

Effect of Spatial Heterogeneities on the Membrane “Space Constant” of the Passive Axon.

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Abstract

Findings that sub-threshold Voltage signals were propagated from Soma to Axon terminal may change the way we view Cortical Coding. How these signals were never considered before is a surprising error in both theoretical and experimental neuroscience. I address this by studying the effects of Heterogeneities in axon parameters, specifically membrane and internal resistances. Numerical studies will show how these heterogeneities affect the spatial decay of Voltage in a passive axon.

1 Introduction and Motivation

Mammalian Cortical coding has long been thought to be digital in nature. It was thought to be governed purely by all or none Action Potentials. Analog Coding was thought to occur only in invertebrates or in the peripheral sensory neurons of mammals. This notion was broken by Alle and Geiger's 2006 paper [1]. In this paper they show that sub-threshold changes in somatic voltage of Hippocampal Granule Cells were able to propagate to the axon terminal. Moreover, these sub-threshold deflections in the terminal had an impact in Action Potential Coding. They hypothesize that this may have functional implications during theta oscillations.

Regardless of functional significance, the propagation of sub-threshold voltage deflections over such a long distance is quite astounding. Cable Theory states that in general the membrane space constant is short. All sub-threshold signals dissipate in close proximity to the origin of the voltage change. This is often used as the segway into why our nervous system needs Action Potentials.

The use of Action Potentials comes at a cost. The metabolic costs of active current propagation are presumably higher than passive diffusion. Additionally joint experimental and theoretical studies suggest the superiority of analog signaling in information coding capacity [2]. But because of the short membrane constant, passive signals are supposedly not able to propagate. We must make the metabolic and coding capacity sacrifices associated with Action Potential generation in order to propagate the signal. This is the general dogma, and the findings by Alle and Geiger are an astounding contradiction.

The presence of these passive analog signals is truly remarkable. The explanation given by Alle and Geiger is that the space constant of the system is actually rather large. A plausible explanation, but I still find it interesting that this wasn't discovered earlier.

I propose that perhaps heterogeneities, specifically in the internal resistance and in the membrane resistance, could lead to non-intuitive effects on the space constant. The inhomogeneous resistances could have an average value, which would lead one to believe in a certain space

constant. Perhaps though the average value does not accurately capture the true dynamics of the cable equation given heterogeneities. This paper will explore that question.

2 Problem Setup

I will analyze how heterogeneities in the membrane resistance and internal resistance of a neuronal axon affects its ability to propagate sub-threshold membrane signals. Most analysis considers the resistances to be constants in space. I will see what happens if I let them have a periodic spatial structure. *f and g are periodic functions whose amplitude is always less than 1, and have average values of 0.*

$$\begin{aligned} r_m(x) &= r_m (1 + f(x)) \\ r_i(x) &= r_i (1 + g(x)) \end{aligned}$$

I will then compare spatial voltage decay in the standard axon to the spatial voltage decay of inhomogeneous axons (with f and g). I will refer to the space and time constant as being the space and time constants derived if one were to just use the average values of the resistances.

I will always set the Voltage at the origin of the axon to be 10mV. This is meant to represent a large depolarization that is still sub-threshold. Given this *boundary condition* I will see how the Voltage changes as we increase our distance from the axon origin.

$$V(0,t) = 10 \text{ for all time values of } t$$

3 Analytical Section

In solving the cable equation over the axon, I will take the standard reduction from three spatial dimensions to one spatial dimension. This results in the circuit diagram shown below (figure taken from Wikipedia's Cable Theory page)

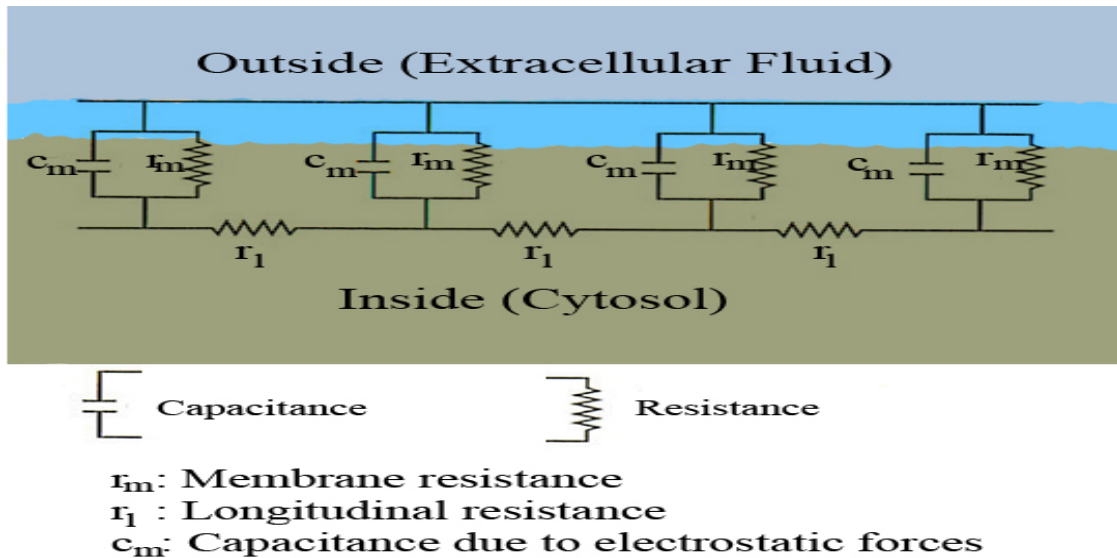


Figure 1: Illustration of Circuit Diagram of Cable Equation

Assuming a uniform neuron, the resulting linear PDE is

$$(1) \quad r_m c_m V_t = (E - V) + (r_m / r_l)(V_{xx})$$

It is typical to use time constant ($\tau = r_m c_m$). We also replace the ratio of resistances by the space constant squared (λ^2). We end up with the following equation.

$$(2) \quad \tau V_t = (E - V) + (\lambda^2)(V_{xx})$$

I simplify by non-dimensionalizing the PDE. I rescale both time and space by the space constant and time constant respectively. Since I am only looking at passive dynamics, I will let V represent the voltage drop from the leak reversal. We come out with a much cleaner equation, where time is in units of the time constant and distance is in units of the space constant.

$$(3) \quad V_t = -V + V_{xx}$$

I will be solving numerically this equation and two variations of it. When I vary the membrane resistance we can still derive an interpretable equation

$$(4) \quad V_t = -(1+f(x))^{-1} V + V_{xx}$$

When I introduce heterogeneities into the longitudinal resistance, the PDE cannot be written cleanly in non-dimensionalized units.

The analytic domain of choice is from 0 to positive infinity. Zero is going to represent the beginning of the axon, which stretches out in the positive x direction. Analytically we will approximate it to be infinitely long. This is a standard approximation technique used to avoid a second boundary condition. We cannot solve equation (4) with standard techniques but we can solve equation (3) for its steady state. Using 10mV as our voltage at the origin of the axon we get the following steady state analytic solution.

$$(5) \quad V_{ss}(x) = 10 \exp(-x)$$

This baseline, representing the homogeneous axon, is what I will use to compare my numerical results from. This represents both the solution of the inhomogeneous system and the solution of the in-homogenous solution if we were to average out heterogeneities.

4 Numerical Implementation

I will be solving a single PDE rather than a system of ODEs. This presents a host of numerical problems that are not present when numerically solving ODEs. I will employ a standard forward finite difference method. The method is most simple in its implementation and interpretation. It is also the easiest to manipulate the resistances in this numerical method. However, what is gained in ease of implementation is lost in numerical stability. Careful choice of time and distance steps is necessary for numerical solutions to converge.

I solve the PDE over a finite mesh that has a spatial dimension of 5 and a time length of 4. (again these are non-dimensionalised and we want to think 5λ and 4τ). The choice of domain was based upon a compromise between computation time and convergence to the steady state solution. After four time steps the simulation of the homogeneous system (equation 3) converges well to the theoretical steady state (equation 5). Additionally five steps of the spatial constant is enough

to properly see the exponential decay, and is long enough so that introducing a numerical boundary condition on the right doesn't interfere too much.

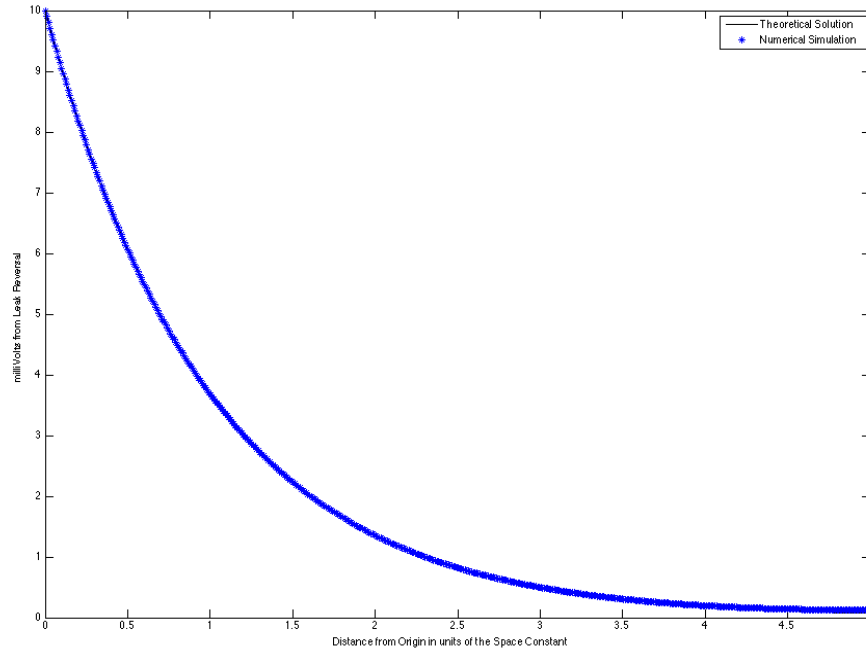


Figure 2: Verifying time-space domain choice: convergence of homogeneous simulation

The right hand side has a no flux boundary condition. I'm not sure what is the theoretically the best for axon terminal. However, I've seen it used in the literature. More importantly it does little to affect the behavior inside of the boundary at our choice of space scale. The mesh was particularly fine in time. I choose $dt=.00001$ and $dx=.01$. The small time steps were necessary to guarantee convergence as the resistances were varied.

4.1 Choice of Inhomogeneity.

$$r_m(x) = r_m (1 + f(x))$$

$$r_i(x) = r_i (1 + g(x))$$

My original conditions on f and g where that they must be periodic, bounded in amplitude by 1, and have an average value of 0. There a wide range of such functions, so I will restrict myself to alternating step functions and sin curves. The period will be fast because I am attempting to create a fast microstructure over the axon. The amplitude will be stepped from .1 to .9. Choice of these functions is also deemed useful in that if the numerics find an interesting solution, these functions will be amenable for some sort of analytical high order averaging argument.

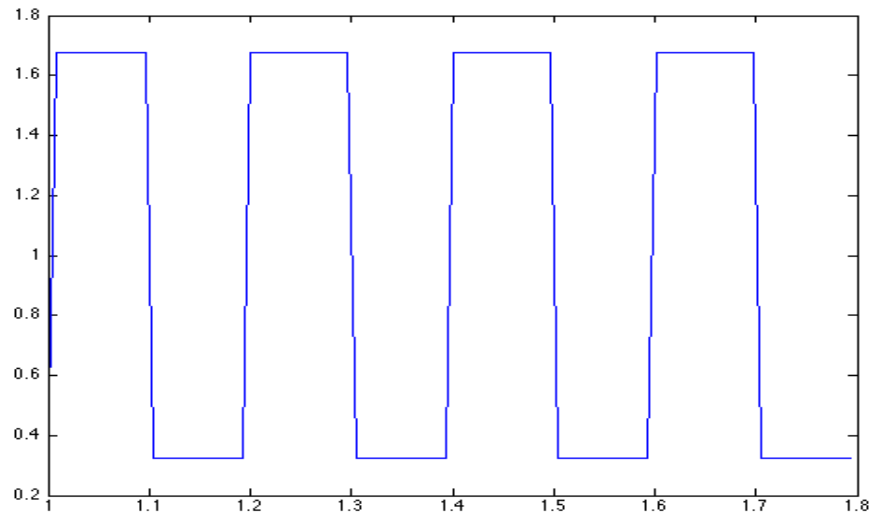


Figure 3: Example of an inhomogeneous resistance function of .7 amplitude

5 Numerical Results

All in all the numerics did not deviate too far from the homogeneous axon. The step functions had more notable results than the smooth sine functions and my results will focus exclusively on the step functions.

5.1 Heterogeneities in Membrane Resistance.

Here we see the most dramatic results. Compared with the theoretical solution after averaging out the heterogeneities, the voltage decays faster. It is imperceptible at first, but gets stronger as the amplitude of the heterogeneity is increased.

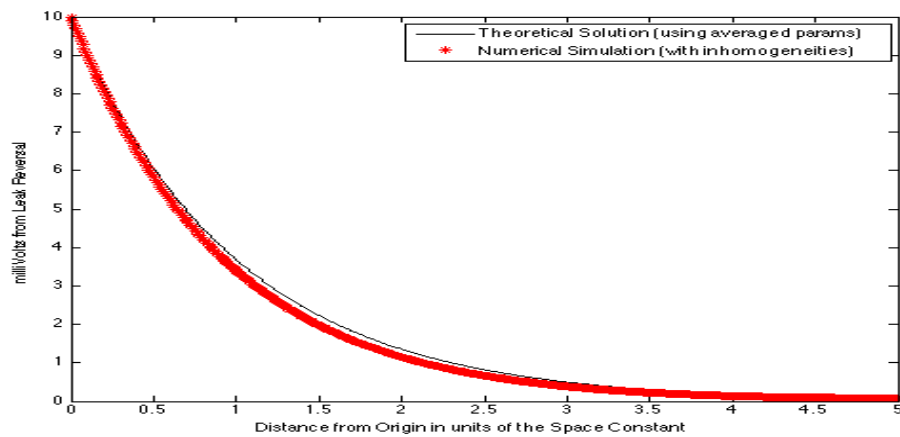


Figure 4: Faster voltage decay with amplitude of $f(x)$ at .5

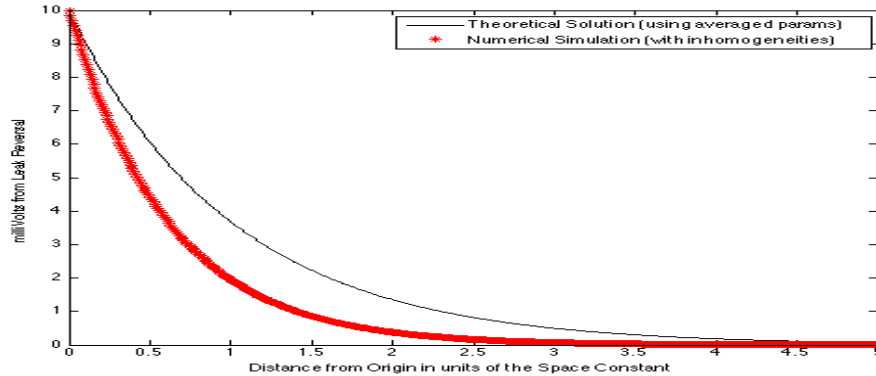


Figure 5: Faster voltage decay with amplitude of $f(x)$ at .8

5.2 Heterogeneities in Internal Resistance.

These results here are less clear. Voltage decay again seemed to stay near the theoretically derived estimate. Additionally, something about the system doesn't allow for the curve to smooth out like it does for the non-uniform membrane resistance. This time we see choppiness in our voltage traces. Even when the oscillation in resistance has a strong amplitude, we do not see a dramatic decrease.

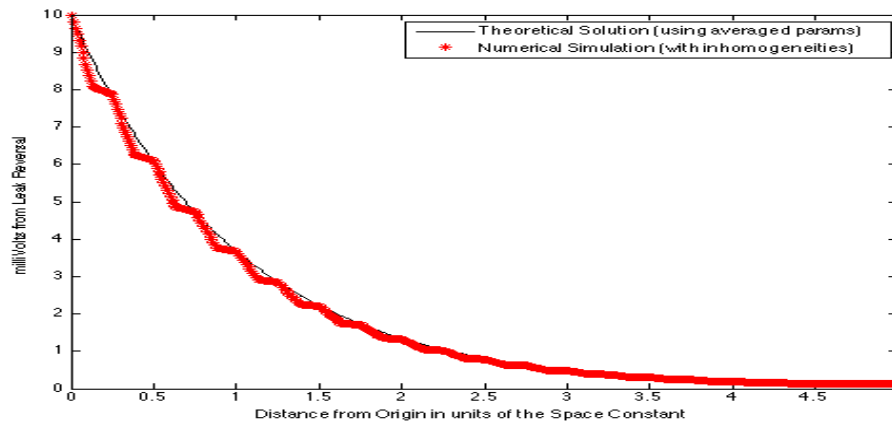


Figure 6: Inhomogeneous internal resistance: Chopy Voltage decay with amplitude of $g(x)$ at .8

5.3 Heterogeneities in Both Resistances.

Having established the effects of each independently, I now let both internal and membrane resistance oscillate. However, there don't seem to be any interesting interaction. The effects essentially summate.

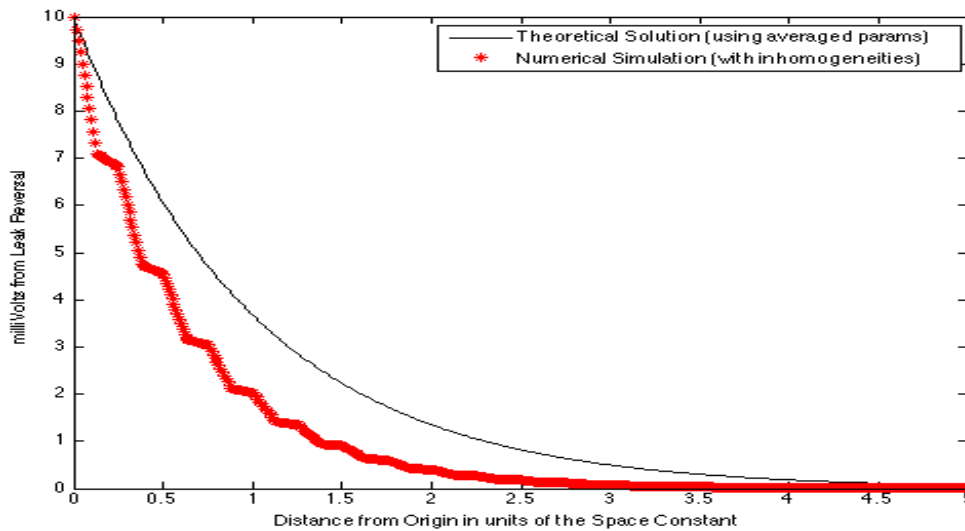


Figure 7: Inhomogeneous in both internal and membrane resistance. Combines the effects of figures 4 and 5.

6 Discussion

The numerical results can be summarized by the following five statements:

- 1) Heterogeneities in Internal Resistances can be averaged out
- 2) Heterogeneities in Membrane Resistance can NOT be averaged out
- 3) Heterogeneities in Membrane Resistance result in faster spatial decay of Voltage
- 4) The two heterogeneities act independently, there are no significant interactions
- 5) The existing effects of the Heterogeneities are stronger as we increase their amplitude

In light of the motivation for this study, these results are disappointing. Heterogeneities of Membrane Resistance were different from “expected” however they were in the wrong direction. I was ultimately looking for something that would slow down the spatial decay of voltage, not speed it up. In light of these findings, I do NOT think it worthwhile to attempt a rigorous mathematical averaging argument.

Perhaps Alle and Geiger's explanation was correct. Perhaps the biologically accurate space constant is surprisingly large. Either way, I am sure that fast oscillatory changes (even fairly large ones) in resistance cannot increase the space constant, if anything they decrease it. Either the space constant is naturally large, or there is a more complicated explanation of propagation of sub-threshold voltage signals. Future directions would be to look for sub-threshold active currents, and perhaps a more detailed look into the geometry of the axon.

7 Citations

- [1] Alle H, Geiger JR., Combined analog and action potential coding in hippocampal mossy fibers. *Science* (2006)
- [2] de Ruyter van Steveninck and Laughlin, The rate of information transfer at graded-potential synapses. *Letters to Nature* (1996)