Electric Field Inhibition of Transiently Induced-Pain

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Abstract

Oscillating electric fields have shown great promise for indirect stimulation of damaged axons, classification of synchronizing neural networks, and inhibition of nociceptive signals. So far, models in this course have focused on modeling the membrane voltage dynamics of neurons based on their ionic components. Without altering the physical properties of neurons, electric fields also induce changes in the membrane voltage. With this in mind, we aim to analyze the effect of an external electric field on primary and secondary afferent neurons immediately following a nociceptive stimulus. The application of a field in this manner is expected to impede the downstream signal, thereby preventing the sensation of transient pain.

1 Introduction

1.1 Problem/Pain Physiology

Injury and pain information is transmitted to the Central Nervous System (CNS) through peripheral nerves. Sensory nerve endings in the skin are capable of detecting chemicals, mechanical stimuli, and heat. These stimuli create action potentials that are carried through long axons to the spinal cord as seen in Figure 1 [Julius].

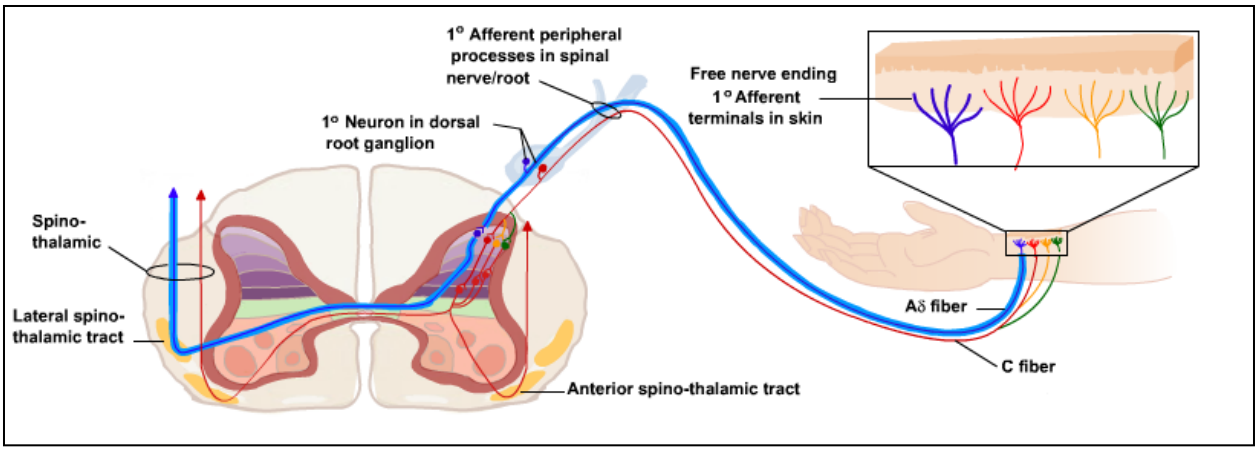


Figure 1: Physiology of nerve fibers

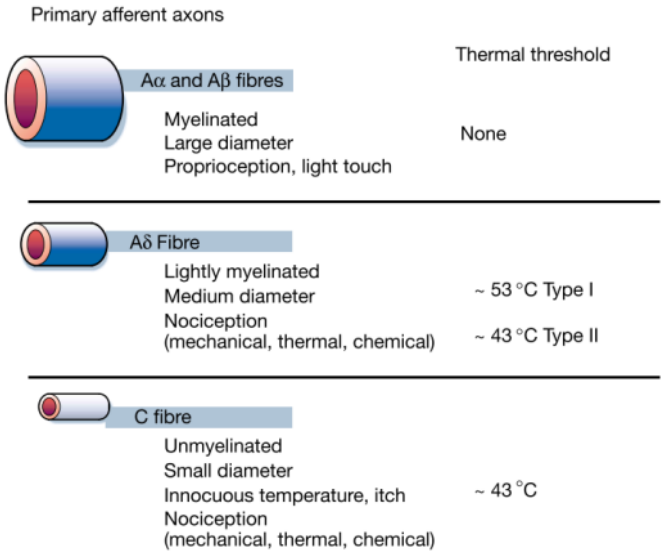


Figure 2: Nerve fibers

There are several different fibers that carry these inputs as seen in Figure 2 [Julius]. We are mainly concerned with the Aδ fiber which detects chemicals released due to cell damage caused by sharp or piercing pain. These fibers are lightly myelinated with one millimeter spacing between the nodes of Ranvier where electrical interactions take place as seen in Figure 1 [Bell]. We modeled the effects of electric fields on this axon.

Gating theory as detailed by Wall [1978] and Melzack [1993] describes how pain is transmitted and controlled by the CNS and spinal cord. The Aδ and C fibers have no electrical interaction until it reaches the spinal cord. At this point there is a "gate" that controls which signals go to the brain. It is thought that larger fibers inhibit the signals of smaller fibers. This is why transcutaneous neural stimulation (TNS) is able to inhibit pain. It activates larger fiber mechano-receptors that inhibit pain receptors. The CNS can also tell the spinal cord to stop passing certain signals up or to release neurotransmitters that bind to the nociceptor nerve endings and block the signal. These interactions will be considered in our future work.

1.2 Problem Setup

Sixty years ago, Alan Lloyd Hodgkin and Andrew Huxley presented a mathematical model depicting the ionic nature of excitable cells, the Hodgkin-Huxley (HH) model. In essence, they described the manner through which action potentials can be modeled using a set of nonlinear ordinary differential equations, overall responsible for gating kinetics of ionic channels and the membrane potential of excitable membranes.[Jiang]

$$\frac{dV}{dt} = -\frac{1}{C_M}\left[\bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_K n^4 (V - V_K) + \bar{g}_l (V - V_l)\right]$$

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

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

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

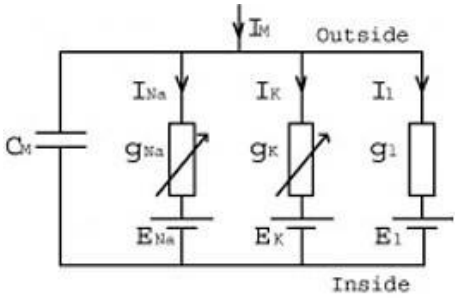


Figure 3: Hodgkin Huxley model

These equations are the basis of a circuit analog to the physical nature of a neuron membrane, the sum of currents representing the differential voltage across a capacitor over time.

Now, we look to the problem at hand: electric field inhibition of pain sensation. An externally applied electric field is expected to effect voltage dynamics of peripheral nociception (so long as it is within close proximity). As such, there should be a similar set of equations that describes the phenomena of an electric field's manifestation in HH dynamics. As it turns out, Warman et al. stated, "The electric fields applied to a fiber are equivalent to a set of current sources applied intracellularly."[Warman] Further literature has since then incorporated electric fields into the HH model in the following manner:

$$C_M \frac{dV}{dt} = I_{ext} - [\bar{g}_{Na} m^3 h(V + V_E - V_{Na}) + \bar{g}_K n^4 (V + V_E - V_K) + g_l (V + V_E - V_l)]$$

$$\frac{dy}{dt} = [\alpha_y(V)(1-y) - \beta_y(V)y] \quad (y = m, h, n)$$

Figure 4: Modified Hodgkin Huxley model

The modified HH model used for this project employs the same approach explained earlier, but now includes the induced electric field voltage in concert with the resting membrane potential, V, and the Nernst reversal potential, V_{ion}. This new voltage, V_E, is defined experimentally [Kotnik]:

$$V_E = \frac{QRK}{4\pi\varepsilon_o r^2} \cos\theta \sin 2\pi f t$$

where Q is the monopole charge magnitude, R is the radius of the cylindrical nerve, K describes the geometrical and electrical properties of the cell, r is the radial distance from the source to the nerve membrane, ε_o is the free space permittivity constant, and θ is the angle between the electric field vector and the membrane.

With these equations, we can begin to investigate the electric field effects on a nerve, and more specifically, effects on induced pain. To simulate this scenario, I_{ext} will be used to represent a pain-inducing stimulus, allowing the nerve to produce a spike train. We anticipate that as electric field properties are fine-tuned this pain spiking will become inhibited, therefore theoretically preventing pain sensation.

1.3 Project Goals

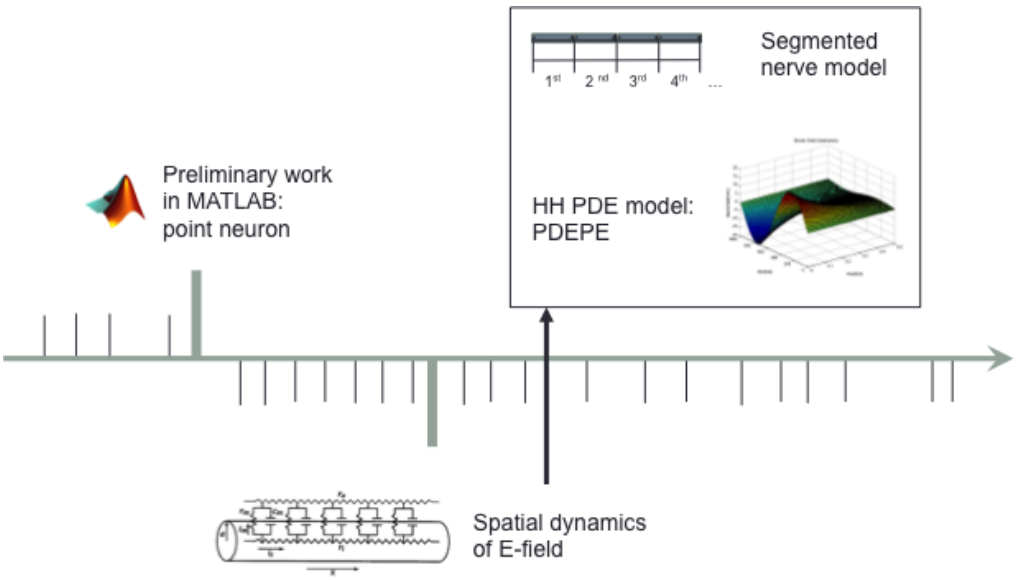


Figure 5: Project timeline

The project was broken down into goals addressing specific aspects of electric field inhibition. Above is a timeline of these goals, broken down into two main features:

1. Analyze nerve HH dynamics in the presence of a time-varying, spatially static electric field.

2. Spatiotemporal modeling of action potential spiking with increasing distance from electric field source. Finite element and numerical approaches used to characterize the voltage-time properties of the nerve.

By investigating such dynamics, we can determine what parameters (e.g. charge magnitude, frequency, source location relative to nerve) need fine tuning to elicit impulse inhibition. First, we modeled HH dynamics in a space-independent manner, also utilizing the modified HH model presented above. Once preliminary results were attained and analyzed, one-dimension in space was incorporated, allowing us to observe the inverse relationship of increased space and overall inhibition.

2 Preliminary Results: Frequency-Dependent Inhibition

In order to assess the effects of an electric field on transiently-induced pain, a pain model was constructed. An external current I_{ext} was fed into the HH neuron in order to simulate a neuron responding to nociceptive input. In this way, the neuron would inherently spike.

The first model consisted of feeding a sinusoid voltage, V_E, into the HH dynamics of a single spiking neuron. This sinusoid voltage corresponds to the E-field external voltage experienced by the axon. V_E=Asin(2*pi*f) , where f is the frequency of the E-field. Frequencies from 1 to 10 Hz were fed into the model with a voltage amplitude, A, of 10 mV.

Figure 6 shows the membrane voltage of the neuron plotted along with V_E for frequencies f=1 and f=10 Hz, respectively. As depicted, the spiking subsides in intervals that are functions of the E-field frequency. As the frequency decreases, the intervals between spike are consequently longer. These preliminary results imply that a sufficiently small frequency E-field may inhibit transient pain and thus validates our model.

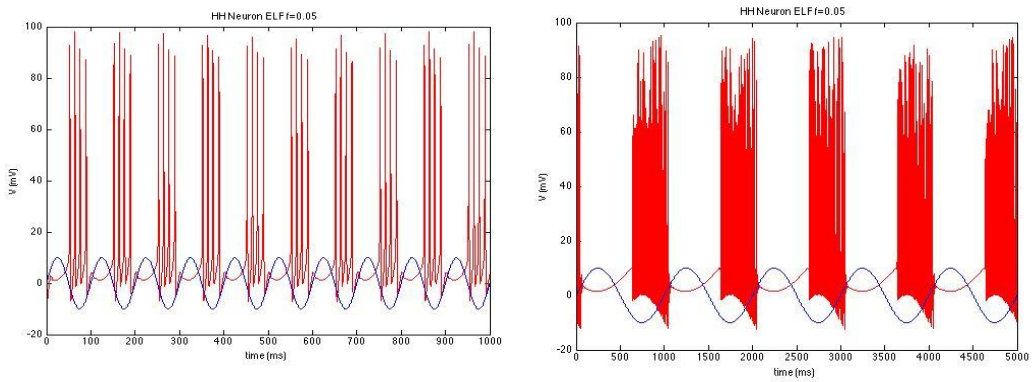


Figure 6: Frequency dependent inhibition

3 Spatio-Temporal Modeling

So far in the course we have explored the temporal dynamics of individual neurons and networks of neurons. In our model, the external E-field source is placed at a specific site along the relatively long nerve fiber and will affect the signal being propagated at different points on the axon. In order to evaluate the effects of the E-field along these different points, we must take into consideration the spatial dynamics of an axon. Using cable theory, an axon can be modeled as a cylinder composed of segments with capacitance and conductance elements in parallel as shown in Figure 7 [Schierwagen].

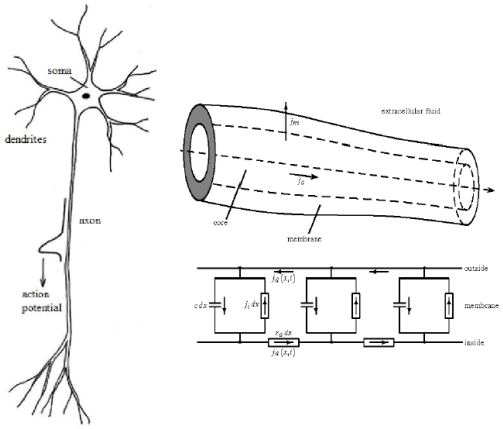


Figure 7: Cable Theory model of axon

From this, we can derive time and space dependence equations. In our model, we assume that myelin completely insulates the axon, and the electric field will induce an external voltage, V_E, only on the nodes of Ranvier, which exhibit HH dynamics. The voltage experienced at each node will vary with the distance and the angle of the axon to the electric field vector, θ.

Figure 8 exemplifies a decaying sinusoidal E-field and the response of a single neuron to the field. We can extend these results to an entire axon by recognizing that as the source of the electric field is placed farther from the cell body, the electric field experienced by that neuron will be attenuated significantly and the inhibition in spiking will subside. Besides taking into consideration the distance from the E-field source to the cell body, we recognize that since each node of Ranvier exhibits active HH elements, V_E may also induce spiking at different sections of the axon.

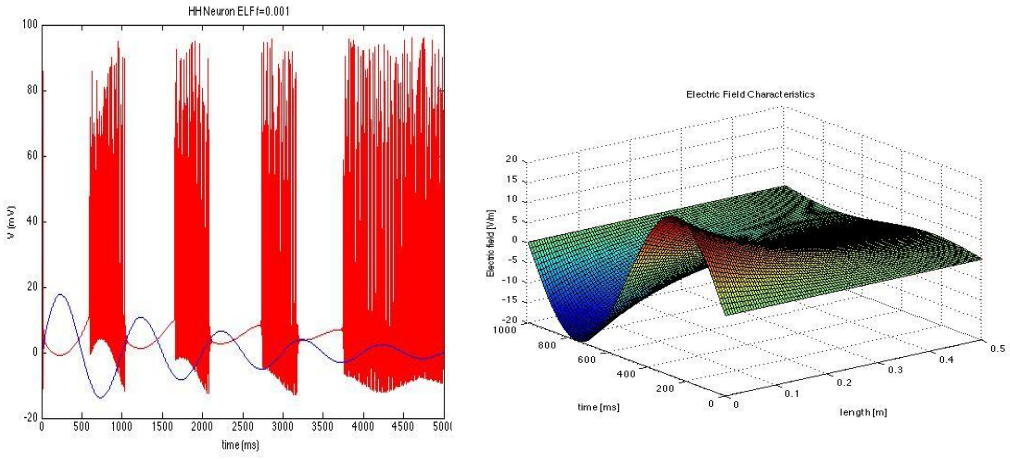
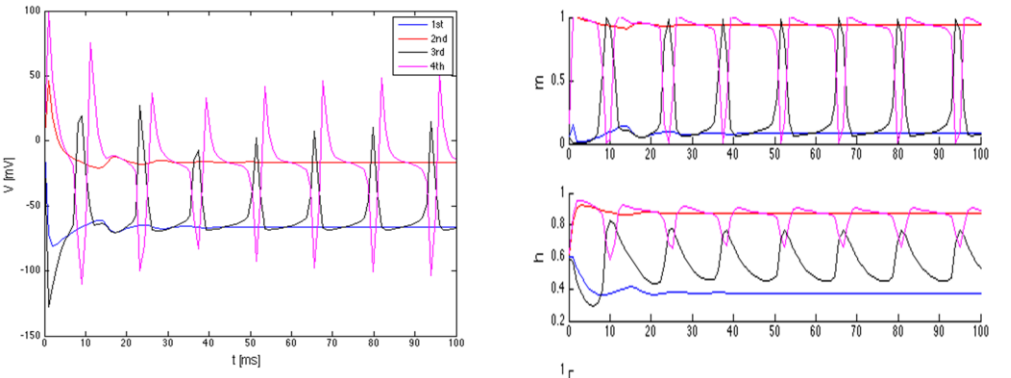


Figure 8: Response of decaying electric field and electric field in 3 dimensions

3.1 Segmented Nerve Model

Our first approach to model the axon, previous to using the cable equation, consisted of axon segments connected through synapse-like dynamics. In this case, the voltage of each segment adjacent to another segment in the direction of propagation was modeled as an extra source voltage V_{pre}. In this way, each segment would be affected not only by the varying electric field voltage V_E, but by the signal propagated by its neighbor. An excitatory current, I_{ext} was fed into the first axon segment.

Figure 9 shows the membrane potential of four connected axon segments and their corresponding gate variables. The first two axon segments, which are closer to the electric field, are inhibited, while the next two axon segments exhibit spiking. This spiking could be a response to a mixture of the spiking of the cell body and the electric field voltage.



Charge (Q) = 150 nC

$$I_{Na} = g_{Na} m^3 h \left(V + V_E - V_{Na} + V_{pre}\right)$$

$$I_K = g_K n^4 \left(V + V_E - V_K + V_{pre}\right)$$

$$I_L = g_L \left(V + V_E - V_L + V_{pre}\right)$$

Figure 9: Segmented model

This approach is a good initial representation of the space dynamics in an axon, but fails to model the conductivity of the axon in a cable theoretic and continuous way.

3.2 Numerical modeling using MATLAB PDEPE

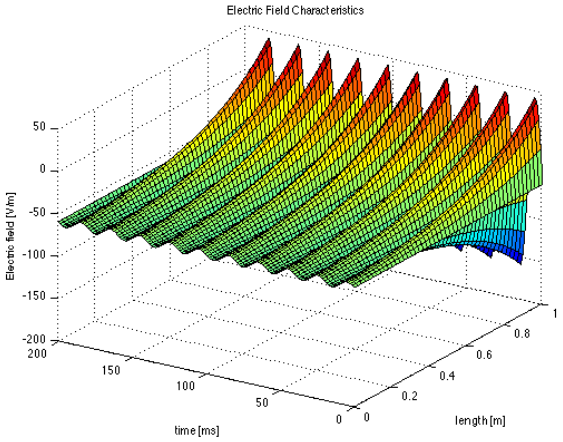
We have already demonstrated a pseudo-spatio-temporal approach towards HH dynamics in a segmented nerve fiber. Now we look to the time and space dependent form of the HH model:

$$\frac{\partial V}{\partial t} - \frac{\partial^2 V}{\partial x^2} = I_{ext} - g_{Na} m^3 h(V - V_{Na} + V_E) - g_K n^4 (V - V_K + V_E) - g_L (V - V_L + V_E)$$

[Evans]

This equation is quite similar to the HH model employed throughout the course, and contains our addition of the externally applied electric field voltage, V_E. The difference here is the 2nd order derivative in the x dimension, making this a two-dimensional model incorporating cable theory. By definition, this modified version of the HH equation is a partial differential equation (PDE). In the same manner as our segmented model, the HH PDE will serve to characterize the time-varying voltage properties of our nerve model while also implementing electric field inhibition as a function of distance from the source. The biggest difference between the two spatio-temporal models is that this PDE will present a *continuum* of action potential voltage values across an arbitrary nerve length, as opposed to modeling segments of the nerve in tandem.

The approach taken here is solely numerical. Although the solution to the HH PDE can be found analytically, it is easiest to manipulate necessary initial and boundary conditions via PDEPE in MATLAB. That being said, we expect to see a pattern as demonstrated in the following figure.



Sinusoid signal emulating space-time varying properties of nerve spike train

Figure 10

This is simply a sinusoid function that simulates the spike-train nature of nerves in time and space as a continuum. As time increases, action potentials are seen. Moreover, decaying of the signal settles to a set steady state value as x → 0 (the field source).

In order to solve the PDE (and end at a similar voltage distribution) we must declare the conditions by which the PDE can be solved uniquely. PDEPE requires definitions for the initial condition as well as boundary conditions at the "left" and "right" bounds of the system, namely x = 0 and x = L, respectively. We must also include conditions for HH gating variables, h, m, and n. Our values for these three parameters are listed in the table below.

Condition	Variable	Definition	Value
Initial	V	(x, t = 0)	-59
	m		0.053
	h		0.596
	n		0.318
Boundary	V, m, h, n	(x = 0, t)	No value
		d/dx (x = 0, t)	1
		(x = L, t)	No value
		d/dx (x = L, t)	0

This, along with the HH PDE, allows us to numerically simulate the nerve action potential signal. Here are the results:

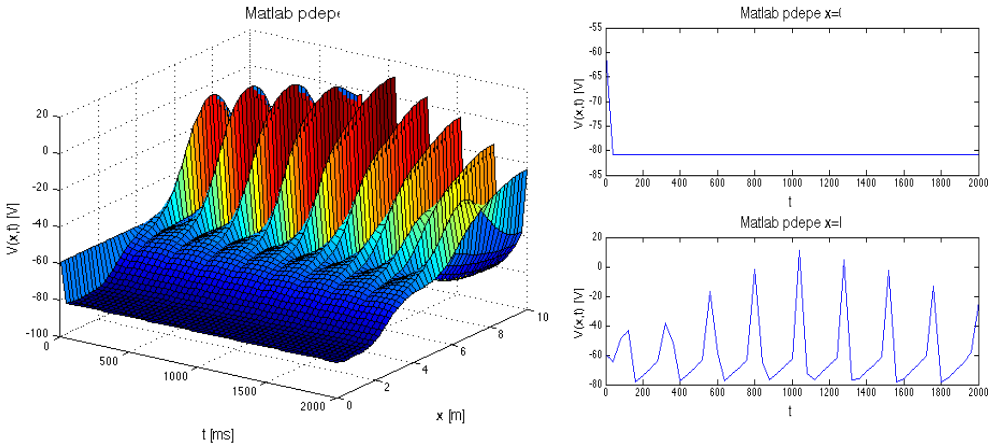
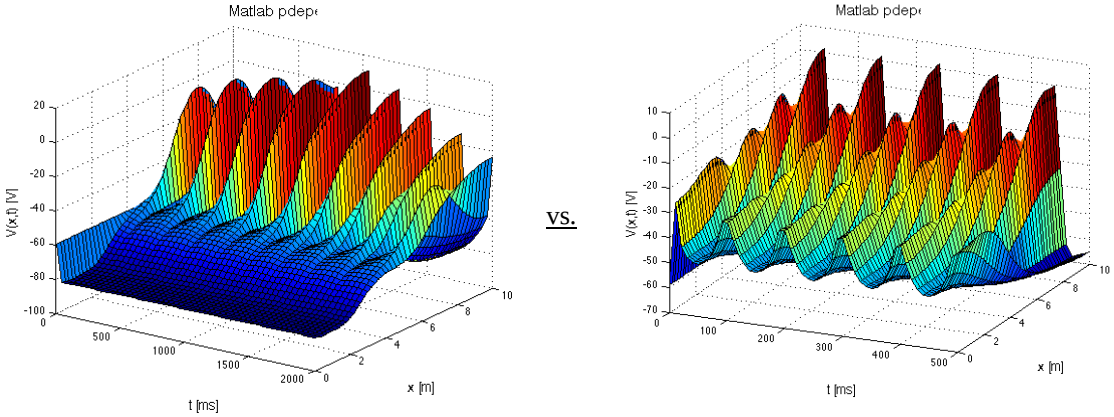


Figure 11

Our surface plot results demonstrate signal decay as x increases from the source (x = 0) to the theoretical end of the nerve (x = L, or x = 10 in this case). Voltage vs. time plots illustrated on the right show that action potential-like spikes form periodically at x = L, but are non-existent at x = 0, suggesting that the electric field inhibition at x = 0 is active. Moreover, the steady state voltage nearest to the source appears to remain in a hyperpolarized state, lower than the normal resting membrane potential of a nerve (80 mV vs. ~65mV), which is likely due to the inhibition strength of the external field. The spiking pattern exhibited at x = L is not entirely identical to those observed earlier, but do appear to function within the range of depolarized/hyperpolarized membrane voltage values.

Utilizing numerical methods such as PDEPE allows us to easily analyze the development of action potentials along a nerve over time. The results above are indicative of typical HH nerve dynamics, and begin to approach our expectations as the BCs for the system improve. This can be seen by comparison with the following image, which utilized zero flux BCs at both ends of the nerve:



For our previous formulation in PDEPE, zero-flux implied that the system retained its dynamics within the time and space boundaries specified. This caused a reflection of the voltage values at both ends (as seen to the right), which masked the true HH dynamics, similar to those in our newer results. Specifying a definitive flux at the end of the nerve allowed this build-up to "exit" the domain, leaving the actual results of the HH PDE. It is likely that flux BCs better associated with actual nerve dynamics would improve the voltage distribution and spike-train characteristics further. Still, our current setup presents promising results for analyzing the spatio-temporal nature of electric field inhibition on afferent nerve signals.

4 Conclusion

In our model, we have considered the spatial and temporal dynamics of an axon by utilizing cable theory. Specifically, we looked at how pain affects spiking throughout the axon.

For future studies, we could take into account the effect of the axon hillock in propagating the signal from the cell body along the axon. We would like to include gating theory interactions. Other solutions to this problem could include activating mechano –receptors with electric fields to gate pain signals in the spinal cord or activating neurotransmitter sites to decrease the effectiveness of the Aδ fiber nerve endings. A combination of these approaches would be interesting to pursue and could show promise.

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