# Impact of Demyelination Disease on Neuronal Networks

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## 1. Abstract

Demyelination has a detrimental impact on conduction of nerve signals. The purpose of this paper is to understand the impact of demyelination and build a mathematical model for it. We will model the impact of demyelination on neuronal characteristics, including capacitance and ion leakage. We will then create a small network of demyelinated nerves and study the impact on various types of connections, such as propagation through the network and inhibition. Performance of the demyelinated network will be compared with a network of standard neurons. This model can help us further understand the medical implications of demyelination-causing diseases.

## 2. Introduction

### 2.1 Neurons

Neurons are information carriers. One function of peripheral neurons is to carry sensory information from the body to the central nervous system (CNS). Information is received at the Dendrite and passed electrochemically through the Axon to a terminal where the signal can be passed to another neuron (see Figure 1). The CNS interprets the information and responds accordingly. The response may be to excite motor neurons to contract muscles. Or the response could be to block muscle contraction.

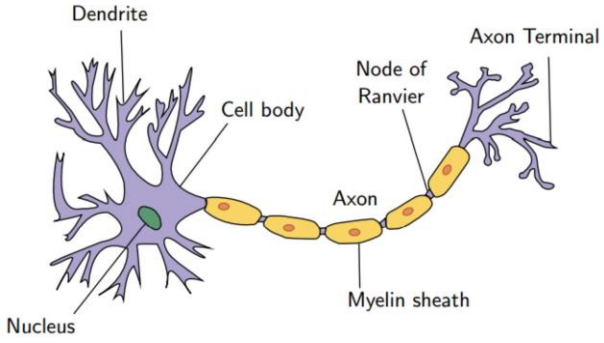


*Figure 1. Healthy neuron with myelin intact [1]*

In humans, Axon length ranges from as short as a millimeter to as long as a meter with a typical diameter of a micrometer [1]. The Axon is electrically insulated by a myelin sheath which allows a signal to efficiently pass between Nodes of Ranvier. Ion channels located at the Nodes of Ranvier rejuvenate the signal as it passes along the axon. When the myelin sheath is damaged signal conductance and rejuvenation through axon is degraded. Demyelinated axons typically become atrophied and may degenerate over time [2]

**Demyelinating Disease**

Demyelination is caused by several physiologies [2]: Inflammatory-caused demyelination is common in diseases such as Multiple Sclerosis and Guillain-Barre Syndrome. Multiple Sclerosis is the most common with 2.5 Million patients world-wide [3]. Other causes may be due to viral infection by papovavirus, JC in HIV or cancer patients, or rare metabolic complications usually caused by excessive alcohol consumption or drugs used in transplantation. More acute cases can be the result of Hypoxic-ischaemia (hypoxia, CO exposure, Leber's Optic Neuropathy) or even focal compression (pinched nerve). Demyelinating diseases affect both the central and peripheral nervous systems. Symptoms of peripheral nerve demyelination include, loss of sensation and movement, pain, neuropathy, and other symptoms depending on the cause.

## 2.3 Myelin Sheath and Saltatory Conduction

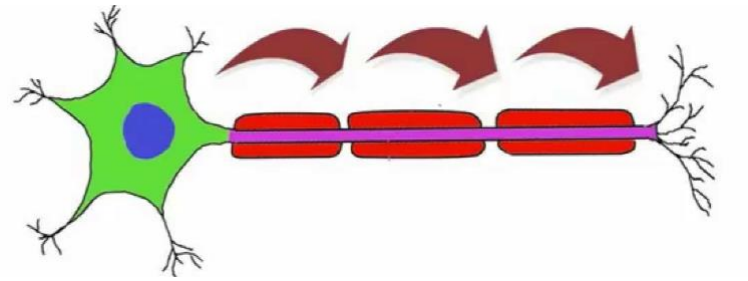

*Figure 2. Saltatory conduction along a myelinated axon [4]*

The myelin sheath is an electrically insulating substance surrounding the axons of many neurons. In the peripheral nervous system it is composed of a combination of fatty materials, protein, and water in layers around axons made up of Schwann cells. In a myelinated neuron, the myelin sheath insulates the axons which prevents current leakage through the membrane of the cell [5]. This is important as it allows a current to not decay below a threshold level of potential while traveling the long distances between nodes (see Figure 2).

In the beginning of this process, an initial action potential in myelinated neural cell occurs at an initial segment of an axon that is produced by a threshold stimulus from the cell body in the dendrites. Consequent action potentials then occur at Na+ voltage-gated channels in the nodes of Ranvier. This causes saltatory conduction in which these nerve impulses then jump from node to node down the myelinated axon [6], Every action potential in each of subsequent the nodes is then activated by a threshold stimulus generated by a passive current from the respective previous node. As the repolarization of the previous node occurs, Na+ channels open within the in the stimulated node causing an influx of Na+ ions causing depolarization in its vicinity. Another passive current is then created because of the attraction of the negative and positive charges of ions in nodes adjacent to each other.

This cycle of action potential and passive current generation propagates repetitively at each node until the axon terminal synapse. This mechanism is highly energy efficient to propagate nerve impulses over long distances as the insulation of the myelin sheath prevents dissipation of signal and increases nerve conduction velocity [5].

### 2.4 Impacts of Demyelination to Neuron

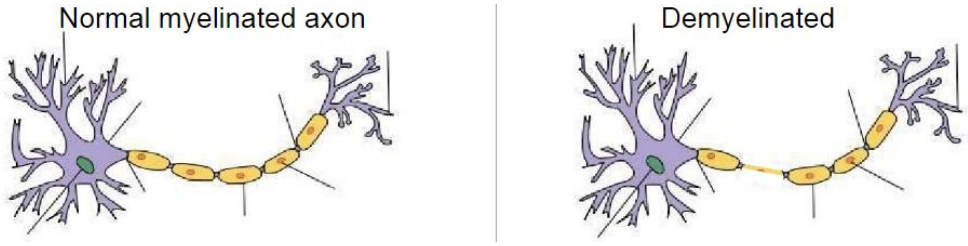


*Figure 3. Two neuronal cells. Normal myelination (left); Partially demyelinated (right). [8]*

In a myelinated axon, the myelin sheath is a relatively thick insulator that covers the axon membrane (see Figure 3, left). The axon is only exposed at the nodes of Ranvier so its overall membrane capacitance is low and resistance is high. This allows the action potential to propagate quickly through the axon [7].

However, a demyelinated axon is exposed to the external interstitial fluid (see Figure 3, right). Without its insulator, the axon membrane experiences increased capacitance and lower resistance. There is increased signal dissipation and the action potential propagating along the axon will be impaired. The loss of saltatory conduction slows conduction velocity of the propagating signals [7].

## 3 Methods

### 3.1 Patellar Reflex Circuit

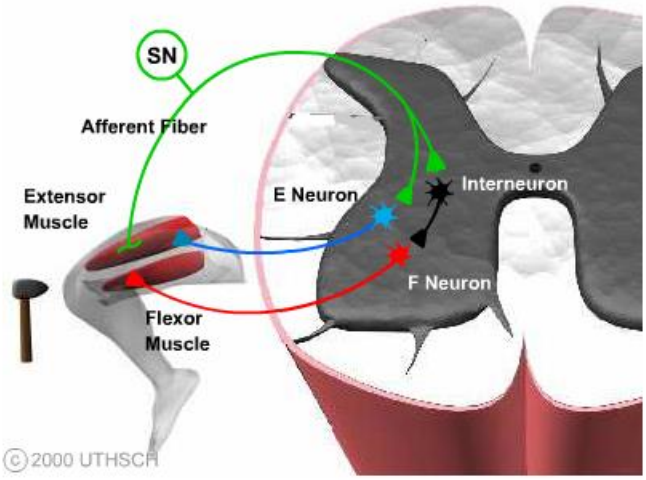


*Figure 4. Patellar reflex circuit; sensory neurons (green), extensor motor neuron (blue), interneuron (black), and flexor motor neuron (red) [9]*

Figure 4 illustrates circuit diagram for the patellar reflex or knee jerk reflex which is a test used to examine the integrity of the sensory and motor pathways of a portion of the lumbar spinal cord [9]. The tap of hammer stretches the leg muscle and leads to the initiation of action potentials in sensory neurons within the muscle that are sensitive to stretch. The action potentials propagate into the spinal cord where the axon splits into two branches. At the E neuron terminal, the action potential propagates directly into an extensor motor neuron. This is a basic example of feedforward excitation pathway. At the interneuron terminal, the action potential expands to an inhibitory interneuron which is interposed before the flexor motor neuron. This leads to an inhibitory postsynaptic potential which makes the action potential less likely to propagate down

the flexor motor neuron so it will decrease the probability of undesired flexion in the leg muscle. This is why when a doctor taps your leg, it will extend instead of flex. This is an example of feedforward inhibition. We will be studying the effects of demyelination of these four neurons in this circuit.

The neuronal relationship of the Patellar Reflex Circuit is represented in the block diagram shown in the Figure 5.

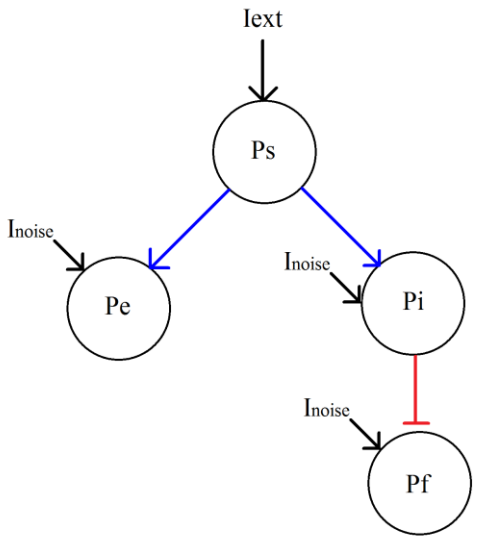


*Figure 5. Block diagram of patellar reflex circuit. Ps: sensory neuron; Pe: extensor neuron; Pi: inhibitory neuron; Pf: flexor neuron; Blue arrow: excited synapse; Red line: inhibited synapse; $I_{ext}$: external current; $I_{noise}$: extraneous signals ("noise").*

### 3.2 Single Neuron Circuit

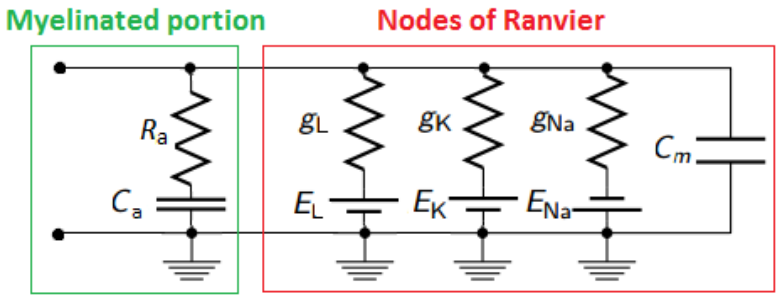


*Figure 6. Circuit diagram of single myelinated neural cell [10]*

Figure 5 describes a circuit model of a single myelinated neural cell. On the right, we have circuit diagram of the exposed axon membrane of a neural cell that contains the conductances and potentials of sodium, potassium, and the leakage. This is connected by the axon circuit on the left which contains our parameters of interest which are the capacitance and resistance along the axon. In a myelinated cell we would keep the resistance high across the membrane because of the insulation of myelin sheath and capacitance low due to the low exposure of the axon membrane. Also since the resistance is very high we will assume it is infinite for this model.

We based our model on the Hodgkin-Huxley (HH) model of action potential in squid giant axons. Since the purpose of this paper is to study the effect of demyelination on signal translation, we chose to simplify some of the potential dynamics of the axon. We will simplify the spatial portion of the HH model [11] and simplify our model into the following circuit (Figure 7).

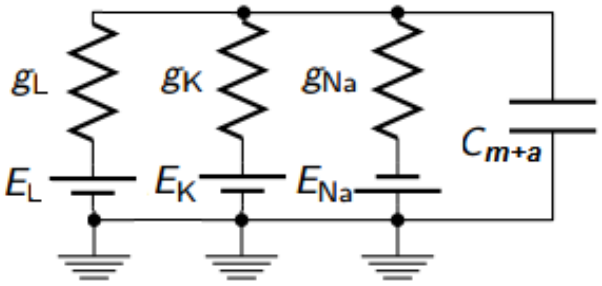


*Figure 7. Circuit diagram of single demyelinated neural cell [10]*

To simplify our demyelinated model we neglected the axonal resistance and represented the increased capacitance by summing all capacitance into one term.

### 3.3 Hodgkin-Huxley equations for our model

$$C_m \frac{dV}{dt} = -I_{Na} - I_K - I_L - I_{syn} + I_{ext} \quad (1)$$

$$I_{Na} = g_{Na}\, m^3\, h\, (V - E_{Na}) \quad (2)$$

$$I_K = g_K\, n^4\, (V - E_K) \quad (3)$$

$$I_L = g_L\, (V - E_L) \quad (4)$$

$$I_{syn} = g_{syn}\, r\, (V_{post} - E_{syn}) \quad (5)$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)\, m \quad (6)$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)\, h \quad (7)$$

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)\, n \quad (8)$$

$$\frac{dr}{dt} = \alpha_r[T](1 - r) - \beta_r\, r \quad (9)$$

$$[T] = [T]_{max} / (1 + e^{-\frac{V_{pre} - V_p}{K_p}}) \quad (10)$$

$$\alpha_m(V) = 0.1\,(V + 45) / (1 - e^{-\frac{V+45}{10}}) \quad (11)$$

$$\beta_m(V) = 4\, e^{-\frac{V+70}{18}} \quad (12)$$

$$\alpha_h(V) = 0.07\, e^{-\frac{V+70}{20}} \quad (13)$$

$$\beta_h(V) = 1 / (1 + e^{-\frac{V+40}{10}}) \quad (14)$$

$$\alpha_n(V) = 0.01\,(V + 60) / (1 - e^{-\frac{V+60}{10}}) \quad (15)$$

$$\beta_n(V) = 0.125\, e^{-\frac{V+70}{80}} \quad (16)$$

Demyelination exposes the neuron to extraneous signals. We incorporated such "noise" as leakage current from the sensory neuron affecting neighboring neurons in the Patellar Reflex Circuit based on Equation 1. ***w*** is the weight coefficient which we set equal to 0.5.

$$I_{noise} = w \times g_L ( E_L - V_s ) \tag{17}$$

## 4 Results

Before studying the complete circuit, we begin with an observation of the impact of capacitance on signal latency from one neuron to another. In this simulation, we consider only an excited synapse from sensory neuron to extender neuron. When capacitance increases, as a function of demyelination, the spike time latency increases between these two neurons (see Figure 8). This demonstrates the expected result that demyelination will cause time delay for signal processing. [11]

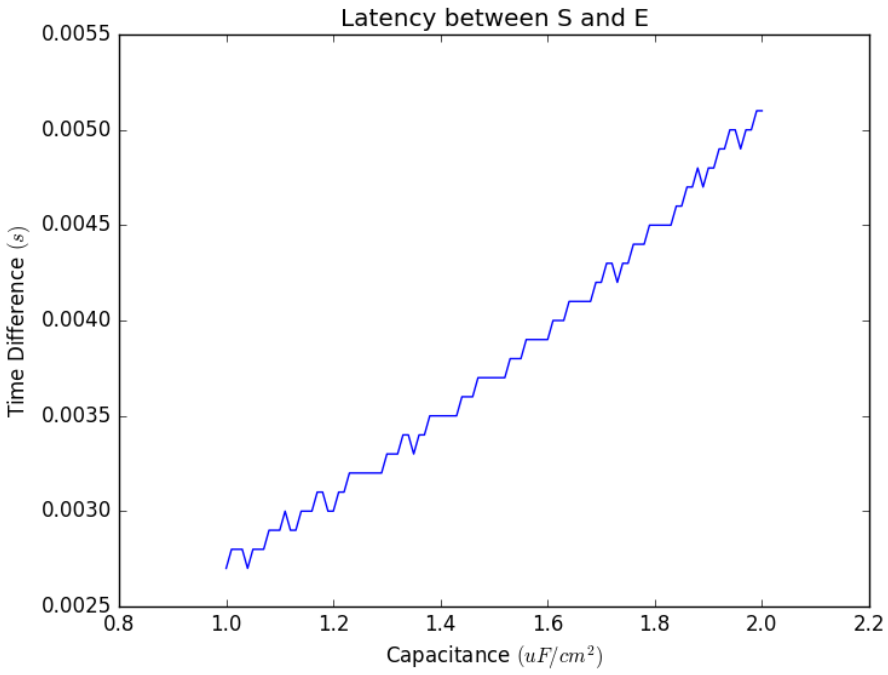


*Figure 8. Latency between sensory and extender neurons.*

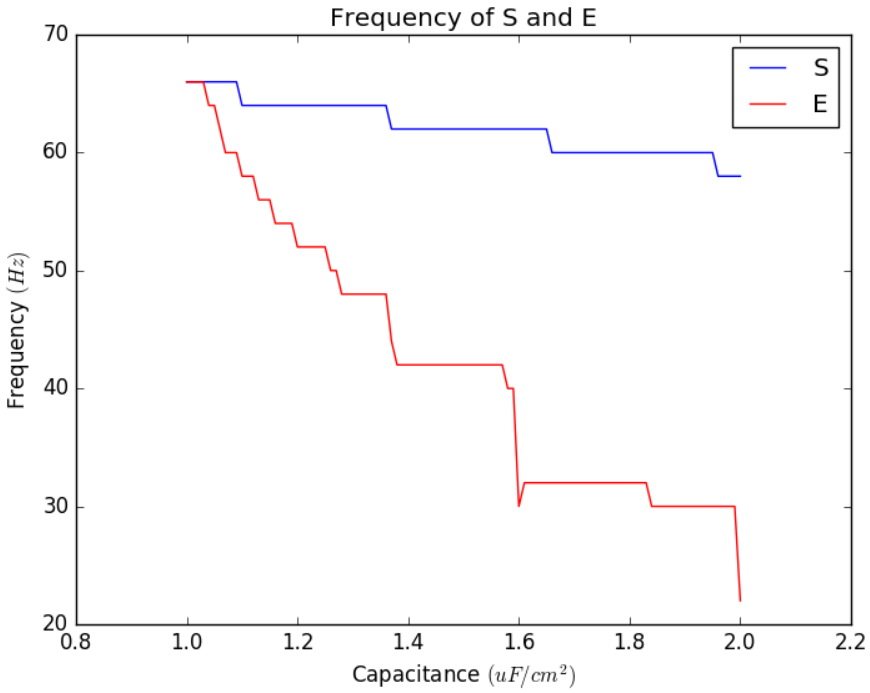


*Figure 9. Frequency of sensory and extender neurons.*

We can also observe this phenomena in the frequency domain (see Figure 9). As we can see, the spike frequency of sensory neuron (blue curve) doesn't change significantly with increased capacitance. However, the frequency of extender neuron (red curve) drops nearly proportionally with increased capacitance. This demonstrates the signal is slowed when progressing from sensory neuron to extender neuron. We found that as the capacitance increases to 5 uF/cm, the extender neuron frequency drops to zero, meaning it does not fire.

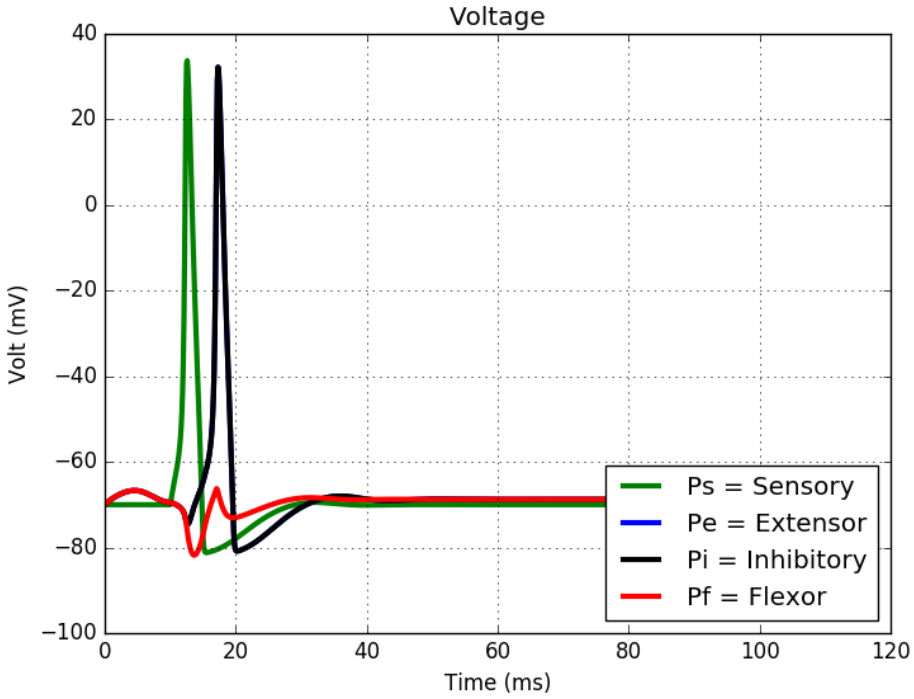


*Figure 10. Normal circuit with single stimulation. (Capacitance of all neurons: 1 uF/cm)*

Next we study circuit reaction with single stimulation. We begin by observing how the normal circuit reacts. Figure 10 shows the sensory neuron fires first, followed by extender and inhibitory neurons operating in parallel. The flexor neuron doesn't fire due to the inhibition from the inhibitory neuron. This matches the doctor's observation that the patient's leg will kick out when they receive a single strike their knee.

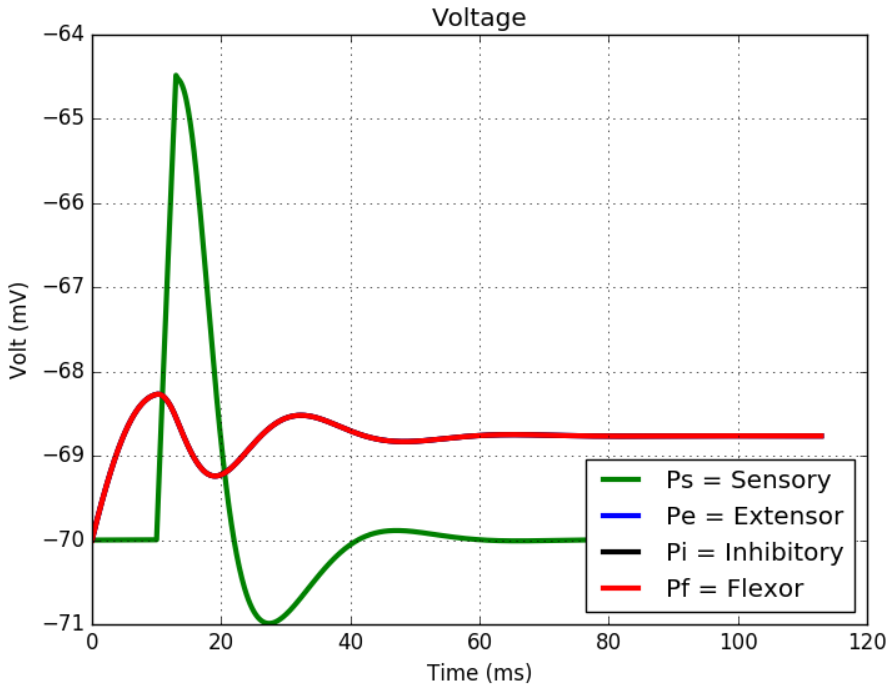


*Figure 11. Single stimulation with all neurons demyelinated (note the voltage scale). Flexor tracing (red) obscures Extensor and Inhibitory tracings. (Capacitance of all neurons: 5 uF/cm)*

Next, we change parameters on all the neurons in circuit to represent the demyelinated state. We set the capacitance equal to 5 $uF/cm^2$ for demyelinated neurons. As Figure 11 shows, no neurons fire (Extensor and Inhibitory tracings are obscured by Flexor tracing (red)). In this condition, the patient's leg will not have any motion because both extensor and flexor are not firing. Moreover, the subject may not even feel the strike because the stimulation is unable to overcome the excessive capacitance and fire the sensory neuron

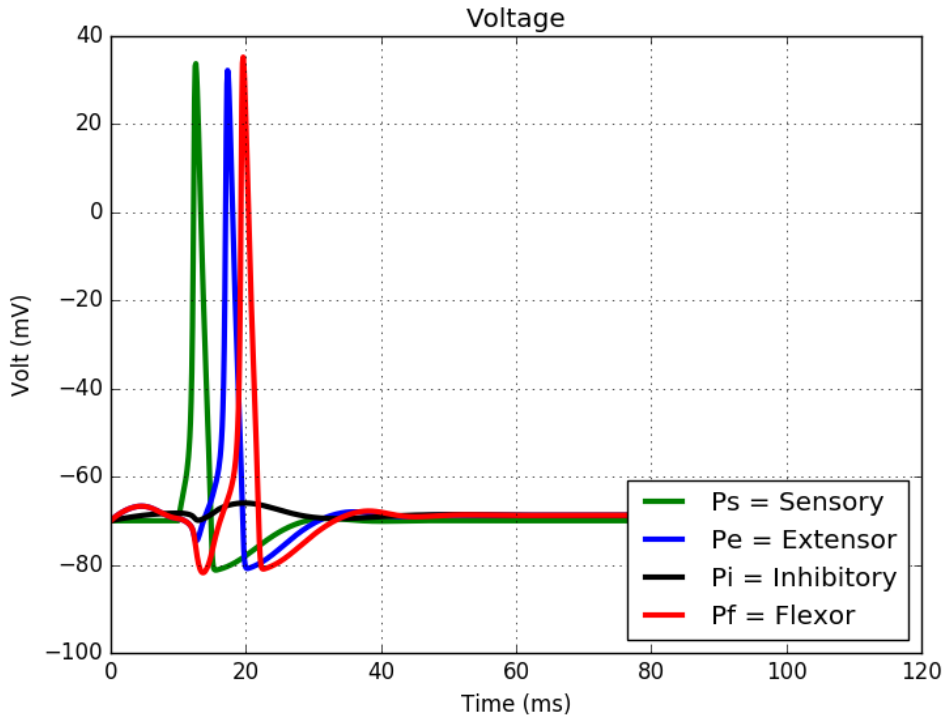


*Figure 12. Single stimulation with demyelinated inhibitory neuron. (Capacitance of Pi: 5 uF/cm; Capacitance of all other neurons: 1 uF/cm)*

Next we observe the effect of the inhibitory neuron on the circuit. We started with myelinated neurons and replaced the inhibitory neuron with a demyelinated neuron. We can see in Figure 12 that the inhibitory neuron is not firing but the uninhibited flexor is indeed firing. This is due to the noise we incorporated via Equation 17. In this case, the patient's leg may tremble after doctor strikes their knee because both extensor and flexor neurons fire.

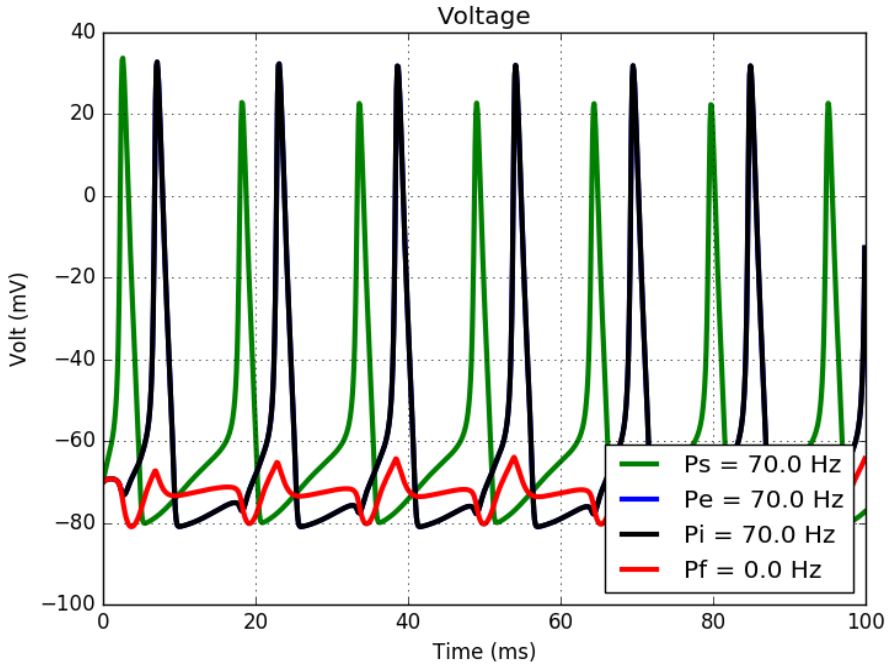


*Figure 13. Continuous stimulation on normal circuit. Inhibitory tracing (black) obscures Extensor tracing. (Capacitance of all neurons: 1 uF/cm)*

Now let's study the effect on continuous stimulation to the sensory nerve as could be initiated by the brain. We begin with a normal circuit of myelinated neurons. As shown in Figure 13, the result is similar to the single stimulation: the sensory neuron fires first, followed by extensor and inhibitory neurons, and a non-firing flexor neuron (Extensor tracing obscured by Inhibitory tracing (black)).

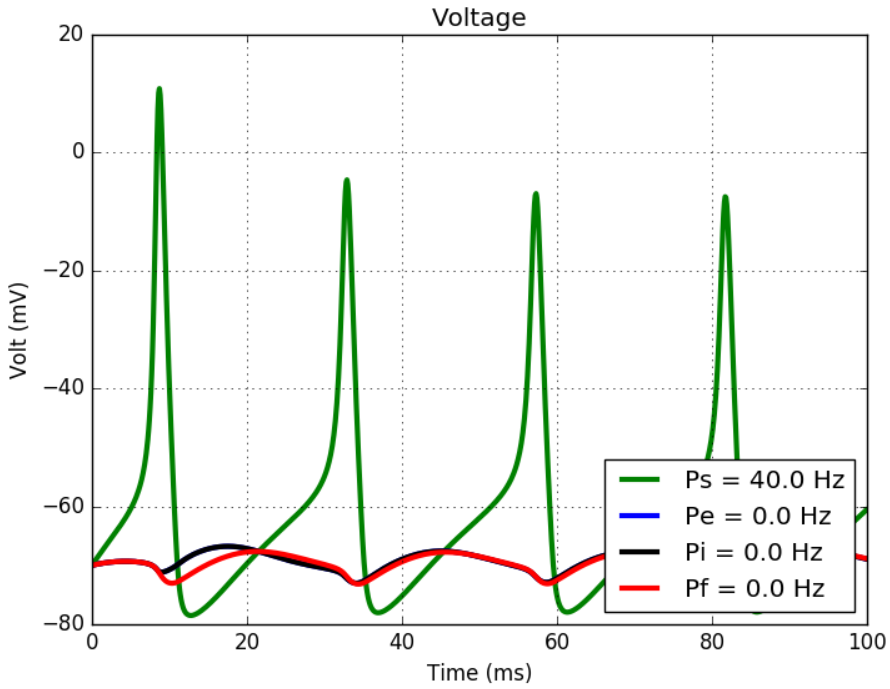


*Figure 14: Continuous stimulation on the all neurons demyelinated circuit. (Capacitance of all neurons: 5 uF/cm)*

Next, we replace all the neurons with demyelinated neurons. We observe that the sensory neuron is firing but none of the other neurons are firing (see Figure 14). Though the sensory neuron fires with a slower pattern, it cannot progress to extensor and inhibitory neuron. Also, the capacitance is so high that the noise is not sufficient to make the other neurons fire.

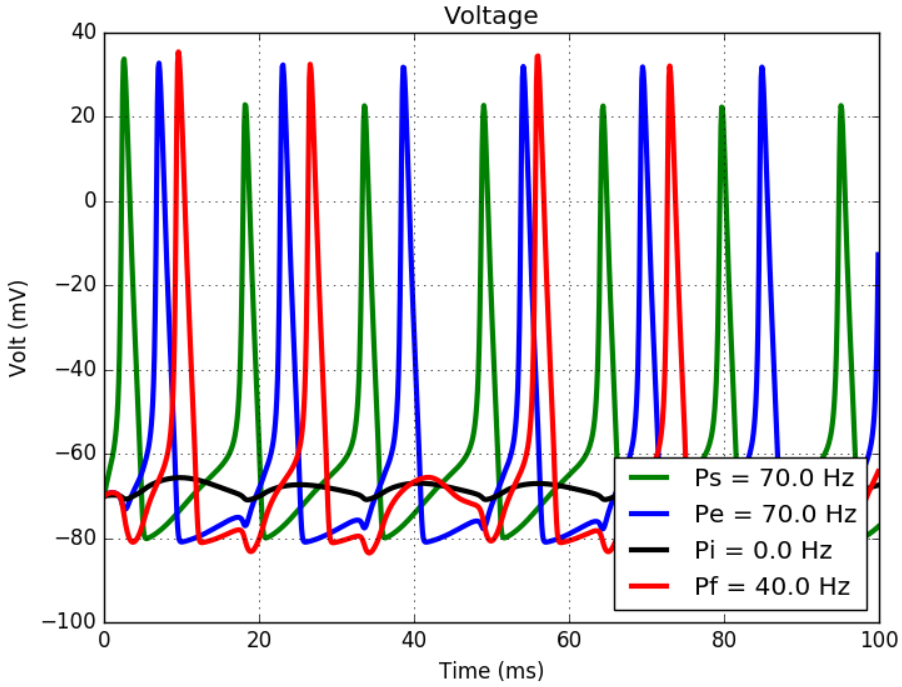


*Figure 15: Continuous stimulation with demyelinated inhibitory neuron. (Capacitance of Pi: 5 uF/cm; Capacitance of all other neurons: 1 uF/cm)*

Finally, we demyelinate only the inhibitory neuron from the firing frequency of each neuron, we can see in Figure 15 that the extensor neuron follows well after sensory neuron. However, because the inhibitory neuron is not firing, the flexor neuron will fire at 40 Hz because of noise. The patient's leg may merely tremble when they want to move their leg.

## 5 Conclusion

We successfully created a model of the Patellar Reflex. As expected, the neuronal response of the model showed propagation of the signal through the sensory neuron to the extensor and inhibitory neurons. The flexor neuron was inhibited, as it would be for a healthy individual. When we increased axonal capacitance, as would be the case in demyelinated neurons, the signal was impeded and the extensor and inhibitory neurons did not fire. This confirms what we found in the literature.

We also studied demyelination of a single neuron in the presence of noise and found that when the inhibitory neuron is demyelinated the flexor neuron behaves erratically. Thus, the model demonstrates the impact on neuronal function caused by variations in demyelination. The next step in this simplified model would be to incorporate greater complexity.

In vivo neurons are often clustered. The model could be expanded to include multiple neurons to demonstrate the convergence and divergence common in neuronal clusters. Variation in axonal length could also be studied by incorporating distributed capacitance and resistance. Also, the impact of various forms of ion leakage on system performance could be studied.

Neuronal models such as this could be useful for studying the medical implications of demyelinating disease. Disease progression in patients could be better understood. Also, models could be helpful for drug development and ancillary therapies.

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