5-2003

Parameter Estimation for a Modified Cable Model Using a Green's Function and Eigenvalue Perturbation.

Scott Lewis La Voie
East Tennessee State University

Parameter Estimation for a Modified Cable Model Using a Green's Function and Eigenvalue Perturbation

---

A thesis

presented to the faculty of the Department of Mathematics

East Tennessee State University

In partial fulfillment of the requirements for the degree

Master of Science in Mathematical Sciences

---

by

Scott La Voie

May, 2003

Jeff Knisley, Ph.D., Chair

Robert Gardner, Ph.D.

Lyndell Kerley, Ph.D.

Keywords: Cable theory, Carleman linear embedding, neuron, somatic shunt.

ABSTRACT

Parameter Estimation for a Modified Cable Model Using a Green's Function and

Eigenvalue Perturbation

by

Scott La Voie

In this thesis we developed the Green's Function for a tapered equivalent cylinder model of dendritic electrical propagation. We then use the Green's Function to develop a Carleman linear embedding scheme which is used to estimate the effects of a nonlinear ion channel hot-spot on the tapered cylinder solution. Mathematica© was used to implement the Carleman embedding scheme.

DEDICATION

I dedicate this thesis to my wife, Casey, and to my daughters Elise and Jada. You fill my life with hope and joy. I love you.

ACKNOWLEDGMENTS

I would like to thank Dr. Jeff Knisley for all of his advice, expertise, and support during the preparation of this thesis. I would also like to thank Dr. Robert Gardner for his friendship and assistance in cultivating my interest in mathematics, and Drs. Kerley and Glenn for their support and technical advice.

Contents

ABSTRACT ii

COPYRIGHT iii

DEDICATION iv

ACKNOWLEDGMENTS v

LIST OF FIGURES viii

LIST OF SYMBOLS 1

1 Introduction to Neuron Models 2

1.1 Historical Notes 2

1.1.1 Definitions 3

1.1.2 Research Overview 4

1.2 Cable Equation 5

1.2.1 Derivation 5

1.3 Delta Function Justification 8

1.4 Green's Function Concept 10

2 Preliminary Work 13

2.1 Eigenvalue Perturbation 13

2.1.1 Introduction 13

2.1.2 Eigenvalue Equation 15

2.1.3 Perturbation Assumption 16

2.1.4 Perturbation Scheme 16

2.2 Estimate of Eigenvalues 16

2.2.1 Recursion Scheme 16

3 Equation of Interest **18**

3.1 Hot-spot Model and Green's Function 18

3.2 Embedding Method and Recursion Scheme 23

4 Conclusions and Future Work **25**

BIBLIOGRAPHY 26

APPENDICES 28

A Mathematica© Code for the Eigenvalue Problem **29**

VITA 30

List of Figures

1 Main components of a typical neuron and synaptic gap. 2

2 Lumped soma RC circuit model. 5

3 Cylinder and RC circuit equivalence. 6

LIST OF SYMBOLS

x	Distance along the cable (cm)
t	Time (s)
R_s	Resistance of the soma (Ω)
R_D	Resistance of the dendritic cable (Ω)
C_s	Somatic capacitance (F)
$R_N = R_s R_D/(R_s + R_D)$	Input resistance of the neuron (Ω)
R_m	Membrane specific resistance (Ω/cm^2)
C_m	Membrane specific capacitance (FΩ)
R_i	Intracellular specific resistance (Ω cm)
R_{ms}	Somatic specific resistance (Ω cm^2)
R_{mD}	Dendritic specific resistance (Ω cm^2)
d	Diameter of cable (cm)
$\lambda = (R_M d/(4R_i))^{1/2}$	Space constant (cm)
$\tau_m = R_m C_m$	Time constant (s)
$\text{X} = \text{x}/\lambda$	Electrotonic distance (dimensionless)
$T = t/\tau_m$	Dimensionsless time variable
$V(X, T)$	Electrotonic potential (resting assumed 0)(V)
l	Physical length of cable (cm)
$L = l/\lambda$	Electrotonic length of cable (dimensionless)
$\tau_s = R_s C_s$	Somatic time constant (s)
$\sigma = \tau_s/\tau_m \in (o, 1]$	Somatic shunt parameter (dimensionless)
$r_i = 4R_i/(\pi d^2)$	Intracellular resistance per unit length (Ω/cm)
$\gamma = \rho_\infty = R_s/(\lambda r_i)$	Dendritic to somatic conductance ratio for semi-infinite cables (dimensionless)
$\rho = \gamma \tanh(L) = R_s/R_D$	Dendritic to somatic conductance ratio (Dimensionless)
$V_s(T)$	Electrotonic potential at the soma (V)
I_0	Magnitude of applied current at the soma (A)
$I_{\text{syn}}(T)$	Synaptic current (A)
T_0	Maximum width (duration) for which the synaptic current is activated (dimensionless)
$g(T)$	Synaptic conductance change (℧)
β	Maximum amplitude of synaptic conductance change ℧
$\alpha = \beta \lambda r_i$	Positive parameter (dimensionless)
K	Separation constant

1 Introduction to Neuron Models

A neuron has three major components: the soma or cell body, the axon, and the dendrites which connect to the axon of other neurons at the synapses. Electrical flow occurs from the axon of one neuron to the dendrites of another through neurotransmitters where it sums either spatially or temporally until a threshold is reached and the neuron then fires down its own axon and onto the dendrites of other neurons. The modelling of neurons is of particular interest because robust models allow for faster, more cost-effective research as opposed to using real neurons from animals.

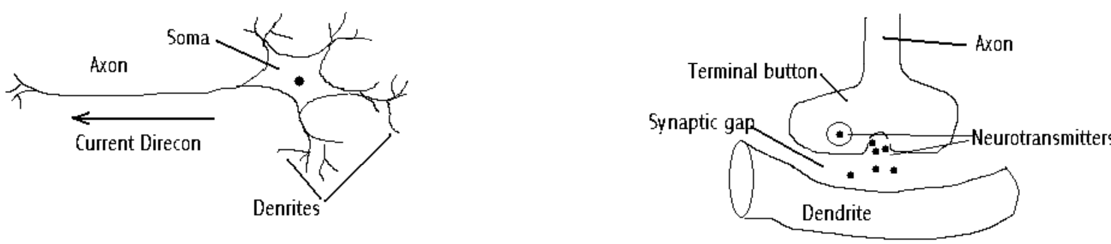

Figure 1: Main components of a typical neuron and synaptic gap.

1.1 Historical Notes

Interest in determining electrical properties of neurons dates back to Galvani and Volta [11]. Cable theory now dominates the research in studying electrical properties of neurons. Lord Kelvin (also known as Professor William Thomson) created cable theory while in correspondence with Professor Stokes to solve the problems faced with the transatlantic telegraph cable then being planned[5]. A very important property of cable theory is that it allows for the reduction to a single spacial dimension along the cable.

Tremendous advances in both the mathematical description of cables as well as the experimental techniques have occurred in the last 100 years. Some of the more important aspects are the use of single axon preparations and the development of space and voltage clamps. There have been two predominant views of cable theory since 1945, one by Hodgkin & Rushton and the other Davis & Lorente de Nó [11].

The modelling work aforementioned was developed with cylinders. Dendrites, however, actually taper, which is caused by a deviation from the 3/2 power law at the branch points [8]. The work completed in this thesis leads to a modified tapered-cylinder model.

1.1.1 Definitions

A **space clamp** is a technique in which membrane potentials are isolated from all other voltage dependent variables, which allows for the study of time dependent membrane potentials since all spacial potentials are set to zero. The technique involves inserting a long electrode with very low resistance per unit length in the axon, which is immersed in a solution of very high conductivity.

A **voltage clamp** is a technique in which the membrane voltage is controlled (fixed) in order to study the normal feedback that occurs between voltage and current. The technique involves the use of two electrodes, one to keep the membrane potential fixed and the other to measure the change in potential across the membrane.

The **somatic shunt**, or a diverted potential to the soma, is a condition thought to be caused in experiments by the damage due to penetration of the membrane by potential measuring instruments. Under specific assumptions the shunt boundary condition is derived.

Rall's **equivalent cylinder** model is a powerful simplifying reduction of branching dendrites to one equivalent cylinder. The advantage is that properties of a whole dendritic tree can be studied with well developed mathematical analysis [11].

1.1.2 Research Overview

This thesis consists of four major parts: development of model, eigenvalue perturbation for a restricted model, a Green's function approach to solving the problem (the main work of the thesis), and future plans.

The development of the model consisted of an introduction to the biological and physical aspects of the problem as well as the development of the mathematical model used to estimate parameters of interest (potentials, currents, conductance, etc.)

The eigenvalue perturbation for a restricted model was a standard technique approach to the somatic shunt. The purpose of this part of the research was to gain a base-level understanding of the research area.

The main work consisted of a Green's function approach to solving the cable equation. The use of a Green's function solves a less restricted cable model and introduces a nonlinearity (a *hot spot.*) The embedding of the nonlinearity from the main equation into one of the boundary conditions renders the problem more accessible.

In the future work we will adapt this work to Poznanski's persistent sodium channel model. [10]

1.2 Cable Equation

The cable equation is the mathematical model by which electrical properties of the neuron are modelled. The equation is a second-order, nonlinear, nonhomogeneous partial differential equation.

1.2.1 Derivation

A dendritic segment is modelled by a cylinder with a membrane and a lumped soma.

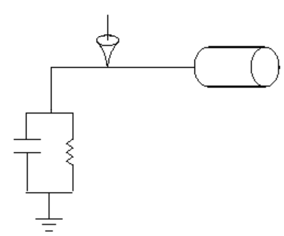

Figure 2: Lumped soma RC circuit model.

The currents through a small patch are given by the membrane current density I_m, the external current densities $I(x,t)$ and the axial current directed toward the soma. In particular, on a small patch we have

$$I_m - \Delta I_{\text{axial}} = -I(x,t)$$

where the membrane current I_m is a sum of a capacitative current and a current across the membrane resistance. Thus,

$$c_m \frac{dV}{dt} + \frac{V}{r_m} - \Delta I_{\text{axial}} = -I(x,t)\Delta x \tag{1.2.1}$$

However, the axial current can be modelled by approximating the cylinder in the following diagram:

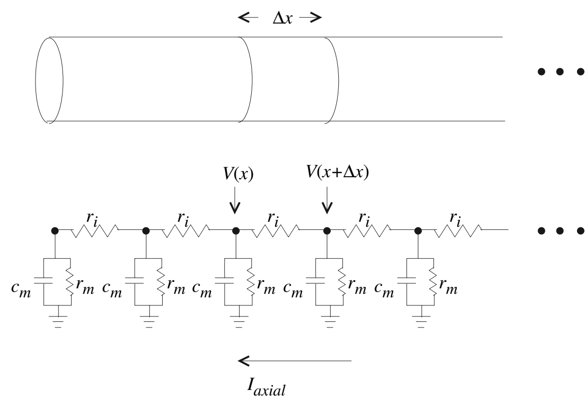

Figure 3: Cylinder and RC circuit equivalence.

Using $r_m = R_m\Delta x,\ c_m = C_m\Delta x$ for the membrane resistance and $r_i = R_i\Delta x$ as the internal resistance we see

$$I_{\text{axial}} = \frac{V\left(x+\triangle x\right) - V(x)}{R_i \triangle x} \implies \lim_{\triangle x \to 0} I_{\text{axial}} = \frac{1}{R_i}\frac{\partial V}{\partial x}.$$

$$\left(C_m \frac{dV}{dt} + \frac{V}{R_m}\right)\Delta x - \Delta I_{\text{axial}} = -I(x,t)\Delta x$$

$$C_m \frac{dV}{dt} + \frac{V}{R_m} - \frac{\Delta I_{\text{axial}}}{\Delta x} = -I(x,t). \tag{1.2.2}$$

Empirical evidence implies that intracellular fluid and membrane thickness are uniform. Thus, internal resistance R_i and membrane capacitance C_m may be assumed to be constant. Now (1.2.2) becomes

$$C_m \frac{dV}{dt} + \frac{V}{R_m} - \frac{1}{R_i} \frac{\partial^2 V}{\partial x^2} = -I(x,t)$$
$$\frac{R_m}{R_i} \frac{\partial^2 V}{\partial x^2} - \tau_m \frac{\partial V}{\partial t} - V = I(x,t).$$

where $\tau_m = C_m R_m$ is the membrane time constant. If we let $\lambda^2 = \frac{R_m}{R_i}$, then $\mathrm{X} = \frac{\mathrm{x}}{\lambda}$ transforms our model into dimensionless form:

$$\frac{\partial^2 V}{\partial \mathrm{X}^2} - \tau_m \frac{\partial V}{\partial t} - V = I(x,t)$$

If we assumed sealed ends (i.e., no current flow), then the boundary conditions and initial condition are

$$\frac{\partial V}{\partial \mathrm{X}}(0,t) = 0$$
$$\frac{\partial V}{\partial \mathrm{X}}(l,t) = 0$$
$$V(\mathrm{X},0) = V_{\mathrm{in}} \equiv \text{constant}.$$

Using subscript notation, our system to be solved is then

$$V_{xx} - \tau_m V_t - V = I(x,t) \tag{1.2.3}$$

$$V_x(0,t) = 0$$

$$V(l,t) = 0$$

$$V(x,0) = 0$$

1.3 Delta Function Justification

This justification is provided by Dr. Jeff Knisley and can be found in [12].

Assume a cable of length l with a point source at $x_0 \in (0,l)$. For each $\varepsilon > 0$, let $V(x,t)$ be a solution to

$$\begin{aligned} \frac{\partial V}{\partial t} &= \frac{\partial^2 V}{\partial x^2} + k\frac{\partial V}{\partial x} - V & (1.3.1)\\ V_x(0,t) &= V_x(l,t) = 0 & (1.3.2)\\ V(x,\varepsilon) &= \frac{1}{\varepsilon\sqrt{2\pi}} e^{-(x-x_0)^2/\left(2\varepsilon^2\right)}. & (1.3.3) \end{aligned}$$

It can be shown that

$$\begin{aligned} \lim_{\varepsilon\to 0^+} V(x,\varepsilon) &= 0 \text{ if } x \neq x_0 & (1.3.4)\\ \lim_{\varepsilon\to 0^+} \int_{-\infty}^{\infty} V(x,\varepsilon)\,dx &= 1 & (1.3.5) \end{aligned}$$

(i.e., it is a Gaussian probability distribution for each $\varepsilon > 0$). This allows the following:

Proposition 1.1 *If* $f(x) \in C^0[0,l]$, *if* $f(x) = 0$ *for* $x < 0$ *or* $x > l_0$, *and if* V *satisfies (1.3.4) and (1.3.5), then*

$$\lim_{\varepsilon \to 0^+} \int_0^l V(x,\varepsilon) f(x)\, dx = f(x_0).$$

Proof:

Let's first notice that we can write

$$\begin{aligned}
\int_0^l V(x,t) f(x)\, dx &= \int_{-\infty}^{\infty} V(x,t) f(x)\, dx \\
&= \int_{-\infty}^{\infty} V(x,t) f(x_0)\, dx + \int_{-\infty}^{\infty} V(x,t)\left[f(x) - f(x_0)\right] dx \\
&= \int_{-\infty}^{\infty} V(x,t) f(x_0)\, dx + \int_{\mathbb{R}\setminus(a,b)} V(x,t)\left[f(x) - f(x_0)\right] dx \\
&\quad + \int_a^b V(x,t)\left[f(x) - f(x_0)\right] dx
\end{aligned}$$

where (a,b) is an interval on which $|f(x) - f(x_0)| < \varepsilon$. Then

$$\lim_{\varepsilon \to 0^+} \int_{-\infty}^{\infty} V(x,\varepsilon) f(x_0)\, dx = f(x_0) \lim_{\varepsilon \to 0^+} \int_{-\infty}^{\infty} V(x,\varepsilon)\, dx = f(x_0).$$

In addition, it is easy to show that

$$\lim_{\varepsilon \to 0^+} \int_{\mathbb{R}\setminus(a,b)} V(x,\varepsilon)\left[f(x) - f(x_0)\right] dx = 0$$

and also that

$$\left| \int_a^b V(x,\varepsilon)\left[f(x) - f(x_0)\right] dx \right| \leq \int_a^b \frac{1}{\sqrt{2\pi}} e^{-(x-x_0)^2/\left(2\varepsilon^2\right)} dx \ \to 0$$

as ε approaches 0.$\square$

In the sequel, we will use the notation

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + k\frac{\partial V}{\partial x} - V \quad (1.3.6)$$

$$V_x(0,t) = V_x(l,t) = 0 \quad (1.3.7)$$

$$V(x,0) = \delta(x - x_0) \quad (1.3.8)$$

to denote the family of functions that satisfy (1.3.1), (1.3.2), (1.3.3), (1.3.4), and (1.3.5).

1.4 Green's Function Concept

The following justification is provided by Dr. Jeff Knisley and can be found in [12].

Let $\mathcal{L}$ be a differential operator with domain $D \subset L^2[0,l]$. Then $\mathcal{L}$ is unbounded since

$$\frac{\|\mathcal{L}x^n\|}{\|x^n\|} = o(n)$$

as $n \to \infty$. Suppose now that the spectrum of $\mathcal{L}$ is discrete. Then the *resolvent* is

$$\rho(\mathcal{L}) = \left\{ z \in C \mid (zI - \mathcal{L})^{-1} \ BLO\ on\ L^2[0,l] \right\}$$

is uncountable and the resolvent operator $R_z = (zI - \mathcal{L})^{-1}$ can be considered a continuous function of z. It follows that $(zI - \mathcal{L})^{-1} f = g$ is a solution to the nonhomogeneous differential equation

$$zg - \mathcal{L}g = f.$$

Moreover, since

$$f(x) = \int_{-\infty}^{\infty} f(u)\,\delta(x-u)\,du,$$

then it follows that

$$\left((zI-\mathcal{L})^{-1}f\right)(x)=\int_{-\infty}^{\infty}f(u)\,(zI-\mathcal{L})^{-1}\,\delta(x-u)\,du.$$

Now we let $G(x,z,u)$ be the solution to

$$(zI-\mathcal{L})^{-1}\,\delta(x-u)=G$$

which is equivalent to

$$zG-\mathcal{L}G=\delta(x-u).$$

Then G is called the *Green's function* of $\mathcal{L}$ and it follows that

$$\left((zI-\mathcal{L})^{-1}f\right)(x)=\int_{-\infty}^{\infty}G(x,u,z)\,f(u)\,du.$$

It is important to point out that *Duhamel's principle* [14] allows us to modify our definition of the Green's function. In particular, suppose that we have

$$\begin{aligned}V_t-(zI-\mathcal{L})\,V &= F(x)\\ V(x,0) &= 0\end{aligned}$$

and let us suppose that we let $W(x,t)=V(x,t)-(zI-\mathcal{L})^{-1}F(x)$. Then

$$\begin{aligned}W_t-(zI-\mathcal{L})\,W &= V_t-(zI-\mathcal{L})\,V-(zI-\mathcal{L})\,(zI-\mathcal{L})^{-1}F(x)\\ &= F(x)-F(x)\\ &= 0\end{aligned}$$

and $W(x,0)=0-\ (zI-\mathcal{L})^{-1}F(x)$. That is, our original non-homogenous equation becomes

$$W_t-(zI-\mathcal{L})\,W=0$$

$$W(x,0) = -\left(zI - \mathcal{L}\right)^{-1} F(x).$$

We thus define a Green's function to be the solution of the main partial differential equation with the delta function imbedded within the initial conditions.

2 Preliminary Work

2.1 Eigenvalue Perturbation

2.1.1 Introduction

In the early stages of the research we used perturbation to solve the hot spot by linearizing with the Laplace transform technique. The problem statement was:

$$\frac{r_m}{r_i}\frac{\partial^2 V_j}{\partial x^2} = r_m c_m \frac{\partial V_j}{\partial t} + V_j - r_{m_j}\, g_j(x_j, t) \tag{2.1.1}$$

where $g_j(x_i, t)$ is the internal ion density and where r_j is the internal resistance.

To illustrate the Laplace Transform method we assume $g_j(x_i, t) = 0$. We then have

$$\frac{r_m}{r_i}\frac{\partial^2 V_j}{\partial x^2} = r_m c_m \frac{\partial V_j}{\partial t} + V_j. \tag{2.1.2}$$

Re-scaling in x and letting $\tau_m = r_m c_m$ [7] leads to

$$\frac{\partial^2 V}{\partial x^2} = \tau_m \frac{\partial V}{\partial t} + V \tag{2.1.3}$$

$$V(0,t) - \gamma V_x(0,t) + \sigma V_t(0,t) = 0$$

$$V_x(l,t) = 0$$

$$V(x,0) = 0$$

which corresponds to the simplification of just one cylinder and a voltage depolarization in the initial conditions.

Using the Laplace operator on derivatives, $\mathcal{L}\left[\frac{df}{dt}\right] = s\hat{f}(s) - f(0)$ [6] we get the Laplace transform of (2.1.3)

$$\frac{\partial^2 \hat{V}}{\partial x^2} = s\tau_s \hat{V} - V(x,0) + \hat{V}. \tag{2.1.4}$$

Working with just one cylinder, the initial assumption (constant V_{in}) implies that $V(x,0) = 0$ so (2.1.4) becomes

$$\frac{\partial^2 \hat{V}}{\partial x^2} = (s\tau_s + 1)\hat{V} \tag{2.1.5}$$

$$V(0,t) - \gamma V_x(0,t) + \sigma V_t(0,t) = 0 \tag{2.1.6}$$

$$V_x(l,t) = 0$$

$$V(x,0) = 0$$

where (2.1.6) is the *somatic shunt* boundary condition [7]. The homogenous form of (2.1.5) has the general solution $\hat{V}(x) = A\cosh\left[\beta\left(l-x\right)\right] + B\sinh\left[\beta\left(l-x\right)\right]$ where $\beta^2 = s\tau_m + 1$. The boundary conditions imply $B = 0$ and

$$A = \frac{1}{(1-\alpha\tau_s)\cosh(\beta l) + \gamma\beta\sinh(\beta l)}. \tag{2.1.7}$$

The solution to (2.1.5) is then

$$\hat{V}(x,s) = A\cosh(\beta l) = \frac{\cosh(\beta l)}{(1-\alpha\tau_s)\cosh(\beta l) + \gamma\beta\sinh(\beta l)}. \tag{2.1.8}$$

2.1.2 Eigenvalue Equation

Separating variables in (2.1.5) yields a solution of the form

$$V(x,t) = \sum_{j=1}^{\infty} c_j(x) e^{-\alpha_j t} \tag{2.1.9}$$

which in Laplace space is of the form

$$\hat{V}(x,s) = \sum_{j=1}^{\infty} \frac{c_j(x)}{s+\alpha_j}. \tag{2.1.10}$$

The α_j's are *simple poles* of $\hat{V}$ with *residues* c_j. The α_j's are the zeros of the denominator of the Laplace space solution (2.1.8).

Next we convert the hyperbolic functions to trigonometric functions by letting $s = -\alpha$ and using the identities

$$\cosh(i\theta) = \cos(\theta)$$

$$\sinh(i\theta) = i\sin(\theta).$$

Thus we convert (2.1.8)

$$\hat{V}(x,s) = \frac{\cosh(\beta l)}{(1-\alpha\tau_s)\cosh(\beta l) + \gamma\beta\sinh(\beta l)} \tag{2.1.11}$$

$$\Downarrow$$

$$\hat{V}(x,s) = \frac{\cos(\beta_1 l)}{(1-\alpha\tau_s)\cos(\beta_1 l) - \gamma\beta_1\sin(\beta l)} \tag{2.1.12}$$

where $\beta_1 = +\sqrt{\alpha\tau_m - 1}$.

2.1.3 Perturbation Assumption

The eigenvalues are the poles of the Laplace Transform of the solution [6], and are thus solutions to

$$\cos(\beta_1 l)(1 - \alpha\tau_s) - \gamma\beta_1 \sin(\beta_1 l) = 0.$$

Empirical evidence implies that $\tau_s << \tau_m$. Let $\tau_s = \varepsilon\tau_m$ for $\varepsilon \approx 0$. Then it can be shown that $\gamma = \varepsilon k$ for some constant k. Our eigenvalue equation is

$$\cos(\beta_1 l)(1 - \alpha\tau_s) - \varepsilon k\beta_1 \sin(\beta_1 l) = 0. \tag{2.1.13}$$

2.1.4 Perturbation Scheme

If we let $x = \beta_1$, the eigenvalues are solutions of $f(x, \varepsilon) = 0$ where

$$f(x) = (x^2 + 1)\varepsilon \cos(xl) - \cos(xl) + k\varepsilon x \sin(xl).$$

We assume a power series expansion in x

$$x = \sum_{n=0}^{\infty} a_n x^n$$

and note that since a_0 is a solution of $f(x, 0) = 0$, this implies that a_0 is a solution to $\cos(xl) = 0$, so $a_0 = \frac{n\pi}{2l}$ for odd n.

2.2 Estimate of Eigenvalues

2.2.1 Recursion Scheme

Using Maple©, the expansion contains five terms and the coefficients for ε^n were collected. The results were

$$
\begin{aligned}
a_0 &= \frac{n\pi}{2l} \\
a_1 &= \frac{n\pi}{l}\left(\frac{kl}{4} - \frac{k}{2l}\right) \\
a_2 &= \frac{n^2}{\pi^2}4l^2 - \frac{k}{l}.
\end{aligned}
$$

Thus, to second order, the eigenvalues are

$$
\begin{aligned}
x_n &= \frac{n\pi}{2l} + \varepsilon\left(\frac{n\pi}{l}\left(\frac{kl}{4} - \frac{k}{2l}\right)\right) + \varepsilon^2\left(\frac{n^2}{\pi^2}4l^2 - \frac{k}{l}\right) \\
\alpha_n &= \frac{1}{\tau_m}\left(x_n^2 + 1\right).
\end{aligned}
$$

These eigenvalues can be used to get the final solution of V by substituting into (2.1.9).

3 Equation of Interest

3.1 Hot-spot Model and Green's Function

We use a modified cable model to represent a tapered equivalent cylinder model with a single hot spot. In particular, if $u(x,t)$ is the membrane voltage at a distance x from the soma at time t, then $u(x,t)$ satisfies

$$\frac{\partial^2 u(x,t)}{\partial x^2} + k\frac{\partial u(x,t)}{\partial x} - \tau\frac{\partial u(x,t)}{\partial t} - u(x,t) = y(t)\delta(x-x_0) \tag{3.1.1}$$

$$u_x(0,t) = 0$$

$$u_x(l,t) = 0$$

$$u(x,0) = 0$$

where $y(t)$ is the voltage at the sodium channel hot spot. In order to solve this, we need to find a Green's Function satisfying the following:

$$\frac{\partial^2 G(x,t)}{\partial x^2} + k\frac{\partial G(x,t)}{\partial x} - \tau\frac{\partial G(x,t)}{\partial t} - G(x,t) = 0 \tag{3.1.2}$$

$$G_x(0,t) = 0$$

$$G_x(l,t) = 0$$

$$G(x,0) = \delta(x-x_0).$$

We assume $G(x,t)$ is separable so that $G(x,t) = \Phi(x)T(t)$. Equation (3.1.2) then becomes

$$\Phi''T + k\Phi' - \tau\Phi T' - \Phi T = 0 \tag{3.1.3}$$

$$\Phi'(0) = 0$$

$$\Phi'(l) = 0.$$

$$\tag{3.1.4}$$

Separating variables yields

$$\frac{\Phi'' + k\Phi' - \Phi}{\tau\Phi} = -\beta^2 \tag{3.1.5}$$

$$\frac{T'}{T} = -\beta^2. \tag{3.1.6}$$

The solution of (3.1.6) is clearly $T(t) = e^{-\beta^2 t}$. The solution to (3.1.7) follows:

$$\frac{\Phi'' + k\Phi' - \Phi}{\tau\Phi} = -\beta^2$$

$$\Phi'' + k\Phi' - \Phi = -\beta^2\tau\Phi$$

$$\Phi'' + k\Phi' - \Phi\left(\tau\beta^2 - 1\right)\Phi = 0. \tag{3.1.7}$$

The characteristic equation for (3.1.7) is $r^2 + kr + (\tau\beta^2 - 1) = 0$ which has roots

$$r = \frac{-k \pm \sqrt{k^2 - 4(\tau\beta^2 - 1)}}{2}.$$

We know that the discriminant $k^2 - 4(\tau\beta^2 - 1) < 0$ so the roots of r in complex notation are $r_1 = \frac{1}{2}\left(-k + 2\imath\sqrt{(\tau\beta^2 - 1) - \frac{-k^2}{4}}\right)$ and $r_2 = \frac{1}{2}\left(-k - 2\imath\sqrt{(\tau\beta^2 - 1)\frac{-k^2}{4}}\right)$.

Using $r = a \pm b\imath$ we see that $a = -\frac{k}{2}$ and $b = \sqrt{(\tau\beta^2 - 1) - \frac{k^2}{4}}$. The solution to (3.1.7) now has the general form

$$\Phi(x) = e^{ax}\left(A\cos(bx) + B\sin(bx)\right) \tag{3.1.8}$$

$$\Phi'(0) = 0$$

$$\Phi'(l) = 0.$$

The derivative of Φ is

$$\Phi'(x) = e^{ax}\left\{[-Ab\sin(bx) + Bb\cos(bx)] + a\,[A\cos(bx) + B\sin(bx)]\right\}.$$

Here we make change of variable letting $x \to l - x$ so

$$\Phi'(x) = e^{ax}\left\{[-Ab\sin(b(l-x)) + Bb\cos(b(l-x))] + a\,[A\cos(bx) + B\sin(bx)]\right\}.$$

Applying the boundary conditions, we see

$$\Phi'(l) = 0 \implies A = -B\frac{b}{a}$$

$$\Phi'(0) = e^{al}\left[B\sin(bl)\left(-1 - \frac{b^2}{a}\right)\right] = 0.$$

The second condition above leads to an expression for β. If we consider the factor $\sin(bl) = 0$ then for n $\in \mathbb{Z}$, we get $b = \frac{\mathrm{n}\pi}{l}$. If we let $\beta = \beta_n$ then from above we see

$$b = \frac{n\pi}{l}$$

$$\sqrt{(\tau\beta_n^2 - 1) - \frac{k^2}{4}} = \frac{\mathrm{n}\pi}{l}. \tag{3.1.9}$$

From (3.1.9) we get for β_n

$$\beta_n = \sqrt{\frac{1}{\tau}\frac{4\mathrm{n}^2\pi^2 + 4l^2 + k^2l^2}{4l^2}}$$

and so $\Phi(x)$ is

$$\Phi(x) = e^{\frac{k(x-l)}{2}}\left[B\sin\left(b(l-x)\right)\right].$$

The separated solution for the Green's function at this point is

$$G(x,t) = \Phi(x)T(t) = Be^{-\frac{k(l-x)}{2}}\left[\sin\left(\left(\sqrt{(\tau\beta_{\mathrm{n}}^2 - 1) - \frac{k^2}{4}}\right)\ (l-x)\right)\right]e^{-\beta_{\mathrm{n}}^2 t}.$$

Thus, with an infinite sum over index n, the generated solution for the Green's function which is of the form

$$G(x,t) = \Phi(x)T(t) = \sum_{\mathrm{n}=1}^{\infty} b_{\mathrm{n}}e^{-\frac{kx}{2}}\left[\sin\left(\left(\sqrt{(\tau\beta_n^2 - 1) - \frac{k^2}{4}}\right)\ (l-x)\right)\right]e^{-\beta_n^2 t}$$

where $\beta_{\mathrm{n}} = Be^{-\frac{kl}{2}}$. To find b_{n} we note that $G(x,0) = \delta(x-x_0)$. For example, if $k=0$ (i.e., the cylinder is not tapered), then

$$\begin{aligned}
\frac{2}{l}\int_0^l G(x,0)\sin\left[\left(\frac{N\pi}{l}(l-x)\right)\right]dx &= \sum_{\mathrm{n}=1}^{\infty} b_{\mathrm{n}}\int_0^l \sin\left(\frac{N\pi}{l}(l-x)\right)\sin\left(\frac{\mathrm{n}\pi}{l}(l-x)\right)dx \\
\int_0^{\infty}\delta(x-x_0)\sin\left[\left(\frac{N\pi}{l}(l-x)\right)\right]dx &= lb_N \\
\frac{1}{l}\sin\left[\left(\frac{\mathrm{n}\pi}{l}(l-x_0)\right)\right] &= b_N.
\end{aligned} \tag{3.1.10}$$

Finally we get

$$G(x,t) = \frac{2}{l}\sum_{\text{n}=1}^{\infty} \sin\left[\left(\frac{\text{n}\pi}{l}(l-x_0)\right)\right] \sin\left[\left(\frac{\text{n}\pi}{l}(l-x)\right)\right] e^{\frac{-k(l-x)}{2}-\beta_n^2 t}$$
$$= \frac{1}{l}\sum_{\text{n}=1}^{\infty} \left\{\cos\left[\left(\frac{\text{n}\pi}{l}(l-x_0)\right)\right] - \cos\left[\left(\frac{\text{n}\pi}{l}(2l-x-x_0)\right)\right]\right\} e^{\frac{-k(l-x)}{2}-\beta_n^2 t}. \tag{3.1.11}$$

To get the full solution $u(x,t)$ we use a convolution with the Green's function.

$$u(x,t) = \int_0^t G(x,t-p)y(p)dp$$
$$= \frac{1}{l}\sum_{\text{n}=1}^{\infty} \left\{\cos\left[\left(\frac{\text{n}\pi}{l}(l-x_0)\right)\right] - \cos\left[\left(\frac{\text{n}\pi}{l}(2l-x-x_0)\right)\right]\right\} \times$$
$$e^{\frac{-k(l-x)}{2}} \int_0^t e^{-\beta_n^2 t - p} y(p)dp. \tag{3.1.12}$$

As an application of the solution we can determine the voltage term $V(t)$,

$$V(t) = \int_0^t G(x,t-p)y(p)dp$$
$$V_x = \int_0^t G_x(x,t-p)y(p)dp$$
$$V_{xx} = \int_0^t G_{xx}(x,t-p)y(p)dp$$
$$V_t = G(x,0)y(t) + \int_0^t G_t(x,t-p)y(p)dp$$
$$V_{xx} - \tau V_t - V = \delta(x-x_0)y(t) + \int_0^t (G_{xx} - \tau G_t - G)(t-p)y(p)dp$$
$$V_{xx} - \tau V_t - V = \delta(x-x_0)y(t) \tag{3.1.13}$$

which has the solution

$$V(t) = \int_0^t e^{-\beta^2(t-p)} y(p)dp.$$

3.2 Embedding Method and Recursion Scheme

A simplified model of the hot spot voltage $y(t)$ is given by

$$y' = ay + mb(y - V_{\text{Na P}})^3.$$

To approximate the solution to the hot spot model we use a modified Carleman scheme [2]. In particular let $V_{\text{n}}(t) = \int_0^t e^{-\beta_{\text{n}}^2(t-u)} \frac{y(u)^{\text{n}}}{\text{n}!} du$. The change of variable $w = t - u \implies u = t - w$ leads to

$$V_{\text{n}}(t) = \int_0^t e^{-\beta_{\text{n}}^2(u)} \frac{y^{\text{n}}(t-u)}{\text{n}!} du.$$

It follows that the derivative of $V_{\text{n}}(t)$ is

$$\begin{aligned}
V_{\text{n}}' &= e^{-\beta_{\text{n}}^2 t} + \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}-1}}{(\text{n}-1)!} y'(t-u)du \\
&= e^{-\beta_{\text{n}}^2 t} + \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}-1}}{(\text{n}-1)!} \left[ay + mb(y - V_{\text{Na P}})^3\right] du \\
&= e^{-\beta_{\text{n}}^2 t} + \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}-1}}{(\text{n}-1)!} \left[ay + mb\left(y^3 - 3y^2 V_{\text{Na P}} + 3y V_{\text{Na P}}^2 - V_{\text{Na P}}^3\right)\right] du \\
&= e^{-\beta_{\text{n}}^2 t} + a\text{n} \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}}}{\text{n}!} du \\
&\quad + mb\text{n}(\text{n}+1)(\text{n}+2) \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}+2}}{(\text{n}+2)!} du - 3mb\text{n}(\text{n}+1) V_{\text{Na P}} \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}+1}}{(\text{n}+1)!} du \\
&\quad + 3mb\text{n} V_{\text{Na P}}^2 \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}}}{\text{n}!} du - V_{\text{Na P}}^3 \int_0^t e^{-\beta_{\text{n}}^2 u} \frac{y^{\text{n}-1}}{(\text{n}-1)!} du.
\end{aligned}$$

The result is an infinite dimensional linear system of equations of the form

$$V_{\mathrm{n}}' = e^{-\beta_{\mathrm{n}}^2 t} + -mbV_{\mathrm{Na\ P}}^3 V_{\mathrm{n}-1} + \left(\mathrm{n}(a + 3mbV_{\mathrm{Na\ P}}^2)\right) V_{\mathrm{n}}$$

$$- 3mb\mathrm{n}(\mathrm{n}+1)V_{\mathrm{Na\ P}} V_{\mathrm{n}+1} + m\mathrm{n}(\mathrm{n}+1)(\mathrm{n}+2)V_{\mathrm{n}+2}.$$

We now have a recursive scheme for the derivative of V_{n} which can be used to set up the system of equations needed to solve for V_1.

4 Conclusions and Future Work

The Carleman linearization worked well for a short period of time. The process became unstable thereafter as the matrix solution produced nearly singular matrices.

The next step in this project is to adapt this work to Poznanski's persistent sodium channel model [10]. This model has been shown to be an accurate representation of a large class of neurons. Currently, approximations are based on the solution to an equivalent Volterra integral equation. Moreover, the original equation must be linearized before transformed to a Volterra integral equation.

The embedding technique does not require a linearization. Moreover, adapting our techniques to other models requires only a modification of the embedding equation.

BIBLIOGRAPHY

[1] Bluman, G. and Tuckwell, H., “Techniques for obtaining analytical solutions for Rall’s model neuron”, *Journal of Neuroscience Methods*, **20** (1987), 151-166.

[2] Gaude, B. W., “Solving Nonlinear Aeronautical Problems Using the Carleman Linearization Method”, *SAND Report* SAND2001-3064, 2001.

[3] Glenn, L. and Knisley, J., “Voltage Transients in Multipolar Neurons with Tapering Dendrites,” in *Modelling in the Neurosciences: From Ionic Channels to Neural Networks*, Roman R. Poznanski, editor, Harwood Academic Publishers, Amsterdam, The Netherlands, (1999), 149 - 176.

[4] Haberman, R., *Elementary Applied Partial Differential Equations* with Fourier Series and Boundary Value Problems, 3$^{\text{rd}}$ ed., Prentice Hall, Upper Saddle River, NJ, 1998.

[5] Kelvin,W. T., “On the theory of the electric telegraph.” *Proc. Roy Soc.* **7** 382-399, 1855.

[6] Kythe, P. K., et. al., *Partial Differential Equations and Boundary Value Problems with Mathematica*, 2^{nd} ed., CRC Press, Baton Rouge, LA, 2003.

[7] Poznanski, R., “Transient response in a somatic shunt cable model for synaptic input activated at the terminal”, *Journal of Theoretical Biology*, **127** (1987), 31-51.

[8] Poznanski, R., "A generalized tapering equivalent cable model for dendritic neurons", *Bulletin of Mathematical Biology* Vol. **53**, No. 3, (1991), 457-467.

[9] Poznanski, R. and Bell, J., "Theoretical analysis of the amplification of synaptic potentials by small clusters of persistent sodium channels in dendrites", *Mathematical Biosciences*, **166** (2000), 123-147.

[10] Poznanski, R. and Bell, J., "A dendritic cable model for the amplification of synaptic potentials by an ensemble average of persistent sodium channels", *Mathematical Biosciences*, **166** (2000), 101-121.

[11] Rall, W., "Core conductor theory and cable properties of neurons," In *Handbook of Physiology: The Nervous System*, E. R. Kandel (ed.), pp. 39-97. Bethesda, MD: American Physiological Society 1977.

[12] Stakgold, I., *Green's Functions and Boundary Value Problems* (Pure and applied mathematics) "A Wiley-Interscience publication," John Wiley & Sons, New York, NY, 1979.

[13] Tuckwell, H., *Introduction to Theoretical Neurobiology, Volume 2, Nonlinear and Stochastic Theories*, Cambridge University Press, Cambridge, MA, 1988.

[14] Zauderer, E., *Partial Differential Equations of Applied Mathematics* 2$^{\text{nd}}$ ed. "A Wiley-Interscience publication," John Wiley & Sons, New York, NY, 1989.

APPENDICES

A Mathematica© Code for the Eigenvalue Problem

- **Computational Loop**

```
Timing[For[i = 1, i ≤ numMatr,
  (* Choose the size*)
  useMatrix =
   Take[workMatrix, {1, numMin + i - 1}, {1, numMin + i - 1}];
  useForceMatrix = Take[forceMatrix, {1, numMin + i - 1}];
  useIdentityMatrix = IdentityMatrix[numMin + i - 1];
  ttime = 0.0; (* Start time loop *)
  inverseMatrix = Inverse[useMatrix + β^2 useIdentityMatrix];
  For[kk = 1, kk <= numTimeSteps,
   V = (MatrixExp[useMatrix ttime] - ⅇ^(-β^2 ttime)
       useIdentityMatrix).inverseMatrix.useForceMatrix;
   (* Here I need storage *)
   soln[[i, kk]] = V[[1]];
   ttime += timeStep;
   kk++;
  ](* end time loop *)
  i++;
 ]](* End for i = 0, choose matrix size *)
```

VITA

Scott La Voie

Address:

1772 Boone's Creek Road
Jonesborough, TN 37659

Education:

East Tennessee State University (ETSU), Johnson City, TN (B.S., Physics 2000)
ETSU (M.S., Mathematical Sciences Applied Mathematics, 2003)

Experience:

Soldier, United States Army, 1991-1998
Graduate Assistant, ETSU, Department of Mathematics, 2000-2003

Organizations:

Kappa Mu Epsilon
Mathematical Association of America
Society for Industrial and Applied Mathematics