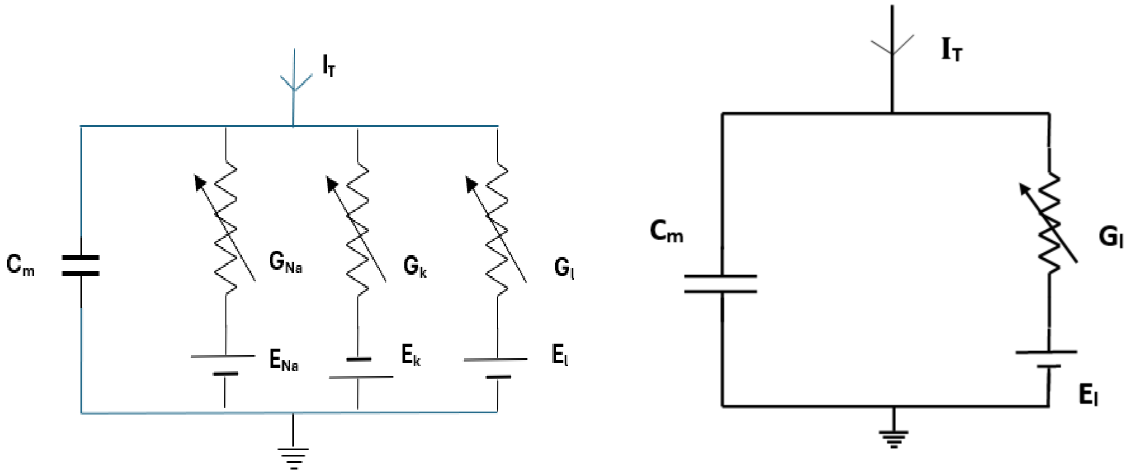
Chapter 2

Literature Survey

This chapter involves an extensive review of the state-of-the-art literatures available on the electrical equivalent model of neuron, the cable representation of a nerve fiber, the ECS and how it impacts neuron dynamics, and the conduction velocity of the neuronal signal. The electrical equivalent representation of a nerve fiber and the cable representation of the same has been incorporated to develop an understanding of how neuronal signals get transmitted along a nerve fiber.

2.1 The Electrical Equivalent Nerve model

Understanding the mechanics underlying nerve signalling and conduction requires equivalent models of the nerves. For communication within the nervous system, these models offer a framework for representing how neurons produce and send electrical impulses. The intricate behaviour of ion channels and membrane potentials may be modelled in terms of circuits, which makes it feasible to model and forecast how nerves react to stimuli, adjust to changes, and suffer from illnesses. In this regard, the electrical equivalent model of a nerve plays an important role as it helps to mimic the characteristics of a real nerve, making signal analysis feasible. It is necessary to have a thorough understanding of the morphology, electrical structure, and localized dynamics of neurons in order to comprehend their computational potential. One must comprehend the dynamic spectrum of computational capabilities resulting from connectivity with other neurons in addition to the physiological features. Several electrical models that mimic the behaviour of neurons include the non-leaky and integrate-and-fire model [92], [93], the Hodgkin and Huxley model [17], the leaky integrate-and-fire model [94] and the exponential integrate-and-fire model [95], [96]. One of the most commonly and extensively used electrical equivalent model of a nerve is the Hodgkin-Huxley model or the H-H model. The Hodgkin-Huxley (H-H) model is a mathematical framework that uses ionic currents across the cell membrane to describe the electrical properties of excitable cells, especially nerve cells. In 1952 Alan Hodgkin and Andrew Huxley developed this model [17], which sheds light on the generation and propagation of action potentials along nerve fibers. The dynamics of ion channels, particularly those involving sodium and potassium ions as they pass through voltage-gated channels are described by equations that are incorporated into the H-H model. In reaction to variations in membrane potential, these channels open and close regulating ion flow and generating electrical signals. Four essential variables are at the heart of the H-H model: a leakage current, sodium conductance, potassium conductance, and membrane potential. The rate constants for each kind of ion channel serve as the foundation for the model's equations which compute the rates at which channels open and close, hence varying the membrane potential over time. Although it is based on the squid giant axon, this innovative model is still fundamental to neurobiology and has been modified to examine a variety of neurons. By offering a foundation for simulating neural behaviour and investigating neurological diseases, the H-H model not only improved our comprehension of nerve physiology but also had an impact on computational neuroscience. The H-H model of nerve can be represented as both an active nerve fiber and a passive nerve fiber depending upon the requirement. While representing the active nerve fiber, the voltage-gated ion channels are incorporated into the model which shows the exchange mechanism of ions in and out of the nerve membrane. While representing the nerve fiber in terms of its passive properties, the active voltage-gated ion channels are omitted from the electrical representation of the nerve.



(a) **(b)**

Fig.2.1 (a) Equivalent Circuit of an Active nerve Membrane Model **(b)** Equivalent Circuit of a Passive nerve Membrane Model

2.2 The Cable Representation of a nerve

Axons in particular are frequently represented as a cable because of their anatomical and functional characteristics. The reason for this is because the cylindrical form of axon enables effective long-distance electrical impulse transmission. This illustration makes it easier to comprehend how signals move through the nervous system by taking into consideration variables that impact signal integrity and speed, such as capacitance and resistance. One of the important representations of a nerve fiber as a cable is given by Wilfrid Rall [91], which is known as Rall’s equivalent cylindrical model. This model, which was first presented by Wilfrid Rall, depicts the dendritic tree of a neuron as a single cylinder enabling researchers to use mathematical concepts to forecast the propagation of electrical signals inside the neurons. The cable theory, which explains how voltage and current vary along the axon or dendritic length, serves as the foundation for the model. Rall made it possible to derive analytical solutions to the cable equation by collapsing the complex branching of dendrites into an equivalent cylinder. This allowed for insights into the spatial distribution of electrical signals and synaptic input effects. This method has impacted current computational models in neuroscience and greatly advanced our knowledge of neural function.

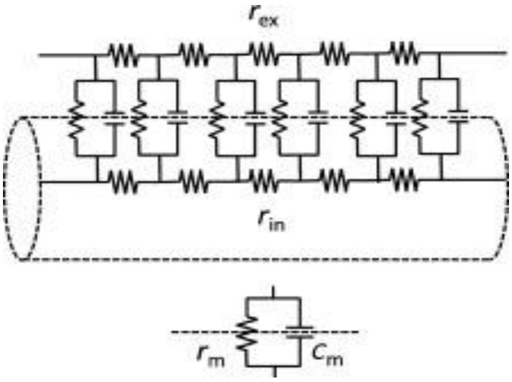


Fig.2.2 Cable representation of a nerve

Wilfrid Rall [91], [97], [98], [99], [100] conducted significant research on the behaviour and characterisation of a passive dendritic fiber, leading to the development of Rall's equivalent cylinder and Rall's 3/2 rule. A principle in neuronal branching, specifically how dendrites split to maintain efficient signal transmission, is described by the Rall 3/2 rule. This rule states that when a dendrite splits into two smaller branches, the diameters of the two smaller branches added together to the power of three-two should equal the diameter of the parent branch increased to the same power. Through this relationship electrical conductance throughout the branching structure is optimized and signal loss is reduced. It is predicated on the notion that information can flow smoothly across intricate dendritic trees because this particular diameter ratio preserves electrical characteristics like resistance and capacitance. The role of non-linearities in dendrites may not be adequately covered by Rall's postulates despite the fact that they support some of the characteristics of a small class of neurons.

2.3 Extracellular Space and its related works

The region around a nerve fiber that consists of a pool of ions is known as the Extracellular Space (ECS) [59], [60], [61], [66], [69]. As the nerve membrane is porous in nature, the effect of the ECS is thus significant in governing neuronal signals. Holt and Koch [75] in their work, has successfully managed to provide a mathematical model of the extracellular potential of the ECS which is known as the Local field Potential (LFP) using the one-dimensional cable theory and the volume conduction theory. However, their work primarily focussed on the LFP calculation and thus the variation of the nerve membrane potential due to the influence of the ECS is still sought about. Nicholson and Hrabětová in their work [60] have observed that the ECS occupies about 20% of the brain tissue with average spacing of about 40 nm. However, Tønnesen et.al [39] 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. Bedard and Destexhe [64], in their work has observed that the phenomenon of resonance is observed due to the diffusive extracellular impedance but, the resonance frequency only depends on the parameters pertaining to the membrane and not the structural parameters.

The ECS is also an effective medium for drug delivery especially during chemotherapy [69]. This region is packed with extracellular matrix and interstitial fluid which makes it easier for therapeutic drugs to diffuse straight to the target cells. Because of its distinct geometry and makeup, the ECS affects how medications transport throughout the brain, enabling targeted therapy with the least amount of systemic side effects. Goldin et.al, in their work [101] has observed that the ECS's spatial organisation changes with sleep, development, and ageing and it is most likely altered in neuropsychiatric and degenerative disorders. Moreover, Bakay has observed that when compared to normal brain tissue (6-7%), the ECS was found to be enlarged in gliomas (20–40%) (type of tumour in brain and spinal cord) during brain tumours [102]. Zamecnik in his work,[70] has also observed that, when compared to the unaffected cerebral cortex, the ECS volume of gliomas substantially increases, which is also correlated with an increase in malignancy. Furthermore, Thorne and Nicholson have observed that the diameter of the ECS falls below 10 nm after severe ischemia (reduced oxygen level in the brain) [103] and Bruehlmeier, et.al, has also seen that during brain edema, the ECS size swells up [99]. Keeping all these factors under consideration, it can be said that the ECS plays a major role in governing neuronal signal and also provides a key pathway for effective drug delivery and treatment.

Thus, incorporating the ECS related parameters into the cable model of nerve would therefore provide a better approach towards studying neuronal signal transmission in-detail as the framework thus developed would be robust and holistic.

2.4 Nerve Conduction Velocity and its derivation

The nervous system depends on nerve conduction velocity (NCV), a crucial measure of how quickly electrical impulses travel through nerves also it is an important parameter for facilitating faster and efficient communication between the brain, spinal cord and other part of the body [79], [81]. Works done by several researchers has highlighted key aspect of the neuron parameters that affects the conduction velocity. Rushton [104] has observed that the conduction velocity of neuronal impulse is proportional to the fiber diameter whereas, similar observation has also been made by Hursh in his work [105] where he proposed that the relationship between the conduction velocity and fiber diameter is linear in nature. Moore et.al, in their work [106] has observed that the nodal region and the precise description of its excitable processes were found to have no effect on the conduction velocity and if the number of myelin insulation turns is kept constant, an increase in diameter can produce a comparable fractional gain in velocity. Goldman and Albus [107] however has observed through mathematical modelling that for non-myelinated fiber, the conduction velocity is proportional to the square root of the diameter of the axon. One of the important works based on NCV and the fiber anatomy was conducted by Hodgkin [81] where he observed that, as long as the membrane's overall area is constant and the stretch does not change the local electric characteristics of the membrane, the velocity in a fiber with a folded membrane should be independent of the fiber's length. Moreover, the conduction velocity of fibers with the identical membranes and axoplasm should change as the square root of the fiber diameter when measured in a large volume but, when evaluated in small volumes, a fiber's conduction velocity should be inversely proportional to the square root of the total resistances, both internal and external per unit length.

Ikeda and oka [89] tried to understand the relation between motor nerve conduction velocity (MCV) and morphological alterations in regenerated nerve fibres at various points following sciatic nerve transection and observed that the MCV remained below the control velocity but gradually rose over time following nerve transection. After nerve transection, the mean fiber diameter (axon plus myelin sheath) likewise grew over time. Despite the fact that regenerating nerves probably comprised a large number of tiny nonconducting fibers, recovery of mean fiber diameter showed a strong correlation with MCV. Col et.al, in their work [108] has observed that the primary cause of activity-induced variations in conduction velocity in unmyelinated axons is a shift in the quantity of sodium channels that are accessible and the interaction between residual sodium channel inactivation after each impulse and the retrieval of channels from inactivation by a concurrent Na^+–K^+-ATPase-mediated hyperpolarization determines the axonal conduction velocity at moderate stimulus frequencies. Since sodium channel availability is the primary determinant of the process, monitoring conduction velocity offers a way to access relative variations in nociceptive neuron excitability. Smith and Koles in their work [109], has proposed that while evaluating the consequences of illnesses or any other condition that causes de-myelination, the myelin internode's contribution to impulse propagation is a crucial phenomenon and they based their work on the basis of Goldman and Albus's work [107]. The above-mentioned literatures did provide some valuable insights into the Nerve Conduction velocity (NCV) study, however these works focussed primarily on the parameters pertaining to the nerve fiber and the ECS parameters are omitted in their works. Since, it is established that the ECS holds a significant influence on the neuronal signal generation and propagation, thus its impact shall not be neglected.

One of the key methods of mathematically modeling the NCV of a nerve fiber has been proposed by Goldstein and Rall [110] in which they gave the relation between the action potential shape and its velocity. To understand the speed at which nerve impulses propagate, they have examined various shaped cylinders in their work. They noticed that, for a cylinder of uniform length or one with a constant diameter, the impulse propagates at a uniform velocity along the length of the cylindrical tube; however, as the cylinder's shape changes, the velocity of propagation neither travels at the same velocity nor at a constant velocity. They calculated the velocity (θ) in their model as dx/dt. They have shown that the value of 'θ' is not only same for all the corresponding points, but its value remains constant as the action potential propagates along the uniform cylinder i.e.

$$\frac{\partial x}{\partial t} = -\theta(\frac{\partial v}{\partial t}) \tag{2.1}$$

Here, V is the deviation from the resting value and this formula demonstrates that, with the proportionality constant denoted by θ, the action potential's shape in the time domain is proportional to its shape in the distance domain. When a cylindrical tube has a non-uniform shape, meaning that its shape changes along the fiber, then Eq.2.1 can be expressed as:

$$\frac{\partial v}{\partial t} = \frac{dv}{dt} - (\frac{\partial v}{\partial \mathrm{x}})(\frac{\partial x}{\partial \mathrm{t}}) \tag{2.2}$$

2.5 Summary

The mathematical models that pertain to the nerve fiber holds key to finding out various intricacies associated with neuronal signal generation and transmission. Mathematical modeling and simulation provide a unique opportunity to understand the neuron in detail as it could potentially mimic the behaviour of a real nerve fiber. However, various works that has been undertaken to study neuronal signals through formulating the membrane potential of the signal through a mathematical model consists of the parameters pertaining to the nerve fiber itself. As it is well established that the ECS plays an important role in governing the neuronal signal, incorporation of its parameters shall not be neglected as incorporation of the ECS related parameters would provide a holistic approach towards studying signal transmission in details. Improved diagnosis of neurodegenerative diseases, improved understanding of network dynamics as a function of individual neurons, and the development of better prosthetic devices are all made possible by individual neurons influencing network level interpretation from the bottom up. Thus, it is essential to develop mathematical models that are robust, holistic yet which are computational and mathematically less complex.