Chapter 1

Introduction

For many years, several scholars have examined and replicated various biological process and phenomena in terms of biologically inspired algorithms or models and in this regard, the evolution of biological nerve model has been a significant achievement in the scientific community [1]. From basic depictions to intricate simulations of cellular functions, the development of nerve models has been essential to the understanding of how neurons transmit information. Additional intricacies such as ion concentration dynamics, signal generation, synaptic inputs, and neural network interactions have been captured by the nerve models as they have evolved over the years. Nerve models are important because they can mimic neuronal behaviours in controlled settings, which can help guide trial design and identify potential therapeutic targets [2], [3]. These models provide a thorough understanding of both normal and abnormal brain activity, which makes them essential resources for clinical applications, neuroscience research, and the development of brain-computer interfaces. Despite this, these systems oversimplified the basic entity of the system's operation. Biological neural systems contain incredibly sophisticated functions, and the emergence of new technologies and techniques has led to the discovery of fresh information about how neurons function[4], [5], [6].

With the developments of recent knowledge in the field of neuroscience and computational setups, the study of such dynamic neuronal behaviour [7], [8], [9] has been extremely popular and has managed to shed light into various key functionalities of neurons. Despite the availability of high-level computation facilities, it is essential to use efficient yet low-computational approaches since they increase efficiency, lower costs, conserve energy, and can be accessible on standard computational systems. Thus, it is essential to have mathematical models that are robust, effective yet computationally and mathematically less complex. But before dwelling into the intricacies of the neuron models, it is essential to understand what the neurons or nerve cells are, how nerve signals are generated, and what effect does the surrounding of the nerve fiber has on neuronal signal generation and transmission.

1.1 The Neuron (Nerve cell)

Neurons or Nerve cell are specialized cells that can be considered as the basic building blocks of the nervous system [10], [11]. They play a vital role in everything from motor control to sensory perception as they are in charge of receiving and sending messages throughout the body. The neuron consists of 3 integral parts viz, axons, cell bodies (soma), and dendrites. The dendrites are extensions that resemble branches and receive signals from the neighbouring neurons, and they are essential for receiving and sending information it to the cell body. The soma houses the nucleus and is in charge of the metabolic processes of the neuron such as the synthesis of proteins and the generation of energy. The axon is an elongated, thin structure that can vary in length and diameter responsible for sending electrical impulses from the cell body to distant places and to the neighbouring neurons [12].

The information travels via the neurons in the form of electrical signal known as action potential (AP) [13], [14], [15], [16]. An action potential is a rapid and transient shift in a neuron's membrane potential that is essential for electrical signals to travel across nerve fibers. It starts with a number of distinct stages that result from a neuron being sufficiently stimulated to reach a threshold level. The unequal distribution of ions across the membrane, mostly sodium (Na^+) and potassium (K^+) maintains the resting potential of a neuron which is typically between -60 mV and -70 mV [17]. Specific ion channels known as Voltage-gated ion channels specifically the sodium (Na^+) and potassium (K^+) ion channels which open and close in response to variations in the membrane potential of the nerve cell are responsible for the

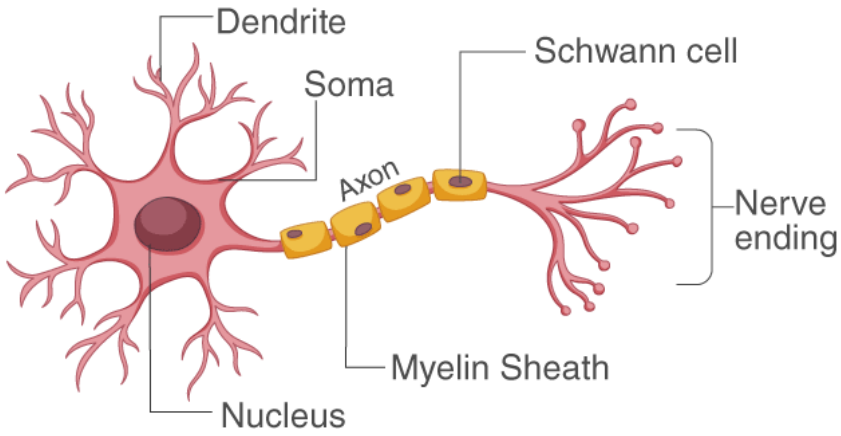

Fig. 1.1 A Myelinated Neuron

generation of an action potential [18], [19]. A powerful enough stimulation causes voltage-gated sodium channels to open, letting sodium ions enter the cell. A chain reaction is started by this voltage change which causes more sodium channels to open along the axon. This inflow of positive sodium ions causes depolarization of the cell membrane which makes the interior of the cell to become more positive. When the membrane potential reaches a maximum value, the voltage-gated sodium channels closes and the voltage-gated potassium channels opens, initiating the repolarization phase. Here, the action potential value falls below the resting membrane potential which occurs as the equilibrium potential of potassium is around -93 mV, this is called the hyperpolarization phase of the action potential [20], [21]. In this scenario, the sodium-potassium pump plays an important role in bringing the membrane potential back to its resting state by pumping out three sodium ions and pumping in two potassium ions. A limited region becomes polarized due to the localized nature of the action potential. By generating and transmitting the action potential through the synchronized opening and closing of sodium and potassium channels, neurons are able to efficiently and quickly transport information throughout the nervous system.

The term impulse refers to the movement of the action potential along its length [22],

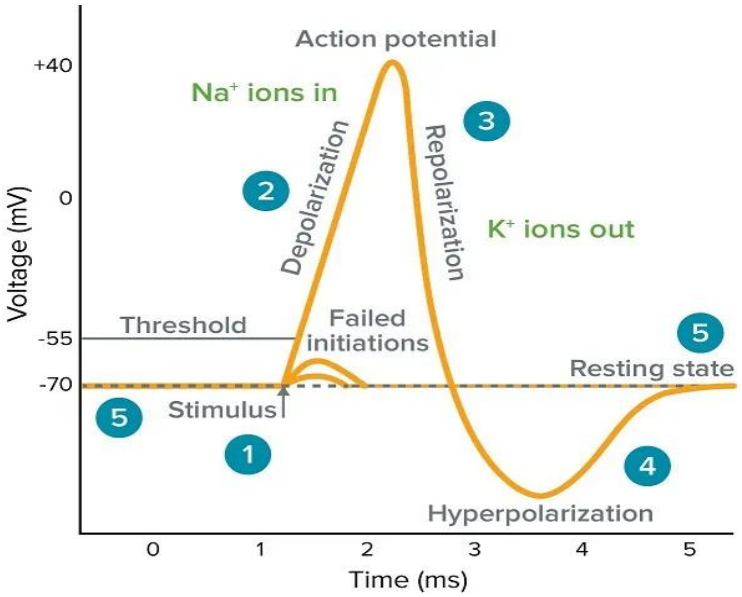

Fig. 1.2 Different phases of an Action Potential

[23], [24]. Opposing charges are found in the neighbouring regions of the nerve membrane and in the vicinity of the excited region. Therefore, it can be said that an electrical circuit forms between these two areas, stimulating the surrounding area and causing an action potential. Because of this repetition process along the fiber's length, the action potential tends to move

through the nerve cell and reach far-off locations. The process of impulse propagation depends on various factors such as whether the nerve fiber is a myelinated one or a non-myelinated one.

1.1.1 Myelinated and Non-Myelinated Neurons

In the nervous system, myelinated and non-myelinated neurons are two different kinds of nerve fibers each having special structural and functional traits [25], [26], [27], [28]. The myelin sheath which is a fatty insulating layer made of glial cells, surrounds myelinated neurons which is produced by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) [29], [30]. The velocity of neuronal impulse propagation is faster for a myelinated nerve fiber than for a non-myelinated nerve fiber as in myelinated nerves, the action potential jumps from one non-myelinated region known as the Node of Ranvier [31], [32] that exists between the myelinated segments to the other Node of Ranvier by a process called Saltatory conduction [33], [34], [35], [36]. Since myelinated neurons can conduct impulses up to 100 times faster than their non-myelinated counterparts, they are essential for processes that are required for fast reactions, like motor control and sensory perception. On the other hand, non-myelinated neurons do not have this protective covering, rather the cytoplasm of the Schwann cell envelops their axons without creating a myelin sheath. Because the action potential must travel continuously down the axonal membrane rather than bouncing between nodes, these neurons conduct impulses more slowly. Usually located in autonomic pathways, non-myelinated fibers are involved in the transmission of signals pertaining to dull pain or other slower processes [37].

1.1.2 Ion channels of neuron

Nerve ion channels are specific protein structures that are embedded in the membrane of the neuron and enable ions to pass through the cell membrane, which is normally impermeable to charged elements [18], [38], [39]. These channels play a crucial role in controlling the membrane potential of the neuron and facilitating the electrical signalling required for nerve activity. A single type of ion such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), or chloride (Cl^-), can normally pass through each selective ion channel. According to their gating mechanism, ion channels can be divided into two categories: ligand-gated which open when particular molecules (ligands) bind to them, and voltage-gated which open in response to variations in membrane potential [40], [41], [42], [43], [44]. Voltage-gated sodium and potassium channels are essential for the generation of an action potentials. The resting membrane potential is maintained in part by other channels, such as the leakage channels which

are constantly open. The various types of Ion channels are essential to the operation of the nervous system because they allow neurons to transfer signals, react to stimuli, and efficiently connect with other neurons through precise control of ion flow.

1.1.3 Active and Passive properties of Neurons

The capacity of the neuron to produce and transmit action potentials by opening the voltage-gated ion channels is referred to as its "active properties" [45], [46]. When the membrane potential hits a threshold, these characteristics become active and set off a series of actions. Upon depolarization, voltage-gated sodium channels open, allowing sodium ions to enter the cell and further depolarize it resulting in the action potential's upstroke. After the depolarization phase, the voltage-gated potassium channels open slowly, allowing potassium ions to leave the cell and resulting in the repolarization phase of the action potential. The action potential either fully occurs or does not exist at all with no variation in size because this process operates on an all-or-none principle [47], [48], [49], [50].

The interval after an action potential when a neuron's capacity to fire another action potential is diminished or momentarily inhibited is known as the refractory period of a nerve [51], [52], [53]. There are two distinct phases of the refractory period: The absolute refractory period and the relative refractory period. Voltage-gated sodium channels become inactive during the absolute refractory phase which precedes an action potential and prevents the neuron from responding to any new input no matter how strong. By preventing the signal from travelling backward down the axon, this period guarantees that action potentials are unidirectional. The relative refractory period, which comes after the absolute refractory period occurs when the voltage-gated potassium channels stay open while some sodium channels start to recover. The neuron can produce another action potential during this period, but it needs a far more powerful stimulation than usual to cross the threshold. In order to enable the neuron, moderate its response to high-frequency stimulation and ensure correct signal storage in neural circuits, the relative refractory time permits a controlled rate of firing. Rapid and coordinated communication across the neurological system is made possible by these active characteristics which are essential for nerve signal transmission.

The passive properties of a nerve are the intrinsic electrical characteristics of the neuronal membrane that affect the transmission of graded potentials or sub-threshold electrical impulses across the cell [54], [55], [56]. Passive properties rely on membrane resistance, membrane capacitance, and axial (internal) resistance rather than voltage-gated channels or

action potential production as in the case with the active properties. Membrane resistance affects the decay of electrical signals over distance by determining how easily ions may pass through the membrane. The capacity of the cell membrane to store charges is known as membrane capacitance and it influences how rapidly the membrane potential may change in response to an incoming signal. Internal resistance or the axial resistance affects how easily ionic currents could travel along the length of the neuron. All of these characteristics work together to control the signal's strength, speed, and range inside the neuron without initiating an action potential. Although passive characteristics cannot transmit long-distance or regenerative signals like active characteristics may, they are essential for early signal integration and aid in the neuron's interpretation of inputs.

1.1.4 Active and Passive Transport

The generation and transmission of electrical signals in neurons depend on both active and passive transport [57], [58]. By using diffusion, passive transport enables ions to follow concentration gradients across the nerve cell membrane without the need for energy input. When a nerve impulse initiates, voltage-gated sodium channels allow sodium ions (Na^+) to passively enter the neuron by following the electrochemical gradient. The membrane is depolarized by this quick inflow of Na^+, which causes the initial rising peak of the action potential. Likewise, during repolarization, potassium ions (K^+) escape the cell and passively diffuse down their concentration gradient to return the membrane to its resting state.

On the other hand, active transport needs energy, usually from ATP in order to move ions against their gradients. One of the most important active transport mechanisms in nerve cells is the sodium-potassium pump (Na^+/K^+-ATPase). A high concentration of Na^+ outside and K^+ inside the neuron is produced by this pump, which transports three sodium ions out of the cell and two potassium ions into the cell, maintaining the resting membrane potential which primes the neuron for the subsequent action potential depends on this imbalance. When ion channels open, the pump makes sure that ions are still unevenly distributed throughout the membrane allowing for quick reactions to stimuli. As passive and active transport work together, the neuron can produce rapid, fleeting changes in membrane potential during action potentials and maintain a steady resting potential. The neuron gets ready for future signals by active transport which restores the resting ionic conditions, while passive transport enables the quick depolarization and repolarization required for signal transmission. In the absence of this interaction between active and passive transport ion gradients would gradually equalize,

stopping signal transmission and the neurons would not be able to sustain repeated action potentials or remain prepared to react quickly. thus, for neurons to communicate and function, this equilibrium is essential.

1.2 Extracellular Space (ECS)

The Extracellular Space or the ECS, is the general term used for the pool of ions that surround a nerve fiber [59], [60], [61] with many studies suggesting its size to range in the nanometer scale with average gap between the spaces being 40 nm. However, Tønnesen et.al [62] has observed that the size of the ECS can be well above 1 μm (minimum = 50 nm, maximum = 3.2 μm, median = 0.27 μm) [62], but the microscope involved in their work failed to resolve structure which are less than 50 nm. This is significant as various other research findings has shown that the size of the ECS ranges in the nanometer scale [59], [60]. An ionic equilibrium for Ca^{2+}, Na^{+}, K^{+}, and Cl^{-} across the cell membrane is maintained by the fluid filled ECS that is similar in composition to that found in the brain ventricles. The cellular resting potential, neural action potentials, and synaptic transmission are all made possible by this ion filled ECS [61].

The ECS also possess a network of proteins and long-chain polymeric polymers in addition to an ionic fluid which is known as the Extracellular Matrix (ECM). The ECM primarily provides support and strength to the nerve fiber thereby providing structural stability and influencing neuronal repair. These matrix molecules frequently branch off from a hyaluronic acid backbone and include tenasin, chondroitin sulphate, and heparin sulphate [63]. Diffusion of ions is influenced by both the characteristics of the Extracellular Matrix and the shape of the ECS as the geometry of the ECS prevents molecules from diffusing freely in general, but the Matrix may behave more selectively towards molecules that bind to it sterically or electrostatically, or it may increase local viscosity.

Since, the ionic make-up of the ECS is similar to that of the interior ionic fluid nerve fiber, a larger ECS would facilitate more ionic flow from inside of the nerve fiber to the outside via the leakage channels due to its decreased resistance resulting in a higher signal attenuation. Similarly, a smaller ECS would provide much hindrance to the mobile ions to get dissipated from within the nerve fiber to the external media via the leakage channels due to its increased resistance resulting in a smaller attenuation of the neuronal signal [64]. Thus, it can be estimated that the size of the ECS has a significant influence on neuronal signalling. It is observed that the size of the ECS can be larger than the diameter of the fiber throughout the

development phase of the neurons [65]. Within the ECS, the Extracellular Matrix (ECM) and interstitial fluid serve as a dynamic environment that can change size in response to developmental needs and cellular activity [61], [63]. As neurons develops, the ECS must create room for the expanding axons and dendrites to facilitate its growth. Ions and signalling chemicals can move more easily through the larger ECS, which is essential for healthy neuronal function and communication. This spatial arrangement enables chemical signals to go across the ECS and reach target cells through effective volume transmission. Thus, it becomes further interesting to dwell into the intricacies of the ECS in influencing neuronal signals.

To have a wider understanding of the functionalities of the brain such as memory, synaptic connections, sleep, etc. a thorough and clear focus on the ECS is of utmost importance. Thus, it can be said that understanding the ECS in-depth holds a great significance in the field of fundamental neuroscience concerning signal propagation, drug delivery, neurological disorders, etc [65]. The fundamental research conducted on the ECS is still not adequate to solve various questions involving signal transmission through the neurons as no clear and credible structural image of the various ECS channels and reservoirs exists; thus, a need to develop such a technique is of utmost importance to map the ECS of the brain in detail [66].

During cortical spreading depression (CSD) (inactivation of brain neuron) and ischemia (lack of oxygen in the nerve tissue), the ECS is found to shrink to about 50% of its initial concentration which is seen from the maximal increase in the concentration of choline and N-TRIS. Moreover, during CSD a 2-fold raise in the brain tissue impedance and during ischemia a marginal increase in impedance is also found during the depolarization phase [67]. Moreover, it is also seen that during ischemia, dead space volume increases from 40% to about 60%. [68]. Furthermore, it is also observed that the ECS serves as an effective medium for drug delivery during chemotherapy [69]. Thus, looking at all the significant attribute of the ECS, it can be justified that the ECS plays a major role in effecting neuronal signal transmission.

1.2.1 Composition and Function of the Extracellular Space

The Extracellular Space (ECS) mainly consists of the following:

i). **Interstitial Fluid:** The interstitial fluid has the same composition as the cerebrospinal fluid which contains essential ions such as sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}). The main functions of these ions are to maintain the

ionic balance which is needed to maintain the normal resting potential of the neuron [60], [65].

ii). **Extracellular Matrix (ECM):** The Extracellular Matrix is mainly functions to provide the structural support to the neuron and is composed of various polysaccharides and proteins [61], [70], [71]. The important components of the ECM are:

- **Proteoglycans** such as chondroitin sulphate and heparan sulphate that interacts with various signalling molecules.
- **Glycoproteins** such as fibronectin and laminins that play an important role in adhesion and migration.
- **Hyaluronic Acid** which functions as the supporting element for other components of the ECS [63], examples include structural support and space filling matrix, formation of perineuronal nets, regulation of the formation of synapse.
- **Metabolites and Signalling Molecules** such as neurotransmitters, hormones, growth factors etc. that are involved in facilitating the communication between the neuron and glial cells.

The ECS performs several key functions which such as **(a)** Volume Transmission i.e., the ECS serves as the pathway for neurotransmitter and other molecules to diffuse over the distance, **(b)** Cellular Interaction between the neuron and the glial cells and **(c)** Regulation and Diffusion i.e., the factors such as tortuosity (complex pathway that a molecule takes) and viscosity which are important for rapid diffusion of neurotransmitters. These features make ECS unique in the sense that the ECS is an important parameter which shall not be neglected while studying neuronal signal transmission.

1.2.2 Local Field Potential (LFP)

The electric potential measured in the ECS of brain tissue, usually with the use of micro-electrodes is known as the Local Field Potential (LFP). Electric currents and charges in brain cells, such as neurons and glial cells produce the LFP [72], [73], [74], [75][76]. The LFPs are different than that of the electroencephalogram (EEG) and Electro-Corticogram (EcoG); an EEG is recorded with macro-electrodes and at the scalp's surface and an EcoG is recorded from the surface of the brain using large subdural electrodes, the LFPs on the other hand are recorded in depth from inside the cortical tissue (or other deep brain structures). Thus, LFP provides signals that are much refined in comparison to an EEG or an EcoG [77], [78]. Apart from these

variations, the oscillations in EEG and LFP signals during wake and sleep states are identical. According to the current understanding, synchronized synaptic currents that arise on cortical neurons possibly as a result of dipole formation produce EEG and LFPs, but the LFP may be influenced by any of the ionic currents in neurons. Although intrinsic voltage-dependent currents and spikes may also play a role, synaptic currents in neurons are thought to be the primary cause of LFPs. It is common practice to model extracellular LFPs as originating from a collection of current sources contained in a homogenous Extracellular medium. This formalism is capable of accurately modelling a number of extracellular LFP features, but it ignores the frequency-dependent attenuation of these potentials with distance, which is a crucial feature for accurately modelling extracellular spikes.

1.3 Nerve Conduction velocity (NCV)

The nervous system depends on the nerve conduction velocity (NCV), a crucial parameter of how quickly electrical impulses travel through nerves [79], [80], [81], [82]. The NCV study is crucial because a detailed understanding of the it can help identify and treat a number of neurological conditions. Changes in the NCV can reveal the health of the nerve fibers, with slower conduction often signifying neuronal diseases or nerve damage. Therefore, understanding the NCV is essential for assessing the extent of nerve dysfunction, diagnosing and monitoring neurological illnesses, and establishing therapies to restore normal nerve function. Faster nerve conduction is crucial for processes requiring quick reflexes and fine motor control, while slower conduction may impair these abilities leading to delayed reactions. Hence, NCV is a crucial marker for clinical evaluations and the study of nervous system disorders.

The Nerve conduction Velocity can be influenced by a variety of factors such as the fiber anatomy, myelination etc. It is understood that fiber with a greater diameter possess a higher NCV than a fiber with a smaller diameter [83], [84], [85], [86]. A nerve fiber with a larger diameter has a higher conduction velocity because the internal resistance of the is decreased by the larger cross-sectional area of the larger nerve fiber. Ions can flow along the nerve fiber more freely and quickly which speeds up the transmission of the electrical signal and in comparison, to a smaller diameter fiber, action potentials can propagate more quickly in larger fibers due to the efficient ionic movement. The conduction velocity also gets affected by the presence or absence of the myelin sheath. It is observed that myelinated nerve fibers possess faster conduction velocity than non-myelinated nerve fiber [87], [88], [89], [90]. The insulating

qualities of the myelin sheath allow myelinated fiber to conduct impulses more swiftly than a non-myelinated fiber. By limiting ion exchange with the ECS, this myelin insulation greatly reduces ion leakage and lowers the capacitance of the membrane, which enables the membrane to store less charge and react to voltage changes faster. Rapid depolarization is made possible by the concentration of voltage-gated ion channels at the Node of Ranvier and due to this structure, electrical impulses can "jump" from node to node (Saltatory conduction) rather than moving continuously along the length of the axon as they do in non-myelinated fibers. The propagation time of the nerve signal is substantially reduced by this jumping mechanism, leading to quicker conduction velocity. Since, the ECS has a substantial role to play in shaping the neuronal signal, it can also be inferred that the ECS play a major role in influencing the NCV. Hence. it is essential to drive deeper into the intricacies of the role the ECS plays in governing the conduction velocity of the neuronal signal in order to develop a holistic understanding of several neurological disease that are synonymous to the slow conduction of nerve signal which could potentially open up avenues for further scientific understanding and developing therapeutic measures to tackle these conditions.

1.4 Motivation

Significant research related to the ECS, synaptic communications, localized active ion channel distribution in the dendritic arbour, active and passive membrane dynamics, and their possible role in forming neuronal signals has previously been reported in the field of neuroscience. Nonetheless, there is a gap between the experimental results regarding the role of the ECS with neuronal morphologies and electro-chemical, electrophysiological, and physicochemical characteristics and their likely contribution to the formation of the neuronal structure-function relationship. Various experimental works pertaining to the ECS, involves modeling the Local Field Potential (LFP) or determining the ionic and matrix component of the ECS. But it is also understood that the size and the related parameters of the ECS has a significant influence in governing the neuronal signal. The basic cable model of the nerve proposed by Rall [91] pertains to the parameters of the nerve fiber only without considering the ECS related terms. Moreover, work done by Holt and Koch [75] that incorporates the ECS related parameters into the cable model involved finding the LFP which involves much complex mathematical and computational operations.

Taking everything into account, it can be concluded that a complete grasp of the ECS holds the possibility of presenting new discoveries in the field of neuroscience and providing

a clear picture of how the ECS affects the signal transmission via a neuron. In this regard, an effective and robust mathematical framework is essential that would be less mathematically and computational complex, could also replicate the working of biological neurons and would be useful in providing a holistic understanding of nerve signal propagation under the effect of ECS.

This thesis aims to address gaps in the existing literature by developing a robust and efficient mathematical framework to investigate the influence of the ECS properties such as its size, resistance, and conductance on neuronal signal generation and transmission. The model seeks to provide deeper insights into how neurons function under the effects of the ECS. Moreover, it is also understood that the biological system possesses a Rescue Protein mechanism to alter the effect of voltage shift that the neuronal signals undergo owing to genetic mutations. But a robust mathematical model to replicate this Rescue Protein mechanism is still warranted. Thus, the thesis also aimed at bridging this gap in the field of neuroscience with a robust mathematical model which also incorporates the parameters pertaining to the ECS in-order to have a holistic approach in studying the Rescue Protein mechanism.

Since the work involved in this thesis is aimed towards developing an understanding of the ECS and its related parameters such as its resistance, diameter and length on influencing neuronal signalling, the calculations of the Local Field Potential (LFP), and the Extracellular Matrix (ECM) components are not considered to avoid the complexity associated with the electric fields and matrix variations. By focusing on the direct impact of ECS on signal dynamics, this method sheds light on how spatial variations alone impact conduction efficiency and signal fidelity rather than being impacted by other extracellular factors.

1.5 Objectives

The objective of the thesis is to understand how the ECS affects neuronal signal for both a passive and active nerve fiber under different conditions. For this, the ECS related parameters are incorporated into the traditional cable model and nerve membrane potential expression has been derived for different scenarios. The proposed thesis also involves work that put forward a robust mathematical framework to study the efficacy of the Rescue Protein mechanism in mitigating the effect of voltage shift to the gating variable owing to genetic mutation. In summary, the main objectives of the thesis are as follows:

- **Mathematical modeling and simulation of Neuronal Axon to understand the effects of Extracellular Space on neuronal signal dynamics.** Works related to the ECS have shown their significant importance in signal propagation as any increment or decrement in its size can cause significant alteration to the propagating signal. Thus, understanding the ECS in-depth is of significant essence when it comes to understanding the nerve signal propagation along the neuronal fiber.
- **Study and modeling of Velocity Profile of Axonal membrane due to Non-Homogeneous Extracellular Space.** The Nerve Conduction Velocity study is crucial as several neurological issues arise due to the slow propagation of the nerve signal. Since a nerve fiber is surrounded by the ECS, its role in influencing the conduction velocity shall not be ignored. Thus, the velocity profile for neuronal signal under different combinations of the ECS size, and fiber anatomy might highlight significant findings.

1.6 Materials and Methods

It is commonly known that a single neuron model is an important computationally intensive unit for investigating basic neuronal behaviour, such as the onset and conduction of action potentials. Studies on the nervous system is aided by its simpler framework for investigating how neurons interact and react to changes. The work conducted in this thesis involves investigating the role of varying ECS on neuronal signal and for this purpose, single nerve model has been used extensively. The well-known Rall's cable model has been modified to incorporate the ECS dependent parameters in order to have a holistic approach in understanding neuronal signal transmission which is also mathematically and computationally less complex. Moreover, the incorporation of the ECS dependent parameters makes the framework relate much closer to a biological neuron, widening the scope for a better interpretation of neuronal signalling.

Local Field Potential (LFP) which is the electrical potential recorded in the ECS and the Extracellular Matrix (ECM) parameters have been omitted in this thesis to avoid the complexity associated with the electric fields and matrix variations and also because the work extensively focusses on the impact of the ECS on neuronal signalling rather than the extracellular potential or the proteins available in the ECS that mainly used for providing support and strength to the nerve fiber.

1.7 Organisation of the Thesis

The thesis is organized as follows:

Chapter 1: Introduction

This chapter 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 nerve fibers and its make-up, the ECS that surrounds a nerve fiber and its importance in governing neuronal signal, and other factors that governs neuronal signals. The chapter concludes with a summary of the primary objectives of the thesis, laying the groundwork for an in-depth investigation.

Chapter 2: Literature Survey

This chapter 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: Extracellular Conductivity and Neuronal Activity: Consequences for Nerve Signal Transmission and Neural Development

This chapter involves examining the effect of neuronal activity and how it influences neuronal growth. Furthermore, this chapter also examines the effects of varying ECS on neuronal signal transmission.

Chapter 4: Effective Nerve Signal Transmission through an Axon without Information Loss in Extracellular Space

This chapter aims to comprehend the similarities in the neuronal signal between two distinct axon locations under the effect of an ECS of constant diameter. An action potential is first originated at a node of Ranvier, then the similarity between the original signal and the signal when it reaches the next node of Ranvier, following its propagation via a myelinated segment, is then analysed to find the similarities or dissimilarities between them.

Chapter 5: Extracellular Space and its role in neuronal signal transmission for both Healthy and Diseased Nerve Fiber

This chapter involves mathematical modeling and simulation to obtain a membrane potential expression incorporating the fundamental parameters of the ECS to study signal transmission in healthy and diseased nerve fiber under the effect of ECS of varied sizes. Moreover, this chapter also involves proposing a robust mathematical model for the Rescue Protein mechanism that biological systems have that could alter the voltage shift in the gating variables that resulted from genetic mutation.

Chapter 6: Study and Modeling on Effect of Extracellular Space on Velocity profile of neuronal signal transmission

This chapter involves mathematical modeling and simulation to understand how the ECS of different sizes affects the conduction velocity of the neuronal impulse. Since, slow conduction of the neuronal impulse is synonymous with various neurological issues, the study attempts to shed light on the possible contribution of the ECS in this regard.

Chapter 7: Conclusion

This chapter aims to present the research findings in depth. Furthermore, this chapter also covers the future scope of the work undertaken in this thesis.