Chapter 7

Conclusion and Future Scope

A comprehensive survey of the state-of-the-art studies has been carried out in this thesis, which has allowed for a better understanding of the problems and difficulties in the field as well as some of the research gaps present in existing literature. Furthermore, the potential future avenues and scopes for extending the work conducted in this thesis has also been incorporated in this chapter.

7.1 Conclusions

The key findings of each chapter of this thesis have been mentioned below for a detailed and comprehensive understanding.

Chapter 1 involves the introduction of the thesis which provides a brief overview of the work that served as inspiration and motivation for the study undertaken. This section aimed to shed light on the ECS that surrounds a nerve fiber and its importance in governing neuronal signal in detail. The chapter concludes with a summary of the primary objectives of the thesis, laying the groundwork for an in-depth investigation.

Chapter 2 consists of the Literature Review which involves an extensive review of the state-of-the-art literatures available on the electrical equivalent model of neuron, and the cable representation of a nerve fiber, the ECS and how it impacts the dynamics of the neuronal membrane, and the conduction velocity at which neuronal signals propagate. Moreover, the chapter also aimed at understanding various neuronal models used for analysis of neuronal signals.

Chapter 3 has been divided into two sections where the first section deals with how neuronal signal itself aid in remyelination and the second section deals with the effects of varying ECS on neuronal signal transmission. It can be inferred from the chapter that the variation in the rate of change in membrane potential ($\frac{dV_m}{dt}$) can have an effect on myelination such as increase in rate of change of membrane potential causes the capacitance value to reduce, signifying remyelination taking place. The rate of change of membrane potential can be increased by a stronger Excitatory Neurotransmitter release like glutamate, decrease release of Inhibitory Neurotransmitter like GABA, temperature and physical activities. However, the

model is a simplified representation of a nerve fiber and for a more detailed model, the effect of periaxonal fluid should be considered which is to be explored further. Moreover, the results obtained from this chapter suggests that larger the ECS, higher is the signal attenuation and vice-versa. This occurs because a larger ECS offers less resistance thus, offering less hindrence to the mobile ions to get dissipated towards the external media via the leak channels resulting in a higher signal attemuation. But, a smaller ECS offers higher resistance thus the the mobile ions finds it much difficulties to get dissipated towards the external media through the leak channels which results in a smaller attenuation of the signal. Additionally, it is also found from the study that if the nerve fiber is surrounded by an uniform ECS, the attenuation of neuronal signal is approximately same whether the fiber is a tapered one or a flared one. The mathematical model used to carry out the work in this chapter involves less mathematical and computational complexity and the incorporation of the ECS related parameters provides a robust framework to study neuronal signal transmission in a detailed manner.

Chapter 4 involves the work that analyses the similarities between the neuronal signals at two successsive active regions (Node of Ranvier). Here, the action potential spike train is first considered to be generated at a Node of Ranvier, which passes via the adjacent myelinated segment to the next Node of Ranvier and how much information content of the original signal is modifed or remained preserved with changing length as it reaches the next Node of Ranvier is tried to be investigated in this work. Initially, a longer fiber was considered and it was found that as the spike train moves from the initial Node of Ranvier to the adjacent myelinated segment, the information content of the signal remained preserved with a slight attenuation of the signal is observed which is due to the decremental conduction of the neuronal signal caused by the combined effects of the axial resistance of the fiber and the length of the fiber. Moreover, a tiny amount of DC shift to the signal is also observed which is because of the passive characteristics of the nerve fiber. When the spike train reaches the next Node of Ranvier after propagating via the myelinated segment, regeneration of the signal takes place due to the active ion channels present at the Node of Ranvier (Saltatory Conduction). It is seen here that the signal more or less remained intact with a negligible amount of ionic loss taking place. In the second scenario, a shorter fiber is considered and the simulation is repeated again. In this scenario, it is seen that when the length is shortened, an additional spike is found to get generated suggesting information mismatch taking place as the signal moves from one Node to the other. This occurs because a shorter consists of fewer open channels to facilitate ionic losses which causes the spike encoding to change significantly. This causes a high amount of

current to be delivered to the subsequent region of the fiber resulting in the generation of an additional spike at the second Node of Ranvier thus modifying the information content of the neuronal signal. Thus, it can be said that myelinated fibers have a certain critical length at which the information content of the signal is preserved and does not change.

Chapter 5 involves proposing a mathematical framework for nerve membrane potential expression which is simple and robust incorporating the fundamental parameters of the ECS in order to have a holistic approach towards studying neuronal signal transmission. Initially, using this framework the study aimed at understanding how injury (disease) to the nerve fiber that alters the opening and closing of the ion channels affects neuronal signal under the effect of the ECS of varying sizes. The results show that the generation and propagation of neuronal signals for both healthy and injured nerves are significantly influenced by the size of the ECS. Moreover, it can also be inferred that there has to be a certain combination of the size of the ECS and the degree of neuronal damage for the nerve signal to propagate without distortion which needs to be further investigated. It is also seen from the study conducted in the chapter that the size of the ECS significantly influences the generation and propagation of neuronal signal for both healthy and injured nerve fibers. Also, for the neuronal signal to travel without distortion, there has to be a certain combination of the extent of the neuronal damage and the size of the ECS that needs to be further investigated. Therefore, a detailed analysis of the ECS and its role in neuronal signal transmission is necessary to understand the underlying cause of various neuronal abnormalities associated with hypoexcitation of the neuronal signal, such as peripheral neuropathy, Guillain-Barré syndrome, Charcot-Marie-Tooth condition, etc., as well as conditions symbolic of hyperexcitation, such as epilepsy and seizures. Thus, it can be inferred that ECS plays a pivotal role in governing the generation and transmission of neuronal signal.

In the second part of Chapter 5, an attempt has been made to mimic the effects of genetic mutations that are known to change how ion channels function by inducing a voltage shift to the rate constant (α and β) parameters, which would eventually change the gating variables of the ion channels and have proposed a rescue protein mechanism that could alter the effect of these mutations. In order to add to our understanding of how minor modifications in channel behaviour can have major physiological effects by influencing gating variables, ionic currents, and the membrane potential, this study aims to determine how both positive and negative voltage shifts to the rate constant parameters affect neuronal excitation. This study is intended in aiding in the development of targeted therapies and interventions for associated medical

disorders. The results show that a positive voltage shift to the rate constant parameters causes a hyperexcitable condition that is characterised by a higher firing frequency and a larger peak amplitude. This occurs when the potassium activation variable (n) and sodium channel variable (m) both activate more quickly, which accelerates the repolarization process. In contrast, a hypoexcitable state caused by a negative voltage shift weakens and delays the action potential. Smaller action potential amplitudes and delayed depolarization are the outcomes of the incapacity of the sodium channels to open. The potassium activation variable (n) not only causes a slower response, but it also prolongs the refractory period and the repolarization phase which results in a decrease in potassium and sodium currents further contributing to the overall hypoexcitation condition. Mutations in sodium channel genes, including as SCN1A, SCN2A, and SCN8A, are important in conditions like epilepsy because they are linked to a positive voltage shift that causes hyperexcitation. The hypoexcitation that results from a negative voltage shift to the rate constants, is linked to genetic mutations of sodium channels (e.g., SCN4A) and potassium channels (e.g., KCNA's, KCNQ2, KCNJ2), which are characterised by longer refractory periods and delayed responses. This suggests that there must be a limit to the degree of mutation at which the signal retains its integrity without changing from its original form which needs to be studied further.

The suggested framework also incorporates a rescue protein mechanism, represented by a rescue protein voltage $R_p(V_m)$, which is thought to be a combination of the original and mutated membrane potentials. The rescue coefficent (k_{Rescue}) acts as a tuning parameter that regulates how much a rescue protein mechanism counteracts the effects of a mutation. The rescue protein voltage $R_p(V_m)$ becomes exactly the same as the mutated voltage ($V_{m,mutated}$) when $k_{Rescue} = 1$, indicating that no rescue is occurring and that the rescue mechanism is unable to counteract the effect of mutation. Conversely, when $k_{Rescue} = 0$, the dynamics of the membrane potential return to their non-mutated (normal) state ($V_{m,original}$), indicating that the rescue protein mechanism has completely succeeded in reversing or mitigating the effect of genetic mutation. The rescue coefficient, or k_{Rescue}, should be determined in such a way that its value falls between 0 and 1 depending on the scope of the rescue. Adjusting the amount of k_{Rescue} allows for precise control over how much the rescue protein corrects for the mutation. Because k_{Rescue} is adaptive, it could be an essential resource for examining the variety of possible consequences of rescue proteins and comprehending their ability to restore normal neuronal function. Moreover, if membrane potential for the non-mutated (original) state, mutated state and the drug induced rescue state could be calculated experimentally, then the

value of the rescue coefficient (k_{Rescue}) could be obtained which would show how much the drug has been able to mitigate the impact of genetic mutation of ion channels with a value close to 1 indicating less effectiveness of the drug to mitigate the impact of the mutation and a value close to 0 indicating that the drug has shown signs of mitigating the impact of these mutations. The proposed rescue protein mechanism would provide pathway which that would aid in therapeutic treatments such as quantifying drug efficacy, predicting long term drug effects, optimization of drug dosage comparing different treatments etc.

Chapter 6 deals with studying the velocity profile of neuronal signal for a passive nerve fiber under the influence of the ECS of varied sizes through a robust mathematical model which is computationally and mathematically less complex. The study takes into account a passive nerve fiber because it allows for a better focus on the important components of the nerve such as membrane resistance, membrane capacitance, and ECS resistance which together regulate how signals attenuate and move along the nerve while neglecting the dynamics of the active ion channel dynamics. This allows for a clearer understanding of how certain passive features, such the effects of leak channels and the ECS influence conduction velocity without the complications of voltage-gated ion channels. Since the ECS has a major impact on the transmission of neuronal signals, the proposed framework has been developed by modifying the well-known cable model by adding the characteristics of the ECS in order to gain a thorough understanding of the velocity profiles of neuronal signals. The study suggests that there exist certain critical points where the conduction velocity spikes up a little causing the conduction velocity to reach the point of observation at different instance of time. The study also shows that the conduction velocity of neuronal signal for a fiber surrounded by a larger ECS is less in comparison to a fiber which is surrounded by a smaller ECS. 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 and a smaller ECS provides significant hindrance to the mobile ion to get dissipated towards the external media thereby causing significantly less signal attenuation.

Moreover, it is known that fiber anatomy also influences conduction velocity of neuronal signals as a fiber with larger diameter have a larger conduction velocity than a fiber with smaller diameter. However, it is observed in this study that when the parameters of the ECS are taken into account, a specific combination of the fiber diameter and the size of the ECS causes the conduction velocity to increase. This suggests that there are critical points where velocity spikes and that these points are generated at uniform duration. According to the

results obtained, the length of the fiber has an impact on conduction velocity as well as the conduction velocity is found to decrease with increasing fiber length. This is mostly caused by the decremental conduction of signals which shows that as fiber length increases, signal strength decreases. Another finding from this study shows that there occurs a phase shift to the propagating signal resulting due to the delay created by the influence 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.

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. As a result, it can be stated that different configurations of fiber bundles may exist based on signal transmission and function formation. This kind of configurations might be achieved during the developmental phase of the dendritic arbors during dendritic growth, rearrangement, and decay.

The velocity profiles obtained by the suggested framework provide some important insights with minimal computational or mathematical complexity. Therefore, as the suggested framework uses the ECS related parameters to derive the velocity equation, it may be helpful in comprehending the impact of the ECS on nerve conduction velocity in a deeper way.

7.2 Future Directions

The current thesis lays a foundation for several possible future directions, as outlined below:

a. The framework proposed in this thesis involves minimal mathematical and computational complexity, making it both efficient and robust, particularly with the inclusion of ECS-dependent components. This simplified yet effective model provides a solid foundation for further exploration across various domains of neuroscience and therapeutic research. Moreover, the proposed framework could be further expanded in studying the effect of length on neuronal signal for flared and tapered nerve fiber under the influence of the ECS of varied sizes.
b. The active membrane potential expression presented in Chapter 5 could be extended to investigate the interplay between ECS size and the extent of neuronal damage,

especially in relation to the propagation of nerve signals with minimal distortion. Understanding this relationship will improve diagnostic tools and intervention strategies for neurodegenerative diseases or nerve injuries.

c. Since ECS plays a critical role in chemotherapeutic drug distribution, the framework could be extended to include drug delivery mechanisms. Incorporating drug-related parameters into the ECS model could assist in predicting and diagnosing the effects of chemotherapeutic drugs offering new opportunities for personalized treatments and optimizing drug distribution to target areas.
d. The proposed Rescue Protein mechanism in this thesis has great potential to advance our understanding of genetic mutations and their impact on voltage shifts in ion channel gating variables. This could lead to the development of new therapies targeting ion channel mutations, which are implicated in various neurological disorders, offering hope for more effective treatments.
e. The nerve conduction velocity model can be extended to active nerve fibers to provide deeper insights into the role of ECS on the conduction velocity of neuronal impulses. This could greatly contribute to understanding neurological issues associated with slow conduction velocity, such as multiple sclerosis or other demyelinating diseases, and inform therapeutic interventions. The work could be further extended to incorporate the Extracellular Matrix (ECM) parameters into the membrane potential expression for both the active and passive nerve fibers which would enable in the better understanding of the functional proteins that take part in proving strength to the neuron and also it would help in a better understanding of the role that the ECM plays in signal transmission. The Local Field Potential (LFP) could also be studied by developing a model that involves less computational and mathematical complexity which would enable in a better understanding of the associated electric field that gets generated due to the propagation of the action potential along the nerve fiber. Finally, the model could be extended for a system of coupled nerve fiber for a more comprehensive analysis of neuronal system.