Chapter 2: Literature survey

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Problems are not stop signs, they are guidelines
-Robert H. Schuller

2.1 Introduction

Over the past century, studies of impulse propagation through myelinated nerves have been made by different professional areas [1]. Since 1960s, these researchers have gathered a huge amount of data corresponding to analytical interpretations, demonstrating the physiological importance of myelination [2]. In this direction, some of the engineering community begun to study the phenomenon of saltatory conduction and started constructing electronic nerve models. Investigations on the properties of the nerve fibers have been always an important and interesting area of research in the field of neuroscience. The descriptions and interpretations made on the basis of the morphology, biochemistry and physical chemistry of the nerve fiber helped the neuroscientists, neurophysicians, neuroengineers, and mathematicians to collect a great number of experimental data and facts to understand the mechanism of physiology of a normal nerve as well as the factors underlying the disease of the abnormal nerves in the nervous system [3, 4].

Before proceeding towards our proposed work, a thorough and comprehensive survey on the nerve excitability properties including the abnormal physiology of the nervous system is required in order to achieve fruitful results and observations. A brief review on some of the important existing electrical circuit models is also necessary for motivation to design our proposed models. In this direction, this chapter is dedicated to the theoretical background and work done for the peripheral nervous system with the inclusion of the primitive mathematical models.

2.2 Electrophysiology of peripheral myelinated nerves: an overview

The myelinated nerves in the peripheral nervous system consist of concentric spiral layers of myelin sheath produced by the Schwann cells in the PNS which wraps around the axon [5] as shown in Fig-2.1 (a) and (b). Nerve fibers with larger diameter may possess around 50 concentric spirals of myelin while smaller fiber contains 2-3 such concentric layers [6]. A major advantage of myelinated nerve is that the myelin sheath wrapping around the axon increases the resistance to flow of ions through the membrane channels and reduces the membrane capacitance, thereby facilitating saltatory

conduction at the nodes by reducing the current across the internodal axonal membrane [7]. The nodes of Ranvier are the small gaps in the nerve without myelin sheath are present at distance of 1mm in larger diameter fibers while it is present at distances ranging from less than 100µm in smaller diameter fibers [8]. A longitudinal section of the PNS myelin sheath gives a clear view of the presence of nodes of Ranvier at the lateral extremities of each internode which supports saltatory conduction in the PNS nerve fiber [9-11] as shown in Fig-2.1 (a) and (b). The theory of saltatory conduction was first proposed by Lillie in 1925, followed by the pioneer works in 1930s by many Japanese workers in Kado's laboratory in the development of techniques dealing with the dissection of a single myelinated nerve to collect evidences about saltatory nerve conduction. Since then many workers started to work on the transmembrane properties along a myelinated nerve fiber to confirm saltatory conduction [12-14].

The myelin sheaths in the PNS possess a typical morphology. The cross sectional view of the myelin sheath provides a compact and spiral structure with basal lamina covered around it and cytoplasm associated with the outer layer [15, 16]. Mesaxon or membranous channel elongates and forms a loose spiral around the axon which announces the commencement of myelination in the PNS. The increase in length of the spiral mesaxon and extrudation of the cytoplasmic content between the layers results in the formation of compact myelin. The association of Schwann cells with the axon flattens out in a chain before the commencement of myelination. The basal lamina of adjustened Schwann cells continues and forms a tube like structure around the fiber [9, 17]. Thus the process of myelination proceeds with the longitudinal migration of lamellae towards the nodes of Ranvier [16-18].

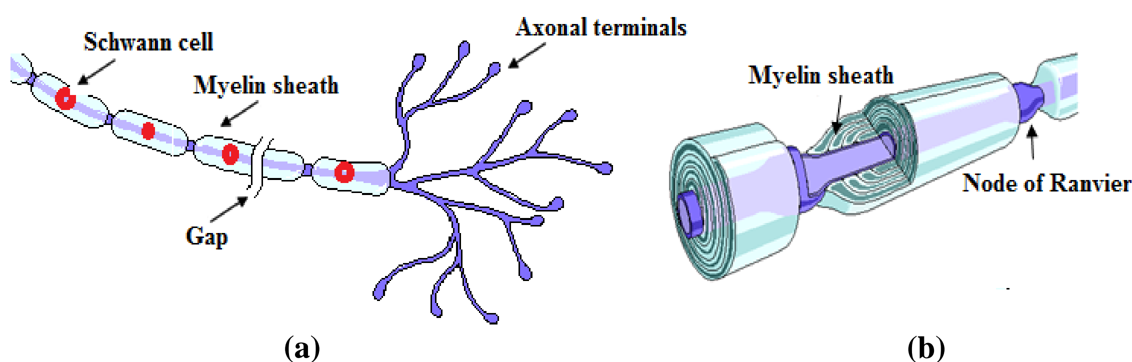


Figure 2.1: (a) Different parts of a myelinated axon and (b) cross sectional view of a myelinated axon.

A myelinated membrane consists of a phospholipid bilayers and membrane proteins. The ability to conduct, transmit and receive electric signals along a myelinated nerve fiber results from opening and closing of specific ion channel protein located in the plasma membrane of the nerve fiber [19]. Each ion channel is selective to flow of specific ions through the channel as shown in Fig-2.2. The generation of action potential is a cyclic process of membrane polarization, hyperpolarization and return to resting potential of the membrane. The conduction of action potential results from change in membrane potential caused by opening and closing of voltage-gated ion channels [20, 21]. The membrane consists of a voltage-gated Na^+ channel, responsible for opening and closing of channels that allows the entry and exit of Na^+ ions through the channel while voltage-gated K^+ channel allows passage of K^+ ions only across it. A small amount of Cl^- ions passes through the Cl^- channel. The opening and closing of the voltage gated ion channels causes a change in voltage across the membrane that leads to the propagation of action potential [22]. The opening of Na^+ channel causes an excess of negative ions on the outer surface of the membrane with more positive ions on the cytosolic surface. This causes depolarization of the membrane potential with less negative membrane potential, while closing of Na^+ channel reverses the action and causes hyperpolarization of the membrane with more negative potential [23]. In the meantime, the opening of K^+ channel hyperpolarize the membrane causing more negative potential with negative ions on the cytosol surface and more positive ions on the outer surface of the membrane. The closing of K^+ channel has a reverse effect on the membrane and again polarize the membrane with less negative membrane potential [24]. At the resting potential, no movement of ions takes place across the channels and the voltage-gated ion channels remain closed. Thus the conduction of axon potential over long distances depends on the opening and closing of the voltage-gated ion channels [21].

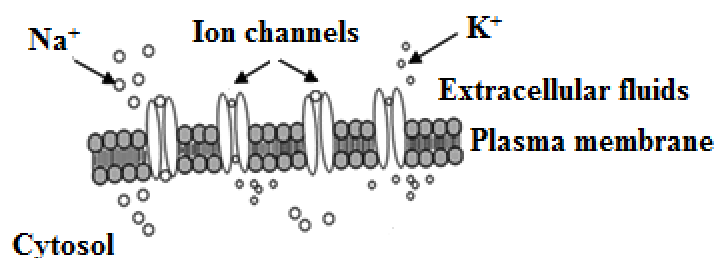


Figure 2.2: Transportation of Na^+ and K^+ through their respective ionic channels.

Another important feature of a myelinated nerve is related to the conduction speed of nerve impulses across the membrane. Myelin acts as an electrical insulator and speeds up propagation of action potential across a myelinated nerve possessing a larger diameter nerve fiber [9]. The action potential jumps from one node to another in a myelinated axon through saltatory conduction and possess a higher conduction velocity than an unmyelinated axon. The loss or degradation of myelin sheath unmyelinated and demyelinated nerve results in absence of saltatory conduction affecting the nerve conduction velocity as it is directly proportional to the diameter of the nerve fiber.

2.3 Some aspects of demyelination: an overview

Demyelination is referred to the disordered state of a nerve where the normal functioning of the nerve is affected due to the loss or degradation of myelin sheaths. The reduction of myelin sheath in demyelinating diseases affects the nerve impulse propagation by reducing the nerve action potential, thereby affecting the nerve conduction velocity in the peripheral nerves [25-27].

2.3.1 Demyelinating diseases associated with peripheral nerves

The disruption in the velocity of signal transmission and disordered domain organization of the myelinated nerve fiber are the important characteristic features of demyelinating diseases. These may sometimes lead to an axonal degradation and conduction block in severe cases [28, 29]. Some of the common demyelinating diseases of the peripheral nerves are Charcot-Marie-Tooth Disease (CMT), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Guillain-Barre Syndrome (GBS), Multifocal Motor Neuropathy (MMN), etc. [30, 31].

2.3.1.1 Charcot-Marie-Tooth Disease (CMT): CMT is a hereditary neuropathy of the peripheral nervous system [32, 33]. The patients suffer from slow and progressive weakness and numbness in the distal limbs. The symptom then proceeds towards the legs and finally ends in the patients' arms. The major types of CMT are:

- *Charcot-Marie-Tooth Disease Type 1(CMT1)* - It is also known as the hereditary motor and sensory neuropathy Type I (HMSN I) and is a type of demyelinating neuropathy. It degrades the myelin sheath of the peripheral nerve fiber [34]. A mutation in the peripheral myelin protein (PMP) 22 gene

causes a disorder of peripheral demyelination. This results in axonal segmentation along the nerve fibers affecting the conduction velocity in the motor and sensory nerves [35].

- *Charcot-Marie-Tooth Disease Type 2 (CMT2)* - It degrades the axon of the nerve fiber and is type of axonal neuropathy. It is also known as hereditary motor and sensory neuropathy Type II (HMSN II) [36]. This of disease results in axonal loss with Wallerian degeneration. However its conduction velocities of the propagated impulses along the axons remain close to its normal range [37, 38].
- *Dejerine-Sottas Syndrome (DSS)* - It is the severe type of demyelinating neuropathy and is recognized as hereditary motor and sensory neuropathy Type III (HMSN III) [39]. This type of disease is characterized by blocking of conduction in the sensory and motor nerves with considerable slow propagation speed of impulse within the range of 2-5 m/s [40].

2.3.1.2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Clinical investigations are still under process to examine the genetic basis and inheritance of this type of disease. In this type of disease, the immune system recognizes one or more component of the myelin sheath to be a foreign particle. As a result, the resultant antigen produced by reaction with antibody is believed to deform the structural integrity of the myelin sheath [41]. It affects the upper limbs of the patients with severe generalized disabilities. Diffused demyelination with slowing or blocking of conduction potentials in the motor and sensory nerves is an important characteristic of this disorder. Both the proximal and distal muscles are affected and may occur simultaneously with other systemic diseases [42, 43].

2.3.1.3 Guillain-Barre Syndrome (GBS): The presence of human immunodeficiency virus (HIV), herpes zoster virus or hepatitis B virus infections in some patients is a characteristic feature of this type of syndrome. The patients with this type of disorder posses slow segmental conduction or blocking in certain parts of the nerves [44]. Based on pathological and electrodiagnotic criteria [45], GBS is classified in the following subtypes: acute inflammatory demyelinating polyneuropathy (AIDP); Fisher syndrome-

acute motor and sensory axonal neuropathy (AMSAN) and acute motor axonal neuropathy (AMAN).

2.3.1.4 Multifocal Motor Neuropathy (MMN): MMN is regarded as a unique variant of CIDP. Conduction block in multiple peripheral nerves is a critical diagnostic feature of MMN [46, 47].

2.3.2 Diagnosis of the demyelinating diseases

Neurologic diagnosis for disorders of peripheral nerves is a challenging issue for the clinicians with unknown nerve anatomy, physiology and pathological patterns. It requires a structured approach to evaluate the peripheral nerve disease by localizing lesion within the nervous system, determination of the pathology and the root cause of the disease [48]. Some major symptoms such as numbness, tingling pain and weakness in the limbs are associated with the demyelinating diseases. Demyelination and axonal loss are the two basic pathological processes to be determined for diagnosis, treatment and prognosis [49].

2.3.2.1 Neuro-diagnostic testing: The two most important components in neuro-diagnostic testing are nerve conduction studies (NCS) and needle electromyography (EMG) [50].It is performed for differentiating axonal loss and demyelinating pathological processes. NCS provides informations about involvement, distribution and severity of involvement of different types of nerves and its underlying pathology. NCS are suitable for the study of distal muscle. NCS are useful for understanding the physiology, pathology and functional state of a nerve [50-52]. It is performed by percutaneous electrical stimulation of all axons in a nerve and thus record the resultant evoked response. The placement of recording electrodes differentiates between sensory nerve conduction studies and motor nerve conduction studies. As the conduction velocity of a nerve is directly proportional to the axon diameter, NCV within a nerve ranges from ~ 35-70 m/s for sensory nerve and ~ 35-55 m/s for motor nerve [53]. Beyond these range, the nerves are treated as abnormal. Sensory and motor nerves are studied separately by varying the placement of the recording electrode. In sensory nerve, the recording electrode are placed over the nerve to study the activity of all sensory nerve action potentials by recording the evoked response (SNAP) [54] whereas, the

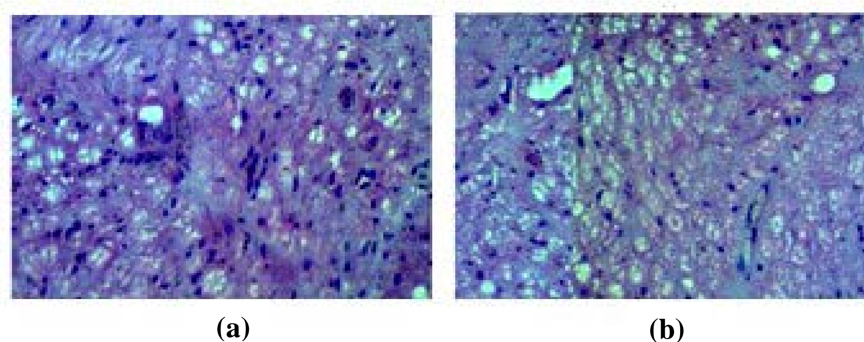
activity of all muscle fiber action potentials is studied by recording the evoked response of compound muscle action potential (CMAP) with recording electrodes placed over the muscle [55]. Motor nerve studies are more useful than sensory nerve studies because the responses required to distinguish between demyelination and axonal loss is absent in sensory nerve studies.

EMG deals with information on motor nerve involvement and chronicity of the process [56]. Needle EMG allows assessment of almost any muscle and provides information on the rate of axonal loss. It is performed by inserting a fine needle into a muscle to compare the amount of electrical activity present in the muscles as shown in Fig-2.3. EMG tests help to differentiate between muscle and nerve disorders [57, 58].

Figure 2.3: Nerve conduction study with Medicaid EMG machine Model No EMG-2000.

2.3.2.2 Biopsy: Biopsy is an invasive procedure performed for the evaluation of degree of disorder by the application of anesthesia. Based on the site of application, biopsy is classified into:

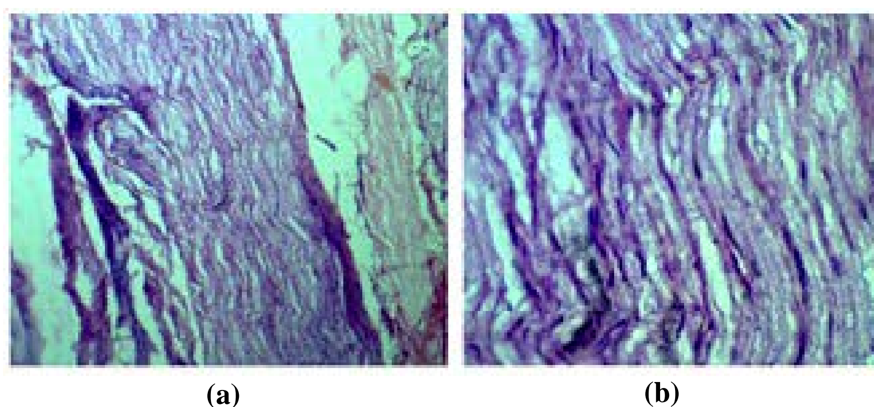
- *Nerve biopsy*: It is performed with a segment of nerve of several centimeter cut into pieces for several pathological processes. Nerve biopsy cannot differentiate between demyelination and axonal loss and are less informative as it is applied over a small segment of sensory nerve as shown in Fig-2.4. Infection due to nerve surgery and healing of the patients are the major drawbacks concerned with nerve biopsy [59].



(a) (b)

Figure 2.4: Nerve biopsy of (a) Patient’s id: 015 and (b) Patient’s id: 058, collected from Pathology Lab, GNRC Hospital, Guwahati, Assam, India.

- *Skin biopsy*: The use of skin biopsy for the study of peripheral neuropathy came into existence in the 1960s to investigate a variety of inherited neuropathy. Skin biopsy is used for observing the structures of sensory receptors and sweat glands. It is an important research tool for measuring small fiber neuropathy, severity and progression of disorder along the nerve fiber [60]. Study of peripheral neuropathy with the use of skin biopsy is a development and is performed by obtaining about 3 mm of the skin after the injection of a local anesthesia. The procedure is well tolerable with a least minimal risk of infection; the healing period of the biopsy site is recovered in about 2 weeks from the period of surgery. Standard light microscopy or confocal microscopy may be used to analyze the biopsy slides. Fig-2.5 represents the skin biopsy of two neuropathic patients collected from Pathology Lab, GNRC Hospital, Guwahati, Assam, India.



(a) (b)

Figure 2.5: Skin biopsy of (a) Patient’s id: 023 and (b) Patient’s id: 027, collected from Pathology Lab, GNRC Hospital, Guwahati, Assam, India

Skin biopsy is often performed in patients suffering from foot pain and numbness with a normal nerve conduction study. An abnormal skin biopsy confirms the occurrence of small fiber predominant neuropathy [61]. Thus skin biopsy is an important research and clinical tool used in the investigation of sensory peripheral neuropathy in the patients involving small diameter nerve fibers.

2.3.2.3 Computed Tomography (CT scan): It is a noninvasive and painless process used frequently for diagnosing the peripheral nerve disease. It is performed by applying X-rays over the nerve at various angles and is detected by computerized scanners. The data processed are displayed as cross sectional images of the nerves. However, the procedure is costly, less reliable and the data achieved may be considered as irrelevant findings leading to unnecessary treatment or surgery [62, 63].

2.3.2.4 Magnetic resonance imaging (MRI): MRI is another important diagnostic tool for the evaluation of peripheral nerve integrity and its architecture. High quality images of the peripheral nerves are obtained from routine clinical MRI scanners using commercially available MRI coils [64]. The advantage of using MRI over X-rays, ultrasonography and CT scans is that it provides sufficient contrast and spatial resolution multiplanar capabilities and flexibilities for evaluating disorder in peripheral nerves and muscles [65].

2.4 Strategies for recovery of neurological disorders

Scientists are concentrating on finding new treatments by refining existing methods and are also looking at the works of the immune system to find out the cells responsible for beginning and carrying out the attack on the nervous system. The fact that so many cases of Guillain-Barre begin after a viral or bacterial infection suggests that certain characteristics of some viruses and bacteria may activate the immune system inappropriately. Investigators are searching for those characteristics. Neurological scientists, immunologists, virologists, and pharmacologists are all working collaboratively to learn how to prevent this disorder and to make better therapies available when it strikes [66].

2.4.1 Cell therapy for neurologic disorders

Cell therapy for neurologic disorders means the use of cells of neural or nonneural origin to replace, repair or enhance the function of the damaged nervous system. This is also called neuro transplantation, and is usually achieved by transplantation of the cells that are isolated and may be modified by genetic engineering. Tissue engineering in the nervous system is the science of designing, creating, and realizing systems where neural cells are organized in a controlled manner, to perform appropriate diagnostic, palliative, and therapeutic tasks in the nervous system. The focus of this clinical summary is on cells used as therapeutic agents. Genetically modified cells that secrete therapeutic substances such as neurotrophic factors, or the use of cells as vectors for gene therapy and vehicles for drug delivery to the central nervous system are described in other clinical summaries. An overlap between cell therapy, gene therapy, tissue engineering, and regenerative medicine provides more effective treatment of nerve disorder [67].

2.4.2 Transplantation- Use of stem cells

Cell replacement therapy has provided the basis for the development of potentially powerful new therapeutic strategies for a broad spectrum of human neurological diseases. The transplantation of stem cells may provide effective treatments due to the self-renewing and multipotential nature of these cells, including delivery of therapeutic factors to provide trophic support or missing gene products, mobilization of endogenous stem cells and replacement of lost or dysfunctional cells [68].

Spinal cord injury invariably results in the loss of neurons and axonal degeneration at the lesion site, leading to permanent paralysis and loss of sensation below the site of the injury. It interrupts between ascending and descending axonal pathways that cause a loss of neurons and glia, inflammation and demyelination. Preclinical studies have been performed on rats with a spinal cord injury and have shown that transplanted Mesenchymal Stromal cells (MSCs) in the injured spinal cord survive, migrate into the host tissue and lead to axonal regeneration and motor function recovery [69].

2.4.3 Myelin repair

Techniques for repairing of damaged myelin sheaths include surgically implanting oligodendrocyte precursor cells in the central nervous system and inducing myelin repair with certain antibodies. While there have been some encouraging results in mice (via stem cell transplantation), it is still unknown whether this technique can be effective in replacing myelin loss in humans [70]. Some researchers hypothesize that those cholinergic treatments, such as acetyl cholinesterase inhibitors (AChEIs), may have beneficial effects on myelination, myelin repair, and myelin integrity. It is argued that increasing cholinergic stimulation also acts through subtle trophic effects on brain developmental processes and particularly on oligodendrocytes and the lifelong myelination process they support. It is possible that by increasing oligodendrocyte cholinergic stimulation, AChEIs and other cholinergic treatments like nicotine could promote myelination during development and myelin repair in older age (Myelin Repair Foundation) [71].

2.5 Historical background on the physiological studies of peripheral nerves

The theory of saltatory conduction by Lilie in 1925 has formed the foundation to many neuroscientists to develop scientific and experimental techniques for collecting evidences of saltatory conduction in myelinated nerves. The pioneer work by Hodgkin-Huxley [72-73] for quantitative description of nerve propagation in a squid giant axon has motivated many research groups to study the quantitative biophysical descriptions of the complete membrane properties of the node of Ranvier. Dodge and Frankenhaeuser [74] and Frankenhaeuser and Huxley [75] performed nerve excitability experiments on Rana pipens while Dodge [76] on Xenopus laevis using H-H equations. Later similar computation experiments were performed by Goldman and Albus [77] and Hardy [78] modifying Dodge equation for frog nerve and Frankenhaeseur and Huxley equation for toad nerve.

The first direct evidence of demyelination causing conduction block in the peripheral nerves come in to existence during World War II. Denny-Brown and Brenner

found that compression of peripheral nerves due to injuries produces a primary demyelination over short segments of about one internode without disrupting the axons. When simulation was applied in the nerves below the compressive lesion, it caused muscle contraction. But a simulation above the lesion was found to be ineffective producing conduction block [79, 80].

The application of saponin, a detergent in nerves was performed by Tasaki [81] to study the conductance and capacitance of a myelin sheath in demyelinated peripheral nerve. He observed that the saponin solution dissolves the myelin sheath and causes a propagation block in about 20-40 minutes. He found that capacitance and conductance increased proportionally with the decreases of the resistance in the degraded myelin sheath.

Mc Donald performed a series of experiments to witness the effects of conduction in the peripheral nerves by administering toxin parenterally into eats causing diphtheria neuritis in the dorsal root ganglia. He witnessed a decrease in maximal conduction velocity of the action potential which is proportional to the severity of demyelination [87-89]

Since then many experimental studies were carried out on animal models to witness the slowing of conduction velocity caused by degradation of myelin and segmented demyelination [85-88].

The first biophysical study of membrane excitability properties of demyelinated nerves was demonstrated by Rasminsky and Sears [89] by modifying the technique used by Huxley and Stampfi to determine the action currents in a single demyelinated nerve fiber. They observed that the conduction remained saltatory in the demyelinated nerve to the point of conduction block. They also examined the transmembrane current in blocked fibers to conclude that internodal capacitance increases while decreasing the internodal resistance in the paranodal area.

In the meantime, a new approach with the aid of computer to study experimental demyelination for quantitative stimulation of conduction in demyelinated nerve fibers

was emerging at a fast rate. Smith and Koles made the first computer simulation to study the effect of myelin thickness on conduction velocity [90].

The concept of nerve fiber coupling came into existence in the mid of 18th century. Since 19th century, many theories and experiments were evolved or performed to show transmission of electrical pulses (i.e. sequences of action potential) through nerve fiber influencing with activity of the surrounding nerve fiber [91]. Bokil et al. [92], Holt and Koch [93] and Katz and Schmitt [94] had already reported that two parallel and closely placed nerves can interact with each other ephaptically, thus creating impact on electrodynamics of one another. In 2011, Anastassiou reported the ephaptic coupling of cortical neurons [95].

The application of electrical stimulation for improving functional recovery in peripheral nerves is increasing rapidly in recent years. Electrical stimulation along with physical exercise increases neural activity enhances axon regeneration. In 2016, Gordon and English [96] reported that electrical stimulation and exercise are promising treatment for regeneration of peripheral nerves which may find its application in clinical use very soon. Chan et al. [97] developed a method of application of low frequency electrical stimulation in surgically repaired nerves to accelerate axon outgrowth at the repair site to enhance peripheral nerve regeneration. The application showed clinical feasibility and the positive impact of the stimulation was effective in patients with severe compressive neuropathy.

Taghipour-Faeshi et al. [98] developed a technique of recording nerve signals based on nerve cuff electrodes using F-N equation. The action potential amplitudes and nerve impulse velocity generated is similar to that of real life measurements. The results obtained can be used in computer simulation to the study the nervous systems. The further concluded that the observations made by using F-N equations can be used to record peripheral nerve signals in order to discriminate active fascicles in a nerve bundle.

The study of the pathophysiology underlying the mechanism of nerve dysfunction is ongoing process. Recently, Otani et al. [99] in 2016 studied the molecular organization and fine structures at and near nodes of Ranvier in a compression

neuropathy model by placing a silastic tube around the mouse sciatic nerve. They observed that show that chronic nerve compression disrupts paranodal junctions and axonal domains required for proper peripheral nerve function when observed through electron microscope.

A number of clinical trials of stem cells in demyelinating patients are being tested worldwide for regeneration of peripheral nerves. However, no such stem cells therapy has been yet approved clinically which could regenerate the nerve cells in neurologic patients [100-102].

Although adjuvant, targeted therapies that exploit the emerging pathways to neurodegenration may be applied to treat or prevent the inflammation in inflammatory demyelinating diseases. In coming years, the use of growth factors which promotes both myelin repair as well as in nerve regeneration will find adverse applications in peripheral neuropathies [103, 104]. Myelin repair for the treatment of peripheral demyelinating neuropathies has become a serious clinical issue for the medical practitioners. During the last 20 years, many researches are going on with the application of drugs which promotes myelin repair in demyelinating diseases [105-108]. Progestogen is one of such promising therapeutic agents which promote myelin regeneration. The role of progestogen in peripheral nervous system was first demonstrated by Koenig in 1995 using mouse and rat model [109]. Since then many research have been performed using potential therapeutic drugs including progestogen and nestorone promoting myelin repair for its application in the treatment of demyelinating diseases in the patients [110, 111]

Mclean and Verge [112] have shown in their work that polarization of the macrophage by electrical nerve stimulation on the neural immune axis plays a vital role in promoting a state of repair in focally demyelinated nerve. Recent studies have revealed many significance of macrophage in the pathologies of demyelination. It has the ability to release toxins and contribute to demyelinating pathologies *via* antigens presentation to cytotoxic lymphocytes [113, 114]. Removal of myelin debris, secretion of growth factors and nerve repair promotion are the specific qualities of macrophage making it a special phenomenon of improving demyelinating neuropathies [115].

2.6 Electric circuit model of nerve propagation

Hodgkin-Huxley model

A series of electrophysiological experiments on a squid giant axon between the period of 1940 to 1950 by Sir Alan Hodgkin and Sir Andrew Huxley have set the foundation for mathematical modeling and understanding the physiology and nerve excitable properties in a biological system. They successfully developed a mathematical model and demonstrated the mechanism of ionic currents in squid axon in terms of change in Na^+ and K^+ conductances in the axon membrane. The pioneer work in a series of experiments lead to the formation of Hodgkin-Huxley (H-H) model in 1952 [72, 73] where they described the ionic basis of action potential in the membrane with the help of an electrical equivalent circuit of an axon as shown in Fig-2.6. In the equivalent circuit, the current across the membrane consists of: (i) capacitive current (C_m) due to membrane capacitance and (ii) ionic current (I_{ion}) due to the flow of ions through resistive membrane channels. The change in membrane potential (V_m) to current flowing across the membrane can be describes by a differential equation of general form:

$$C_m \frac{dV_m}{dt} + I_{ion} = I_{ext} \tag{2.1}$$

Where, I_{ext} is applied current across the membrane.

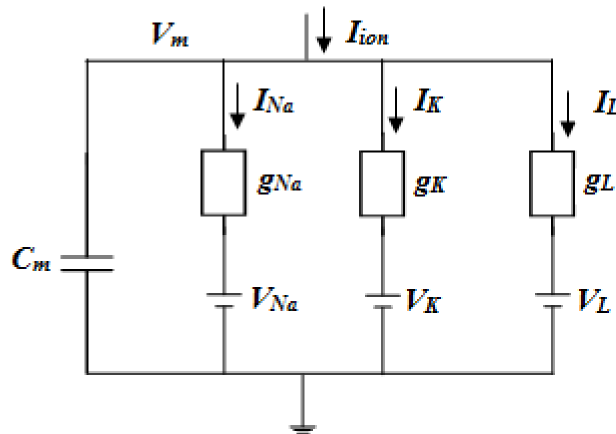


Figure 2.6: An equivalent electric circuit of H-H model.

The ionic current is again subdivided into three components: (a) sodium current (I_{Na}), (b) potassium current (I_K) and (c) small amount of leakage current (I_L), due to flow of Cl^-.Thus, the total ionic current can be written as:

$$I_{ion} = I_{Na} + I_K + I_L \tag{2.2}$$

The equation in terms of respective ionic conductances (g_{Na}, g_K and g_L) membrane potential (V_m) and equilibrium potentials of the individual ions can be written as:

$$I_{ion} = g_{Na}(V_m - V_{Na}) + g_K(V_m - V_K) + g_L(V_m - V_L) \tag{2.3}$$

Further, individual ion channel in the circuit is governed by one or more physical gates of permissive and non-permissive states that regulate the flow of ions through the channel. The two states indicate the opening and closing of the channels. The sodium channel is controlled by three '*m*' type and one '*h*' type gates while the potassium channel is controlled by four '*n*' type activation gates. The leakage channel lacks such type of gates. The conductances for sodium and potassium can be denoted by the generalized notation as:

$$g_{Na} = G_{Na}m^3h \tag{2.4}$$

and,

$$g_K = G_K n^4 \tag{2.5}$$

Thus equation (2.3) takes the standard notation as:

$$I_{ion} = G_{Na}m^3h(V_m - V_{Na}) + G_K n^4(V_m - V_K) + G_L(V_m - V_L) \tag{2.6}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m \tag{2.7}$$

$$\frac{dh}{dt} = \alpha_h(1-n) - \beta_h h \tag{2.8}$$

$$\frac{dn}{dt} = \alpha_n(1-h) - \beta_n n \tag{2.9}$$

The six rate constants α_m, α_h, α_n, β_m, β_h and β_n depends on the membrane voltage in the circuit. The equation (2.6) along with equation (2.7), (2.8) and (2.9) specify the behavior of the membrane potential of the squid giant axon in the H-H model.

2.6.1 Models based on H-H model of nerve propagation

In 1995, Schwarz et al. [116] demonstrated the action potential and membrane currents in single isolated human myelinated nerve fibers based on current and voltage clamped conditions. Using membrane currents, the quantitative analysis for Na^+ current measured in two axons was found to be

$$I_{Na} = I'_{Na}[1-\exp(-t/\tau_m)]^3 \exp(-t/\tau_h) \tag{2.10}$$

Where, I'_{Na} is the amplitude of sodium current and τ_m and τ_h are the time constant of activation and inactivation of Na permeability. The equations for voltage clamp and current clamp is given by:

Voltage clamp:

$$E = E_{command} - I_{total}R_{series} \tag{2.11}$$

Current clamp:

$$dE/dt = -(I_{total} + I_{stimulus} + I_{polarizing})/C_{nodal} \tag{2.12}$$

Where, I_{total} is the total ionic current in the membrane and C_{nodal} is the capacitance at the node of Ranvier. Generally R_{series} and $I_{polarizing}$ are condered as zero. Similarly, the quantitative analysis for fast K^+ current measured in four axons was found to be

$$I_{Kf} = I'_{Kf}[1-\exp(-t/\tau_n)]^4 \tag{2.13}$$

The rate constants α_m, β_m, α_h and β_h for Na^+ current, α_n and β_n for fast K^+ and α_s and β_s for slow K^+ current are respectively derived from the following equations:

$$\alpha_m, \alpha_n, \alpha_s = A(E-B)/\{1-\exp[(B-E)/C]\} \tag{2.14}$$

$$\alpha_h, \beta_m, \beta_n, \beta_s = A(B-E)/\{1-\exp[(E-B)/C]\} \tag{2.15}$$

$$\beta_n = A/\{1+\exp[(B-E)/C]\} \tag{2.16}$$

Schwarz et al. used H-H formulation for quantitative analysis of membrane currents for easy comparison of models previously described for other species and to minimize the number of parameters required to describe the behavior of nerve excitable properties.

In recent years, numerous studies were carried out to examine the characteristics of axons including the axonal length using mathematical and computational models. In 2013, Namazi and Kulish developed a mathematical model of the generating potentials in action to determine the characteristic length of a myelinated segment in axons using diffusion phenomenon [117, 118].

Recently in 2016, Takieh et al. [119] demonstrated a mathematical model to study the propagation of action potential in a deformed neuron. They modified the cable equation by considering the effects of ionic currents from H-H model and obtained a equation for the neuron with deformed geometry as

$$C_m\left(\frac{\partial V_m(z,t)}{\partial t} + I_{ion}\right)\frac{ds}{dz} = \frac{r}{2(R_e+R_i)}\frac{\partial^2 V_m(z,t)}{\partial z} + \frac{1}{(R_e+R_i)}\frac{dr}{dz}\frac{\partial V_m(z,t)}{\partial z} \tag{2.17}$$

And the gating variables are given by

$$\frac{dy}{dt} = \alpha_y(V)(1-y) - \beta_y(V)y = \frac{y_\alpha(V)-y}{\tau_y(V)} \tag{2.18}$$

$$y_\alpha(V) = \frac{\alpha_y(V)}{\alpha_y(V)+\beta_y(V)} \tag{2.19}$$

$$\tau_y(V) = \frac{1}{\alpha_y(V)+\beta_y(V)} \tag{2.20}$$

Where y is the rate of gate closing state, $\alpha_y(V(t))$ is the rate of gate opening state while $y_\alpha(V)$ is the steady state fraction of open gate. $\tau_y(V)$ is the time constant related to the change in fraction of open gates. $y_\alpha(V)$ and $\tau_y(V)$ are obtained experimentally from H-H voltage clamp data.

They concluded from the observed results that deformation affects the propagation speed, refractory period and the action potential of the nerve.

Previously, three different electric circuit models representing a single myelinated axon, demyelinated axon and a couple model between a myelinated axon and a demyelinated axon is presented to estimate the NCV in the three modeled axons using the equivalent electric circuits [120].

An electric circuit model of a single myelinated axon:

A single myelinated axon is modeled from Kirchhoff's law analysis by the system of difference-differential equation. Fig-2.7 represents an electric circuit model of a single myelinated axon. In the figure the index n indicates successive active nodes, each of which is characterized by a transverse (inside to outside) voltage across the membrane (V_n). A second dynamic variable is the current (I_n) flowing longitudinally through the fiber from node n to node $n+1$. Also, R is the sum of the inside and outside resistances. R_i and R_o are the internal and external resistances with membrane capacitance C and ionic conductance G_{Na}, G_{Kf}, G_{Ks} and $G_{L,}$ corresponding to sodium (Na) ions, fast potassium (Kf) and slow potassium (Ks) and leakage (L) ions such as chlorine and calcium ions respectively. I_{ion} is the total ionic currents. I_{Na}, I_{Kf}, I_{Ks} and I_L are the ionic currents responsible mainly due to flow of sodium, fast potassium, slow potassium and other ions known as the leakage currents. The NCV of the myelinated axon using the electric circuit model was estimated by the equation

$$v_c = \sqrt{\frac{G_{Na}}{RC^2}}\left(\frac{V_{Na} - 2V_{th}^{Na}}{\sqrt{2V_{Na}}}\right) + \sqrt{\frac{G_{Kf}}{RC^2}}\left(\frac{V_K - 2V_{th}^{Kf}}{\sqrt{2V_K}}\right)$$

$$+\sqrt{\frac{G_{Kf}}{RC^2}}\left(\frac{V_K - 2V_{th}^{Kf}}{\sqrt{2V_K}}\right) + \sqrt{\frac{G_L}{RC^2}}\left(\frac{V_L - 2V_{th}^{L}}{\sqrt{2V_L}}\right) \quad (2.21)$$

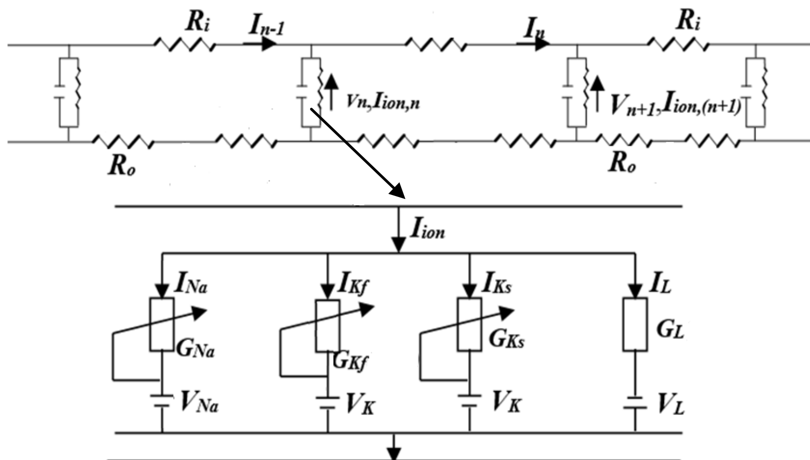


Figure 2.7: An electric circuit of a single myelinated axon [120].

Using the above expression, the conduction velocity of the myelinated nerve of human is calculated numerically which comes out to be 59.4691 m/s.

An electric circuit of a demyelinated axon:

Generally, the process of demyelination decreases the amount of myelin, thereby affecting the myelin resistance of the nerve which in turn affects the internal resistance of the axon by decreasing the total resistance of the axon. On the other hand, capacitance and the ionic conductance of the respective ions namely sodium ion, fast potassium, slow potassium and the other ions (leakage) increases with the increase in demyelination. Fig-2.8 shows an electric circuit model of a demyelinated axon along with the circuit model displaying the ionic currents present in it.

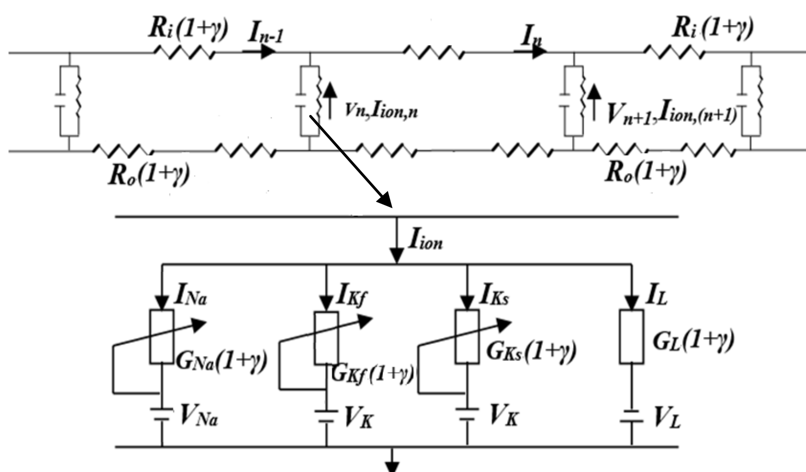


Figure 2.8: an electric circuit of a single demyelinated axon [120].

In this model, a demyelination factor, gamma (γ) is introduced to describe the change in the parametric values of resistance, capacitance and ionic conductance respectively. Thus, the change in internal resistance becomes $R_i(1-\gamma)$, while $R_o(1-\gamma)$ being the external resistance. Therefore the total resistance is $(R_i + R_o)(1-\gamma)$ and the change in capacitance due to demyelination is $C(1+\gamma)$. The ionic conductance are $G_{Na}(1+\gamma)$, $G_{Kf}(1+\gamma)$, $G_{Ks}(1+\gamma)$ and $G_L(1+\gamma)$ respectively. To this end, the NCV of a demyelinated axon is given by

$$v_c = \sqrt{\frac{G_{Na}(1+\gamma)}{R(1-\gamma)\{C(1+\gamma)\}^2}}(\frac{V_{Na}-2V_{th}^{Na}}{\sqrt{2V_{Na}}})(1-\gamma)$$

$$+\sqrt{\frac{G_{Kf}(1+\gamma)}{R(1-\gamma)\{C(1+\gamma)\}^2}}(\frac{V_K-2V_{th}^{Kf}}{\sqrt{2V_K}})(1-\gamma)$$

$$+\sqrt{\frac{G_{Kf}(1+\gamma)}{R(1-\gamma)\{C(1+\gamma)\}^2}}(\frac{V_K-2V_{th}^{Kf}}{\sqrt{2V_K}})(1-\gamma)$$

$$+\sqrt{\frac{G_L(1+\gamma)}{R(1-\gamma)\{C(1+\gamma)\}^2}}(\frac{V_L-2V_{th}^{L}}{\sqrt{2V_L}})(1-\gamma) \tag{2.22}$$

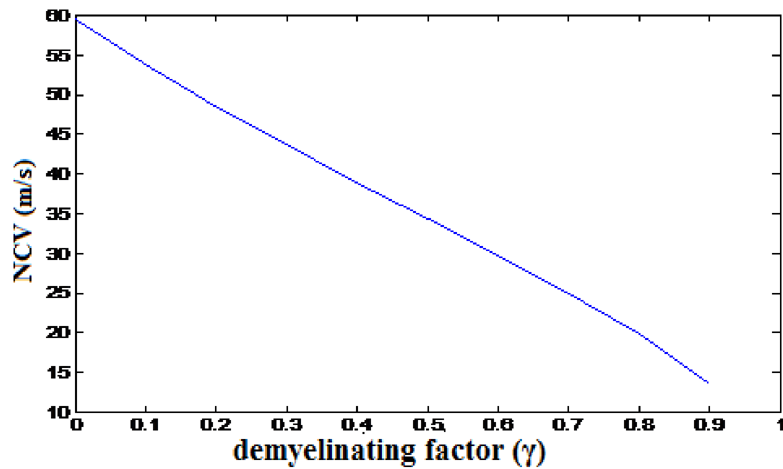


Figure 2.9: NCV versus demyelination factor (γ) [120].

The reduction of NCV increases with increase in demyelination factor in the demyelinated axon as seen in Fig-2.9. At γ=0, the axon possess a NCV value of 59.4691 m/s which is equal to that of a myelinated axon. But as the demyelination factor increases, the reduction of NCV increases gradually and ultimately tends to diminish as it becomes fully demyelinated.

An electric circuit of a coupled model of an axon:

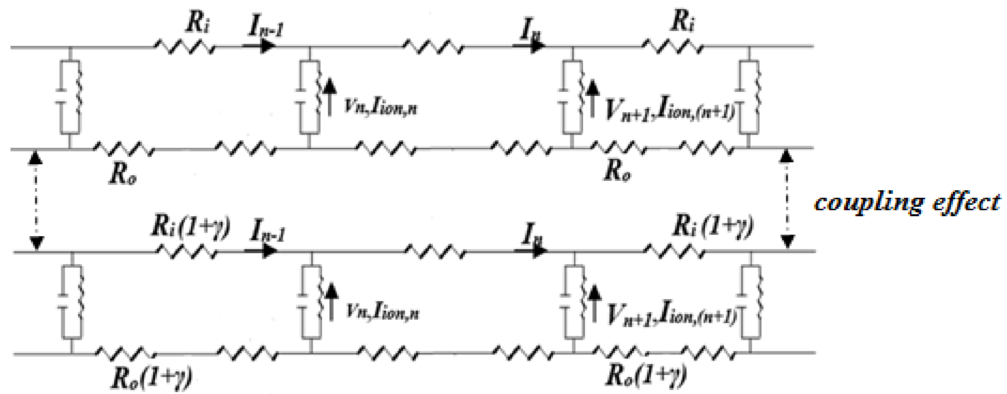


Figure 2.10: An electric circuit of a coupled model of axon [120].

Fig-2.10 represents an electrical circuit model of coupling between a myelinated axon with a demyelinated axon consisting of a demyelination factor γ. The I_n and V_n are nodal ionic current and voltage at node n whereas I_{n+1} and V_{n+1} are nodal ionic current and voltage at node *(n+1)* respectively. In the circuit the voltage V_n at node n depends on V_{Na}, V_{Kf}, V_{Ks} and V_L which are Nernst potentials of sodium, fast potassium, slow potassium and leakage ion at which corresponding currents return to zero. As seen in case of a myelinated and a demyelinated axon, the NCV for the coupled model is given by

$$v_c = \sqrt{\frac{G_{Na}(2+\gamma)}{R(2-\gamma)\{C(2+\gamma)\}^2}}\left(\frac{V_{Na}-2V_{th}^{Na}}{\sqrt{2V_{Na}}}\right)(2-\gamma)$$

$$+\sqrt{\frac{G_{Kf}(2+\gamma)}{R(2-\gamma)\{C(2+\gamma)\}^2}}\left(\frac{V_K-2V_{th}^{Kf}}{\sqrt{2V_K}}\right)(2-\gamma)$$

$$+\sqrt{\frac{G_{Kf}(2+\gamma)}{R(2-\gamma)\{C(2+\gamma)\}^2}}\left(\frac{V_K-2V_{th}^{Kf}}{\sqrt{2V_K}}\right)(2-\gamma)$$

$$+\sqrt{\frac{G_L(2+\gamma)}{R(2-\gamma)\{C(2+\gamma)\}^2}}(\frac{V_L-2V_{th}^L}{\sqrt{2V_L}})(2-\gamma) \tag{2.23}$$

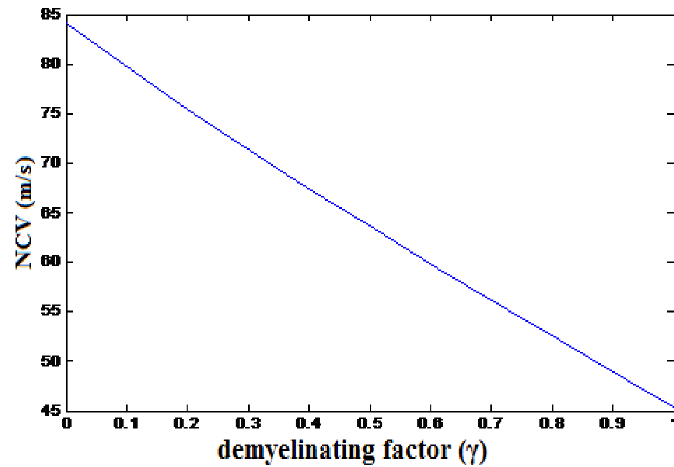


Figure 2.11: NCV versus demyelination factor (γ) in a coupled model of axons [120].

Fig-2.11 clearly shows a recovery of NCV when a demyelinated axon is coupled with a myelinated axon in the coupled model. When a fully demyelinated axon is interacted to a myelinated axon, the coupled model of axon seems to possess a NCV value with the normal range, indicating a recovery of the demyelinated axon of the demyelinating patients.

2.7 Some recent patents/ patent applications for the development of myelinated nerve fibers

During the last 30 years, many physical innovations such as chemicals, pharmaceuticals, medical equipments, etc and clinical processes are filed as the intellectual property rights which are aimed for the betterment of peripheral myelinated nerves and worked to repair the myelin sheaths in demyelinating diseases [121]. These patents/ patent applications served to be very useful and reduce the workload for the scientists while conducting research on myelin of peripheral nerves. In 1998, Vogt invented a method for extracting axon fibers and clusters through transmission electron monograph (TEM) to reduce the workload of neuroanatomist. The method uses grey level operators to identify the co-occurrences and multiplicity of myelinated axon fibers in a cluster of axons. The method successfully identified about 95 percent of the axon fibers in the clusters [122].

Schnaar et al. in 1999 [123] invented certain compounds dealing with the neuronal inhibitory activity of myelin associated glycoprotein (MAG) which stimulate its neuronal growth function by inhibition. The invention also describes a technique of identifying the stimulating compounds which inhibits MAG inhibition of axonal outgrowths.

In 2000, Chum and Weiner provided a method for promoting of survival of myelin producing cells which are used in therapeutic methods and other applications related to myelin disorder [124]. Meanwhile the use of suitable dose of autoantigen or administration of myelin protein came into existence for the treatment of peripheral nerve diseases [125-127].

Moore and Novak in 2003 [128] invented a method for promoting myelination by promoting the expressions of myelin or myelin protein in the Schwann cells of the peripheral nervous system. This method is especially applicable for the treatment of demyelinating diseases such as GBS, CIDP, etc. In the meantime many innovations are made by inventors to detect the compositions of the compounds promoting regeneration of axons. The inventions also describe about the use of the methods for the treatment of myelin disorders in the peripheral nervous system [129-131].

Recently in 2016, Scanlan et al. [132] filed a patent application where subjects with neurodegenerative disorders related to demyelination, insufficient myelination or underdevelopment of myelin sheaths are treated with the administration of sufficient amount sobetirome or a pharmaceutically accepted salt.

Table 2.1: Lists of patents/ patent applications in recent years

Sl. No.	Title	Patent/ Patent Application Publication Number	Source
1.	Method of extracting axon fibers and clusters.	US 5,850,464	[122]
2.	Compounds for stimulating nerve growth.	US 5,962,434	[123]
3.	Methods for promoting survival of myelin producing cells.	US 6,150,345	[124]
4.	Use of recombinant myelin protein for treating T-cell-mediated autoimmune diseases of the peripheral nervous system	US 6,319,892	[125]
5.	Use of Ulip and/ or ULIP2 in the treatment of myelin disorder.	US 2002/0119944	[127]
6.	Methods for promoting production of myelin by Schwann cells.	US 6,569,419	[128]
7.	Axon regeneration with PKC inhibitors.	US 2003/0176423	[129]
8.	Induced regeneration and repair of damaged neurons and nerve axon myelin.	US 6,776,984	[130]
9.	Chlamydial peptides and their mimics in demyelinating disease.	US 2004/0038920	[131]
10.	Sobetirome in the treatment of myelination diseases.	US 2016/0081955	[132]

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