Journal of Electronics, Electromedical Engineering, and Medical Informatics
Multidisciplinary: Rapid Review: Open Access Journal **Vol. 6, No. 2, April 2024, pp: 206-218; eISSN: 2656-8632**

RESEARCH ARTICLE **OPEN ACCESS**

Manuscript received February 10, 2024; revised February 26, 2024; accepted April 10, 2024; date of publication April 20, 2024
Digital Object Identifier (**DOI**): https://doi.org/10.35882/jeeemi.v6i2.394

How to cite: Biswajit Das, Satyabrat Malla Bujar Baruah, Sneha Singh, and Soumik Roy, Insights into Nerve Signal Propagation: The Effect of Extracellular Space in Governing Neuronal Signal for healthy and injured Nerve Fiber using Modified Cable Model, Journal of Electronics, Electromedical Engineering, and Medical Informatics, vol. 6, no. 2, pp. 206-218, April 2024.

Insights into Nerve Signal Propagation: The Effect of Extracellular Space in Governing Neuronal Signal for healthy and injured Nerve Fiber using Modified Cable Model

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ABSTRACT Nerve injuries are complex medical conditions that may arise from a variety of traumatic events or diseases, altering the intricate structure of neural pathways. During neuronal injury, the potassium and sodium ion concentration that controls signaling endures significant changes such as the ion channels getting blocked or an increase in the intracellular ionic concentration. The Extracellular Space which surrounds a nerve fiber has a significant impact on the neuronal signal and variation in its size can alter neuronal signal transmission. Hence, to fully understand neuronal signal transmission, it is essential to explore the effect that the Extracellular Space exerts on the neuronal signal. The aim of this study is to develop a mathematical model which yields a simplistic yet robust mathematical expression of the nerve membrane potential, incorporating the Extracellular Space dependent parameters for having a holistic approach towards understanding neuronal signal transmission in healthy and injured nerve fiber. The conventional cable model focuses solely on the intrinsic properties of the nerve fiber, but the current work expands this model by incorporating the Extracellular Space dependent parameters into the final membrane potential expression. The results obtained from this study shows that certain combination of the Extracellular Space and fiber diameter could bring about hyperexcitation whereas in some cases it may lead to hypoexcitation to the neuronal signal as it propagates along the nerve fiber. Moreover, prolonged refractory period and delayed refractory period are also observed in certain combination of the Extracellular Space and fiber diameter. The proposed framework manages to show trends associated with certain medical conditions and may also be useful to further understand, and early diagnosis of various neurological conditions under the effect of an Extracellular Space of varied sizes.

INDEX TERMS Extracellular Space, Information loss, Information mismatch, Ion concentration, Modified Cable Model; Neuronal signal transmission

I. INTRODUCTION

Neurons send and analyze electrical signals that drive our thoughts, emotions, and actions. Extracellular Space or the ECS that surrounds neurons is as important as their inner workings. The brain's cerebrospinal fluid flow, glial cell support and modulation, and neuronal metabolic activity all have an impact on the dynamic and highly controlled ECS. Studies have shown that the ECS's composition affects neuronal excitability, synaptic transmission, neural circuit function, cognition, behavior, and disease states [1][2]. Moreover, the size of the ECS has an important role to play in governing the neuronal signal. A larger Extracellular Space allows for greater mobility of ions from the fiber to the extracellular medium than a smaller one. Since a larger Extracellular Space has a lower resistivity, it increases the mobility of ions from the fiber to the external medium [1], [2], [3][4] resulting in attenuation of signal due to this leakage of ions towards the external medium.

The ECS with thickness ranging in the nanometer scale is found to occupy about 20 % of the brain tissue and its resistive properties are essential for the generation of the extracellular potential also known as the Local Field Potential [1]. Moreover, during neurological conditions such as ischemia and cortical spreading depression (CSD), shrinkage of the ECS by about half of its initial volume is also observed [5]. Studies have also shown that, during edema (brain swelling), the size of the ECS has been found to increase [6]. The ECS can be an effective tool for drug delivery in the brain during treatment such as chemotherapy [7]. Thus, it can be inferred that ECS is an important mechanism that can affect nerve signal transmission and variation in its size can help in predicting various neurological conditions and the ways to tackle them.

Several factors, including trauma, ischemia, neurodegenerative diseases, and toxic exposure, can cause neuronal damage [8], [9], [10], [11], [12]. When neurons are

injured, a series of events are triggered, leading to cellular dysfunction and, in extreme cases, neuronal mortality. The disruption of potassium (K+) and sodium (Na+) ion concentrations, which are essential for maintaining the normal functioning of neurons, is one of the primary effects of neuronal injury [12]. Any injury to the nerve fiber may lead to ion channel blocking or may also induce increased ion concentration.

The normal operation of ion channels can be interfered due to nerve damage, leading to sensory or motor impairments. Ion channels may be redistributed as a result, which may reduce their responsiveness or cause them to group in unusual manners. These modifications may have an impact on the regular inflow and outflow of potassium and sodium ions during an action potential which may ultimately result in decreased nerve conduction [13].

Blocking of sodium ion channels can lead to the reduced ability of neurons to generate an action potential while potassium ion channel blocking can prolong the duration of an action potential [14][15], [16], [17].

Hubel et al. in their work [12] have shown that large Extracellular Space in the upper brain regions impairs Na+/K+–exchange pumps so that they function at a lower-than-normal capacity and are unable to bring the cell out of anoxic depolarization (AD) once oxygen and glucose are restored, nonetheless, its underlying cause has not yet been uncovered. Their result suggests that Na+/K+ATPase must function at 15 times the physiological rate during ischemia to let cells recover from AD. Wang-Mi Liu et al. [18] suggested that the secondary pathology of spinal cord injury is intricate and entails disruptions in the homeostasis of potassium, sodium, and calcium ions. Mori et. Al [19] have shown in their study that Ischemic cellular swelling (decreased ECS) occurs concurrently with phase 1 potassium ion increase but before phase 2 ionic membrane homeostasis disturbance and mild hypothermia delays these events but does not impact ECS or ion concentrations. Thus, from the mentioned literature it can be deduced that ECS swelling or increase in its size has a substantial role in governing neuronal signal transmission.

Existing literature emphasizes the importance of Extracellular Space (ECS) in neuronal signal transmission, which is overlooked by the conventional cable model, which only focuses on the intrinsic features of the nerve fiber. The current study includes incorporating the ECS dependent parameters in addition to the intrinsic fiber properties into the traditional cable model to obtain a simplistic yet robust mathematical expression for nerve membrane potential for comprehensive understanding of neuronal signal transmission which would be less computationally complex, cost effective, and can be used for rapid prototyping.

As the mathematical model effectively analyzes the passage of electric currents and voltages between adjoining sections in a nerve fiber, it can be viewed as the corresponding electrical circuit equivalent of a nerve fiber. The current investigation is based on the observation that the transmission of neuronal signal for a healthy and injured nerve fiber strongly depends upon the size of the ECS and the variation in its size can play a crucial role. The idea of the study is to have a generalized view on the subject which would help in providing an overall understanding of how the ECS affects neuronal signal transmission. The following are the contributions of this work.

1. A simplistic yet robust framework which yield a mathematical expression of the nerve membrane potential that can properly replicate the working of a nerve fiber, incorporating the fundamental parameters of the Extracellular Space (ECS) to have a holistic approach in understanding neuronal signal transmission in healthy and injured nerve fiber that would be less computational complex, cost efficient, and can be used for rapid prototyping.

2. An exhaustive experimentation with various combinations of electrophysiological parameters of the Extracellular Space (ECS) and biological nerve fiber to simulate many biological circumstances which provide valuable understandings about the functions of the Extracellular Space (ECS) and how it can influence neuronal signal transmission in healthy and injured nerve fiber.

III. PROPOSED METHODOLOGY AND EQUATIONS

The individual tank circuit given in FIGURE 1(a) is inspired from the traditional Hodgkin and Huxley membrane model [20] shown in FIGURE 1(b) that successfully justifies its equivalence with a nerve fiber. Calcium dynamics has been neglected in the study as it would only slightly change gating dynamics since calcium currents have little direct effect. However, a model for neurotransmitter release and synaptic communication should account for calcium dynamics.

In this study, the active nerve membrane is analyzed, and the changes in ionic composition that occur during injury and in healthy condition in a nerve fiber are investigated by varying the ionic concentrations. Moreover, the variation in the size of the ECS and its effect on healthy and injured fiber are also analyzed in this work.

From FIGURE 1(a), using the Kirchhoff's voltage law, the potential equation can be deduced as,

$$\frac{\partial V_i}{\partial x} = -R_i I_i(x) \quad (1)$$

And

$$\frac{\partial V_e}{\partial x} = R_e I_e(x) \quad (2)$$

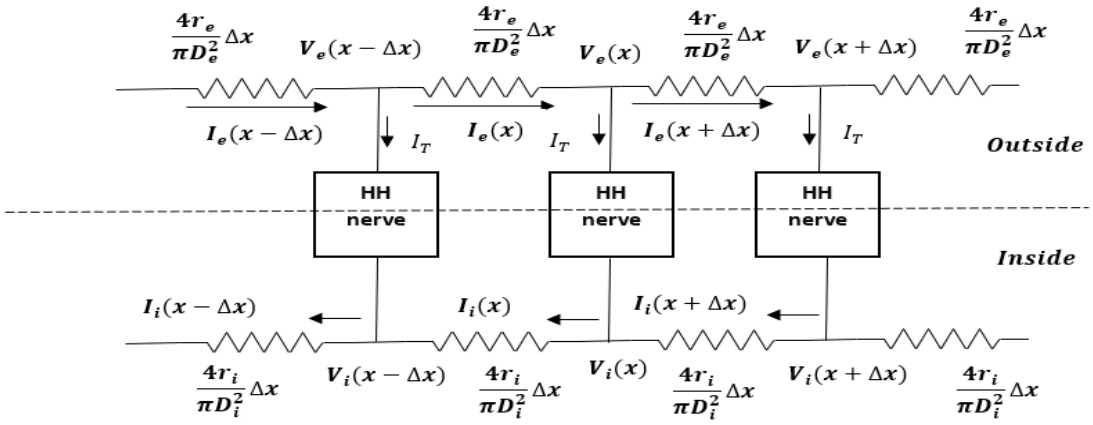
Since transmembrane potential is obtained by subtracting (1) from (2) that is V_e-V_i =V_m, is shown as,

$$\frac{\partial V_m}{\partial x} = I_a(R_e + R_i) \quad (3)$$

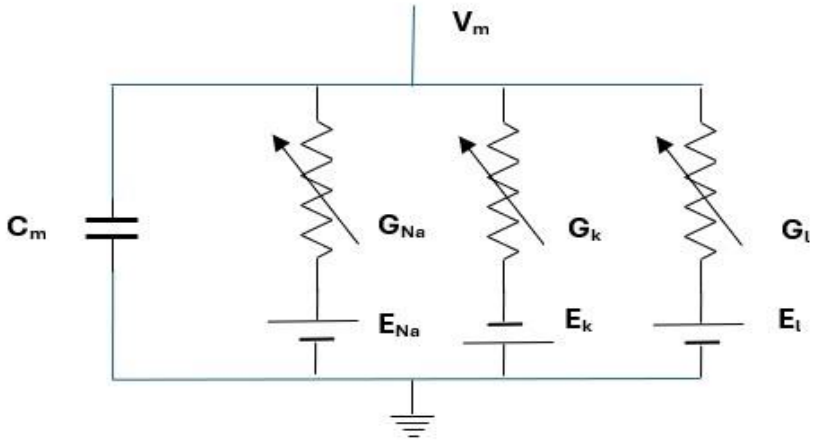
Here, (3) gives the transmembrane potential with respect to distance x. Since, $\frac{\partial I_a}{\partial x}$ gives the transmembrane current, I_T. Thus, we have differentiated (3) with respect to x, the expression obtained is

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{\partial I_a}{\partial x}(R_e + R_i) \quad (4)$$

In (4), I_a is the axial current, $R_e = \frac{4r_e}{\pi {D_e}^2}\Delta x$ and $R_e = \frac{4r_e}{\pi {D_e}^2}\Delta x$ are the volumetric internal and external resistance which together



(a)



(b)

FIGURE 1. (a) The cable model, (b) Hodgkin-Huxley (H-H) nerve

gives the overall axial resistance. V_i, V_e and r_i, r_e are the internal and the external voltages and characteristic internal and external resistances respectively. I_i and I_e are the internal and external currents and D_i, D_e are the internal diameter and the Extracellular Space diameter respectively. Rearranging (4), the equation obtained is,

$$\frac{\partial^2 V_m}{\partial x^2}\left(\frac{1}{R_e+R_i}\right) = I_T \qquad (5)$$

where, $\frac{\partial I_a}{\partial x} = I_T$ is the transmembrane current for an active nerve which was expressed by Hodgkin-Huxley membrane equation given in [20] as,

$I_T = C_m \frac{\partial V_m}{\partial t} + I_{Na} + I_k + I_l$, this equation can be further expanded as,

$$I_T = C_m \frac{\partial V_m}{\partial t} + G_{Na}(V_m - E_{Na}) + G_k(V_m - E_k) + G_l(V_m - E_l) \qquad (6)$$

Here, C_m is the overall membrane capacitance given by the expression $C_m=c_m\pi D_i l$ [21]. Where, c_m is the characteristic membrane capacitance, I_{Na}, I_k, and I_l are the currents due to sodium, potassium, and leakage ions. G_{Na}, G_k and G_l are the equivalent conductance's of sodium, potassium, and the leakage ions respectively. Moreover, E_{Na}, E_k and E_l are the equivalent potentials of sodium, potassium, and leakage currents which are suggested in [20].

Hodgkin and Huxley proposed that potassium conductance takes the form $g_K n^4$, where n is the potassium activation variable and g_k is the maximum potassium conductance. The sodium conductance is given by $g_{Na}m^3h$, where m^3 and h are the activation variable and activation state variable for sodium and g_{Na} is the maximum sodium conductance respectively.

To represent the changes in ionic conductance caused by nerve damage, the values of g_{Na} and g_k were changed in this experiment to produce the appropriate outputs. The Hodgkin-Huxley parameters can be shown as [20],

$$\frac{dn}{dt} = \propto_n (V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \propto_m (V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \propto_h (V_m)(1-h) - \beta_h(V_m)h,$$

where I is the current per unit area,

$\propto_i$ and β_i are rate constants for the i-th ion channel that depends on voltage but not time , $\overline{g_n}$ is the maximal value of the conductance 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 and are represented by Boltzmann equations as functions of V_m. By H-H, the functions α and β are given by [20]:

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

$$\propto_h (V_m) = 0.07 \exp\left(\frac{V_m+60}{-20}\right),$$

$$\beta_n(V_m) = 0.125\exp\left(\frac{V_m+60}{-80}\right)$$

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

Putting (6) in (5), the resultant expression obtained is,

$$\frac{\partial^2 V_m}{\partial x^2} - [C_m(R_e+R_i)\frac{\partial V_m}{\partial t} + (R_e+R_i)G_{Na}(V_m - E_{Na}) + (R_e+R_i)G_k(V_m - E_k) + (R_e+R_i)G_l(V_m - E_l)] = 0 \quad (7)$$

Considering the region of the fiber to be equipotential, i.e., $\frac{\partial V_m}{\partial x} = 0$, and I_{inj} is the injected current into the system then (7) gets converted into,

$$-[C_m(R_e+R_i)\frac{\partial V_m}{\partial t} + (R_e+R_i)G_{Na}(V_m - E_{Na}) + (R_e+R_i)G_k(V_m - E_k) + (R_e+R_i)G_l(V_m - E_l)] + I_{inj} = 0 \quad (8)$$

Therefore, rearranging (8), the resultant membrane potential can be represented as,

$$\partial V_m = \frac{\partial t}{C_m(R_e+R_i)}[I_{inj} - (R_e+R_i)(G_{Na}(V_m - E_{Na}) + G_k(V_m - E_k) + G_l(V_m - E_l))] \quad (9)$$

Hence, (9) can be rewritten in terms of the ionic currents as,

$$\partial V_m = \frac{\partial t}{C_m(R_e+R_i)}[I_{inj} - (R_e+R_i)(I_{Na} + I_k + I_l)] \quad (10)$$

Equation (10) is final expression for nerve membrane potential which is used to obtain the simulation results. Here, (R_e+R_i) which is the axial resistance is a combination of both the internal resistance of the fiber and the resistance of the ECS. Thus, the above model unique as it manages to successfully incorporate ECS dependent resistivity term into the final membrane potential expression of the standard cable model allowing for the analysis of the Extracellular Space's impact on the propagation of neuronal signals with minimal mathematical and computational complexity.

IV. RESULTS

For analysis purpose, GNU Octave is used, and (10) which consists of the ECS related parameters is simulated using the standard parameters. The simulation parameters for the model are listed in TABLE I which are derived from standard Hodgkin-Huxley model [20].

TABLE 1
Simulation parameters

Symbol	Quantity	Values
L	Length of the fiber	80 µm
D_i	Diameter of the fiber	5 µm
Vm	Resting membrane potential	-60 mV
cm	Characteristic membrane capacitance	1 µF/cm^2
E_{Na}	Equivalent potential of sodium ion	55 mV
E_k	Equivalent potential of potassium ion	-72 mV
E_l	Equivalent potential of leakage ion	-49 mV
g_l	Leakage conductance	0.3 m.mho/cm^2
g_{Na}	Sodium conductance	120 m.mho /cm^2
g_k	Potassium conductance	0.36 m.mho /cm^2

A. SPIKE TRAIN FOR A HEALTHY NERVE FIBER

Initially, a spike train is generated using (10) here the size of the ECS of 50 nm**.** The generated spike train when it propagates to a distance of 80 µm along the nerve fiber is shown in FIGURE 2 which is used as a reference and the subsequent plots which are obtained further in this study are analysed by comparing them to the spike train obtained in FIGURE 2. The common H-H parameters are used to obtain the action potential spike train.

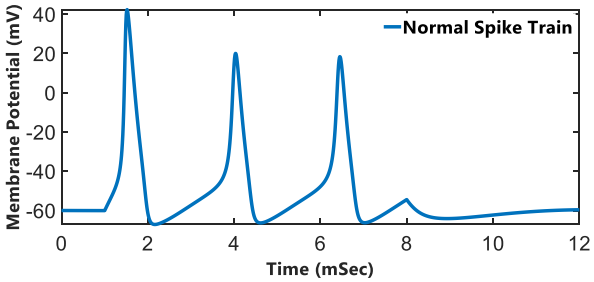


FIGURE 2. Normal Spike train

It can be seen in (2) that the initial spike has an amplitude of about 42.34 mV and the subsequent spikes have a slightly lesser amplitude which are 20.02 mv and 18.37 mv respectively. This is true as any neuronal signal undergoes decremental conduction as it travels down the fiber [22][23], [24] which is the phenomenon wherein an electrical signal weakens as it passes through a nerve fiber. Thus, the model validates the decremental conduction of neuronal signal appropriately. It is already understood that variation in the size of ECS has a significant impact on the neuronal signal as a larger ECS tends to decrease the strength of neuronal signal significantly in comparison to a

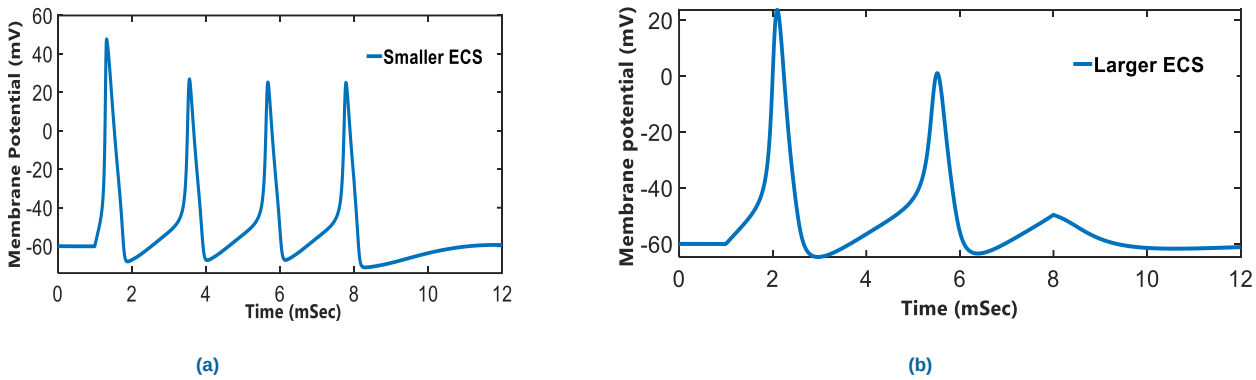


FIGURE 3. (a) Spike train when Size of ECS is smaller (b) Spike train when Size of ECS is larger

smaller ECS. This is because when Extracellular Space is larger, the resistance of the spacing decreases, causing mobile ions to disperse further into the space and attenuating the signal, which is also seen in multiple literatures as mentioned previously.

FIGURE 3(a) shows a spike train when the size of the ECS is smaller i.e. of 10 nm and FIGURE 3(b) shows the spike train when the size of the ECS is larger i.e., the size of the ECS is considered to be of 100 nm and the internal diameter of the fiber is taken to be of 5 µm respectively. It is observed that, when the ECS is smaller, the amplitude of the initial spike increases to 47.69 mV which is slightly higher than the first spike seen in FIGURE 2 and the subsequent spikes have amplitude slightly increased when comparing to that in FIGURE 2. Moreover, an additional spike is also found to be generated suggesting hyperexcitation. This rise in signal amplitude results from the fact that with the decrease in the size of the ECS, the hindrance to mobile ions to pass to the external media is significantly higher. So, at the same point of reference in the nerve fiber and with a smaller ECS, the amplitude of the signal is found to be marginally improving. The additional spike which is seen in FIGURE 3(a) arises because with the decrease in the size of the ECS, spike encoding changes significantly and with less possibility of the mobile ions to dissipate to the Extracellular Space, high amount of charged ions are accumulated and delivered to nearby region resulting in the generation of an additional spike within the same time frame. This condition can be associated with diseases like Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome [25], [26], [27], [28], [29], [30], [31].

In FIGURE 3(b), it is seen that as the size of the ECS is larger, the signal tends to undergo more attenuation and the number of spikes decreases. The initial spike is observed to have an amplitude of 23.75 mV and the subsequent spike also tends to have a lower amplitude. This reduction in amplitude results from the fact that the neuronal signal attenuates more when the ECS is larger due to the higher possibility of the mobile ions dissipating to the extracellular media. Moreover, due to this, the number of spikes also gets reduced suggesting hypoexcitation as the accumulation of the ions to sustain the intensity of neuronal signal decreases which may eventually lead to signal getting died down before reaching its intended target. Thus, this proposed framework incorporates the ECS dependent parameter and its impact on neuronal signal effectively. This condition of hyperexcitation of neuronal signal can be associated with diseases like Guillain-Barré Syndrome, Charcot-Marie-Tooth Condition [32], [33], [34] .

B. SPIKE TRAIN FOR AN INJURED NERVE FIBER THAT RESULTS IN THE BLOCKING OR ALTERATION OF ION CHANNELS

In this section, the simulation is carried out considering the nerve fiber to be injured. When a nerve undergoes any injury; the sodium and potassium ion concentrations are affected greatly. In this section, ion channel blocking and alternation of ion channels viz increase in ion concentration due to neuronal injury and its effect on the neuronal signal under the influence of the ECS is studied.

1. SPIKE TRAIN WHEN SODIUM ION CHANNELS ARE BLOCKED

Here, the sodium ion channels are considered to be blocked due to an injury keeping the potassium ion channels as usual. The blocking condition is applied to the maximum conductance of sodium ion in the H-H parameters, i.e. g_{Na} is taken to be so small (0.01) which can be considered as nearly zero which symbolizes that only a few sodium ion channels are kept open to initiate an action potential in this case. The resultant plot obtained is shown in FIGURE 4(a). It is observed from FIGURE 4(a) that the initial action potential has a reduced amplitude (-43.5 mV) and the subsequent spikes observed in FIGURE 2 are not generated. This happens because the sodium ions are essential for the generation of an action potential, blocking of these ion channels hampers the inward flow of sodium ions thus leading to the change in shape and duration of the action potential. The initiation threshold for an action potential is raised by sodium channel blockade. The action potential's amplitude is decreased, yet with a powerful enough depolarizing stimulation, it is still feasible to cross this higher threshold. The remaining leakage channels and subsequent H-H parameters might still contribute to produce an action potential when the membrane potential exceeds this high threshold, however due to unavailability of adequate sodium ion channels to boost up the signal, it would not be strengthened enough, and its overall amplitude would diminish drastically as it travels along the length of the fiber i.e., the decremental conduction in this case is significantly higher and the signal might quickly die. Moreover, observing FIGURE 4(a) it is also seen that the signal undergoes prolonged refractory period, and the resting membrane potential undergoes a dc shift and is found to be less negative (about -52.4 mV) than usual also the subsequent spikes in the spike train as observed in FIGURE 2 ceases to occur. This might be because when the sodium ion

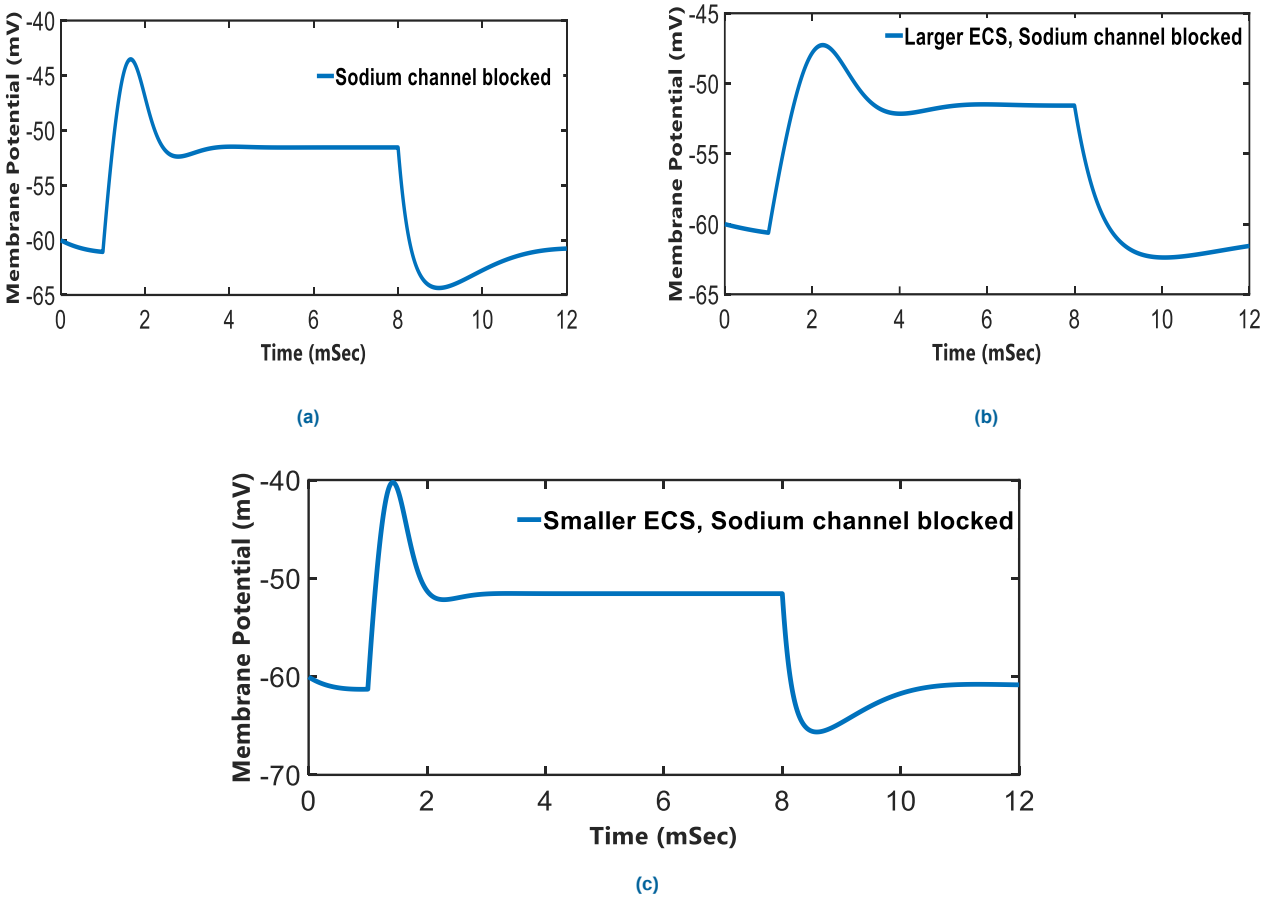


FIGURE 4. (a) Spike train when Sodium channels are blocked, (b) Spike train when Sodium channels are blocked and the size of ECS is larger (c) Spike train when Sodium channels are blocked and the size of ECS is smaller

channels are blocked, there is a dearth of sufficient sodium ion channels to initiate another action potential thereby hampering the generation of the other spikes and instead increases the duration of the refractory period within the same time frame. Prolonged refractory periods, or the interval following an action potential during which the neuron is unable to produce another action potential, can also result from a decrease in sodium conductance. The duration required for voltage-gated sodium channels to reactivate after being inactivated determines the refractory period. An extended refractory period may result from a decrease in sodium conductance because voltage-gated sodium channels require more time to reactivate after being inactivated. A depolarizing change in membrane potential, or a shift in the resting membrane potential towards more positive values, can also result from a decrease in sodium conductance. The equilibrium of ionic currents flowing across the membrane establishes the resting membrane potential, which is impacted by the membrane's permeability to various ions. Because the voltage-gated sodium channels oversee the quick depolarization of the membrane during an action potential, a decrease in sodium conductance may result in a dc shift in the membrane potential. These symptoms are usually associated with medical conditions like Sodium Channelopathies [35], [36], [37]. Moreover, traits of Guillain-Barré Syndrome are also seen during sodium channel blocking conditions according to [38][39]. Now, the simulation is undertaken in an environment where the size of the ECS is considered to be larger i.e., the size of ECS is taken to be of 100 nm and the internal diameter is taken to be of 5 µm and sodium ion channels are considered to be blocked and the resultant plot is shown in FIGURE 4(b). FIGURE 4(b) shows result similar to the one observed in FIGURE 4(a) but here the amplitude of the action potential further diminishes to about -47.4 mv. Moreover, the resting membrane potential was also found to be less negative experiences a dc shift and undergoes a dc shift to about -52.1 mV. This further reduction in amplitude is because a larger ECS facilitates further movement of ions towards the external medium and thus combined effect of a larger ECS along with the sodium channel blocking further degrades the amplitude of the signal and the subsequent spikes are also not generated. Moreover, there is a prolonged refractory phase taking place which is evident from the observations made in FIGURE 4(a) due to the reasons mentioned above. This condition can be associated with diseases associated with sodium channelopathies [35], [36], [37] and Guillain-Barré Syndrome [38], [39]. FIGURE 4(c) shows a similar arrangement of sodium ion channel blocking in a nerve surrounded by the ECS but here the size of ECS is taken to be smaller i.e., the ECS is taken to be of 10 nm and the internal diameter is taken to be of 5 µm respectively. Here, the amplitude of the action potential increases to about -40 mV this slight increment in the amplitude arises from the fact that the size of the ECS is taken to be smaller in this case and as it is already understood from previous sections that a smaller ECS obstruct the movement of ions towards the extracellular medium thus increasing the strength of the signal. Here, the influence of the ECS makes this improvement in the amplitude. Moreover, the resting membrane potential also experiences a dc shift to about -52.1 mV and the occurrence of prolonged refractory period is also observed in this case which is similar to the one observed in FIGURE 4(a) and FIGURE 4(b) due to the reasons discussed above. This condition can be

associated with diseases associated with sodium channelopathies [35], [36], [37] and Guillain-Barré Syndrome[38], [39]. The observations made from this section show the significance of the ECS on neuronal signals as the combined effect of ECS along with the sodium channel blocking can affect the generation and propagation of neuronal signal significantly.

2. SPIKE TRAIN WHEN SODIUM ION CONCENTRATION IS INCREASED

In this section, it is assumed that an injury to the nerve fiber leads to an increase in the sodium ion concentration.

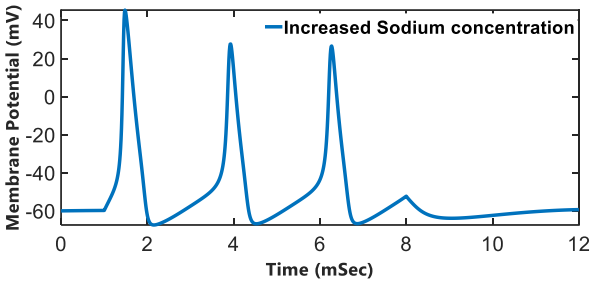


FIGURE 5. Spike Train with increased Sodium concentration in an injured nerve fiber

Here, it is seen that increase in sodium ion concentration does not alter the nerve signal significantly and the obtained graph is similar to FIGURE 2. This is because sodium ions are essential for the generation of action potentials, a substantial increase in extracellular sodium concentration is typically not required for hyperexcitability to occur as the equilibrium of potassium and sodium ions determines the membrane potential at rest as the normal extracellular sodium concentration exceeds intracellular sodium concentration, producing a concentration gradient that favors sodium influx during depolarization. Therefore, as the concentration gradient for sodium influx is already established, further increase in extracellular sodium concentration may not cause hyperexcitability. It may alter action potential production and ion channel function.

3. SPIKE TRAIN WHEN POTASSIUM ION CHANNELS ARE BLOCKED

In this section, it is assumed that the potassium ion channels are blocked because of a nerve injury and sodium ion channels are kept as usual. The blocking condition is applied to the maximum conductance of potassium ion in the H-H parameters, i.e. g_k is taken to be zero in this case. Initially, the simulation is carried out by considering the internal diameter of the fiber to be of 5 µm and the ECS to be 50 nm respectively.

When compared to the blocking events of the sodium ion channel blocking, it can be seen from FIGURE 6(a) that the action potential's amplitude here is greater i.e., about 55.1 mV. As the sodium ion channels, which are crucial for the generation of an action potential, are not blocked, the action potential gets formed and sustained easily. However, the repolarization phase of the action potential is delayed suggesting prolonged depolarization. This event develops because of the potassium ions being blocked, which are essential for bringing an action potential to the repolarization phase and maintain resting state. This eventually results in a longer duration of the action potential. As the potassium ion channels are important in regulating the repolarization phase and refractory periods of excitable cells, blocking them can cause the initial spike to sustain for the entire duration of the spike train and thus the subsequent spikes fails to get generated as there is a dearth of potassium ion channels to repolarize the initial spike which is evident from FIGURE 6(a) as the subsequent spikes failed to get generated and the initial spike is sustain for the entire duration of the spike train. Moreover, an increase to the strength of the signal is also observed. This is because, by impeding the neuron's ability to repolarize effectively, blocking potassium channels might cause a protracted depolarization phase. The action potential may amplify more as a result, resulting in a stronger signal. This situation eventually suggests conditions similar to Potassium Channelopathies[40], [41], [42].

Now the simulation is conducted considering the ECS to be larger and the resultant plot is shown in FIGURE 6(b). Here, the ECS is taken to be of 100 nm in size and the internal diameter of the fiber is taken to be of 5 µm respectively. Here, the action potential gets generated effectively, but its amplitude decreases marginally to 53.7 mV which is true as in this case, the size of the ECS is taken to be larger. Moreover, similar to the observations made from FIGURE 6(a), there is a delayed repolarization suggesting prolonged depolarization taking place, and the subsequent action potential spikes fails to generate due to the reasons discussed above. This condition can be associated with diseases associated with potassium channelopathies [40], [41], [42].

The experiment is now conducted considering the ECS to be and the resultant plot is shown in FIGURE 6(c). The ECS is taken to be of 10 nm in size and the internal diameter of the fiber is taken to be of 5 µm respectively**.** It is seen from FIGURE 6(c) that the action potential manages to get generate efficiently but the amplitude of the action potential increases marginally to about 55 mV. Because the ECS in this case is considered to be smaller, there is more hindrance to the outward migration of the mobile ions thereby increasing the amplitude. Similar to the observations made in FIGURE 8 and 9, there is a delayed repolarization and the next action potential spikes do not form for the reasons mentioned above. This condition can be associated with diseases associated with potassium channelopathies [40], [41], [42].

4. SPIKE TRAIN WHEN POTASSIUM ION CONCENTRATION IS INCREASED

In this section, the simulation is carried out considering the potassium ion concentration to increase due to any injury. The increased potassium ion condition is applied to the maximum conductance of potassium ion in the H-H parameters, i.e. g_k is considered to increase by a factor of 2.

The function of potassium ions in establishing the resting membrane potential of neurons is crucial. Normal resting potential is maintained by an equilibrium of ion concentrations and with higher potassium ion concentrations inside the cell and higher sodium and chloride ion concentrations outside the cell. This concentration gradient generates an electrochemical potential that contributes to the regulation of neuronal excitability. The disruption of the equilibrium of ion concentrations caused by an increase in potassium ions can result in quick repolarization of the cell membrane and due to the presence of the sodium ions in normal concentration which is crucial for the depolarization of the cell membrane, additional spike is found to be generated thus resulting in hyperexcitability of the cell membrane as seen in FIGURE 7(a) suggesting in information mismatch taking place when potassium ion concentration increases owing to an injury. However, it is also observed that the strength of the signal does not change

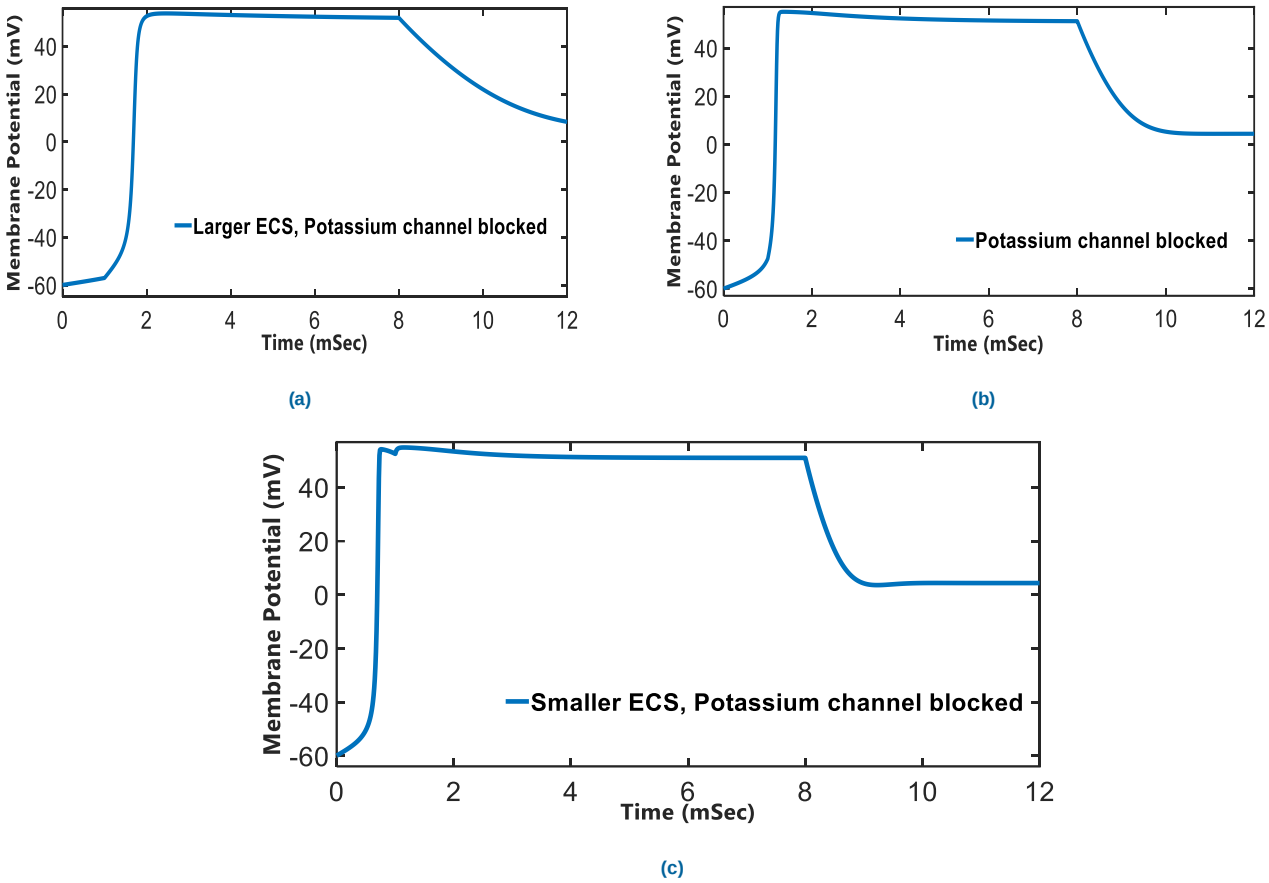


FIGURE 6. (a) Spike train when potassium channels are blocked (b) Spike train when potassium channels are blocked and size of ECS is larger (c) Spike train when potassium channels are blocked and size of ECS is smaller

significantly, this is because, in this case the size of the ECS is considered to be normal and only the effect of ionic disruption due to injury is considered for the study as it is already understood from literature that the changes to the size of the ECS affects neuronal signal. Hyperexcitability brought on by an increase in extracellular potassium levels can have a variety of effects on neuronal functions such as spontaneous activation of action potentials, increased sensitivity to stimuli, and abnormal signaling patterns. These alterations may contribute to conditions such as epilepsy, in which the brain experiences recurrent and uncontrolled bouts of excessive neuronal activity. This condition can be associated with diseases associated with Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome [25], [26], [27], [28], [29], [30], [31].

In FIGURE 7(b) it is observed that an injured nerve fiber of internal diameter 5 µm, that results in an increased in the potassium ion concentration surrounded by a larger ECS of 100 nm, there is a reduction in signal amplitude like what is observed in FIGURE 3(b) , but the additional spike observed in FIGURE 7(a) because of an increase in potassium conductance is absent. The reduction in signal amplitude or intensity suggests that a larger ECS has a significant impact in hampering the strength of the signal, which is consistent with the general understanding that larger the ECS, the greater the signal attenuation. The fact that the number of spikes has not increased due to the increase in potassium concentration in this scenario indicates that in a system with a larger ECS and more potassium ions owing to an injury to the fiber, the influence of the ECS over the nerve fiber is significantly higher. Here, signal modulation may not occur, meaning that the information may remain intact, but there is a possibility of information loss as the signal travels down the fiber due to a decrease in signal amplitude. This decrease in signal strength is a typical indication of problems like peripheral neuropathy, Guillain-Barré syndrome, Charcot-Marie-Tooth condition etc. [32], [33], [34] .

In FIGURE 7(c), the ECS is taken to be smaller in size i.e., 10 nm and internal diameter of the fiber is taken as, 5 µm. The potassium concentration is considered to increase due to injury to the fiber. The result shows that the number of spikes has increased significantly as compared to FIGURE 7(a) and FIGURE 7(b), also the signal's amplitude has increased too. The amplitude increased since the size of the ECS is considered to be smaller thus it provides less resistance for the movement of the ions to the external space and thus resulting in accumulation of the ions causes the signal strength to increase. However, the abrupt increase in number of spikes is because the combination of smaller ECS along with the increase in the number of potassium ion concentration resulted in the hyperexcitability of the nerve membrane. This result signifies that in an environment of smaller ECS in an injured nerve fiber, the possibility of information mismatch is significantly higher than that of an ECS which is of the normal size or larger. This is a typical symptom of neurological conditions such as seizures, epilepsy etc. as discussed earlier [25], [26], [27], [28], [29], [30], [31].

The proposed framework provides a simpler mathematical expression, and it is able to replicate the observations made in the traditional literature regarding the impact of the ECS on neuronal signals. This framework may be useful for rapid

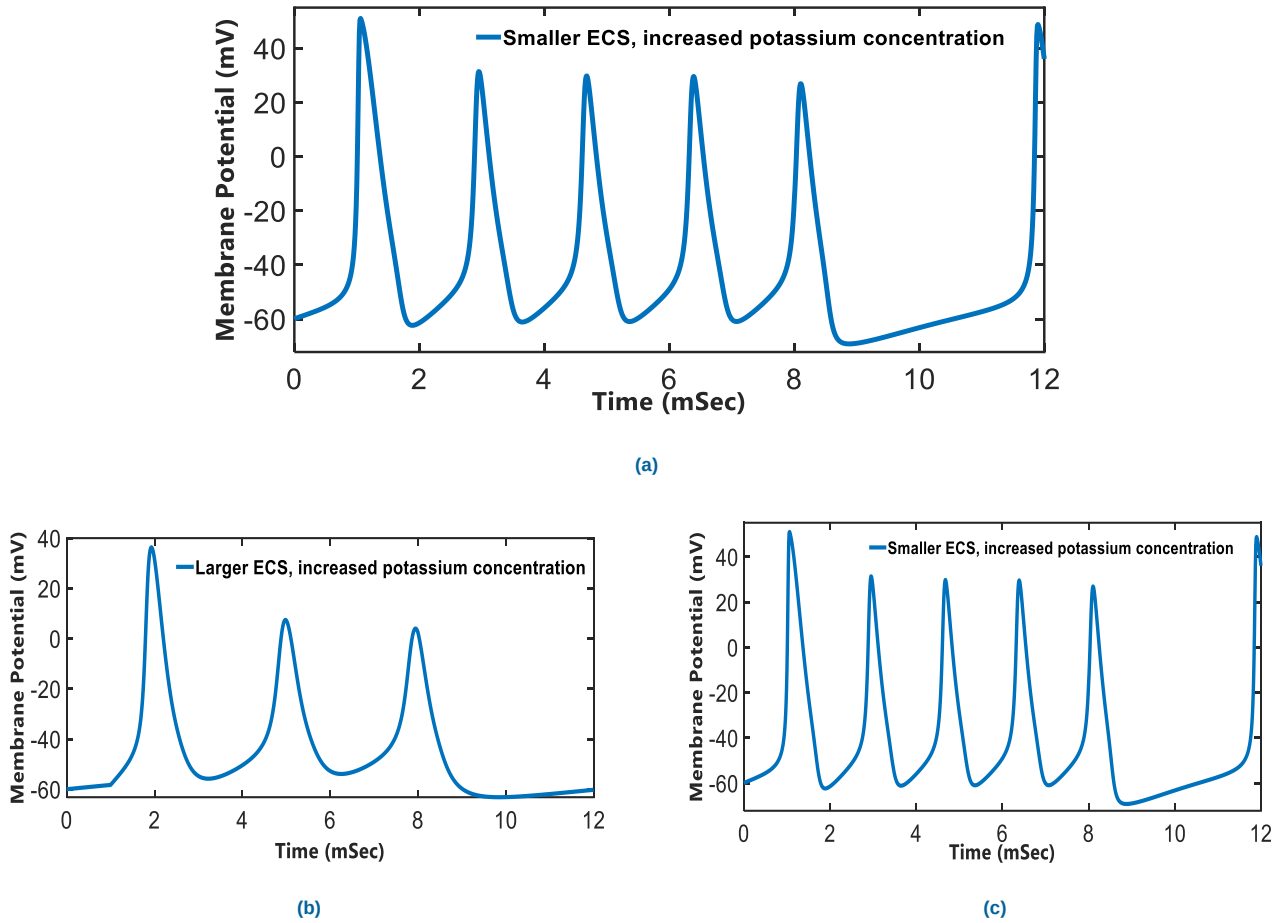


FIGURE 7. (a) Spike train when potassium channels are increased (b) Spike train when potassium channels are increased and size of ECS is larger (c) Spike train when potassium channels are increased and the size of ECS is smaller.

prototyping as well as providing results concerning the impact of the ECS on various neurological illnesses. The findings in this study also signify the role of ECS that facilitates local action potential stimulation as well as effectively controlling the neural signal losses as a factor of Extracellular Spaces.

Thus, it is essential to consider the ECS-related characteristics when assessing signal transmission since variation in the size of the ECS has a substantial impact on preserving the total information content of a signal.

A summary of the results has been listed in TABLE 2, which is shown below.

V. DISCUSSION

The present study involves proposing a mathematical model to obtain the nerve membrane potential expression that incorporates the fundamental parameters of the Extracellular Space (ECS) to study how the ECS affects neuronal signal transmission in a healthy and injured nerve fiber. To develop and run the proposed model, the well-known neuronal cable model has been modified to incorporate the Extracellular Space dependent parameters and conventional electrophysiological parameters from the literature. The conventional cable model considers only the intrinsic parameters of the nerve fiber, and it does not consider the parameters pertaining to the ECS for studying neuronal signal transmission. However, it is understood that the ECS has a major role to play in governing neuronal signals as the variation in the size of the ECS affects neuronal signal propagation. Therefore, it is necessary to address this issue and to have a mathematical model pertaining to the nerve membrane potential that not only consists of the intrinsic parameters of the nerve fiber such as the well-known cable model, but also the parameters pertaining to the ECS which is simple and yet robust and produces results that are consistent with existing literature.

In the current study, the ECS related parameters such as its volumetric resistance (R_e), diameter (D_e), ECS effected axial current (I_e), extracellular potential (V_e) has been incorporated to the standard cable model. The final obtained membrane potential expression is much simpler in comparison to other available methods and yields results that are consistent with existing literature. This approach offers advantages since it has a low level of computational complexity and works well for rapid prototyping.

The simulation of the proposed framework manages to produce a spike train as observed in FIGURE 2 suggesting that the model is effective in the generation of a realistic spike train similar to what is observed from the Hodgkin-Huxley model [20]. This shows that the proposed framework is efficient, and it can be used to analyze and study neuronal signal transmission.

The results obtained from the simulation show that, for a healthy nerve fiber surrounded by a larger ECS, the strength of the signal drops. This is because a larger ECS provides less

TABLE 2
Summary of the results suggesting different combinations of fiber anatomy and the size of the ECS shows symptoms of certain medical conditions

Size of the ECS	Condition of the fiber	Ionic condition	Signal strength	Signal condition	Symptoms of possible Medical conditions
Smaller	Healthy	Normal	Increased	Hyperexcitation	Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome
Larger	Healthy	Normal	Decreased	Hypoexcitation	Guillain-Barré Syndrome, Charcot-Marie-Tooth Condition
Normal	Injured	Sodium channels blocked; Potassium channels normal	Decreased	Prolonged refractory period; dc shift to membrane potential; Hypoexcitation	Sodium Channelopathies, Guillain-Barré Syndrome
Larger	Injured	Sodium channels blocked; Potassium channels normal	More decreased	Prolonged refractory period; dc shift to membrane potential; Hypoexcitation	Sodium Channelopathies, Guillain-Barré Syndrome
Smaller	Injured	Sodium channels blocked; Potassium channels normal	Marginal increased	Prolonged refractory period; dc shift to membrane potential; Hypoexcitation	Sodium Channelopathies, Guillain-Barré Syndrome
Normal	Injured	Increased Sodium concentration; Normal Potassium concentration	No significant change	Similar to normal spike train	-
Normal	Injured	Potassium channels blocked; Sodium channels normal	Increased	Delayed repolarization; Prolonged depolarization; Hypoexcitation	Potassium Channelopathies
Larger	Injured	Potassium channels blocked; Sodium channels normal	Marginal decreased	Delayed repolarization; Prolonged depolarization; Hypoexcitation	Potassium Channelopathies
Smaller	Injured	Potassium channels blocked; Sodium channels normal	Marginal increased	Delayed repolarization; Prolonged depolarization; Hypoexcitation	Potassium Channelopathies
Normal	Injured	Increased Potassium concentration; Normal Sodium concentration	No significant change	Hyperexcitation	Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome
Larger	Injured	Increased Potassium concentration; Normal Sodium concentration	Decreased	Similar to normal spike train	-
Smaller	Injured	Increased Potassium concentration; Normal Sodium concentration	Increased	Severe Hyperexcitation	Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome

resistance to the ions present in the nerve to propagate towards the external media resulting in attenuation of the signal, which is seen in FIGURE 3(b) moreover, the opposite is also true as observed in FIGURE 3(a). A smaller ECS can also aid in the generation of additional spike/s because the spike encoding changes significantly and with less possibility of the mobile ions to dissipate to the Extracellular Space, high amount of charged ions are accumulated and delivered to the nearby region resulting in the generation of an additional spike within the same time frame. The generation of the additional spikes when the nerve is surrounded by a smaller ECS indicates hyperexcitability of the neuronal signal which are associated with conditions such as Epilepsy, peripheral Neuropathy, Restless Legs syndrome. Moreover, hypoexcitability of neuronal impulse which is observed in case of nerve being surrounded by a larger ECS can be indication of medical conditions such as Guillain-Barré Syndrome, Charcot-Marie-Tooth Condition. This result confirms the validity of the proposed framework as the result is in coherence with the standard literature.

An injury to the nerve fiber can bring changes to the ionic concentration. The proposed model is also run to investigate the changes that the neuronal signal undergoes during nerve injury and the nerve being surrounded by an ECS of varying size. When an injury causes the sodium or potassium ion channel blocking, the obtained results suggest showing trends that are similar to what is obtained during sodium channelopathies, Guillain-Barré Syndrome and potassium channelopathies respectively. Moreover, the variation in the size of the ECS under similar conditions suggests that the strength (amplitude) of the signal is also affected. With the ECS being larger, the strength of the signal deteriorates in comparison to that of a smaller ECS. This shows that the ECS has a significant influence over the neuronal signal.

Furthermore, if any injury to the nerve fiber results in an increase in the intracellular ionic concentrations, the proposed framework is tested for increased potassium ion concentration for a nerve surrounded by an ECS of normal size. The simulated results suggest showing hyperexcitation of the neuronal signal, which is similar to medical conditions such as Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome. Moreover, if the ECS is larger under similar situation, there is only a slight decrease in the signal strength, but the signal is similar to that of

TABLE 3
Modified cable model's parameter and their physiological relevance

Parameter	Description	Units	Physiological relevance
Resting Membrane Potential (V_m)	Electrical Potential difference between outside and inside of nerve membrane at resting state	mV	Important for the generation of Action Potential in response to a stimuli
Characteristic Membrane Resistance (r_m)	Hindrance to ionic flow across the membrane	Ω·cm	Higher r_m, weaker the signal
Characteristic internal resistance (r_i)	Hindrance to ionic flow within the axoplasm	Ω·cm	Higher r_i, obstruction in the spread of electrical current in the forward direction
Characteristic Extracellular Space resistance (r_e)	Hindrance to ionic flow within the Extracellular Space	Ω·cm	Higher r_e, obstruction in the spread of electrical current towards the extracellular media
Characteristic Membrane Capacitance (c_m)	Ability of storing electrical charges	μF/cm^2	Higher c_m, stronger current is needed to alter the voltage
Sodium Conductance (gN_a)	Shows the highest Sodium ion flow achievable from the voltage-gated Sodium channels	m.mho/cm^2	A greater sodium current influx is made possible by a higher g_{Na} ; has a key function in the initiation and spread of action potentials
Potassium Conductance (g_k)	Shows the highest Potassium ion flow achievable from the voltage-gated Potassium channels	m.mho/cm^2	A greater Potassium current influx is made possible by a higher g_k; controls the rate of repolarization and affects the duration of the action potential
Leakage Conductance (g_l)	Shows the flow of ions through the opened (always) non-specific channels	m.mho/cm^2	Establishes the neuron's resting membrane potential (V_m); higher the g_l harder the generation of action potential
Equivalent Potential of Sodium ions (E_{Na})	There is no net flow of Sodium ions if V_m and E_{Na} are equal	mV	Establishes the sodium current's direction and force of action
Equivalent Potential of Potassium ions (E_k)	There is no net flow of Potassium ions if V_m and E_k are equal	mV	Establishes the Potassium current's direction and force of action.
Equivalent Potential of Leakage ions (E_l)	There is no net flow of leakage ions if V_m and E_l are equal	mV	Effects Resting membrane Potential (V_m)

a healthy nerve fiber. But, if the ECS is smaller, the simulation results show severe hyperexcitation to the neuronal signal, a trend similar to what is observed during Epilepsy, Peripheral Neuropathy, Restless Legs Syndrome.

The proposed framework is advantageous as the final membrane potential expression is simpler, robust, and consists of the parameters pertaining to the nerve fiber and the ECS thereby proving a holistic approach towards studying neuronal signal transmission. The proposed framework has its advantage towards understanding and predicting various neuronal conditions which arise due to changing ionic concentrations and changes to the size of the Extracellular Space. However, it must also be noted that it is an approximate model and inclusion of micro-level parameters might give refined results.

VI. CONCLUSION

This study demonstrates that the size of the ECS has a significant effect on the generation and propagation of neuronal signal through a healthy and an injured nerve. Also, it can be inferred that there must be some critical combination between the size of the ECS and the extent of the neuronal injury for the nerve signal to propagate without being distorted which is to be studied further. Hence, an in-depth analysis of the ECS and its role in neuronal signal transmission is essential to understand the root cause of several neuronal abnormalities that are associated with hypoexcitation of the neuronal signal like peripheral neuropathy, Guillain-Barré syndrome, Charcot-Marie-Tooth condition etc. and the conditions that are symbolic to hyperexcitation like seizures, epilepsy etc. Moreover, understanding the effect of the ECS on neuronal signals might also help in better understanding of issues such as ischemia, trauma etc.

The current work involves proposing a framework that yields a simplistic yet robust mathematical expression of the nerve membrane potential that can properly replicate the working of a nerve fiber, incorporating the fundamental parameters of the Extracellular Space to have a holistic approach in understanding neuronal signal transmission in healthy and injured nerve fiber. The simulation results appear to be consistent with the existing literature and may be crucial for comprehending how the ECS affects neuronal signals. The framework is very useful for obtaining an approximate result, having less computational complexity, cost effective and useful for rapid prototyping. It has already been recognized that the ECS is crucial in controlling the generation and propagation of action potentials and the proposed framework manages to incorporate the fundamental parameters of the ECS in the final expression of the membrane potential thereby making it possible to study signal transmission in detail.

The results obtained from the study show that certain combination of the ECS and nerve fiber diameter suggests showing trends which are similar to certain medical conditions as listed in TABLE 2 that are typically associated with changes

to the ionic concentrations in nerves. Hence, the current study suggests that the ECS has a deeper role to play in governing neuronal signals in healthy and injured nerve fiber.

Given that the Extracellular Space (ECS) plays a critical role in chemotherapeutic drug distribution, the suggested framework with its simplistic membrane potential expression may find use in this field in the future and may also be useful to further understand, predict, and diagnosis of various neurological conditions under the effect of ECS of varied sizes. However, more in-depth investigation is required to fully examine this idea. Moreover, it must also be noted that it is an approximation model and incorporation of micro-level parameters might give refined results. The detailed explanations of the modified cable model's parameters and their physiological relevance are listed in TABLE 3.

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest related to the manuscript.

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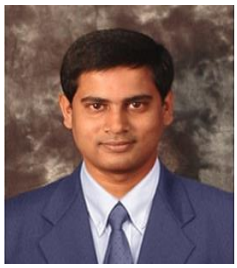

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