Chapter1: Introduction

Contents

The secret of getting ahead is getting started.
-Mark Twain

1.1 Introduction

Over the last two decades, neuroscience has experienced an extensive progress within the practice of refining and understanding of the etiology and pathogenesis for diseases related to peripheral nervous system (PNS) and central nervous system (CNS). These have led to the development of new diagnostic and therapeutic approaches towards these diseases [1, 2]. In this direction, the progress of neuroscience along with the spectacular growth of computer science has made it possible to analyze the complexity of flow of neuro signals in the nervous system theoretically [3-5]. The introduction of neuroengineering techniques have paved a path to engineer the systems that interact with, augment or mimic the nervous system functionality [6, 7] and are also used to understand, repair, replace, and enhance the performance of the nervous systems [8, 9].

Neuroscience deals with the study of the anatomical and physiological studies of the nervous system with the use of various allied sciences such as psychology, neurology, neuroethics, neurolaw and neurophysics [10, 11]. The origin of neuroscience started dating back in 1700 BC in ancient Egypt where the Egyptians had little knowledge about the symptoms of brain damage [12]. Since then many prominent scientists have indulged themselves to study the various problems and issues and also started their pioneer works associated with the nervous system.

With the advent of the various recent advances in neuroscience, its goal is dedicated to understand the basic mechanism of clinical and laboratory diagnosis of neuromuscular diseases which includes the symptoms and pathology of the diseases. Its aim is also extended to device new effective treatment and therapies for these disorders to prolong and improve the quality of the patient's life [13]. During the last decade, neurophysiology and neuromodulation are the two emerging fields where research is accelerating at a fast rate [13, 14]. The emergence of new diagnostic and therapeutic applications in this field develops new concepts and technologies to improve neuromuscular disorders and eliminate patient sufferings [15]. In this regard, the application of electrical stimulation and chemicals in the PNS or CNS is used for therapeutic purpose of the nervous system. Neurons can communicate among themselves to modify their anatomy and physiology thereby alternating the pathophysiology of the

diseased nerves, thus improving the neural function caused by cellular alterations in disordered nervous system [16]. In this context, different electric circuit models are required to design for the study of physiology in normal peripheral nerves as well as disordered nerves affected by demyelination. For treatment of demyelinated diseases such as Guillain-Barre Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, etc., non-invasive quantification of demyelination is required to study by using electric circuit model of human nerve consisting of bundle of axons.

1.2 Motivation

Some of the key issues which motivated for this research are discussed below:

- *Electrical circuit modeling and its theoretical analysis*: Electrical circuit modeling of the PNS and its theoretical analysis has always been an important problem in characterizing and understanding the operations and functions of the nervous system. It is difficult to recognize appropriate procedure of modeling for a particular problem or disorder which may leads to faulty experimental data. So, the model has to be designed based on anatomical, physiological and circuitry by taking into consideration of computational and theoretical information that will help the neuroscientists to predict and interpret the behavioral and cognitive importance of the functions of the nervous system.
- *Relation between biological and theoretical studies*: The interaction between theoretical studies and actual nervous system is another issue for accurate modeling of the PNS. The primary approach is to design a theoretical model taking biological conditions into consideration to study and analyze the abnormalities in the peripheral nerves affected by myelin disorder.
- *Root cause of the disorder*: Though immense advances in medical neuroscience have taken an extreme height, yet there is a deficit in the fundamental theoretical aspects of the physiological stability and normal functioning of PNS. Moreover, the mechanism underlying the root cause of the nerve disorder is yet to be discovered and advancement in appropriate

diagnostic techniques and its therapeutic techniques for its complete recovery has to be explored.

- *Quantification*: Quantification of demyelination (disorder due to myelin damage) in nerves is another important issue to be addressed.
- *Recovery of disorder*: With the increase in number of patients suffering from different nerve diseases, the growth of advanced technologies has facilitated medical science with many sophisticated diagnostic tools and therapeutic techniques. However, the patients often suffer from many discomfort and surgical pain. So, emphasis should be applied on complete recovery of the disorder by reducing patients' sufferings.

The above issues in nerves consisting of bundle of axons lead to study quantification of demyelination of peripheral nerves (caused by GBS, CIDP, etc.) and its recovery with coupling between a demyelinated nerve and a normal nerve by using electric circuit model.

1.3 Research objectives

Considering the issues of PNS (discussed in section 1.2), the disorder of demyelination is recognized to be one of the root causes of signal transmission failure in peripheral nerves. Moreover, complete recovery from these disorders is still under the dawn. So, through this research work, it is intended to investigate to the depth and contribute in the field of neuroscience considering toad model with its sciatic nerves being demyelinated using *Naja kaouthia* (Nk) snake venom. Accordingly, the major objectives of the research work are listed as follows-

- To design an electric circuit model of a myelinated nerve consisting of a bundle of axons.
    - To estimate the nerve conduction velocity (NCV) using the electric circuit model.
    - NCV determination in sciatic nerves of toad.

- Modeling of a demyelinated nerve (consisting of a bundle of axons) considering basic electrical parameters.

    - Formulation of NCV from the modeled demyelinated nerve.
    - Experimental validation of the modeled nerve using animal (toad) model.

- To design a recovery model by interacting two different nerves.

    - Estimation of NCV in the recovery model.
    - To perform experiment on toad model to validate the recovery model.

1.4 Methodology adopted

The following approaches have been applied in order to fulfill the objectives for the completion of the thesis:

- A complete literature survey on the selected existing mathematical models of the nervous system related to the area of interest to study the nerve excitability properties is carried out. Information regarding the importance of myelin and work done to develop myelin in demyelinated nerves are also thoroughly studied.
- Designing of electric circuit model of a myelinated nerve considering bundle of axons and formulation of NCV using the electric circuit model.
- Electric circuit model of a demyelinated nerve and estimation of reduction of NCV from the electric circuit model of demyelinated nerve in terms of demyelinated factor (reduction of myelin thickness) for quantification of demyelination.
- Establishment and hands on training on the instrumental set up as well as on isolation of nerves from toad to determine neuro signals in the isolated sciatic nerves of toad and verification of demyelination by using Nk venom treated demyelinated sciatic nerves of toad.
- Modeling and formulation of NCV in a recovery model (coupled model) where the demyelinated nerve is interacted with a normal myelinated nerve to

witness an increase in NCV. This coupling approach is also verified by experimental validation using toad nerve model.

1.5 Research achievements

The major contributions of the thesis are listed below:

1. Hodgkin-Huxley (H-H) electric circuit model for a single axon is revised to model a myelinated nerve, consisting of a bundle of axons contributed by ionic currents due to Na^+ and K^+ and small amount of Ca^{2+}, Mg^{2+}, Cl^-, etc., (considered as leakage current). The normal range of NCV formulated from the electric circuit model using human data is found to be 35-65 m/s. Validation of the model was carried out on isolated, normal sciatic nerves of toad. It was seen that the NCV was found to be 32.90±0.21m/s with myelin thickness of 1.79±0.05µm at γ=0 (normal), observed through SEM image. Both the values range within the normal range of a human and a toad myelinated nerve. However, the rate of NCV is directly proportional to the nerve fiber diameter [17]. So, human nerve with greater nerve fiber diameter conducts nerve impulse at a higher speed than that of a toad nerve.
2. Reduction of myelin thickness is obtained from the proposed model of demyelinated nerve considering demyelinating factor (γ) in the equivalent circuit as a function of myelin thickness. It is also seen that the speed of conduction decreases with an increase in demyelinating factor. The conclusion derived from the model is that the reduction of myelin thickness leads to the decrease of NCV.
3. Crude Nk venom is used as a candidate to demyelinate sciatic nerve of toad because of the presence of high percentage of phospholipase A_2 (PLA_2) that causes degradation of myelin sheath. It is observed when the nerve is demyelinated with 0.1µg/ml, 1.0µg/ml and 10µg/ml of venom concentration, the reduction of myelin thickness is found to be 1.22±0.15µm, 1.00±0.9µm and 0.91±0.08µm respectively with their corresponding NCV of 26.62±0.58m/s, 18.25±0.22m/s and 15.87±0.15m/s which are far below normal value. Further, when the nerve is treated with same concentration of

Nk-PLA_2 (purified from crude Nk venom), myelin degradation with thickness of 1.18±0.32µm, 0.99±0.27µm and 0.89±0.12µm with their corresponding reduced NCV of 25.62±0.81m/s, 17.10±0.13m/s and 14.46±0.58m/s respectively. However, three finger toxin (3FTx) extracted from the crude venom does not show any activity in the degradation of myelin sheath. It acts only as a channel blocker.

4. Coupled model of nerve fiber is modeled by interacting a demyelinated nerve with a myelinated nerve to function as a recovery model and compensate the loss in the physiological properties observed in nerve disordered patients. The results obtained clearly indicated a gain in amplitude as well as NCV in the proposed recovery model.
5. The reduced NCV due to demyelination is recovered in the coupled nerve and are found to be 40.36±0.12m/s, 37.50±0.11m/s and 34.85±0.14m/s respectively for their corresponding crude Nk venom concentrations. Similarly, for nerves demyelinated by using 0.1µg/ml, 1.0µg/ml and 10µg/ml of purified Nk-PLA_2, the increased values of NCV are 39.24±0.26m/s, 36.36±0.35m/s and 33.66±0.38m/s respectively. It is seen that the reduced NCV due to the mentioned demyelination factor increases in the coupled model due to the coupling effect of the normal myelinated nerve in the model. Also, the blocking property of 3FTx is suppressed by the electrophysiology of the normal nerve.

1.6 Thesis organization

The thesis has been organized into six chapters. In this context, each chapter has been summarized briefly as follows:

Chapter 1: *Introduction*- Chapter one describes about a general introduction to the thesis. A general summary of the topic is outlined in this chapter along with its motivation and objectives of the thesis.

Chapter 2: *Literature survey*- Chapter two provides an overview on the primitive study of the nervous system and comprehensive literature survey on the ancient information required to fulfill the objectives in the thesis. The chapter describes a brief history on the

works and its inventions/discoveries related to our area of research. It describes some of the existing mathematical models which motivated us to carry out our research in this field of neuroscience for the benefit of the mankind.

Chapter 3: *Electric circuit model of a myelinated nerve and study of its nerve excitable properties via toad nerve model*- In this chapter, a theoretical model of human peripheral myelinated nerve consisting of a bundle of axons is proposed considering electric parameters such as myelin resistances, membrane capacitance and ionic conductances along with other important coupling parameters that actually exists in the bundled nerve. All the components are equally important and must be considered to model a myelinated nerve with significant functioning of nerve conduction in the nervous system. The model is also validated experimentally with a toad model as experimental validation is an important part of research in the process of mathematical modeling as witnessed from literature survey.

Chapter 4: *Modeling of a demyelinated nerve and quantification of demyelination*- This chapter deals with the theoretical modeling of a demyelinated nerve to formulate the change in NCV considering the conditional change in the components of a disordered nerve due to degradation of myelin sheaths. It also gives a description about the quantification process of degree of disorder in the nerves of demyelinating patients. Snake (Nk) venom is used as an agent to demyelinate sciatic nerve of toad in the experimental validation process performed to study the electro-physiological properties in the demyelinated nerve.

Chapter 5: *Modeling and validation of a recovery model via coupling between myelinated and demyelinated nerve fibers using toad nerve model*- This chapter deals with the designing of a coupled model, proposed by interacting a myelinated and a demyelinated nerve to serve as a recovery model in demyelination through myelin repair. The validation of the coupling model is performed on the sciatic nerves of toad to witness a gain in the electro-physiological process lost due to demyelination in the proposed model.

Chapter 6: *Conclusion and future scope*- The summary of the interpretations obtained from the various results of the research carried out in the thesis is concluded in this

chapter. The contribution discussed in chapter 3, chapter 4 and chapter 4 in the thesis is summarized in this chapter. Some aspects on this part of research are suggested in this chapter to carry out research in the future.

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