MNS CP Project '19/20: Action Potential Propagation

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1 Introduction

Neurons have widely varying dendritic structures and branching patterns, affecting how they transmit and process signals. Cable theory allows researchers greater accuracy in modeling how a neuron's axonal/dendritic structure affects signal processing. Simplifying assumptions are used to construct an equivalent circuit of the electrical properties of the axonal/dendritic segment. In this project, an axon has been modeled through this method. At first the axon is modeled as passive, i.e. without ion channels propagating the action potential along the axon. The axon is subjected to a steady current injection. Further exercises model the axon as "active", and investigate the effect of applying the Hodgkin-Huxley model of action potential propagation in a squid giant axon. Further work investigates the effect of injecting current into an axon from two ends, and the biophysical rationale for this. Finally, the effect of myelinating axonal segments is studied. The Crank-Nicolson algorithm is applied to solve the cable equation numerically; it is used to allow for greater accuracy.

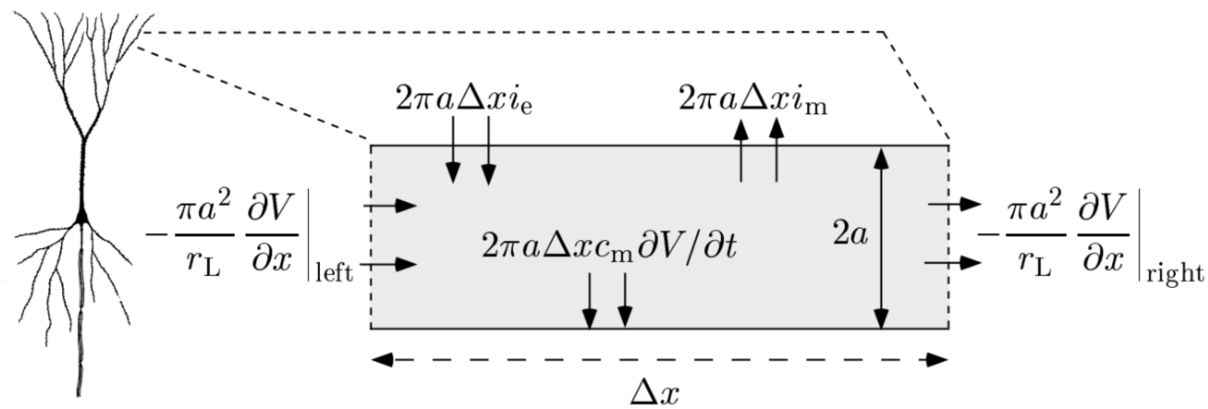


Figure 1: The Cable Equation current fluxes (Figure 6.6 Dayan and Abbott, 2001).

In figure 1, illustrated is a portion of neuron used to derive the cable equation. There are four currents that determine the rate of change the membrane potential within this segment has: two longitudinal, a membrane, and an electrode current. Due to Kirchhoff's current law, the sum of these currents must equal zero. Thus, we are able to result in the partial differential equation that is the cable equation, equation 1.

2 Solving the PDE

2.1 Crank-Nicolson Method: Theory

The cable equation, below, describes how the axonal membrane potential (relative to resting potential),v, varies with time and distance. Solving for the change v with time and distance involves finding the voltage at several points in space (along the axon) and how the voltage at each of these points varies over time.

$$c_m \frac{\partial v}{\partial t} = \frac{1}{2ar_L}\frac{\partial}{\partial x}\left(a^2 \frac{\partial v}{\partial x}\right) - i_m + i_e \tag{1}$$

For problems which involve an update in both time and space, to minimize error, "implicit" methods of numerical analysis are preferred. Implicit methods differ from explicit methods in the following way: explicit methods solve for the state of a system in the future, using the known current state of the system; implicit methods use both the current and future state of the system. One commonly used implicit method is the Crank-Nicolson scheme. The Crank-Nicolson scheme evaluates the time derivative with the basic ”forward differencing” approach, but evaluates the spatial derivative at a time in between the current and next timepoint. This is the average of the calculation performed at j and at j+1. The increased number of unknowns means that the resulting set of linear equations need to be solved simultaneously, which is possible given spatial and temporal boundary conditions.

For the basic form:

$$\frac{\partial v}{\partial t} = \frac{\partial v}{\partial x^2} \tag{2}$$

the Crank-Nicolson scheme can be applied as follows:

$$\frac{v_{i,j+1} - v_{i,j}}{\Delta t} = \frac{v_{i+1,j+1/2} - 2v_{i,j+1/2} - v_{i-1,j+1/2}}{\Delta x^2} \tag{3}$$

$$= \left(\frac{v_{i+1,j+1} - 2v_{i,j+1} - v_{i-1,j+1}}{\Delta x^2} + \frac{v_{i+1,j} - 2v_{i,j} - v_{i-1,j}}{\Delta x^2} \right) \tag{4}$$

2.2 Crank-Nicolson Method: Application

The Crank-Nicolson method is applied to the multicompartment axon model to update the voltage in each compartment in both space and time. The update rule applied is below:

$$\Delta V_\mu = a_\mu \Delta V_{\mu 1} + b_\mu \Delta V_\mu + c_\mu \Delta V_{\mu+1} + d_\mu \tag{5}$$

Starting from one end of the cable, we calculate the voltage change in terms of the voltage change in the next compartment, as in the below equation. At the end of the cable, we calculate ΔV using boundary conditions, and then substitute backwards to the first compartment to find the ΔV in each one.

$$\Delta V_{\mu-1} = \frac{c_{\mu-1} \Delta V_\mu + d'_{\mu-1}}{1 - b'_{\mu-1}} \tag{6}$$

3 Passive Membrane with Steady Current Injection

The first exercise in the project illustrates how a steady current injection, in the middle of an axon, propagates along the axon. As the membrane is passive, the current decays exponentially with distance. As the current is steady, the voltage in each compartment does not change with time. Propagation is symmetric on either side of the injection site.

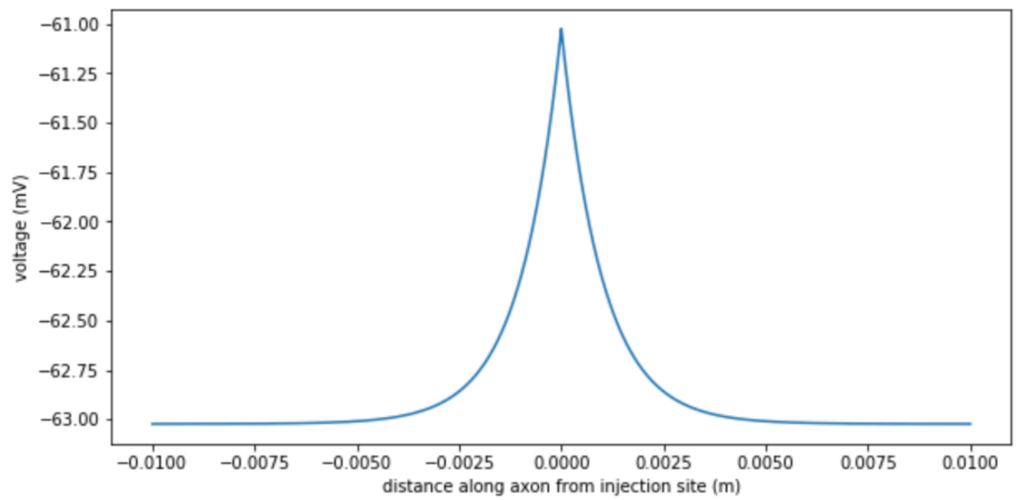


Figure 2: Exponential decay of membrane voltage when a steady current is injected in the middle of an axon with a passive membrane.

4 The Hodgkin-Huxley Model

For the generation of the action potential the Hodgkin-Huxley model is used. It is constructed by defining the membrane current as the sum of a leakage current, a potassium current, and a sodium current.

$$i_m = \bar{g}_L(V - E_L) + \bar{g}_{Na}m^3h(V - E_{Na}) + \bar{g}_K n^4(V - E_K) \tag{7}$$

Here, the gating variables n, m, and h are defined by equation 8. By integrating these equations with those of the cable equation we will be able to obtain results of the Hodgkin-Huxley model in its multi-compartment form.

$$\frac{dx}{dt} = \alpha_x(V)(1 - x) - \beta_x(V)\,x \tag{8}$$

In figure 3 a few example action potential spikes measured in a single compartment with a constant current input can be seen.

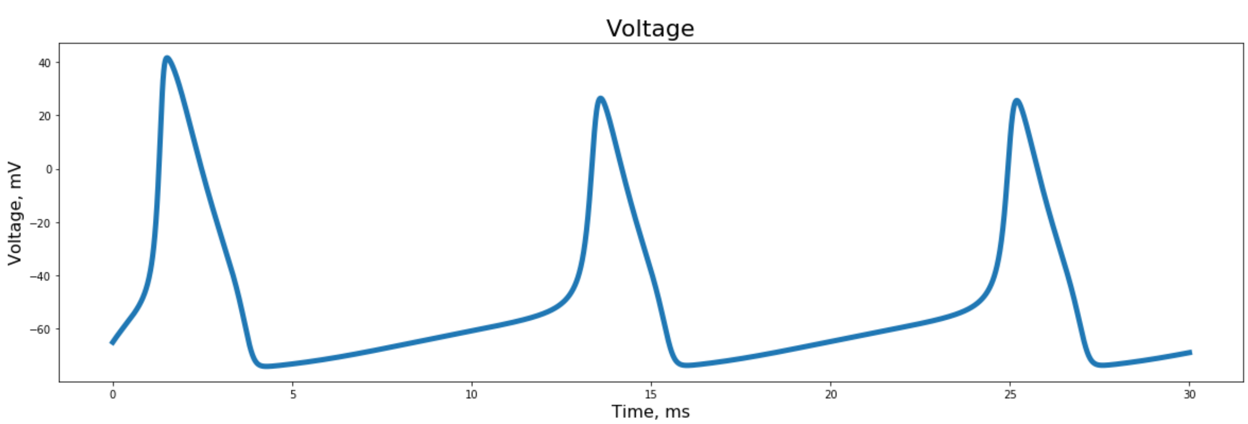
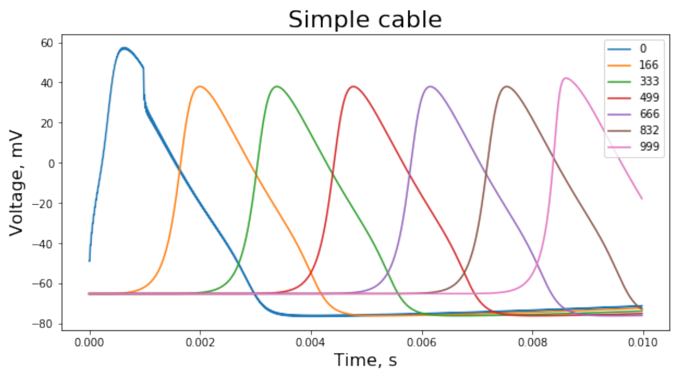


Figure 3: A graph of characteristic action potential spikes from the Hodgkin-Huxley model.

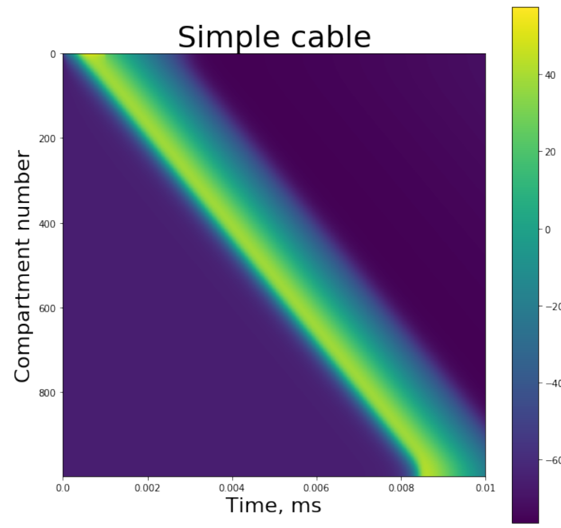
5 Initiation of an Action Potential

5.1 Simple Cable

In this section we modeled a squid giant axon using the Hodgkin-Huxley model. To do this we created a 100mm long cable comprised of identical 2μm long compartments. The first compartment was stimulated with a 10μA current for 1ms. The results of the simulation showed the AP propagating at a constant speed along the cable, with the shape of the AP remaining the same throughout.



(a) Action potentials at various compartment numbers.



(b) Voltage along the entire cable over time.

Figure 4: A single action potential initiated in the terminal compartment of an unmyelinated axon.

5.2 Velocity of an Action Potential

To see how cable radius affects the velocity of an AP 11 simulations were conducted from 2μm to 200μm. Cable length and stimulating current were changed according to the formulas:

$$Ie = 1nA * (r/2\mu m)^2$$

$$L = 8mm * \sqrt{r/2\mu m)^2}$$

These values were found empirically to be sufficient to stimulate the cable and so that the AP can travel approximately the length of the cable within the simulated time of 10ms. The results showed that the AP velocity is proportional to the square root of the radius, as can be seen by how well the sqrt function approximates the results.

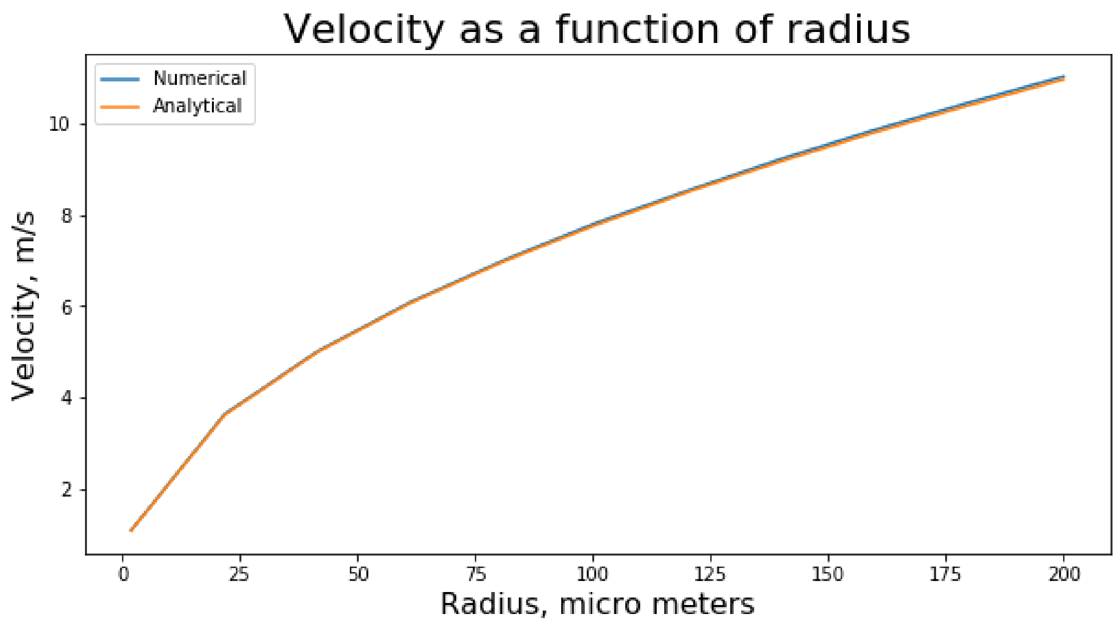
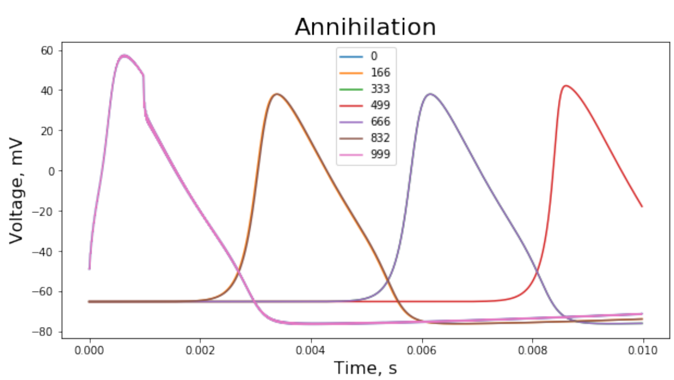


Figure 5: The numerical and analytical solution of the action potential propagation velocity.

5.3 Annihilation Cable

In this section we used the previous model, but instead stimulated from both ends of the cable. The resulting simulations showed the two propagating APs meeting in the middle and cancelling each other out. This phenomenon can be explained by the fact that at the moment of collision all nearby compartments are in their refractory period and cannot produce another spike, thereby ending the AP propagation.



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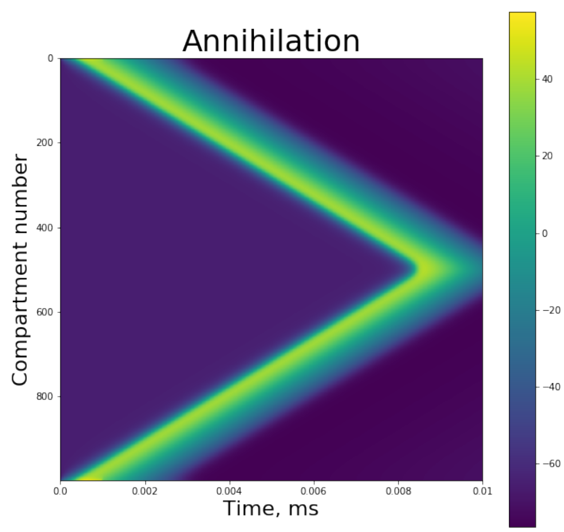


(b) Voltage along the entire cable over time.

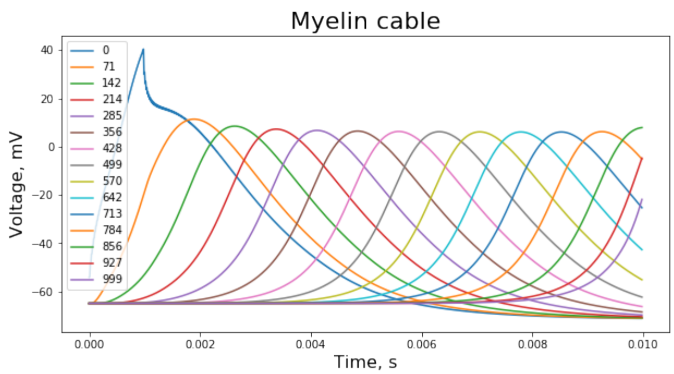
Figure 6: Two action potentials initiated at both ends of an axon.

6 Myelinated Axons

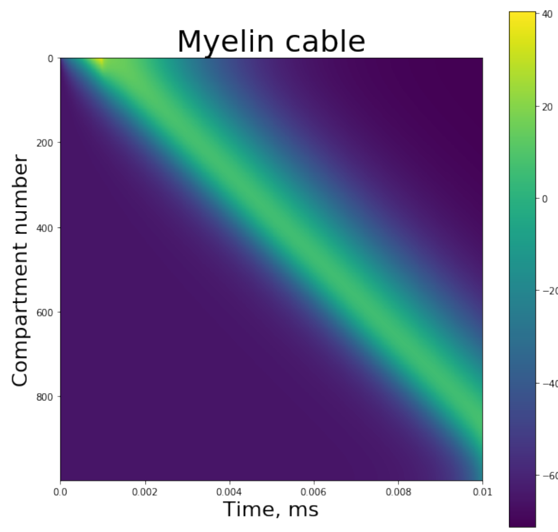
To simulate myelination the following changes were implemented:

- Nodes of Ranvier are every 1mm and are identical to a normal cable.
- Between nodes all compartments are myelinated and have their resistance increased by a factor of 5000 and their capacitance decreased by a factor of 50.
- The stimulating current was decreased to 1μA.
- The length of the simulated cable was increased to 500mm to account for the greater velocity.

The results of the simulation showed an AP that was more than 4 times faster than an unmyelinated one with the same radius. Also the shape of the AP became smoother and the peak voltage decreased to about 10mV. Taking into account the results on AP velocity, one would need an unmyelinated cable with a radius 16 times larger to match the speed of a myelinated cable.



(a) Action potentials at various compartment numbers.



(b) Voltage along the entire cable over time.

Figure 7: A single action potential initiated in the terminal compartment of a myelinated axon.

7 Cable Branching

Previously, we have only been observing the effects of an action potential in a single cable with constant radius and no branching. Now, we shall inspect the analytical solution to the cable equation solved for a branching cable.

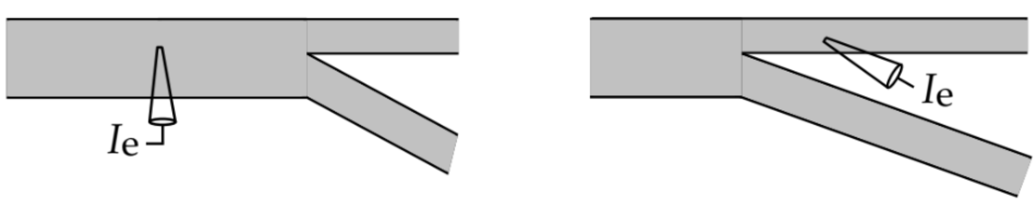


Figure 8: Diagrams illustrating a branching cable with a current injection into both the thick and thin sections of the axon. (Figure 6.9 Dayan and Abbott, 2001)

To do so, we define the potentials along each of the three segments as V_1, V_2, and V_3. Here, we will call V_2

the segment that current is injected into. The variable y will be the distance from the junction of the branching. By setting the boundary conditions $V_1(0) = V_2(0) = V_3(0)$ and $\sum a_i^2 \partial V_I/\partial x = 0$, we must find solutions that satisfy the cable equation, equation 1. These solutions are the following:

$$V_1(x) = p_1 I_e R_{\lambda_1} exp(\frac{-x_1}{\lambda_1} - \frac{y}{\lambda_2}) \tag{9}$$

$$V_2(x) = \frac{I_e R_{\lambda_2}}{2}[exp(\frac{-|y-x_2|}{\lambda_2}) + (2p_2 - 1)exp(\frac{-(y+x_2)}{\lambda_2})] \tag{10}$$

$$V_3(x) = p_3 I_e R_{\lambda_3} exp(\frac{-x_3}{\lambda_3} - \frac{y}{\lambda_2}) \tag{11}$$

where, for i = 1,2, and 3,

$$p_i = \frac{a_i^{3/2}}{a_1^{3/2} + a_2^{3/2} + a_3^{3/2}}, \quad \lambda_i = \sqrt{\frac{a_i r_m}{2r_L}}, \quad R_{\lambda_i} = \frac{r_L \lambda_i}{\pi a_i^2} \tag{12}$$

For the branching cable, the radius of the thick cable and the two thinner cables was 2 µm and 1 µm, respectively. Inspecting the results, as seen in figure 9, we can see that the two smaller branches has little effect on the declination of the potential away from the site of the current injection. This is because the thin branches do not contribute a large heat sink. The thick branch has a larger impact on attenuation of the potential because of its larger radius and from equations 12 the radius of the cable has an exponential effect on the resultant voltage.

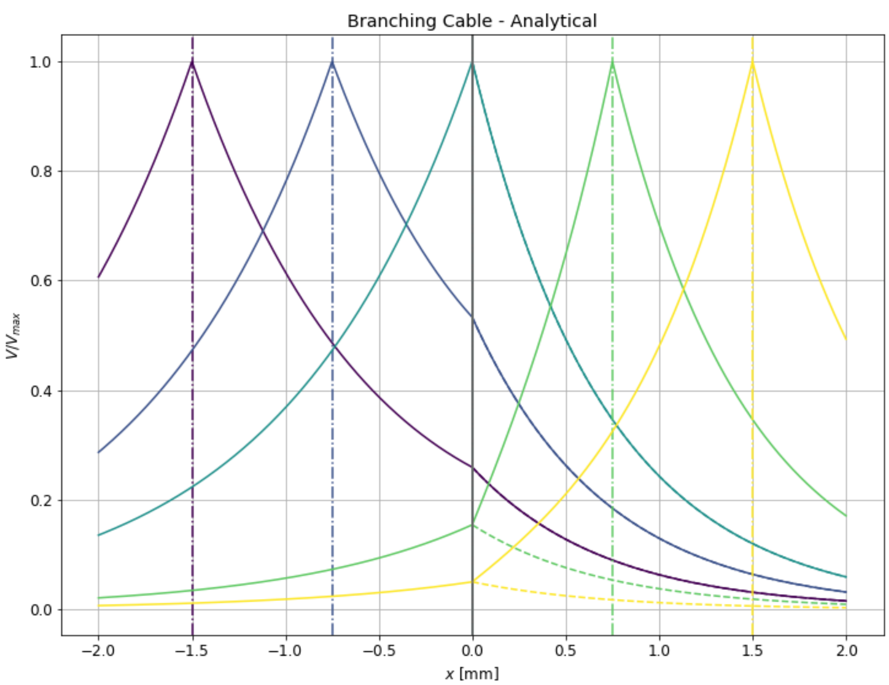


Figure 9: The analytical solution of a branching cable with various injection sites. The point $x = 0$ represents where the branching of the cable begins. Vertical dash-dotted lines represent sites of current injection, with each color corresponding to the resultant voltage divided by its voltage max for normalization. The solid lines represent the voltage in the thick branch and branch where current is injected. The dashed lines represent voltage in the branch where current was not injected. Notice that for a current injection in the thick branch, the voltages in the two thin branches is identical.

8 Conclusion

Through inspection and solving, both analytically and numerically, of cable equation, we have been able to gain insight on the characteristics of action potential propagation across an axon. It is useful to study the characteristics of the action potential in a multi-compartment model in order to gain insight on how different features, such as changes in cable radii, length of axon, myelination, and branching nodes, impact the information transfer of the neuron. This has use in future studies to have a reliable and accurate way of measuring the potential along an axon from a mathematical model.