The future of the treatment of multiple sclerosis using mathematical models

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Abstract

In this project, we will delve, to the best of our abilities, into the difference between the transmission of an electrical signal through a myelinated and a non-myelinated axon of a neural cell. We will examine, using research conducted by experts, manipulating and presenting the data collected, the insulating effect that the myelin sheath has on the axon of a neuron. The modeling strategies that we will show here are similar to those used in the Hodgkin-Huxley model. The purpose of myelin is to provide an insulating layer around the axon, which in turn, greatly increases the speed by which the electrical pulse travels along the length of the axon. Modeling the electrical signals in axons in this way can help to quantitatively look at diseases in humans where they have a considerably lesser amount of myelination, causing their brain activities to be restricted or impaired. This is because the decrease in speed of the electrical signal can have detrimental effects on thinking abilities, brain growth, memory, etc.

1 Modelling Myelin Sheath using the Hodgkin Huxley Model

In class we explored and modelled the Hodgkin-Huxley model for neuron firing. A very important thing that was missed, was the effect of Myelin Sheath. So in the former part of this project we will be discussing the Hodgkin-Huxley model modified with Myelin Sheath simulation designed by Richardson, McIntyre And Grill in 2000.

There were three models of Myelin- perfectly insulating single cable (Model A), finite impedance single cable (Model B) and a finite impedance double cable model (Model C). In this project we will be looking at Model C since it was the closest to the experimental results.

1.1 Method

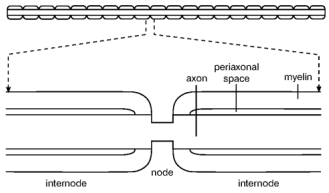

Figure 1: Biological Structure with of the neuron

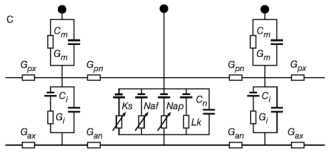

Figure 2: The schematic of the simulated neuron- Model C

There were further three divisions involved: i)Extracellular simulation of the axon through electrode current, ii) Intracellular current injections, iii) Reduced set of intracellular injuctions that accurately simulate extracellular potentials. For this model, there are four axonal current equations and four periaxonal current equations (I will write them in detail after this draft). The simulations were carried out through PSPICE simulations and the results verified the derived equations.

1.2 Results

They carried out a number of comparisons between the three models, Strength-Duration, Current-Distance, Action Potential Characteristics, and Conduction Velocity.

There was a major difference in the Conduction Velocities of the three models, with C having the least CV. It was also that model C exhibited a depolarising potential after excitation, which was not the case in A or B.

Now that we have seen the effect of Myelin on neurons Conduction Speed, and how it can be modelled through the Hodgkin Huxley Model, we will now turn to the main idea of this project- how can we similarly model brain pathologies? More specifically, Multiple Sclerosis, which involves majorly demyelination.

2 Modelling Multiple Sclerosis

Although there are many theories for what causes demyelination; a single cause has yet to be found. One of the potential candidates according to Taylor et al is" the apoptosis of the oligodendrocyte". The oligodendrocyte is a category of neuralgia (a type of cells that aid in the correct positioning of nerve cells labelling them to work efficiently.

A mathematical biochemical system theory can be used to model three states: one without MS with MS and lastly one in a treatment stage. Before the setup of this system, it is essential go understand the ions and chemicals involved in the decline of oligodendrocyte production in multiple sclerosis effected cells. Firstly, the excessive production of "reactive oxygen and nitrogen species" harms the nerve cell by damaging essential components of nerve cells such as DNA or mRNA and can cause cell death in extreme cases as well. Secondly, the accumulation of calcium ions leads to the production of the aforementioned reactive oxygen and nitrogen species as well in a multiple sclerosis effected cell. The mathematical model for the diseased state of the nerve cell will have all variables of ions and other factors attenuated according to their concentration and behaviour in real life cells which is higher than normal.

In the model for the third state, the "activation of pro-inflammatory cytokines" is suppressed so as to put a stop to the production of all their other by products such as RONs which cause harm to the nerve cells and oligodendrocytes. Taylor et al cites these as doing the same job as a potential drug as it reduces the production of chemicals which lead to apoptosis. It also prevents the production of NO which causes the death of oligodendrocytes.

The comparison of both models shows that MS can be accurately depicted using the diseased state experimental model. Therefore, this can be a promising way to study MS in a cost-effective manner which can lead to the possibility of this models incorporation with drug developmental programs. (We will add the technicalities here after this)

After learning about how MS can be modelled, it is time that this project proposes solutions that might be helpful in dealing with MS.

3 Possible solutions to Multiple Sclerosis

The thorough analysis of the effects of myelination leads to experiments to do with trying to manipulate the myelin present in neural cells. As we have seen, the presence of myelin leads to an electrical pulse traveling in much shorter time as opposed to an axon without myelin. The fundamental role of myelin is to provide insulation for the electrical signal to be able to transmit quickly and efficiently along the length of the axon.

In the case of multiple sclerosis, there may be the option of increasing the amount of myelin in the cells by perhaps an artificial method of myelination: by means of drugs, hormones, or steroids. To test if this is a viable solution to the problem, the velocity of electrical signals can be monitored by using electrodes and conducting a similar process as highlighted above. This, of course, is a rough outline of a method that must be refined and conducted in a controlled manner by experts in the field of neuroscience.

Another application of the effects of myelin may be to try and create a body with a neural system that can conduct "super-reflexes". That is to say: to increase the myelination so much so that the speed of electrical signal transmission drastically increases, perhaps even exponentially. In theory, this seems entirely possible but may have limitations in real-life application and experimentation. A logical question would be to ask: is there an upper limit to how much a neuron can be myelinated? As in: is there a specific maximum after which the signal cannot possibly travel any faster? Moreover, myelination of the central nervous system cells can significantly improve memory and learning skills; this can, in theory, be used as a method to improve intelligence or aid in providing solutions to illnesses that lead to memory loss.

Lastly, an alternative to try and increase signal transmission in neurons is to increase ion concentration in the intracellular and extracellular fluid to make up for the lack in myelination. This too may be considered a way to improve the condition of people with multiple sclerosis. Since there would be higher concentrations of the ions that conduct the action potential, the diffusion of these ions would take place faster because of the greater concentration gradient. This, in turn, would improve signal transmission and would perhaps make up for the lack of myelin in neural cells. However, the drawback to this would be that the imbalance of ions could affect the condition of other cells present in the body and cause damage.