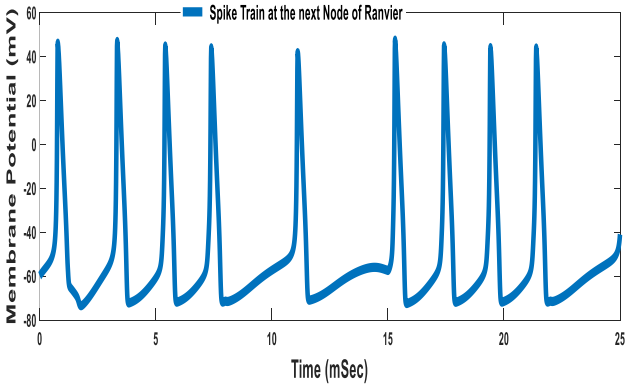

Fig.4.10 Spike train at the next Node of Ranvier

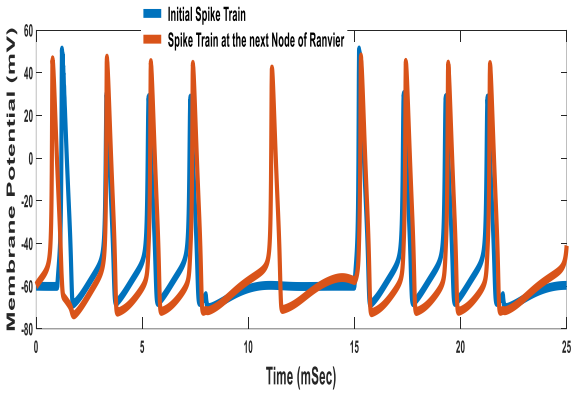

Fig.4.11 Overlaying plots of initial Spike train and Spike train at the next Node of Ranvier

Fig.4.10 shows that an additional spike is produced at the second Ranvier Node when the fiber's length is reduced, indicating the possibility of an information mismatch due to an additional amount of current being delivered to the next Node of Ranvier. It can be deduced that for a fiber, $I_{inj} = I_{delivered} + I_{losses}$. Here, $I_{delivered}$ is the current delivered at the fiber's outlet, I_{inj} is the initial current due to the action potential at the fiber's intake, and I_{losses} is the propagation loss caused by the endoplasm's axial resistance, which is inversely proportional to the fiber's length. According to the above equation, a shorter fiber length leads to a smaller axial resistance and loss due to propagation of axial current, which in turn results in a higher current at the outlet causing an additional spike to be generated at the next Ranvier node. Therefore, it may be inferred that information mismatch may occur for a shorter fiber as a result of high current being delivered at the node.

In this work, the variable l is referred to as the fiber length, which, within the scope of the modelled system, represents the segment of axon over which signal transmission occurs specifically, the distance between two adjacent nodes of Ranvier. In myelinated axons, the conduction of electrical signals involves saltatory propagation, where current flows passively across internodal regions and is regenerated at the nodes. In this work, the resistance Ri is calculated over the segment through which intracellular current flows using the conventional cable model equation $R_i = \frac{4r_i}{\pi {D_i}^2} l$. Although l is referred to as "fiber length" for generality, it accurately and efficiently represents the internodal distance in the context of myelinated fiber. Depending on the biological context and spatial resolution of the model, l can represent either a whole fiber or a compartmental segment. This duality in the interpretation of l is consistent with normal modeling technique. The usage of l is consistent with the internodal length because the emphasis is on the propagation between nodes and each segment that is simulated spans a single internode. Thus, for the first scenario when l is taken to be of 80 μm, it effectively shows the internodal distance to be of 80 μm, and in the second scenario when l is taken as 50 μm, it effectively shows that the internodal distance is of 50 μm respectively. Thus, l can be used to represent the entire length of the fiber, or it can also be used to represent the region between two successive nodes depending upon the work undertaken. The comparison table for the work with standard literature is shown in Table 4.1.

Comparison Table:

Table 4.1: Comparison Table for the current finding with the existing literatures

Work	Methods Used	Results	Remarks
Ford, M. C., Alexandrova, O., Cossell, L., Stange-Marten, A., Sinclair, J., Kopp-Scheinpflug, C., ... & Grothe, B. (2015). Tuning of Ranvier node and internode properties in myelinated axons to adjust action potential timing. *Nature communications*, *6*(1), 8073.	The methodology used in this work evaluates the characteristics of myelinated axons using morphometric techniques, statistical analysis, and simulations.	Myelinated axons with shorter internodal lengths transmit nerve signals more effectively because they increase sodium current at synaptic terminals, which speeds up conduction velocities. On the other hand, thicker axons with longer internodal lengths are better able to optimize energy efficiency and modify action potential arrival times.	ECS parameters are not considered.
Arancibia-Cárcamo, I. L., Ford, M. C., Cossell, L., Ishida, K., Tohyama, K., & Attwell, D. (2017). Node of Ranvier length as a potential regulator of myelinated axon conduction speed. *Elife*, *6*, e23329.	The optic nerve of Sprague-Dawley rats was examined using electron microscopy, with particular attention paid to the structural features of myelination and internodal lengths. This method sought to examine how these anatomical characteristics affected the effectiveness of nerve signal transmission.	Conduction speed may be increased by shorter internodal lengths because of more effective depolarization spread, whereas conduction speed may be decreased by longer internodal lengths as efficiency declines.	ECS parameters are not considered.
Current work	**Modeling and Simulation method is used to compute the similarities of signal between two successive Node of Ranvier under different fiber length.**	**For a longer fiber, the information content of the signal remains intact at the next Node of Ranvier. For a shorter fiber, there is a**	-

		possibility of signal modulation taking place when the neuronal signal reaches the next Node of Ranvier. There must be some critical length where the information content of the signal does not alter.	

4.6 Summary and Future Remarks

The similarity between two segments of nerve fiber i.e., the first Node of Ranvier, where the action potential is generated, and the second Node of Ranvier, that emerges after passing through a myelinated segment is computed in this work. Initially a nerve fiber of length or effectively the internodal distance of 80 μm is considered and in the second scenario a shorter nerve i.e. a shorter internodal distance of length 50 μm is considered for the simulation purpose. An input spike train of duration 1-8 mSec and 15- 22 mSec is considered to trigger the action potential at the initial Node of Ranvier. When the length of the fiber or the internodal distance under consideration is 80 μm; it is observed that when the spike train propagates to the myelinated section of the nerve fiber, the information content of the signal remains intact with only attenuation in the signal strength is observed. This attenuation of the signal is due to the decremental conduction of nerve signal that occurs due to the longitudinal (axial) resistance present along the fiber's length which is a combination of the volumetric internal resistance of the fiber and the volumetric resistance of the ECS as per Eq.4.5. Since a myelinated segment has negligible leakage channels to facilitate losses, the axial resistance contributes to the decremental conduction of nerve fiber resulting in a reduction in the signal amplitude. Because of the nerve fiber's passive membrane characteristics, which are mostly caused by its capacitive characteristics, a tiny amount of DC shift is also seen in the passive region. The spike train then moves to the next Node of Ranvier after propagating via the myelinated region. In the second Node of Ranvier, regeneration of the spike train takes occurs due to the availability of the active ion channels (saltatory conduction) as discussed previously. Observing the spike train at the second Node of Ranvier, it is seen that the signal more or less remains intact with very little amount of ionic loss taking place.

When the simulation is undertaken considering a fiber with shorter internodal length i.e., of 50 μm. It is observed that, there is an additional spike getting generated at the second Node of Ranvier which suggests that there is a possibility of information mismatch for a shorter fiber. Because a shorter length between the two Nodes of Ranvier has fewer open channels to facilitate ionic losses, spike encoding changes significantly. As a result, a high amount of current is delivered to the subsequent region of the fiber, resulting in the generation of an extra spike at the second node of Ranvier, which can significantly reduce the signal's information content. Therefore, it may be stated that myelinated fibers have a critical length at which point the information content of the signal is preserved and does not change. It could also be stated that for a longer fiber or longer internodal length, signal attenuation might be higher due to a greater number of open channels resulting in higher leakage of ions, but for a shorter fiber, the possibility of information mismatch might be higher due to the reasons discussed above.

The proposed framework offers a holistic and a robust approach as the ECS dependent parameters are also incorporated into the study which is fundamentally important in understanding nerve signal transmission in detail. In addition, the suggested framework would yield results rapidly and is less sophisticated in terms of mathematically and computationally. Furthermore, the framework could be further expanded to study how length affects neuronal signal transmission for a flared and tapered nerve fiber under the condition of varying ECS.

Publications:

Book chapter:

1. **Das, B**., Baruah, S. M. B., & Roy, S., “Modeling and Simulation of Successful Signal Transmission Without Information Loss in Axon”, Book name (Lecture Notes in Electrical Engineering), Vol. 1061, pp. 397-409, 2023, Springer Nature Singapore, DOI: https://doi.org/10.1007/978-981-99-4362-3_36 (ISBN: 978-981-99-4361-6).