Chapter 6

Study and Modeling on Effect of Extracellular Space on Velocity profile of neuronal signal transmission

The chapter involves investigating the effect of ECS on the conduction velocity of neuronal signal through a mathematical model in which the ECS dependent parameters have been incorporated. The results obtained indicates that the ECS has a significant influence on the conduction velocity in terms of velocity variations, signal delay, and phase shift. In order to mimic a significant number of biological situations, the suggested model has been simulated using various combinations of the ECS and biological nerve characteristics. Since, slow conduction of neuronal impulse is synonymous with various neurological issues. The goal of the study is to understand how the ECS may affect the velocity at which information travel through neurons.

6.1 Introduction

Nerve conduction velocity (NCV), a critical indicator of how fast electrical impulses travel through nerve fibers and is essential to the operation of the nervous system [81], [82], [90], [110]. The velocity at which nerve signals travel is crucial for facilitating quick and effective communication between the brain, spinal cord, and other parts of the body. Variations in NCV may indicate the health of nerve fibers with slower conduction velocity indicating nerve injury or other neuronal disorders. For this reason, determining the degree of nerve dysfunction, diagnosing and tracking neurological disorders, and directing therapy plans to restore normal nerve function, depends on the understanding of and ability to measure the NCV. Fast nerve conduction is particularly important for processes that need fine motor control and fast reflexes, whereas slower conduction might hinder these functions resulting in delayed reactions and possible harm. Thus, NCV is an important indicator in studying nervous system disorder and for clinical assessments.

Slow nerve impulse conduction velocity is an indicator of several degenerative diseases, such as Guillain-Barré syndrome [200], [201], [202], [212], [213], where the immune system of the body attacks the peripheral nervous system usually occurring after an infection such as a respiratory or gastrointestinal disease, this immune response causes inflammation and damages the myelin sheath resulting in a disruption of nerve signals which can lead to tingling, muscle weakness, and occasionally paralysis. Charcot-Marie-Tooth disease which is caused by genetic mutations affecting the peripheral nerves that control movement and sensation [198], [199] and these mutations impair the myelin coating or the nerve fibers themselves which alters the structure and function of the nerves and causes gradual muscle weakening, loss of feeling, and trouble walking. The autosomal dominant gene mutation is the most prevalent way that the disease is inherited while there are other patterns as well. Carpal tunnel syndrome [214], [215], [216] which is associated with the compression of the median nerve while passing through the carpal tunnel of the wrist which often results from repetitive hand movements, fluid retention, injury to the wrist or conditions such as arthritis or diabetes leading to tingling sensation, numbness and weakness in the fingers and hands. Sciatic nerve problems, or sciatica [217], [218] is associated with irritation or compression of the sciatic nerve due to herniated disc, or spine related issues resulting in numbness and weakness that moves from the lower back down through the leg. Multiple sclerosis [131], [132], [133], [138], [141] is associated with the immune system attacking the myelin layer of the nerve fibers especially of the Central Nervous System leading to its damage or inflammation. This results in a range of neurological issues such as coordination issues, vision related issues, difficulty in walking, and cognitive issues. Since these neurological conditions limit a person's natural movement, it is essential to understand the nerve conduction as quickly and effectively as possible.

Studies show that the conduction velocity is significantly influenced by the geometry of the nerve fiber as a fiber with a the greater the diameter offers faster conduction velocity than for a fiber with smaller diameter [89], [90], [105], [219]. this occurs because a fiber with greater diameter offers less resistance to the ions in its forward propagation resulting in a faster velocity. Moreover, the myelin sheath plays a crucial role in enhancing the transmission of neuronal signals, as the myelin layer acts as an insulating barrier, preventing leakage of ions from the nerve fiber towards the external media thereby maintaining the signal strength [87], [100], [106], [220]

The literature has already demonstrated that a larger ECS results in more signal attenuation than a smaller ECS [64]. This is because a larger ECS provides less resistance for the mobile ions to be dissipated towards the external media via the leak channels, which in turn causes a significant reduction in signal strength. A smaller ECS on the other hand, provides more barrier to the mobile ions to get dissipated into the external environment thus enhancing signal strength. Therefore, it is very much essential to fully understand the role of the ECS in influencing the conduction velocity of neuronal signal as the size of the ECS has a major role to play in influencing the signal strength. Thus, to fully comprehend how the ECS might affect the conduction velocity of neuronal signal, it is essential to consider a passive nerve fiber model that could comprehend the passive characteristics such as the impact of the leak channels without involving the complexities of the ion channels. This would enable in developing a broader idea about the impact of the ECS on the conduction velocity of neuronal signal.

6.2 Contribution

The work done involves computing the velocity profile for a passive nerve fiber through a mathematical model which is mathematically and computationally less complex using various combination of parameters pertaining to the nerve fiber and the ECS to develop a view of how the ECS and fiber dynamics influences the conduction velocity of the nerve signal. This study focuses on a passive nerve fiber, allowing emphasis on key factors such as membrane resistance, membrane capacitance, and ECS resistance, which together influence signal attenuation and propagation along the nerve, without the complexities of active ion channel dynamics. Without the complexities of voltage-gated ion channels, this makes it possible to comprehend how these passive characteristics such as the impacts of leak channels and the ECS influence conduction velocity more clearly. The results obtained from this study shows that the ECS has a significant influence on the conduction velocity in terms of critical points, phase shift and delayed reaction.

6.3 Proposed Methodology

The proposed framework shown in Fig.6.1, uses the cable model [91] where the ECS dependent parameters have been incorporated [75]. The individual tank circuit shown in Fig.6.2 is the passive nerve model inspired from Hodgkin and Huxley [17] passive nerve model. The parameters pertaining to the ECS provides a robust approach in analysis of the nerve conduction velocity as a holistic approach would be attained through incorporation of these parameters.

From the Fig.1, using Kirchhoff's voltage law, the potential equations used are given in Eq.1 and Eq.2.

$$\frac{\partial V_i}{\partial x} = -R_i I_i(x) \tag{6.1}$$

And

$$\frac{\partial V_e}{\partial x} = R_e I_e(x) \tag{6.2}$$

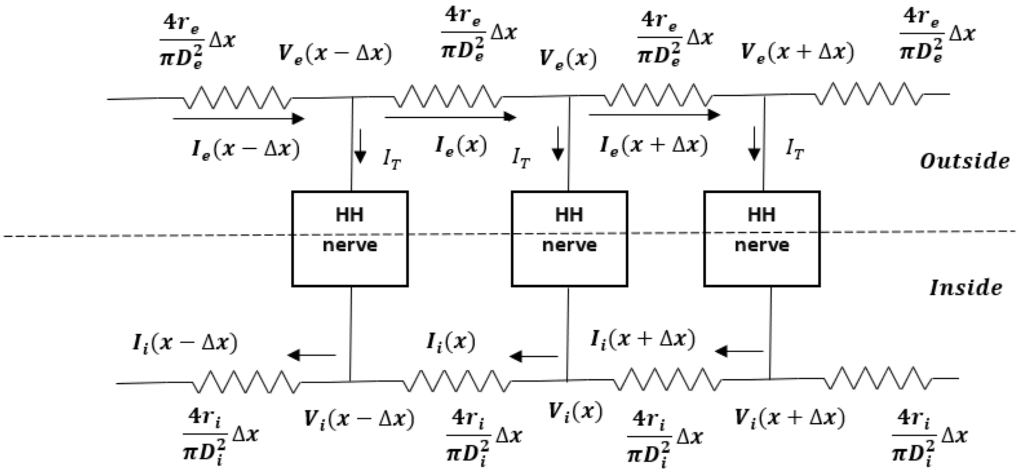

Fig.6.1 Equivalent Circuit of Passive Membrane Model

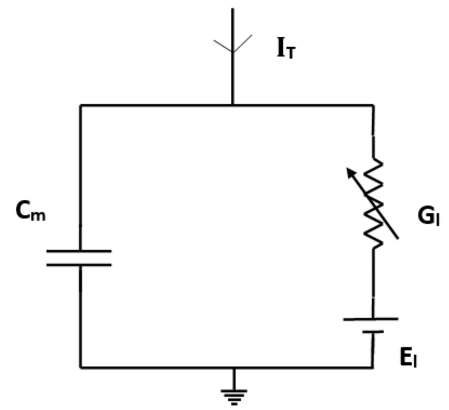

Fig.6.2 Hodgkin-Huxley (H-H) passive nerve

The transmembrane voltage could be obtained from subtracting Eq.2 from Eq.1 which can be shown as,

$$\frac{\partial V_m}{\partial x} = -I_a(R_e + R_i) \tag{6.3}$$

Where, $R_i = \frac{4r_i}{\pi {D_i}^2}\Delta x$ and $R_e = \frac{4r_e}{\pi {D_e}^2}\Delta x$ are the volumetric internal and external resistances that give the overall axial resistance (R_a) and r_e, r_i are the characteristic resistance of the ECS and the nerve fiber [97]. V_i and V_e represents the internal and the external voltages and r_i and r_e represents the characteristic internal and external resistances respectively. I_i, I_e are the internal and external currents which are assumed to be equal in magnitude and can be represented as I_a, which is the axial current. D_i and D_e are the internal diameter and the ECS diameter respectively. The model under consideration is a passive model, thus the transmembrane current (I_T) according to Hodgkin and Huxley can be shown as,

$$I_T = C_m \frac{\partial V_m}{\partial t} + \left(\frac{V_m - E_l}{R_m}\right) \tag{6.4}$$

Here, C_m is the volumetric membrane capacitance which can be expressed in terms of its characteristic membrane capacitance (c_m) as $C_m = c_m \pi D_i l$, E_l is the equilibrium potential of the leakage ions, and R_m is the equivalent leakage resistance which can be expressed in terms of its characteristic resistance as $R_m = r_m \pi D_i l$. Thus, Eq.4, can be rearranged as,

$$\frac{\partial V_m}{\partial t} = \frac{I_T R_m - (V_m - E_l)}{R_m C_m} \tag{6.5}$$

The conduction velocity, V_e could be obtained from dividing Eq.6.5 by Eq.6.3 which is inspired from [110] and can be shown as,

$$\frac{\partial x}{\partial t} = V_e = -\frac{(I_T R_m - (V_m - E_l))}{I_a R_m C_m (R_e + R_i)} \tag{6.6}$$

For a myelinated nerve, the transmembrane current becomes almost negligible and hence, I_T is considered as zero. Hence, Equation. 6 becomes,

$$V_e = \frac{(V_m - E_l) D_e^2}{I_a R_m C_m (R_e + R_i)} \tag{6.7}$$

Now, representing Eq.6.7 by its characteristic parameters or values gives,

$$V_e = \frac{(V_m - E_l) D_e^2}{4 I_a \pi r_m c_m l^3 \left(r_e D_i^2 + r_i D_e^2\right)} \tag{6.8}$$

Where, the axial current I_a, can be shown as,

$$I_a = \frac{(v_{in} - v_m)(\pi D_e^2 D_i^2)}{4 r_e l D_i^2 + 4 r_i l D_e^2} \tag{6.9}$$

Eq.6.8 represent the proposed mathematical expression for the conduction velocity in which the ECS dependent parameetrs are incorporated. In this work, Eq.6.8 is simulated for various combination of the fiber parameters and the ECS parameters to obtain the desired results. The relationshipt between the conduction velocity (V_e), and the diameter of the ECS (D_e) suggests that, for a small value of D_e, the conduction velocity (V_e) grows and for a larger D_e, the conduction velocity decreases accordingly.

6.4 Simulation Considerations

The length (l) of the fiber is considered to be 100 µm, the length is so considered as small axons typically fall within this range and the value could capture physiological behaviour while also being computationally viable. The resting membrane potential is considered to be -60 mV. The leakage conductance (g_l) is considered to be 0.0003 Siemens /cm^2 and the characteristic membrane potential (c_m) is considered to be 1µF/cm^2. The equilibrium potential for leakage ions (E_l) is considered to be -49 mV and the simulation is conducted on MATLAB platform. The fundamental values used for the simulation has been considered from H-H equation given in [17].

6.5 Results and Discussions

This section presents a detailed discussion on the results generated based on the implementation of the proposed framework. The results are generated by keeping certain parameters constant and the other varied to understand how different combination of fiber anatomy and the size of the ECS influences neuronal signal. The main aim towards this study is to understand how different combinations of the size of the ECS and fiber anatomy can influence conduction velocity of neuronal signals. Since, it is understood that the ECS that surrounds a nerve fiber has a crucial role in influencing neuronal signal transmission, it also becomes essential in understanding how the ECS affects the velocity of signal transmission. To achieve this, mathematical modeling and simulation method is used which is efficient and also computationally and mathematically less complex.

6.5.1 Velocity Profile for a Uniform Fiber with Varying Extracellular Space

In this section, the nerve fiber is considered to be of a constant diameter i.e. of 5 µm and the length of the fiber is considered to be of 100 µm respectively. The diameter of the ECS is varied for each observation which are at 50 nm, 80 nm, 110 nm, and 140 nm. The resultant plot for the velocity profile generated using Eq.6.8 with the above mentioned conditions is shown in Fig.6.3 and the same plot in the logarithmic scale is shown in Fig.6.4 respectively.

Fig.6.3 shows the velocity profile for a fiber for a constant length, constant diameter and a varying ECS for each observation and Fig.6.4 represents the same plot in the logarithmic scale for better visualization. Observing Fig.6.3, it can be said that for a larger ECS, the conduction velocity is lesser (magenta plot) and for a smaller ECS, the conduction velocity is higher (blue plot). This is so observed due to the influence of the ECS over the nerve fiber as

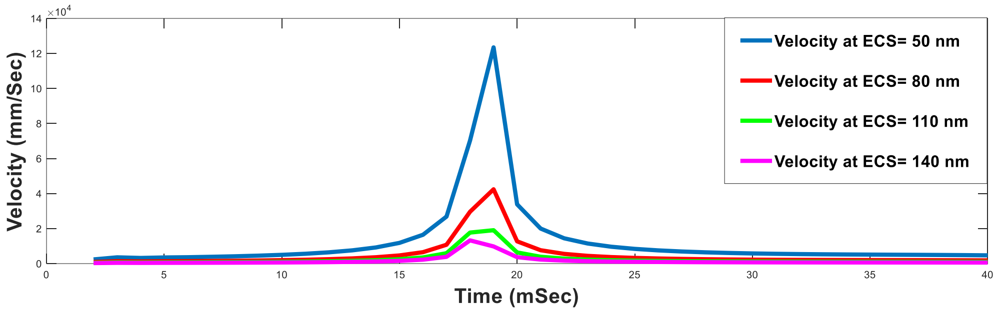

Fig.6.3 Velocity profile for a fiber of constant diameter, constant length and increasing Extracellular Space for each observation

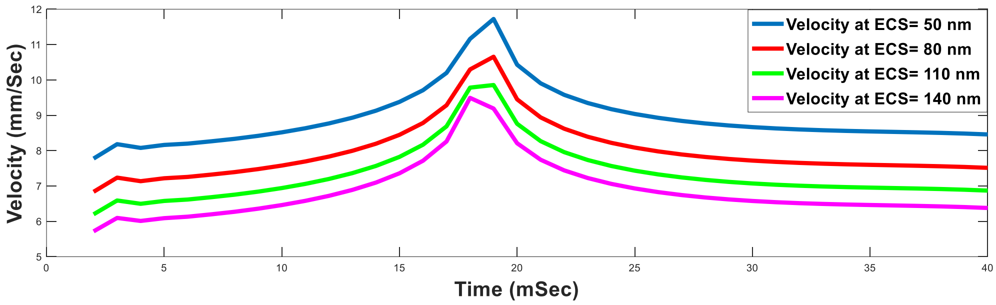

Fig.6.4 Velocity profile for a fiber of constant diameter, constant length and increasing Extracellular Space for each observation in Logarithmic scale

a larger ECS facilitated more leakage of mobile ions to the external media due to its reduced resistivity causing more signal attenuation. This decreased strength eventually contributing to the decrease in conduction velocity of the neuronal signal. Moreover, the opposite is observed when the size of the ECS is considered to be smaller under same fiber anatomy. Here, it is seen that due to the smaller size of the ECS, there is a hindrance to the leakage of the mobile ions to the external media which eventually preserves the strength of the signal resulting in an increased in the conduction velocity. Thus, from the above observation it can be said that larger the ECS less is the conduction velocity and vice-versa.

6.5.2 Velocity Profile for a Fiber with varying internal Diameter

In this section, the length of the fiber and the size of the ECS are kept constant which are at 100 μm and 50 nm, but the diameter of the fiber is varied for each observation which are at 5 μm, 6 μm, 7 μm, and 8 μm respectively. The sets of diameters are meticulously selected to illustrate the relationship between conduction velocity and fiber diameter. The resultant plot for the velocity profile generated using Eq.6.8 with the above-mentioned conditions are shown in Fig.6.5 and the same plot in logarithmic scale is shown in Fig.6.6.

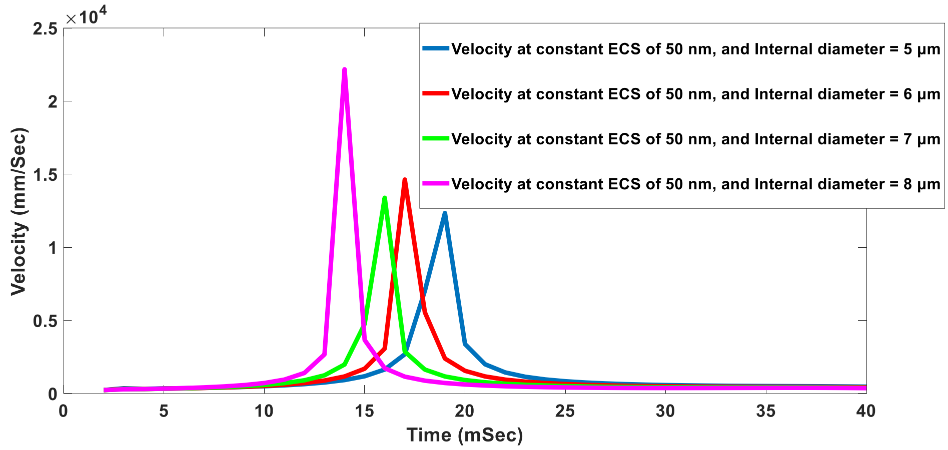

Fig.6.5 Velocity profile for a fiber of varying internal diameter, constant length and a constant Extracellular Space

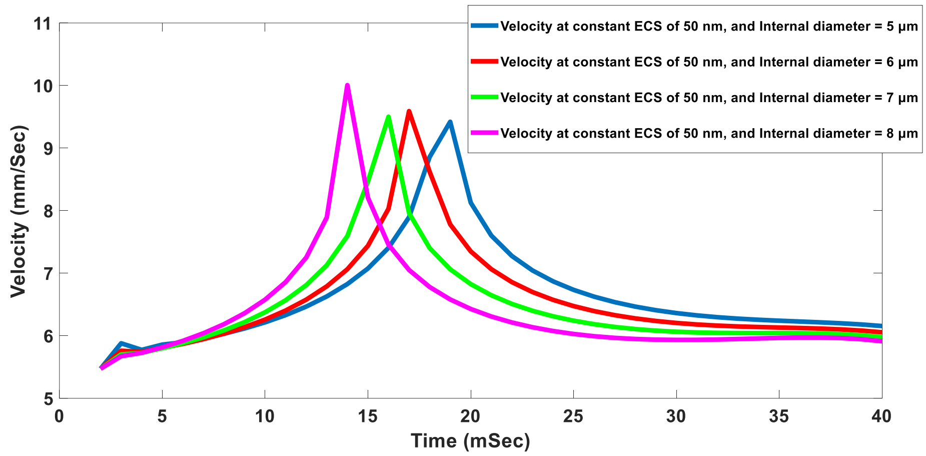

Fig.6.6 Velocity profile for a fiber of varying internal diameter, constant length and a constant Extracellular Space in Logarithmic scale

Fig.6.5 shows the velocity profile for a fiber for a constant length, constant ECS and a varying diameter of the fiber for each observation and Fig.6.6 represents the same plot in the logarithmic scale for better visualization. It can be seen from Fig.6.5 that the conduction velocity is found to be directly proportional to the fiber diameter i.e., for a fiber with greater diameter (8 µm) the velocity reaches the point of observation quicker (about 13 mSec), this matches the general understanding that larger the fiber diameter, greater is the conduction velocity. However, it is also seen from Fig.6.5 that when the diameter of the fiber is 6 µm (red plot), there is a sudden spike in the velocity and also there is a delayed reaction to the velocity spike. This observation suggests that there are certain critical points where the conduction velocity marginally increases, and these points are found to be located at uniform duration. The observations made from section 6.5.2 suggests that the impact of the ECS is such that it can induce slower response on one occasion and faster on the other. Moreover, these critical points induce a phase shift to the signal that results in the velocity to reach at different instance of time.

6.5.3 Velocity Profile for a Fiber with varying Fiber Length

In this section, the diameter of the fiber and the size of the ECS are kept constant at 1.5 µm and 50 nm respectively. The length of the fiber is varied for each observation i.e., at 50 µm, 53 µm, 62 µm, and 80 µm respectively. The sets of fiber length are meticulously selected to illustrate the relationship between conduction velocity and the length of the fiber. The resultant plot for the velocity profile generated using Eq.6.8 with the above-mentioned conditions are shown in Fig.6.7 and the same plot in logarithmic scale is shown in Fig.6.8.

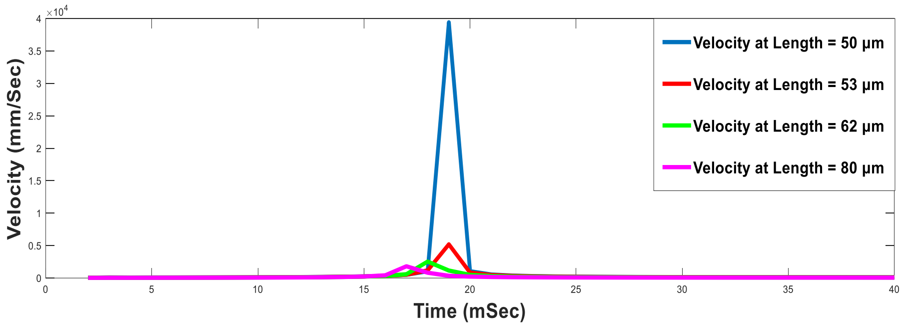

Fig.6.7 Velocity profile for a fiber of constant internal diameter, constant ECS and varying length of fiber

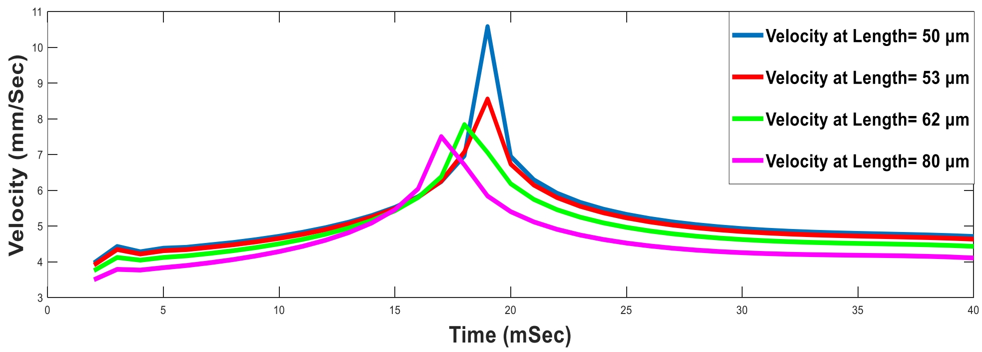

Fig.6.8 Velocity profile for a fiber of constant internal diameter, constant ECS and varying length of fiber in Logarithmic scale

It is seen from Fig.6.7 that as the length of the fiber increases, the conduction velocity decreases; this phenomenon is true for a passive nerve fiber due to the phenomenon of decremental conduction of nerve fiber where the amplitude of the propagating signal reduces during its forward propagation. However, it is also observed from Fig.6.7 that when the length is 50 µm and 53 µm, the conduction velocity reaches the observed point at different instance of time and with different amplitude of velocity. Furthermore, for the length 62 µm and 80 µm, the amplitude of the velocity is lower but reaches the observed point faster. This instances further suggests that there exist certain critical points where the conduction velocity spikes a little similar to observations made from section 6.5.2. This instances further suggests that the influence of the ECS is such that it can cause faster conduction velocity on one occasion and slower on the other. These critical points induce a phase shift to the propagating signal resulting in the velocity to reach the observed point at different instance of time.

6.5.4 Velocity profile for varying internal diameter, varying length of the fiber

In this section, the diameter of the fiber and the length of the fiber are varied for each observation and the size of the ECS is kept constant at 50 nm. The diameter of the fiber are considered to be of 1.5 µm, 1.9 µm, 2.9 µm, 4.9 µm and 6 µm; whereas the length of the fiber are considered to be of 50 µm, 65 µm, 80 µm, 95 µm and 100 µm respectively. The resultant plot for the velocity profile generated using Eq.6.8 with the above-mentioned conditions are shown in Fig.6.9.

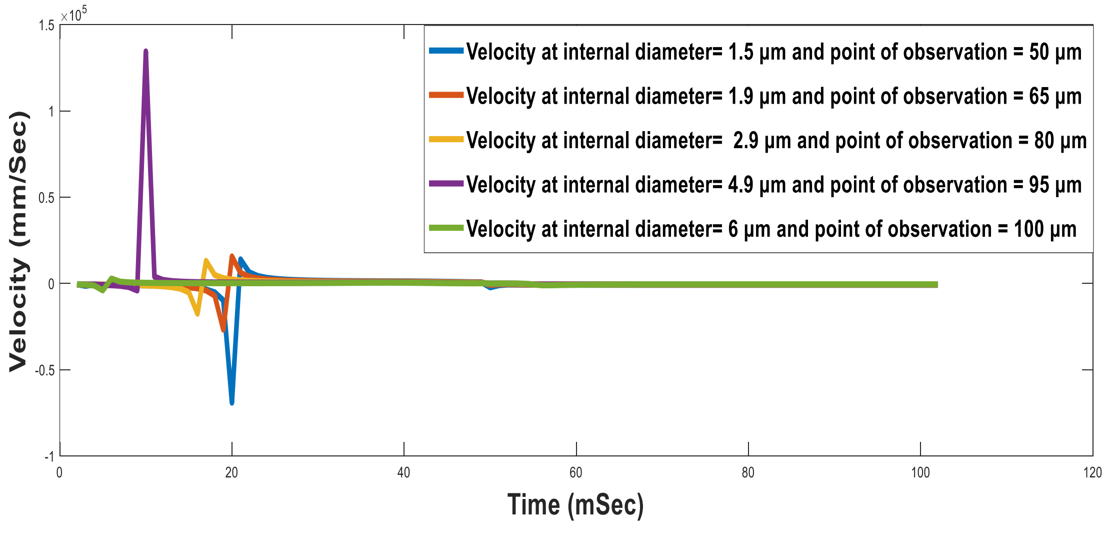

Fig.6.9 Velocity profile for a fiber of varying internal diameter, varying length of a fiber, and a constant Extracellular Space

Observing Fig.6.9, it can be seen that when the diameter of the fiber is 6 µm and the point of observation at length is 100 µm, the conduction velocity reaches faster i.e. at 8 mSec than for a fiber with a smaller diameter and length, but its amplitude is significantly lower. This occurs because of the larger fiber offering less resistance to the axial or forward flow to the ions, fastening the conduction velocity. This reaction delay results in the phase of the propagating signal to be shifted. It is understood that the conduction velocity exponentially decreases with fiber length, however observing Fig.6.9, it is seen that the velocity is maximum when the diameter of the fiber is 4.9 μm and the length is at 95 μm. This suggests that there must exist certain critical points for different combination of the membrane resistance, membrane capacitance, membrane conductance and the ECS which affects the signal significantly. These critical points induce a phase shift to the propagating signal that causes reaction delay. This observation has also been in section 6.5.2 and section 6.5.3 respectively.

6.5.5 Conduction velocity with respect to the changing Extracellular Space (ECS)

The pattern of conduction velocity with respect to the changing ECS is shown in Fig.6.10. this plot shows that the conduction velocity decreases with increasing size of the ECS with the occasions of the velocity spiking at certain critical points which are distributed uniformly.

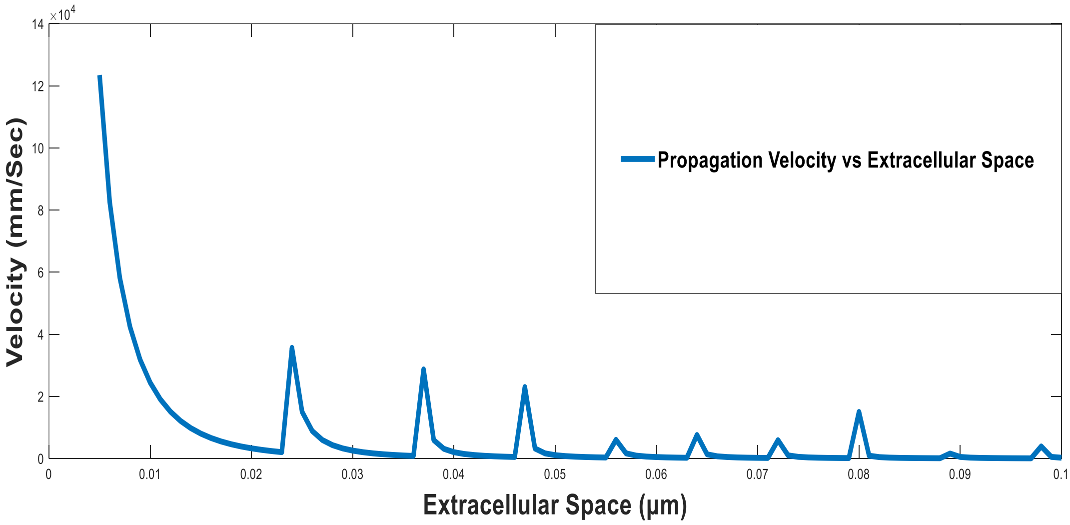

Fig.6.10 Velocity vs Extracellular space with the velocity spiking at certain critical points

The conduction velocity is significantly influenced by the time constant; a high time constant indicates an accumulation of ions in the region, which increases the settling time; a low time constant indicates ion dissipation that reduces the time constant. It is evident from the velocity equation given in Eq.6.8 that there are multiple time constants, namely those induced by the membrane's parameter, the membrane-to-Extracellular Space parameter, and the intracellular-to-membrane parameter. The model thus suggests that the conduction velocity significantly depends on the mentioned time constants. Therefore, as seen in Fig.6.10, there are critical points where the propagation velocity resonates and occasionally causes an increase in the conduction velocity due to changes in the membrane-to-extracellular time constants for various combinations of membrane capacitance, membrane conductance, membrane resistance, and ECS resistance.

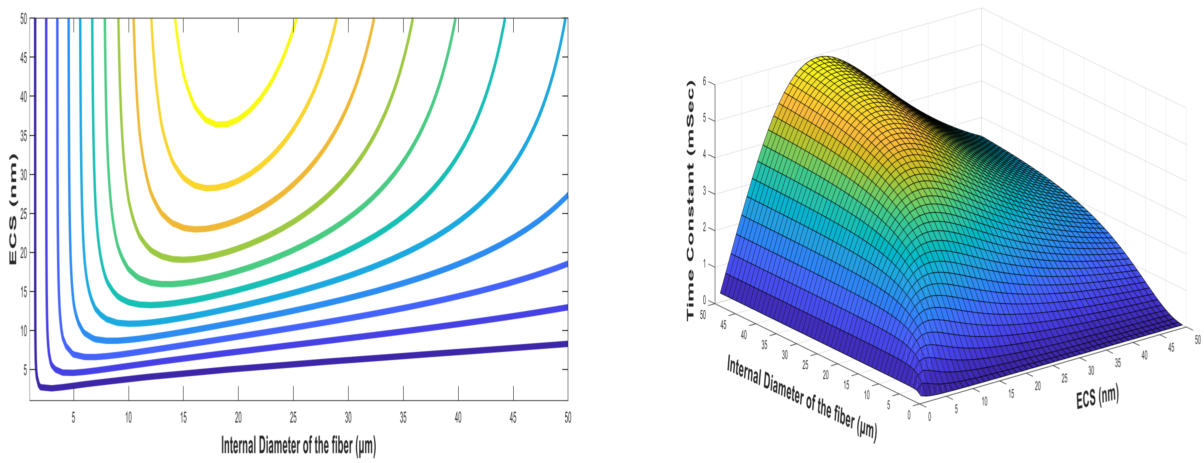

Fig.6.11(a) Change in time constant with the variations in internal diameter and ECS size (b) Change in time constant with the variations in internal diameter and the size of ECS

The initial trend seen in Figure 6.10 also implies that the amplitude of the conduction velocity is influenced by the size of the ECS, with a bigger ECS leading to a drop in conduction velocity and vice versa. However, there are a few critical points where there is a minor increase in the velocity and these points are found to be produced at uniform duration. Furthermore, the contours in Fig.6.11(a) and Fig.6.11(b) also show that these points exist on the contours that are roughly equally spaced apart while moving horizontally, vertically, or diagonally along the axis. The various combinations of the fiber anatomy and ECS used for this study is shown in Table 6.1. The study shows that the conduction velocity of neuronal impulse is significantly dependent on the interaction of various factors such as the structural parameters of the nerve fiber like the fiber diameter, length of the fiber, and the diameter of the ECS that surrounds the nerve fiber. The intricate relation between the fiber anatomy and the ECS plays an important factor in shaping velocity of the neuronal signal as observed from the study. Understanding these dependencies could provide many insights into the biological processes and implications for nerve related disorders especially for targeting issues that are related to the conduction velocity of neuronal impulses.

Table 6.1: Different combinations of the fiber anatomy and the ECS used for the study

Section	Figures	Parameters	
		Kept Constant (Fixed)	**Varied**
6.5.1	6.3 and 6.4	Length of the fiber, Internal Diameter of the fiber	Diameter of the ECS
6.5.2	6.5 and 6.6	Diameter of the ECS, Length of the fiber	Internal Diameter of the fiber
6.5.3	6.7 and 6.8	Diameter of the ECS, Internal Diameter of the fiber	Length of the fiber
6.5.4	6.9	Diameter of the ECS	Length of the fiber, Internal Diameter of the fiber

6.6 Summary and Future remarks

In order to acquire an in-depth understanding of the velocity profiles of neuronal signals, the suggested framework has been established by altering the well-known cable model by including the parameters of the ECS since the ECS has a significant influence on the neuronal signal transmission. The result obtained from the proposed study suggests that the proposed framework is effective and is computationally and mathematically less complex. This study suggests that there exist certain critical points where the conduction velocity may spike a little making the velocity to reach the point of observation at different instance of time.

The results also suggests that the conduction velocity decreases with larger ECS and vice-versa, this is because a larger ECS offers less resistance to the mobile ions to get dissipated towards the external media through the leak channels, resulting in a weaker signal and slower velocity; the opposite is also observed for a fiber which is surrounded by a smaller ECS which is consistent with the general understanding regarding the size of the ECS and its influence over the neuronal signal.

It is already understood that fiber anatomy plays a significant role in in influencing conduction velocity, as a fiber with larger diameter tend to have higher conduction velocity than for a fiber with lower diameter. In this study however, it is seen that when the ECS parameters are taken into consideration then certain combination of the fiber diameter and the size of the ECS results in the conduction velocity to spike up which suggests that there exist certain critical points where velocity spikes and these points are generated at uniform duration. Conduction velocity also gets affected by the length of the fiber and the results generated form the study also confirms this. It is seen form this study that the conduction velocity drops as the length of the fiber increases. This is basically due to the decremental conduction of signal where the signal strength decreases as the length of the fiber increases.

Another finding from this study shows that there occurs a phase shift to the propagating signal resulting due to the delay created by the effect of the non-homogeneous ECS. The effect of the ECS is such that it may cause faster response on one occasion and slower on the other.

As this work indicates, the link between conduction velocity, ECS, and fiber diameter is complex and not straightforward. According to the findings, different combinations of fiber structure and ECS size can result in different neuronal signal transmission results. This study sheds light on a crucial component of neural transmission by showing how variations in fiber structure and ECS dimensions can have a significant effect on how signals propagate.

The velocity equation shows that there exist multiple time constants related to the membrane, intracellular-to-membrane, and membrane-to-Extracellular Space as seen from the velocity equation and the conduction velocity is highly dependent on these time constants. Therefore, there are certain critical points where the propagation velocity resonates, causing a slight increase in conduction velocity as well as a delayed or faster response of the velocity, with changes in membrane-to-extracellular time constants for various combinations of membrane capacitance, membrane conductance, membrane resistance, and ECS resistance.

Thus, it can be said that there might be multiple arrangements of fiber bundles depending on the signal transmission and function formation and this kind of arrangement might be achieved during the developmental phase of the dendritic arbors during dendritic growth, rearrangement, and decay.

The velocity profiles generated using the proposed model show some key insights without much mathematical or computational complexities. Thus, it can be said that the proposed framework could be useful in understanding the effect of the ECS on nerve conduction velocity in much deeper manner since the proposed framework involves the ECS related parameters to obtain the velocity equation. The proposed model could be extended towards studying nerve conduction velocity for an active nerve fiber and also in studying various neurological issues that are synonymous with slow conduction velocity of neuronal signal and also could help in its therapeutic cures.

Publications:

Journal:

1. **Das, B.,** Baruah, SMB., Bhattacharyya, DK & Roy, S., “An Effective Framework to Study Signal Transmission due to Non-Homogeneous Extracellular Space in Neuron”, Journal name (Journal of Biological Physics), Springer (Scopus, SCIE), (Under Review).