RICE UNIVERSITY

Functional inference of conductances in the LGMD neuron

by

Etienne Rudolph Ackermann

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE Master of Arts

APPROVED, THESIS COMMITTEE:

Steven J. Cox
Professor
Computational and Applied Mathematics

Tariq Dabaghian
Assistant Professor
Computational and Applied Mathematics

Mark Embree
Professor
Computational and Applied Mathematics

Danny C. Sorensen
Noah Harding Professor
Computational and Applied Mathematics

Houston, Texas
May, 2013
RICE UNIVERSITY

Functional inference of conductances in the LGMD neuron

by

Etienne Rudolph Ackermann

A Thesis Submitted
in Partial Fulfillment of the Requirements for the Degree
Master of Arts

Approved, Thesis Committee:

________________________
Steven J. Cox
Professor
Computational and Applied Mathematics

________________________
Yuri Dabaghian
Assistant Professor
Computational and Applied Mathematics

________________________
Mark Embree
Professor
Computational and Applied Mathematics

________________________
Danny C. Sorensen
Noah Harding Professor
Computational and Applied Mathematics

Houston, Texas
May, 2013
**Summary**

**Functional Inference of Conductances in the LGMD Neuron**

by

Etienne Rudolph Ackermann

Master of Arts (Computational and Applied Mathematics)

Supervisor: Professor Steven J. Cox

Rice University

This thesis develops an approach to determine spatially-varying membrane conductances throughout the dendrites of the Lobula Giant Movement Detector (LGMD) neuron from distal transmembrane potential recordings in response to distributed subthreshold current injections. In particular this approach is demonstrated on a straight cable approximation to the LGMD neuron with two types of spatially-varying ionic channels.

Knowledge of these conductances can help neuroscientists to characterize, better understand, and predict neuronal behavior—and topographic integration in the LGMD neuron in particular—but it is extremely difficult to measure these conductances directly. As a consequence, these membrane conductances are commonly estimated by searching for several parameters that lead to simulated responses that are consistent with recorded behavior. In contrast, the approach presented here uses the method of moments to directly recover the underlying conductances, eliminating the need to simulate responses, making this approach both faster and more robust than typical optimization approaches since the solution cannot get trapped in local minima.
This thesis is dedicated to:

God Almighty, for all the countless opportunities that He has given me;
My loving family and friends, for their support, encouragement and good advice.

“My soul, wait thou only upon God;
for my expectation is from Him.”

Psalm 62:5 (KJV)
I wish to extend my heartfelt gratitude to *almost everyone*, but in particular to my thesis committee: Dr. Steven Cox—who has taught me much of what I know—and who was always patient, kind, and extremely supportive in every situation; as well as Drs. Dabaghian, Embree, and Sorensen.

I am also indebted to everyone in CAAM (faculty, staff, and students) who gave me this fantastic opportunity, as well as the Fulbright Science and Technology program for their generous support over the last two years.

Furthermore I want to thank my fellow CAAMsters (in no particular order\(^1\)): Anthony, Caleb, Charles, David, Jed, Jun, Lisa, Mario, Muhong, Nichole, Rose, Sebastián, and Zhimin.

I would also like to express my appreciation for everyone from my RGCF, Bridges International\(^2\) and Mission 24 families: you all made a \[\text{huge}\] difference\(^3\).

Finally, I would like to thank my family and friends back home, for their unwavering love, support, and ignorance\(^4\).

---

**PS. If I have failed to mention you, please amend this thesis by printing and completing this page, and consider yourself acknowledged.**

I hereby—somewhat reluctantly—acknowledge ____________ for the (☐ insignificant ☐ small ☐ unmistakable) contribution that (s)he has made.

---

\(^1\)Just kidding: these are clearly listed in alphabetical order.

\(^2\)When I first typed this draft, I missed the ‘g’ in Bridges International—it was quite comical.

\(^3\)There’s a \LaTeX{} joke in here somewhere :D...

\(^4\)I say this in a tongue-in-cheek fashion, and in the most affectionate way imaginable.
# Table of Contents

Table of Contents  

## Introduction  
1. Background and problem formulation  
   1.1 Mathematical modeling and simulation  
   1.2 Problem statement  
1.2 Proposed solution and contributions  
1.3 Organization of this thesis  

## Literature review  
2.1 Dendritic computation  
2.2 Looming sensitive neurons  
2.3 Recovering ionic conductances  

## Models, simulation, and recovery of ionic conductances  
3.1 Introduction  
3.2 Compartamental models  
3.3 The passive cable  
   3.3.1 Model: passive cable  
   3.3.2 Simulation: the discrete passive cable  
3.4 The nonuniform active cable  
   3.4.1 Model: active cable  
   3.4.2 Simulation: the discrete active cable  
3.5 The nonuniform quasi-active cable  
   3.5.1 Model: quasi-active cable  
   3.5.2 Simulation: the quasi-active cable  
   3.5.3 Eigenfunction expansion: uniform quasi-active cable solution  
3.6 The method of moments  
   3.6.1 Method of moments for the passive cable  
   3.6.2 Method of moments for the active cable  


# TABLE OF CONTENTS

## 4 Results

4.1 Simulation parameters and slow $I_h$ dynamics .......................... 43
  4.1.1 Simulation parameters ............................................. 44
  4.1.2 Slow $h$-channel dynamics ......................................... 48

4.2 Recovery of leak conductances in passive cables ....................... 53
  4.2.1 Uniform passive cable .............................................. 54
  4.2.2 Nonuniform passive cable ......................................... 58
  4.2.3 Convergence of approximate moments as $T_{\text{fin}} \rightarrow \infty$ .. 59

4.3 Recovery of conductances in active cables ............................. 61
  4.3.1 Uniform active cable ............................................... 61
  4.3.2 Nonuniform active cable .......................................... 63
  4.3.3 Non-uniqueness of solutions to the BVP ......................... 65

## 5 Conclusion and future work .................................................. 69

Bibliography ............................................................................. 71

List of Abbreviations ............................................................... 75
CHAPTER 1

INTRODUCTION

“Notatio naturae, et animadversio perperit artem.
Art is born of the observation and investigation of nature.”

Marcus Tullius Cicero (106–43 BC)

In this thesis I develop an approach to determine spatially-varying ionic membrane conductances along a simplified morphology of the dendritic tree of the LGMD neuron from distal transmembrane potential recordings in response to current injection in the dendrites. In particular, I solve an inverse problem in which two spatially-varying conductances\(^1\), corresponding to unknown coefficients in a parabolic Partial Differential Equation (PDE), are recovered in a finite-length, one-dimensional diffusion (cable) equation. Knowledge of these conductances can help neuroscientists to characterize, better understand, and predict neuronal behavior—and topographic integration in the LGMD neuron in particular—but it is extremely difficult to measure these conductances directly.

As a consequence, these membrane conductances are commonly estimated by searching for several parameters which lead to simulated responses that are consistent with recorded behavior (see Figure 1.1 on the following page).

\(^1\)Conductances corresponding to chloride (leak), and hyperpolarization-activated \(h\) currents.
Figure 1.1: Typical workflow to recover ionic conductance using optimization. Several neuronal responses are recorded, after which a parametric form for the underlying ionic conductance is assumed. An iterative optimization strategy is then followed to tune the parameters such that the simulated neuronal responses closely approximate the recorded responses.

In contrast, the approach presented here uses the method of moments, developed by Cox (1998), to directly recover the underlying conductances (see Figure 1.2), eliminating the need to simulate responses, thereby making this approach both faster and more robust than typical optimization methods since the solution cannot get trapped in local minima.

Figure 1.2: Typical workflow to recover ionic conductances using method of moments. Several neuronal responses are recorded, after which moments are computed, and then with some additional work (simple algebraic manipulations, solution of BVPs etc., see section 3.6 for details), the underlying conductance is recovered directly.

A large amount of work has already been done on the recovery of constant cable parameters, but the recovery of spatially-varying cable parameters (for both passive and active cables) is significantly more challenging. Nevertheless, it is important to recover spatially-varying cable properties, especially because significant spatial variations of ionic conductances and other cable properties are commonly observed experimentally (Bell, 2005). In this thesis, the method of moments is used to recover spatially-varying ionic conductances in the straight cable approximation to the LGMD.
1.1 Background and problem formulation

The work presented in this thesis is motivated by the desire to better understand information processing at an individual cellular level, and more specifically, to better understand topographic information processing in the LGMD neuron of a locust. The LGMD neuron is large, uniquely identifiable, and is believed to be principally responsible for making a decision whether or not to jump away when the locust is approached by some object on a collision course.

In addition to the LGMD being large and uniquely identifiable (which makes recordings easier), its subcellular topography has been well established, and can be accessed in vivo. The subcellular topography can be accessed by spatially modulating a visual stimulus across the compound eye of the locust, where each facet maps to a unique (and known) location in the dendritic tree of the LGMD, so that illuminating a particular facet will induce a small synaptic input at its corresponding location in the dendritic tree. See Figure 1.3 for an illustration.

Figure 1.3: Overview of experimental setup.
An individual facet on the retina of the locust is illuminated, leading to synaptic input (which we model as current injection) at a corresponding location in the dendritic tree of the LGMD. The neuronal response to this current injection is then recorded close to the SIZ. Another facet is then illuminated, and the procedure is repeated.
1.1.1 Mathematical modeling and simulation

To better understand the information processing of the LGMD, a well established and widely-used mathematical neuron model is assumed, namely a conductance-based Hodgkin-Huxley type model (see Chapter 3 for more details). A spatio-temporal form of the model is used, with the model inputs being localized current injections at the locations in the dendritic tree corresponding to stimulated facets on the locust’s retina, and the model output being the transmembrane potential. The model is further characterized by spatially-varying (but constant in time) ionic channel conductances, as well as additional parameters describing the ionic channel dynamics.

The parameters describing channel dynamics can be determined experimentally, and will be assumed known. Furthermore, input-output recordings can be obtained experimentally (and usually they would be), but in this thesis I consider simulated responses and recordings instead².

Mathematically speaking, the forward problem is then to predict the output (the transmembrane potential) given knowledge of the synaptic inputs, as well as all the model parameters including the spatially-varying conductances and parameters describing channel dynamics. However, the spatially-varying conductances are seldom known, and they are very difficult to measure experimentally, with many prohibitive factors ranging from the large number of branches in the dendritic tree that has to be measured to the size of the recording electrode, which is typically too large to accurately record from a single and precise location in the dendritic tree.

As a consequence, this thesis develops an inverse problem approach to recover the

²Except for issues regarding recording noise, the procedure described in this thesis should apply equally well to either measured or simulated data.
unknown spatially-varying conductances from a collection of known input-output pairs, which will ultimately allow for the careful investigation of topographic integration in the LGMD. A further challenge, however, is that the output (transmembrane potential) will only be known at a single spatial location, for experimental simplicity.

1.1.2 Problem statement

The task of recovering the spatially-varying conductances (and indeed the focus of this thesis) can then finally be stated as follows:

\textbf{Problem statement:}

Given a collection of known synaptic inputs, their corresponding neuronal responses (outputs) at a single spatial location, and the parameters describing channel dynamics, can we reliably recover the spatially-varying conductances? If so, how?

1.2 Proposed solution and contributions

In this thesis, I will consider a simplified morphology of the LGMD consisting of a discretized, compartmentalized straight cable approximation (see section 3.2).

By using integrals of the neuronal responses over all time (i.e., the \textit{method of moments}), expressions for the unknown conductances will then be derived explicitly for the passive cable (where only a leak conductance is assumed), and for the active cable (where an additional hyperpolarization-activated current is assumed) an expression for the additional unknown conductance will be derived in terms of the moments and a solution to a particular BVP.

Furthermore, to test the method, neuronal responses to uniformly spaced current injections will be \textit{simulated} for a range of underlying conductances, storing and using...
only those datapoints which correspond to the recording location for the recovery of the conductances.

To the best of my knowledge this thesis presents the first attempt to recover spatially-varying conductances in a direct manner using the method of moments, and it is also the first time that the recovery of spatially-varying conductances within the LGMD is considered in a computational manner.

Unfortunately there are three important and significant challenges that remain before this method can be of real practical use, namely (i) a more realistic morphology will have to be considered, (ii) recording noise will have to be dealt with intelligently, and (iii) the formulation of the aforementioned BVP will have to be reconsidered, since it appears that a unique solution does not always exist, sometimes leading to incorrect and non-physical conductance estimates. These challenges are beyond the scope of this thesis, however.

1.3 Organization of this thesis

The most important and relevant literature is reviewed in Chapter 2, followed by the mathematical formulation and solution of the inverse conductance recovery problem in Chapter 3. In particular, section 3.2–section 3.5 describes the various mathematical models that are considered, along with details on their simulation, followed by the method of moments in section 3.6.

Simulated recovery results are then presented in Chapter 4, including the recovery of leak conductances (section 4.2), as well as the recovery of hyperpolarization-activated $h$-conductances (section 4.3).

Finally, Chapter 5 briefly describes future directions and remaining work.
Chapter 2

LITERATURE REVIEW

“Questions of personal priority, however interesting they may be to the persons concerned, sink into insignificance in the prospect of any gain of deeper insight into the secrets of nature.”

Baron William Thomson Kelvin (1824–1907)

One of the most important and fundamental questions in neuroscience is how decisions are made by neural networks (London and Häusser, 2005). It is commonly assumed that the decisions—as well as the underlying computations—can be explained or at least characterized by investigating properties of synapses and the connectivity of neurons in a network. London and Häusser (2005) argue that this widely-held view is too simplistic, and that the intrinsic excitability of single neurons is perhaps equally if not more important to understanding elementary computations in neural networks. In particular, London and Häusser (2005) reviewed recent work, which showed that dendrites participate in elementary but essential computations, and they gave several examples ranging from coincidence detection in auditory neurons (see e.g. Agmon-Snir et al., 1998) to the looming sensitive neurons in the locust (see e.g. Gabbiani et al., 1999) which I will consider in this thesis.
2.1 Dendritic computation

It should be mentioned that even though London and Häusser (2005) present a more contemporary view which emphasizes the importance of dendritic computation in single cells, they still assume the existence of a “threshold” above which a neuron will fire an action potential. In contrast, Izhikevich (2007) clearly demonstrated that this view, too, is overly simplistic and naïve, and that the dynamics underlying dendritic computation are often much more subtle and interesting.

“Although dendrites have been studied for decades, the field of dendritic computation is still in its infancy. This is partly because dendrites remain relatively inaccessible and have only recently begun to yield their secrets to the onslaught of multiple new experimental tools. . . . The accessibility of the LGMD neuron to dendritic recordings and optical imaging in vivo makes it a promising candidate for understanding the biophysics of a high-level computation in dendrites in the near future.” (London and Häusser, 2005)

2.2 Looming sensitive neurons

The Lobula Giant Movement Detector (LGMD) is a uniquely identifiable neuron in the locust visual system that responds most strongly to objects approaching on a collision course, referred to as looming stimuli (Peron and Gabbiani, 2009). The LGMD neuron has a complex and unique dendritic structure (see Figure 3.1 on page 14) consisting of three distinct subfields (A–C). Subfield A consists of thousands of branches receiving motion-sensitive excitatory inputs, whereas subfields B and C receive inhibitory inputs that depend on the size of the object (O’Shea et al., 1974). Note that the soma lies outside the signal propagation path, and that the SIZ is
located at the point where the axon is thinnest (London and Häusser, 2005).

Spikes propagate down the axon of the LGMD in a one-to-one fashion to its post-
synaptic target, the Descending Contralateral Movement Detector (DCMD) neuron, which in turn is connected to interneurons and motorneurons that are responsible for controlling jumping, as well as flight steering mechanisms in the locust (Cox and Gabbiani, 2009; O’Shea et al., 1974). Consequently, it is commonly believed that the LGMD/DCMD-pair is responsible for collision avoidance behaviors, including escape responses to potential predators (Cox and Gabbiani, 2009).

The fact that the computation for a particular behavioral function (collision avoidance) seems to be performed entirely in a single neuron (the LGMD), together with the fact that the LGMD neuron is relatively easily accessible, make it an ideal neuron in which to study dendritic computation.

2.3 Recovering ionic conductances

A slightly easier task than explaining how dendritic computation affects an or-
ganism’s behavior is to simply explain how dendritic computation affects neuronal behavior in a single cell. Spatially-varying membrane conductances greatly affect the neuronal response arising from synaptic inputs (see Reyes, 2001, for a review), and therefore knowledge of these membrane conductances is crucial to better our understanding of neuronal behavior in general. These membrane conductances can either be determined experimentally (see e.g. Lörincz et al., 2002, where immunolocalization was used in the rat brain), or computationally, where the membrane conductances are typically recovered from transmembrane potential recordings made some distance away from the dendritic tree.
The simple classification into experimental and computational approaches to determine the membrane conductances is perhaps a little troublesome. After all, experimental approaches often do not measure the conductances directly, and so a fair amount of post-processing (or computation) is still involved. Similarly, the computational approaches ultimately rely on some experimental data from which to recover the desired conductances. Nevertheless, it is helpful to distinguish between these two (sometimes overlapping) approaches, with the understanding that better computational approaches generally require simpler experimental setups. Indeed, it is often prohibitive to perform sophisticated (read costly and invasive) experiments. As a result, computational approaches that only require a small set of easy-to-obtain transmembrane potential recordings are highly desirable. The method of moments presented in this thesis is such an approach.

Even though this thesis specifically deals with the determination of spatially-varying membrane conductances, other important electrical and morphological characteristics of the neuron must be determined too. In vitro determination of the morphological characteristics of neurons (see e.g. Jaeger, 2001) has essentially become routine (Cox, 2006). In contrast, the neuron’s electrical characteristics are more difficult to obtain, and include the cell’s passive properties such as the membrane capacitance, $C_m$, and the axial resistance, $R_a$, as well as its active properties, including the location, conductance and kinetics of a myriad of associated ion channels (Cox, 2006). In this thesis I will assume that the passive cable properties are known, and will focus on recovering the spatially-varying conductances of (i) a chloride channel, as well as (ii) a hyperpolarization-activated ion channel.

One of the first approaches that have been used to determine the electrical charac-
Characteristics of neurons is so-called peeling analysis (see e.g. Rall, 1960, 1969) in which the transient neuronal response is approximated as a sum of exponentials. The passive electrical membrane parameters are then obtained from the estimated exponential time constants and exponential coefficients. Apart from the fact that peeling methods are not well suited to determine the active electrical properties of neurons, these methods have, for the most part, also been superseded by constrained optimization methods. D’Aguanno et al. (1986) compared peeling methods to optimization methods and found that optimization methods were superior in almost every respect: optimization methods were found to be more accurate and less sensitive to recording noise. Optimization methods can also handle more parameters and a wide array of models as opposed to the multiexponential model used in peeling methods.

Optimization methods have their own drawbacks, however. In most optimization methods a parametric model is first selected, after which the parameters are chosen such that simulated responses are consistent with recorded behavior. The process of searching for the best set of parameters often requires a large number of transient responses to be computed or simulated (see e.g. Tabak et al., 2000, in which both simplex and gradient-based methods were used). In contrast, the approach presented in this thesis uses integrals of transients (i.e., the method of moments) to directly recover the underlying conductances, thereby eliminating the need to simulate transient responses.

The method of moments has previously been used to recover neuronal parameters. More specifically, Cox (1998) used the method of moments to recover passive cable properties and the maximal membrane conductance from measurements of a cell’s input impedance, and the approach was later extended to recover passive cable properties
from dual potential recordings of tapered dendrites (Cox and Raol, 2004). Other notable uses of the method of moments, or similar techniques, to recover passive cable properties include the work by Adrian et al. (1974), Agmon-Snir (1995), and Engelhardt et al. (1998).

Despite the fact that Adrian et al.’s work on the method of moments has been called a “breakthrough”, the method of moments has not received significant attention in the computational neuroscience community (Cox and Raol, 2004). This thesis will extend the method of moments beyond the maximal (i.e., constant) conductance case by recovering spatially-varying membrane conductances.
Chapter 3

Models, simulation, and recovery of ionic conductances

“He does not study nature because it is useful; he studies it because he delights in it, and he delights in it, because it is beautiful. If nature were not beautiful, it would not be worth knowing, and if nature were not worth knowing, life would not be worth living.”

Jules Henri Poincaré (1854–1912)

The main contribution of this chapter—and indeed of this thesis—is to develop the method of moments for the recovery of spatially-varying ionic conductances. To this end, several standard discretized neuronal models are first presented along with details on their simulation (section 3.2–section 3.5), followed by the development of the method of moments first for passive, and then for quasi-active cable models (section 3.6.1 and section 3.6.2, respectively). Results are presented in the next chapter.

3.1 Introduction

As mentioned previously, neuroscientists want to understand how, and how much, information processing is done at the single cell level (Bell, 2005). To answer questions
related to single cell processing, one needs to consider both theoretical (modeling and simulation) and experimental studies. In this thesis I consider the modeling and simulation of the LGMD neuron (see Figure 3.1) in the locust, and I show how to recover spatially-varying ionic conductances from single-site recordings of the neuronal response to current injection throughout the dendrites. However, much of the motivation for this present study stems from a well established and ongoing research effort—including a large amount of experimental work—to study and understand the LGMD neuron and topographic dendritic integration in particular.

![Figure 3.1: Example of an LGMD reconstruction from an intracellular, Lucifer yellow stained, 2-photon confocal scan (adapted from Peron et al. (2007)). Subfield A is excitatory, whereas B and C are inhibitory. Recordings typically take place at the SIZ.](image)

Indeed, the passive membrane properties of the LGMD have already been characterized by Peron et al. (2007), and the main active conductance, an inward rectifying conductance mediating a hyperpolarization-activated current $I_h$, has also been identified. Studying the LGMD is particularly attractive because (i) it is uniquely identifiable and quite large, (ii) its function is fairly well understood (that of collision detection) and (iii) because its topography can be accessed in vivo. More specifically, precise spatio-temporal synaptic inputs can be induced by modulating a visual stimulus in the form of a laser beam across the facets of the locust’s compound eye (Peron et al.,

---

Department of Computational and Applied Mathematics
Assumptions underlying this thesis. The large body of experimental work on the LGMD, together with the ability to induce subthreshold synaptic inputs throughout the dendrites of the LGMD, coupled with the physical constraint of only being able to record neuronal responses at a few easily accessible locations then finally motivate the assumptions underlying this thesis.

To be precise, it is assumed that the transmembrane potential $V(x, t) \equiv V$ of the LGMD obeys a general cable equation of the form

$$C_m \frac{\partial V}{\partial t} = G_a \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

(3.1)

where $I_{ion}$ is a sum of ionic current densities depending (possibly nonlinearly) on $V$. It is also assumed that the dynamics of $V$ are dominated by two types of (possibly spatially-varying) ionic channels, namely those associated with a leak current $I_{Cl}$, and with a hyperpolarization-activated $h$-current, denoted by $I_h$; and that the $h$-channel can be blocked pharmacologically, resulting in a purely passive cable. It is further assumed that the ionic channel kinetics are known, along with the associated reversal potentials, and that precise spatio-temporal current injection can be induced throughout the dendritic tree. Finally, it is assumed that the neuronal response to subthreshold current injection can be recorded from at least one spatial location, for a sufficient amount of time (typically much less than a second). The question remains:

How can we recover underlying ionic conductances from a collection of distal single-site neuronal response recordings/simulations?

Here I only develop a possible answer for simulated data, so I start with a model.
3.2 Compartmental models

A common approach to model neurobiological cells with spatially-varying parameters is to divide the cell into a collection of connected isopotential compartments such that the network of compartments closely approximates the geometry of the original neuron (see Figure 3.2 for an illustration).

A significant reduction in model as well as computational complexity can be obtained by simply approximating the model geometry by a straight cable as shown in Figure 3.2(c), and this simplification will be considered throughout this thesis\(^1\).

Furthermore, the compartments considered in this thesis are all cylindrical, isopotential compartments as illustrated in Figure 3.3, each having length \(dx\) and radius \(a\), leading to a surface area of \(2\pi adx\). Compartments are also connected to their neighbors via an axial coupling resistance, \(R_a\).

\(^1\)The straight cable approximation is indeed a very severe simplification, but it remains a natural place to start, and an extension to more realistic geometries is planned for the near future.
Chapter 3 Models, simulation, and recovery of ionic conductances

Figure 3.3: Discretized straight cable of length $\ell$, radius $a$, with $N = 5$ compartments.

It is natural to expect that increasing the number of compartments $N$ will lead to a more accurate model, and this is generally true. However, it is interesting to note that whereas the transmembrane potential is continuous in space, the ionic channels are inherently discrete, so that increasing $N$ could lead to better channel localization, as illustrated in Figure 3.4.

The passive cable is introduced next, first in its continuous form, followed by a compartmental discretization as described in this section.

3.3 The passive cable

The passive cable is important both because it is a simple and natural place to start an investigation, but also because it will be used in the 2-phase method of moments presented in section 3.6.2 to recover the spatially-varying ionic conductances.
3.3.1 Model: passive cable

The neuronal response \( V(x,t) \) to current injection \( I_{\text{stim}}(x,t) \) as observed along a straight passive cable segment of length \( \ell \) in the LGMD neuron obeys the following Hodgkin-Huxley-type (conductance-based) linear cable equation:

\[
C_m \frac{\partial V(x,t)}{\partial t} = G_a \frac{\partial^2 V(x,t)}{\partial x^2} - g_{C1}(x)(V(x,t) - V_{C1}) + \frac{I_{\text{stim}}(x,t)}{(2\pi a)} \tag{3.2}
\]

where frequently \( V \equiv V(x,t) \) will be used for convenience. As before, \( C_m \) is the membrane capacitance, \( G_a \equiv a/(2R_a) \) is the axial conductance, \( R_a \) is the coupling resistance, \( a \) is the cable radius, and \( g_{C1} \) is the leakage conductivity (due to chloride) with an associated reversal potential \( V_{C1} \). Refer to Table 3.1 on the facing page for additional information on the parameters appearing in (3.2) and elsewhere in this thesis.

If current injection is constrained to only occur at the interior of the cable, (3.2) has the following Neumann boundary conditions (we say that the cable is sealed at both ends):

\[
\frac{\partial V}{\partial x}(0,t) = \frac{\partial V}{\partial x}(\ell,t) = 0, \quad t \geq 0, \tag{3.3}
\]

and if the cable is initially at rest (with no current injection) then

\[
V(x,0) = V_{C1}, \quad 0 \leq x \leq \ell. \tag{3.4}
\]

3.3.2 Simulation: the discrete passive cable

Consider a discrete approximation to the passive cable of (3.2) with \( N \) isopotential cylindrical compartments, each of length \( dx = \ell/N \), surface area \( 2\pi a dx \), cross-sectional area \( \pi a^2 \), and with a coupling resistance \( R_a \) between compartments (see Figure 3.3).
<table>
<thead>
<tr>
<th>Description</th>
<th>Units</th>
<th>Source/Assumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V(x,t)$  neuronal response</td>
<td>mV</td>
<td>simulation/recording</td>
</tr>
<tr>
<td>$q(x,t)$  gating variable</td>
<td></td>
<td>simulation/irrelevant</td>
</tr>
<tr>
<td>$V_r(x)$  resting potential</td>
<td>mV</td>
<td>simulation/estimation</td>
</tr>
<tr>
<td>$C_m$ membrane capacitance</td>
<td>$\mu$F/cm$^2$</td>
<td>assumed known</td>
</tr>
<tr>
<td>$G_a$ axial conductance</td>
<td>S</td>
<td>assumed known</td>
</tr>
<tr>
<td>$R_a$ coupling resistance</td>
<td>$\Omega$·cm</td>
<td>assumed known</td>
</tr>
<tr>
<td>$a$ cable radius</td>
<td>cm</td>
<td>assumed known</td>
</tr>
<tr>
<td>$l$ cable length</td>
<td>cm</td>
<td>assumed known</td>
</tr>
<tr>
<td>$V_{Cl}$ chloride channel reversal potential</td>
<td>mV</td>
<td>assumed known</td>
</tr>
<tr>
<td>$V_h$ hyperpolarization-activated channel reversal potential</td>
<td>mV</td>
<td>assumed known</td>
</tr>
<tr>
<td>$q_\infty(V)$ equilibrium response for gating variable $q$</td>
<td>–</td>
<td>assumed known</td>
</tr>
<tr>
<td>$\tau_q(V)$ time constant associated with gating variable $q$</td>
<td>ms</td>
<td>assumed known</td>
</tr>
<tr>
<td>$I_{stim}(x,t)$ stimulus via current injection</td>
<td>$\mu$A</td>
<td>assumed known</td>
</tr>
<tr>
<td>$g_{Cl}(x)$ leakage conductivity</td>
<td>mS/cm$^2$</td>
<td>unknown</td>
</tr>
<tr>
<td>$g_h(x)$ $h$-current conductivity</td>
<td>mS/cm$^2$</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Table 3.1: Common parameters and units associated with the cable equation.
Now following a similar approach as in §6.1 of Gabbiani and Cox (2010), we first define the following circuit elements:

\[ C = (2\pi adx)C_m, \quad G_n = (2\pi adx)g_{Cl}^n, \quad \text{and} \quad R = dxR_a/(\pi a^2) \]

where \( g_{Cl}^n \) is the leakage conductance in the \( n \)th compartment. Current balance at the nodes in Figure 3.5 then leads to

\[
\frac{d\mathbf{v}(t)}{dt} = \mathbf{B}\mathbf{v}(t) + \mathbf{f}(t), 
\]

where \( \mathbf{v}(t) = (v_1 \ v_2 \ ... \ v_N) \), with \( v_n = \phi_n - \phi_0 - V_{Cl} \), and where

\[
\mathbf{B} = \left( \frac{a}{2R_a} \mathbf{S} - \text{diag}(g_{Cl}^1, g_{Cl}^2, \ldots, g_{Cl}^N) \right)/C_m
\]

where \( \mathbf{S} \in \mathbb{R}^{N \times N} \) is the second difference matrix, and \( \text{diag}(\lambda_1, \lambda_2, \ldots, \lambda_N) \in \mathbb{R}^{N \times N} \).
has $\lambda_n$ in the $n$th diagonal entry:

$$
\begin{align*}
S = \frac{1}{dx^2} & \begin{bmatrix}
-1 & 1 & 0 & 0 & \cdots & 0 \\
1 & -2 & 1 & 0 & \cdots & 0 \\
0 & \ldots & 0 & 1 & -2 & 1 \\
0 & \ldots & 0 & 0 & 1 & -1 \\
\end{bmatrix} \\
\end{align*}
$$

and where the synaptic input is modeled by

$$
f(t) = \frac{I_{\text{stim}}(t)}{(2\pi adx) C_m} \mathbf{e}_k \quad \text{where} \quad \mathbf{e}_k = (0 \ 0 \ldots 0 \ 1 \ 0 \ldots 0)^T
$$

for the stimulus, and

$$
v^j \approx v((j-1)dt)
$$

for the response associated with (3.5). Applying the trapezoidal rule to (3.5) then leads to

$$
v^j - v^{j-1} = B(v^j + v^{j-1})dt/2 + (f^j + f^{j-1})dt/2
$$
which is equivalent to

\[ \text{set } r^2 = (dt/2)(f^2 + f^1) \]

and for \( j = 2, 3, \ldots, N_t \)

\[ \text{solve } (I - (dt/2)B)v^j = r^j \text{ and set } r^{j+1} = 2v^j - r^j + (dt/2)(f^{j+1} + f^j). \quad (3.6) \]

The trapezoidal scheme of (3.6) is demonstrated for a nonuniform passive cable with \( I_{\text{stim}}(x, t) = 100 \left( \delta(x-0.06)1_{(1,2)} + \delta(x-0.04)1_{(2,3)} \right) \) and \( g_{Cl} = 10x \) on \( x \in [0, 0.1] \) in Figure 3.6.

Figure 3.6: Simulated neuronal response to dual location current injection in a nonuniform passive cable (trapcabnonuniform.m). (Based on Gabbiani and Cox, 2010, Figure 6.4, where a uniform passive cable was simulated.)

### 3.4 The nonuniform active cable

Adding a hyperpolarization-activated cation \( h \)-current to the passive cable of (3.2) leads to a so-called active cable, which is capable of generating an action potential.
3.4.1 Model: active cable

Similar to the passive cable case, the neuronal response \( V(x, t) \) to current injection \( I_{\text{stim}}(x, t) \) as observed along a straight cable segment of length \( \ell \) can be modeled by the following Hodgkin-Huxley type nonuniform active (and nonlinear) straight cable:

\[
C_m \frac{\partial V(x, t)}{\partial t} = G_a \frac{\partial^2 V}{\partial x^2} - g_{\text{Cl}}(x)(V - V_{\text{Cl}}) - g_h(x)q(x, t)(V - V_h) + \frac{I_{\text{stim}}}{(2\pi a)} \frac{\partial q(x, t)}{\partial t} = q_\infty(V) - q \frac{q}{\tau_q(V)},
\]

where \( V \equiv V(x, t) \) and \( q \equiv q(x, t) \) are used for convenience. Furthermore, \( g_h \) is the conductivity due to the hyperpolarization-activated \( h \)-current with an associated reversal potential \( V_h \), and \( q \) is a voltage dependent gating variable that has been introduced to capture the most important dynamics of the \( h \)-channel. The cable is also assumed to be sealed at both ends, that is

\[
\frac{\partial V}{\partial x}(0, t) - \frac{\partial V}{\partial x}(\ell, t) = 0,
\]

with initial conditions

\[
V(x, 0) = V_r \quad \text{and} \quad q(x, 0) = q_\infty(V_r)
\]

where \( V_r \equiv V_r(x) \) denotes the rest potential. In contrast to the passive cable, the rest potential for the active cable is no longer assumed known, and is often spatially varying. This spatial variation makes it difficult to determine the rest potential experimentally.

Finally it is assumed that the channel kinetics have already been determined experimentally\(^2\). In particular, assume that the hyperpolarization-activated \( h \)-current,

\(^2\)The expressions describing the channel kinetics may indeed change at a later stage as more experiments are done, but changing it is not expected to influence the approach presented here.
\( I_h = g_h q(x, t)(V - V_h) \) is characterized by

\[
q_\infty(V(x, t)) = q_\infty(V) = \frac{1}{1 + \exp((V + 69)/7.1)},
\]

with an associated time constant \( \tau_q \) (in ms), defined as

\[
\tau_q(V) = \frac{10}{\exp((V + 66.4)/9.3) + \exp(-(V + 81.6)/13)}.
\]

A summary of all the variables, coefficients, and functions used in the nonuniform active cable model is given in Table 3.1 on page 19, where the dependence on space \((x)\) and time \((t)\) have been made explicit. For example, \( g_{Cl}(x) \) is assumed to depend on space but not on time, and \( C_m \) is assumed to be independent of both space and time.

### 3.4.2 Simulation: the discrete active cable

An approximate solution to (3.7) on the discretized straight cable can be obtained numerically by means of a staggered backward Euler type method, originally due to Hines (1984). (See §9.1 of Gabbiani and Cox (2010) for more details.) In particular, consider again the same space-time grid and compartmentalization as for the passive cable of section 3.3.2 and define for each \( i = 1, \ldots, N_x \), and for each \( j = 1, \ldots, N_t \)

\[
V_i^j \approx V((i - 1/2)dx, (j - 1)dt),
\]

\[
q_i^j \approx q((i - 1/2)dx, (j - 3/2)dt),
\]

\[
I_i^j = I_{stim}((i - 1/2)dx, (j - 3/2)dt) / (2\pi a),
\]

\[
g_h_i = g_h((i - 1/2)dx), \quad \text{and} \quad g_{Cl_i} = g_{Cl}((i - 1/2)dx),
\]

where \((i - 1/2)dx\) is the midpoint of the \(i\)th compartment.
Chapter 3 Models, simulation, and recovery of ionic conductances

The gating variable $q$ can be advanced via

$$q_i^j = \frac{1/dt - \left(\alpha_q(V_i^{j-1}) + \beta_q(V_i^{j-1})\right)/2}{1/dt + \left(\alpha_q(V_i^{j-1}) + \beta_q(V_i^{j-1})\right)/2} q_i^{j-1} + \alpha_q(V_i^{j-1})$$

\[ i = 1, \ldots, N_x, \quad (3.11) \]

where expressions for the rate functions, $\alpha_q$ and $\beta_q$, were obtained by requiring that $q_\infty = \alpha_q \tau_q$ and $\tau_q = 1/(\alpha_q + \beta_q)$. These two requirements can be expressed as

$$\begin{bmatrix} q_\infty - 1 & q_\infty \\ \tau_q & \tau_q \end{bmatrix} \begin{bmatrix} \alpha_q \\ \beta_q \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

which may be solved to yield

$$\alpha_q(V) = -\frac{q_\infty(V)}{\tau_q(V)} \quad \text{and} \quad \beta_q(V) = \frac{1 - q_\infty(V)}{\tau_q(V)}.$$

Now for each time index $j$, define the vector of $N_x$ transmembrane potentials as

$$V^j = (V_1^j \ V_2^j \ \cdots \ V_{N_x}^j)^T$$

so that for each $i = 1, \ldots, N_x$, the transmembrane potential $V_i^{j-1}$ can be advanced by the half-step backward Euler method as follows:

$$C_m \frac{V_i^{j-1/2} - V_i^{j-1}}{dt/2} = G_a \left(SV_i^{j-1/2}\right)_i - g_{h_i} q_i^j (V_i^{j-1/2} - V_h) - g_{c_{i1}} (V_i^{j-1/2} - V_{c_{i1}}) + I_i^j$$

\[ (3.12) \]

where $S \in \mathbb{R}^{N_x \times N_x}$ is the second difference matrix as before.

Next, rewrite (3.12) as the following linear system

$$(\text{diag}(d^j + 2C_m/dt) + G_a S)V^{j-1/2} = (2C_m/dt)V^{j-1} + f^j$$

\[ (3.13) \]

See §4.3 of Gabbiani and Cox (2010) for a detailed argument on advancing the gating variables using a trapezoid-like approximation.
where
\[ \delta_j^i = g_{h_i} q_j^i + g_{Cl_i} \quad \text{and} \quad f_j^i = g_{h_i} q_j^i V_h + g_{Cl_i} V_{Cl} + I_{j}^i. \]

Finally, compute the half-step update
\[ \psi^j = 2\psi^{j-1/2} - \psi^{j-1}. \tag{3.14} \]

Note the advantage of this staggered approach: if the backward Euler method was used, we would have had to solve a nonlinear system of equations at each time step.

**Computing the nonuniform rest potential** To initialize the simulation, set
\[ V_1^i = V_r((i - 1/2)dx) \quad \text{and} \quad q_1^i = q_{\infty}(V_r((i - 1/2)dx)), \]
where the (nonuniform) rest potential \( V_r \) is the solution to \( G_a V_r''(x) = I^{ss}(x) \):
\[ I^{ss}(x) \equiv g_{Cl}(x)(V_r - V_{Cl}) + g_{h}(x) q_{\infty}(V_r)(V_r - V_h) = G_a \frac{d^2 V_r}{dx^2} \tag{3.15} \]
subject to \( V_r'(0) = V_r'(<0) = 0 \), and where \( V_r(x) \equiv V_r \) has been used for notational convenience. That \( V_r \) has to satisfy (3.15) is a fairly natural requirement, since clearly \( \partial V_r / \partial t = 0 \), and demanding that the net current flowing through the membrane along the cable should be zero then leads to (3.15), where \( q_{\infty} \) defines the steady-state of the gating variable \( q \).

To determine the rest potential at the compartment midpoints (as required for the initialization of the simulation), consider the following problem:
\[ \text{find } V \text{ such that } F(V) \equiv G_a S V - I^{ss}(V) = 0, \tag{3.16} \]
where \( F : \mathbb{R}^{N_x} \rightarrow \mathbb{R}^{N_x}, F(V) = G_a S - I^{ss}(V), V \in \mathbb{R}^{N_x} \) is the column vector of rest potentials such that \( V_i = V_r((i - 1/2)dx) \), and \( I^{ss} : \mathbb{R}^{N_x} \rightarrow \mathbb{R}^{N_x} \) is a vector of steady-
state currents defined as $$I_{ss}^{i}(V) = g_{C1}(V_i - V_{Cl}) + g_{h1}q_{\infty}^{i}(V_i)(V_i - V_{h})$$. To aid in the solution of (3.16), compute the Jacobian matrix $$J$$ of $$F$$:

$$J_{ij} = G_a S_{ij} - \frac{\partial I_{ss}^{i}(V)}{\partial V_j},$$

where

$$\frac{\partial I_{ss}^{i}(V)}{\partial V_j} = \begin{cases} g_{C1} + g_{h1}q_{\infty}'(V_i)(V_i - V_{h}) + g_{h1}q_{\infty}(V_i), & i = j; \\ 0, & i \neq j. \end{cases}$$

Finally then the Jacobian matrix can be used in a Newton update rule:

$$V^{k+1} = V^k - J^{-1}(G_a S V^k - I_{ss}^{k}(V^k)),$$

or any other suitable numerical scheme that can utilize the Jacobian matrix to solve for $$F(V) = 0$$. Alternatively, the rest potential can be solved using the \texttt{fsolve} subroutine in \texttt{Matlab}, where the Jacobian matrix should be provided to improve the performance of the solver.

### 3.5 The nonuniform quasi-active cable

The nonlinear active cable model presented in (3.7) is unfortunately very difficult to analyze. (Note the source of the nonlinearity: $$q(x,t)V(x,t)$$ where $$q$$ itself depends nonlinearly on $$V$$). As a consequence I consider instead a linearization of (3.7), referred to as the quasi-active cable, which more readily lends itself to some analysis, and which will prove very useful in the development of the method of moments to recover the unknown ionic conductances later in section 3.6.2. The idea of linearization in cable theory is fairly common, see e.g., §5.1 of Gabbiani and Cox (2010) or Koch (1984).
3.5.1 Model: quasi-active cable

For a small stimulus, \( I_{\text{stim}} = \varepsilon \tilde{I} \), with \( \varepsilon \ll 1 \), it is natural to expect the transmembrane potential \( V(x, t) \) to remain close to the rest potential, \( V_r \). That is, it is natural to expect

\[
V(x, t) = V_r(x) + \varepsilon \tilde{V}(x, t) + \mathcal{O}(\varepsilon^2)
\]

(3.17)

for \( \varepsilon \) sufficiently small, and similarly for the gating variable \( q \):

\[
q(x, t) = \bar{q}(x) + \varepsilon \tilde{q}(x, t) + \mathcal{O}(\varepsilon^2).
\]

(3.18)

Substituting (3.17) and (3.18) into (3.7) and identifying terms of order \( \varepsilon \) then leads to the following quasi-active system of linear partial differential equations:

\[
\begin{align*}
C_m \frac{\partial \tilde{V}}{\partial t} &= G_a \frac{\partial^2 \tilde{V}}{\partial x^2} - g_h(x) \{ q \tilde{V} + \bar{q} v_h \} - g_{\text{Cl}}(x) \tilde{V} + \tilde{I} / (2\pi a) \\
\frac{\partial \tilde{q}}{\partial t} &= (\bar{q}_{\infty} \tilde{V} - \bar{q}) / \tau_q
\end{align*}
\]

(3.19)

where

\[
\tilde{V} \equiv \tilde{V}(x, t), \quad \tilde{q} \equiv \tilde{q}(x, t), \quad v_h \equiv V_r(x) - V_h,
\]

and where

\[
q \equiv q_{\infty}(V_r(x)), \quad \bar{q}_{\infty} \equiv q'_{\infty}(V_r(x)), \quad \text{and} \quad \tau_q \equiv \tau_q(V_r(x)).
\]

More specifically, to arrive at (3.19) notice that

\[
q(V - V_h) = \left( \bar{q} + \varepsilon \tilde{q} + \mathcal{O}(\varepsilon^2) \right) \left( V_r + \varepsilon \tilde{V} + \mathcal{O}(\varepsilon^2) - V_h \right)
\]

\[
= \bar{q}(V_r - V_h) + \left( \bar{q} \tilde{V} + \bar{q}(V_r - V_h) \right) \varepsilon + \mathcal{O}(\varepsilon^2),
\]
and that the Taylor expansion of $q_\infty(V)$ about the resting potential $V_r(x)$ is given by

$$q_\infty(V) = q_\infty(V_r) + q_\infty'(V_r)(V - V_r) + q_\infty''(V_r)(V - V_r)^2/2 + \cdots$$

so that with $V = V_r + \varepsilon\tilde{V} + \mathcal{O}(\varepsilon^2)$, it follows that

$$q_\infty(V) = q_\infty(V_r) + \varepsilon q_\infty'(V_r)\tilde{V} + \mathcal{O}(\varepsilon^2).$$

Similarly for $\tau_q(V)$, so that substitution leads to

$$\frac{\partial q(x, t)}{\partial t} = \frac{q_\infty(V) - q}{\tau_q(V)} = \frac{q_\infty(V_r) + q_\infty'(V_r)(\varepsilon\tilde{V}) + \mathcal{O}(\varepsilon^2) - (\bar{q}(x) + \varepsilon\bar{q}(x, t) + \mathcal{O}(\varepsilon^2))}{\tau_q(V_r) + \tau_q'(V_r)(\varepsilon\tilde{V}) + \mathcal{O}(\varepsilon^2)}$$

which ultimately, upon identifying terms of order $\varepsilon$, leads to (3.19).

Recall the definition of $q_\infty$ given in (3.8), so that

$$q_\infty' = \left. \frac{dq_\infty(V)}{dV} \right|_{V=V_r} = -\frac{\exp\left((V_r + 69)/7.1\right)}{7.1\left(1 + \exp\left((V_r + 69)/7.1\right)\right)^2}.$$

The quasi-active system (3.19) can be expressed as the linear system

$$\frac{\partial \mathbf{y}}{\partial t} = \mathbf{B}\mathbf{y} + \mathbf{f}$$

(3.20)

where

$$\mathbf{y} = (\bar{q} \ \tilde{V})^T \quad \text{and} \quad \mathbf{f} = (0 \ \bar{I}/2\pi a C_m)^T,$$

and where $\mathbf{B}$ is the matrix differential operator

$$\mathbf{B} = \begin{bmatrix} -1/\tau_q & \bar{q}_\infty/\tau_q \\ -g_h v_h/C_m & G_a/C_m \partial_{xx} - (g_{Cl} + g_h \bar{q})/C_m \end{bmatrix}. \quad (3.21)$$
3.5.2 Simulation: the quasi-active cable

Let \( z(t) = (\tilde{q}_1 \tilde{q}_2 \ldots \tilde{q}_{N_x} \tilde{V}_1 \tilde{V}_2 \ldots \tilde{V}_{N_x})^T \) where \( \tilde{q}_i \) corresponds to \( \tilde{q}(x, t) \) at the midpoint of the \( i \)th compartment, and similarly for \( \tilde{V} \). That is, for each \( i = 1, 2, \ldots, N_x \)

\[
\tilde{q}_i(t) = \tilde{q}( (i - 1/2)dx, t ) \quad \text{and} \quad \tilde{V}_i(t) = \tilde{V}( (i - 1/2)dx, t ).
\]

Also define \( g(t) = \tilde{I}(t)/(2\pi adx C_m)(0_{N_x} e_k^T)^T \) where \( 0_N \) is a column vector of \( N \) zeros, and as before \( e_k = (0 0 \ldots 0 1 0 \ldots 0)^T \) corresponds to current injection at the \( k \)th compartment.

Then a spatial discretization of (3.20) is given by

\[
\frac{dz}{dt} = Qz + g \tag{3.22}
\]

where

\[
Q = \begin{bmatrix}
Q_{11} & Q_{12} \\
Q_{21} & Q_{22}
\end{bmatrix}
\]

with

\[
Q_{11} = \text{diag}(B_{11}^1 B_{11}^2 \ldots B_{11}^{N_x}), \quad Q_{12} = \text{diag}(B_{12}^1 B_{12}^2 \ldots B_{12}^{N_x}),
\]

\[
Q_{21} = \text{diag}(B_{21}^1 B_{21}^2 \ldots B_{21}^{N_x}) \quad \text{and} \quad Q_{22} = \left( G_a S - \text{diag}(B_{22}^1 B_{22}^2 \ldots B_{22}^{N_x}) \right)/C_m
\]

where \( S \) is again the second difference matrix, and where

\[
B_{11}^i = -1/\tau_q \left( \psi_r^i \right), \quad B_{12}^i = q_\infty \left( \psi_r^i \right)/\tau_q \left( \psi_r^i \right),
\]

\[
B_{21}^i = -g_h^i (\psi_r^i - \psi_h)/C_m, \quad \text{and} \quad B_{22}^i = -\left( g_{Cl}^i + g_h^i q_\infty (\psi_r^i) \right)/C_m
\]

with

\[
\psi_r^i \approx \psi_r ((i - 1/2)dx), \quad g_{Cl}^i = g_{Cl}((i - 1/2)dx), \quad \text{and} \quad g_h^i = g_h((i - 1/2)dx).
\]
Chapter 3 Models, simulation, and recovery of ionic conductances

Here $V_i \approx V_r \left( (i - 1/2)dx \right)$ because $V_r$ is in general not known, so that it often has to be approximated numerically before running a simulation.

Finally then an approximate solution to (3.22) can be obtained in exactly the same way as for the approximate solution to (3.5) described in section 3.3.2. That is,

$$ \text{set } r^2 = (dt/2)(g^2 + g^1) $$

and for $j = 2, 3, \ldots, N_t$

$$ \text{solve } (I - (dt/2)Q)z^j = r^j \text{ and set } r^{j+1} = 2z^j - r^j + (dt/2)(g^{j+1} + g^j). $$

3.5.3 Eigenfunction expansion: uniform quasi-active cable solution

Here we develop an exact solution to (3.20) in the form of an eigenfunction expansion for the uniform quasi-active cable. Let $w = (w_1, w_2)^T$, and consider $Bw(x) = \zeta w(x)$, from which it follows that

$$ \left( \frac{q'_\infty}{\tau_q} \right) w_2 - w_1/\tau_q = \zeta w_1 \implies w_1 (1 + \zeta \tau_q) = \frac{q'_\infty}{\tau_q} w_2 \implies w_1 = \frac{q'_\infty}{(1 + \zeta \tau_q)} w_2. $$(3.23)

Hence $w = (q'_\infty w_2 / (1 + \zeta \tau_q) w_2)^T$ is an eigenfunction of $B$. Furthermore, from $Bw = \zeta w$ the quasi-potential $w_2$ reads

$$ \frac{1}{C_m} \left( G_a \partial_{xx} - \frac{g_h v_h \gamma_\infty}{1 + \zeta \tau_q} - gc_{Cl} - gh \gamma \right) w_2 = \zeta w_2 $$

or equivalently

$$ \frac{G_a}{C_m} \frac{d^2 w_2}{dx^2} - \frac{1}{C_m} \left( \frac{g_h v_h \gamma_\infty}{1 + \zeta \tau_q} + gc_{Cl} + gh \gamma \right) w_2 = \zeta w_2. $$

(3.25)

Now since the cable is assumed to be uniform (i.e., both $gc_{Cl}$ and $g_h$ are constants)
the rest potential $V_r$ can be shown to be constant as well, so that the large bracketed term above is independent of $x$. Hence

$$w_2''(x) = \vartheta w_2(x)$$

(3.26)

for some constant $\vartheta \in \mathbb{R}$, and since the cable is sealed, it is natural to expect the quasi-potential to also satisfy

$$w_2'(0) = w_2'(\ell) = 0.$$ 

It can further be shown that (3.26) together with its boundary conditions have solutions of the form

$$\vartheta_0 = 0, \quad \vartheta_n = -n^2 \pi^2 / \ell^2, \quad w_{2,0} = 1 / \sqrt{\ell}, \quad w_{2,n}(x) = \sqrt{2 / \ell} \cos(n\pi x / \ell), \quad n = 1, 2, \ldots$$

from whence it follows that with $w_2''(x) = \vartheta w_2(x)$, (3.25) becomes

$$G_a C_m \vartheta_n w_{2,n} - \frac{1}{C_m} \left( \frac{g_h v_h q'_{\infty}}{1 + \zeta \tau_q} + g_{Cl} + g_h q \right) w_{2,n} = \zeta w_{2,n},$$

(3.27)

so that division by $w_{2,n}(x)$ leads to

$$G_a C_m \vartheta_n - \frac{1}{C_m} \left( \frac{g_h v_h q'_{\infty}}{1 + \zeta \tau_q} + g_{Cl} + g_h q \right) = \zeta,$$

(3.28)

from which it is easy to see that $\zeta$ must be a root of

$$P_n(\zeta) = \left( \zeta - G_a \vartheta_n / C_m + (g_{Cl} + g_h q) / C_m \right) \left( 1 + \zeta \tau_q \right) + g_h v_h q'_{\infty} / C_m$$

$$= \tau_q \zeta^2 + \left( 1 + \frac{\tau a}{C_m} \left( g_{Cl} + g_h q - G_a \vartheta_n \right) \right) \zeta + \frac{1}{C_m} \left( g_{Cl} + g_h q - G_a \vartheta_n + g_h v_h q'_{\infty} \right).$$

(3.29)

Now label the roots as $\zeta_{n,j}$ for $n = 0, 1, 2, \ldots$ and $j \in \{0, 1\}$ so that the eigenfunc-
tions of $B$ can be expressed as

$$w_{n,j}(x) = \left( \frac{q_\infty}{1 + \zeta_{n,j} \tau_q} w_{2,n}(x) w_{2,n}(x) \right)^T$$

and so if $I_{\text{stim}}(x,t) = \sum_{n=0}^{\infty} I_{\text{stim},n}(t)w_{2,n}(x)$ then the stimulus vector is given by

$$f = \sum_{n=0}^{\infty} \sum_{j=0}^{1} c_{n,j}(t)w_{n,j}(x)$$

where

$$c_{n,0}(t) = \frac{I_{\text{stim},n}(t) 1 + \zeta_{n,0} \tau_q}{2 \pi a C_m \tau_q (\zeta_{n,0} - \zeta_{n,1})}, \quad \text{and} \quad c_{n,1}(t) = \frac{I_{\text{stim},n}(t) 1 + \zeta_{n,1} \tau_q}{2 \pi a C_m \tau_q (\zeta_{n,1} - \zeta_{n,0})}.$$

Then finally, we have

$$\tilde{V}(x,t) = \sum_{n=0}^{\infty} w_{2,n}(x) \left( \int_0^t c_{n,0}(s) \exp((t-s)\zeta_{n,0})ds + \int_0^t c_{n,1}(s) \exp((t-s)\zeta_{n,1})ds \right).$$

**Eigenfunction expansion solution for localized instantaneous current injection**

The synaptic input that results from (very) briefly illuminating a single facet on a locust’s retina can be modeled by a precise spatio-temporal current injection $I_{\text{stim}}(x,t) = I_0 \delta(x - x_k) \delta(t - t_{\text{stim}})$, where current injection occurs at location $x_k$ and where the stimulus is applied at time $t_{\text{stim}}$. For such a particular stimulus, it follows that

$$I_{\text{stim},n}(t) = \int_0^t I_{\text{stim}}(x,t)w_{2,n}(x)dx$$

$$= \int_0^t I_0 \delta(x - x_k) \delta(t - t_{\text{stim}})w_{2,n}(x)dx$$

$$= I_0 \delta(t - t_{\text{stim}})w_{2,n}(x_k)$$
so that
\[ c_{n,0} = I_0 \frac{\delta(t - t_{\text{stim}}) w_{2,n}(x_k)}{2\pi a C_m} \frac{1 + \zeta_{n,0} \tau_q}{\tau_q (\zeta_{n,0} - \zeta_{n,1})} \] and \[ c_{n,1} = I_0 \frac{\delta(t - t_{\text{stim}}) w_{2,n}(x_k)}{2\pi a C_m} \frac{1 + \zeta_{n,1} \tau_q}{\tau_q (\zeta_{n,1} - \zeta_{n,0})} \]

Notice that
\[
\int_0^t c_{n,j}(s) \exp((t-s)\zeta_{n,j}) \, ds = \begin{cases} 0 & t \leq t_{\text{stim}} \\ I_0 \frac{w_{2,n}(x_k)}{2\pi a C_m} \frac{1 + \zeta_{n,j} \tau_q}{\tau_q (\zeta_{n,j} - \zeta_{n,k})} \exp\left((t - t_{\text{stim}})\zeta_{n,j}\right) & t > t_{\text{stim}} \end{cases}
\]

and define
\[
K_{n,0} = I_0 \frac{w_{2,n}(x_k)}{2\pi a C_m} \frac{1 + \zeta_{n,0} \tau_q}{\tau_q (\zeta_{n,0} - \zeta_{n,1})} \quad \text{and} \quad K_{n,1} = I_0 \frac{w_{2,n}(x_k)}{2\pi a C_m} \frac{1 + \zeta_{n,1} \tau_q}{\tau_q (\zeta_{n,1} - \zeta_{n,0})}
\]

so that
\[
\int_0^\infty \int_0^t c_{n,j}(s) \exp((t-s)\zeta_{n,j}) \, ds \, dt = I_0 \frac{w_{2,n}(x_k)}{2\pi a C_m} \frac{1 + \zeta_{n,j} \tau_q}{\tau_q (\zeta_{n,j} - \zeta_{n,k})} \int_{t_{\text{stim}}}^\infty \exp\left((t - t_{\text{stim}})\zeta_{n,j}\right) \, dt
\]
\[
= K_{n,j} \int_{t_{\text{stim}}}^\infty \exp\left((t - t_{\text{stim}})\zeta_{n,j}\right) \, dt
\]
\[
= K_{n,j} \frac{\exp\left((t - t_{\text{stim}})\zeta_{n,j}\right)}{\zeta_{n,j}} \bigg|_{t_{\text{stim}}}^\infty
\]
\[
= -\frac{K_{n,j}}{\zeta_{n,j}}
\]

where we have used the fact that \( \zeta_{n,j} < 0 \) for all \( n = 1, 2, \ldots \).

Finally then, for all \( t > t_{\text{stim}} \) the exact quasi-active potential in (3.19) is given by

\[
\tilde{V}(x, t) = \sum_{n=0}^{\infty} w_{2,n}(x) \left( K_{n,0} \exp\left((t - t_{\text{stim}})\zeta_{n,0}\right) + K_{n,1} \exp\left((t - t_{\text{stim}})\zeta_{n,1}\right) \right) \quad \text{(3.30)}
\]

whenever the cable is uniform, and \( I_{\text{stim}}(x, t) = I_0 \delta(x - x_k) \delta(t - t_{\text{stim}}) \).

The method of moments is finally presented next.
3.6 The method of moments

This section develops an approach to recover the ionic membrane conductances from distal transmembrane potential recordings in response to particular known stimuli, by using the method of moments. First the method of moments is developed for the passive cable in section 3.6.1, followed by the active cable in section 3.6.2.

3.6.1 Method of moments for the passive cable

Recall that the passive cable of (3.2) has a leak conductance, $g_{Cl}(x)$, which is allowed to vary over space. Now consider a sealed cable and define for each $k = 1, 2, \ldots, N_k$ the stimulus $I_{stim}(x,t;k) = I_0 \delta(x - x_k)\delta(t - t_{stim})$. That is, current of magnitude $I_0$ is injected at location $x = x_k$ at time $t = t_{stim}$. The perturbation of the membrane potential from rest ($v \equiv V - V_r$) then obeys the following passive cable equation:

$$C_m \frac{\partial v(x,t;k)}{\partial t} + g_{Cl}(x)v - G_a \frac{\partial^2 v}{\partial x^2} = \frac{I_0}{2\pi a} \delta(x - x_k)\delta(t - t_{stim})$$

(3.31)

with boundary conditions

$$\frac{\partial v}{\partial x}(0,t) = \frac{\partial v}{\partial x}(\ell,t) = 0.$$

Integration of each side of (3.31) over all time then gives the zeroth moment\(^4\), defined as

$$M(x,x_k) \equiv \int_0^\infty v(x,t;k)\,dt$$

which clearly obeys

$$g_{Cl}(x)M(x,x_k) - G_a M_{xx}(x,x_k) = \frac{I_0}{2\pi a} \delta(x - x_k), \text{ with } M_x(0,x_k) = M_x(\ell,x_k) = 0.$$

\(^4\)In general, the $n$th moment is defined as $M_n(v) = \int_0^\infty t^n v(t)\,dt$. 

Department of Computational and Applied Mathematics

35
Recall that for constants \(a\) and \(b\) and for sufficiently smooth \(f\)
\[
\int_a^b \frac{\partial^2 f(x,t)}{\partial x^2} \, dt = \frac{d^2}{dx^2} \left( \int_a^b f(x,t) \, dt \right),
\]
so that in the limit as \(b \to \infty\), it follows that
\[
\int_0^\infty \frac{\partial^2 v(x,t;k)}{\partial x^2} \, dt = \frac{d^2}{dx^2} \left( \int_0^\infty v(x,t;k) \, dt \right) = \frac{d^2}{dx^2} M(x,x_k) = M_{xx}(x,x_k).
\]

Note also that the cable is initially at rest (with \(v(x,0) = 0\)) and that as \(t \to \infty\), the cable returns to rest. As a result, it follows that
\[
\int_0^\infty \frac{\partial v(x,t;k)}{\partial t} \, dt = 0.
\]

Let us fix a recording location \(x = 0\). Now as \(x_k \mapsto M(0,x_k)\) is recorded, and since \(M(x,x_k) = M(x_k,x)\) we can recover \(g_{Cl}\) by simply computing
\[
g_{Cl}(x_k) = G_a \frac{M_{xx}(0,x_k)}{M(0,x_k)} = G_a \left( \frac{\partial^2}{\partial x_k^2} M(0,x_k) \right) / M(0,x_k). \tag{3.32}
\]

Indeed, suppose that we are interested in recovering \(g_{Cl}\) at some location \(y \neq 0\), and since we are free to specify the stimulus site, let us “assume” it to be 0. It follows that
\[
g_{Cl}(y) M(y,0) - G_a M_{yy}(y,0) = \frac{I_0}{2\pi a} \delta(y - 0) = 0.
\]
However, in reality we do not know \(M(y,0)\) since we have set our recording location to \(x = 0\). That is, we only know \(M(0,y)\), where \(y\) is the “true” stimulus location. But since \(M(y,0) = M(0,y)\) it follows that
\[
g_{Cl}(y) M(0, y) - G_a M_{yy}(0, y) = \frac{I_0}{2\pi a} \delta(y) = 0,
\]
so that choosing the stimulus location to be \(y = x_k\) finally leads to (3.32).

The entire procedure to recover the leak conductances along a passive cable can then be summarized as in Algorithm 1.

**Algorithm 1** Method of moments for passive cable.

1: for \(k = 1\) to \(N\) do
2: light up \(k\)th facet
3: record neuronal response at \(x = x_{\text{rec}}:\ v(x_{\text{rec}}, t; k)\)
4: compute moment \(M(x_{\text{rec}}, x_k) = \int_0^\infty v(x_{\text{rec}}, t; k)\,dt\)
5: end for
6: compute \(M_{x_k x_k}(x_{\text{rec}}, x_k)\)
7: recover \(g_{\text{Cl}}(x_k)\) at each \(x_k\) from \(M(x, x_k)\) and \(M_{x_k x_k}(x, x_k)\)

3.6.1.1 Exact moments for the uniform passive cable

When the leak conductance \(g_{\text{Cl}}\) is constant, the moment \(M(x, x_k)\) obeys

\[
M(x, x_k) - \frac{G_a}{g_{\text{Cl}}} M_{xx}(x, x_k) = \frac{I_0}{2\pi a g_{\text{Cl}}} \delta(x - x_k), \quad M_x(0, x_k) = M_x(\ell, x_k) = 0,
\]

which has an exact solution given as (cf. (6.48) of Gabbiani and Cox, 2010):

\[
M(x, x_k) = \frac{I_0}{2\pi a \lambda g_{\text{Cl}}} \frac{1}{\sinh(x_k/\lambda) + \cosh(x_k/\lambda) \tanh((\ell - x_k)/\lambda)} \psi(x),
\]

(3.33)

where \(\lambda^2 \equiv G_a/g_{\text{Cl}}\) and

\[
\psi(x) = \begin{cases} 
\cosh(x/\lambda), & \text{if } 0 \leq x \leq x_k; \\
\frac{\cosh(x_k/\lambda) \cosh((\ell - x)/\lambda)}{\cosh((\ell - x_k)/\lambda)}, & \text{if } x_k \leq x \leq \ell.
\end{cases}
\]

An example of the moments computed for a uniform passive cable is given in Figure 3.7, where the “simulated” moment was obtained by numerically integrating
the rest-adjusted approximate solutions to (3.5), whereas the “analytic” moment refers to (3.33).

![Graph showing comparison of simulated and exact moments for a uniform passive cable.](exactmompassive.m)

Figure 3.7: Comparison of simulated and exact moments for a uniform passive cable; recording at \(x = 0.0205\) cm with a stimulus at location \(x_k\) (exactmompassive.m).

### 3.6.2 Method of moments for the active cable

The recovery of the ionic membrane conductances for the quasi-active cable proceeds in a two phase approach: first, the hyperpolarization-activated \(h\)-channel is chemically blocked, resulting in a purely passive cable for which the leak conductance \(g_{Cl}(x)\) can be recovered by following the approach detailed in section 3.6.1. Second, the extended approach presented in this section can then be used to further recover \(g_h(x)\) as well as the nonuniform rest potential \(V_r(x)\).

It is henceforth assumed that the leak conductance \(g_{Cl}(x)\) is known.

Consider again the sealed nonuniform active cable from (3.7):

\[
C_m \frac{\partial V(x,t)}{\partial t} = G_a \frac{\partial^2 V}{\partial x^2} - g_{Cl}(x)(V - V_{Cl}) - g_h(x)q(x,t)(V - V_h) + \frac{I_{stim}}{2\pi a} \frac{\partial q(x,t)}{\partial t} = \frac{q_{\infty}(V) - q}{\tau_q(V)},
\]
with boundary conditions
\[ \frac{\partial V}{\partial x}(0, t) = \frac{\partial V}{\partial x}(\ell, t) = 0 \]

and where, as before, the nonuniform rest potential \( V_r(x) \) is given as the solution to
\[
I_{ss}(x, V_r) \equiv g_{Cl}(x)(V_r - V_{Cl}) + g_h(x)q_{\infty}(V_r)q_{\infty}(V_r - V_h) = G_a \frac{d^2 V_r}{dx^2}.
\] (3.34)

Also recall the quasi-active cable from (3.19), repeated here for convenience, where for each \( k = 1, 2, \ldots, N \) the stimulus \( I_{stim}(x, t; k) = \varepsilon \tilde{I}_0 \delta(x - x_k)\delta(t - t_{stim}) \):
\[
C_m \frac{d\tilde{V}}{dt} = G_a \frac{d^2 \tilde{V}}{dx^2} - g_h(x)\{\tilde{q}\tilde{V} + \tilde{q}v_h\} - g_{Cl}(x)\tilde{V} + \frac{\tilde{I}_0}{(2\pi a)}\delta(x - x_k)\delta(t - t_{stim})
\]
\[
\frac{\partial \tilde{q}}{\partial t} = (\tilde{q}_{\infty}\tilde{V} - \tilde{q})/\tau_q,
\] (3.35)

where
\[ \tilde{V} \equiv \tilde{V}(x, t), \ v_h \equiv V_r(x) - V_h, \ \tilde{q} \equiv q_{\infty}(V_r(x)), \ \tilde{q}' \equiv q'_{\infty}(V_r(x)), \ \text{and} \ \tau_q \equiv \tau_q(V_r(x)). \]

Integrating both sides of (3.35) over all time, and defining the moments
\[
W(x, x_k) \equiv \int_0^\infty \tilde{V}(x, t; k)dt, \quad \text{and} \quad Q(x, x_k) \equiv \int_0^\infty \tilde{q}(x, t; k)dt
\]
leads to (whenever \( x \neq x_k \))
\[
G_a \frac{d^2 W(x, x_k)}{dx^2} = g_h(x)\{\tilde{q}(x)W(x, x_k) + v_h(x)Q(x, x_k)\} + g_{Cl}(x)W(x, x_k)
\]
\[
Q(x, x_k) = \tilde{q}'_{\infty}W(x, x_k).
\] (3.36)
To be a little more careful, define \( \tilde{I} \equiv \tilde{I}_0 \delta(x - x_k) \delta(t - t_{\text{stim}})/(2\pi a) \) and consider

\[
\int_0^\infty C_m \frac{\partial \tilde{V}}{\partial t} \, dt = \int_0^\infty \left( G_a \frac{\partial^2 \tilde{V}}{\partial x^2} - g_h \left( \tilde{q} \tilde{V} + \tilde{q}v_h \right) - g_{Cl}(x) \tilde{V} + \tilde{I} \right) \, dt
\]

\[
= G_a \frac{d^2 W}{dx^2} \int_0^\infty \tilde{V} \, dt - g_h \left( \tilde{q} \int_0^\infty \tilde{V} \, dt + v_h \int_0^\infty \tilde{q} \, dt \right) - g_{Cl} \int_0^\infty \tilde{V} \, dt + \int_0^\infty \tilde{I} \, dt
\]

\[
= G_a \frac{d^2 W}{dx^2} - g_h (\tilde{q}W + v_h Q) - g_{Cl} W + \frac{\tilde{I}_0}{(2\pi a)} \delta(x - x_k),
\]

where as before, and since \( \tilde{V}(x, 0) = \lim_{T \to \infty} \tilde{V}(x, T) \) it follows that

\[
\int_0^\infty C_m \frac{\partial \tilde{V}}{\partial t} \, dt = 0,
\]

so that

\[
G_a \frac{d^2 W(x, y)}{dx^2} = g_h(x) \left( \tilde{q}(x) W(x, y) + v_h(x) Q(x, y) \right) + g_{Cl}(x) W(x, y) - \frac{\tilde{I}_0}{(2\pi a)} \delta(x - x_k),
\]

where the dependence on the recording location \( x \) and the stimulus location \( x_k \) have been made explicit.

Furthermore, integrating the second equation of (3.35) yields

\[
\int_0^\infty \frac{\partial \tilde{q}}{\partial t} \, dt = \int_0^\infty \frac{\partial \tilde{q}}{\partial t} \left( \tilde{q}'(t) \tilde{V} - \tilde{q} \right)/\tau_q \, dt
\]

\[
= \frac{1}{\tau_q(\tilde{V}_r(x))} \left( q'_r(\tilde{V}_r(x)) \int_0^\infty \tilde{V} \, dt - \int_0^\infty \tilde{q} \, dt \right)
\]

\[
= \frac{1}{\tau_q(\tilde{V}_r(x))} \left( q'_r(\tilde{V}_r(x)) W(x, x_k) - Q(x, x_k) \right)
\]

and since \( \tilde{q} \) depends on \( \tilde{V} \), the same argument as above shows that \( \tilde{q} \) is initially at rest, and that it too returns to rest after a transient stimulus, so that

\[
\int_0^\infty \frac{\partial \tilde{q}}{\partial t} \, dt = 0.
\]
It follows then that

\[ Q(x, x_k) = q'_\infty(V_r(x))W(x, x_k) \equiv q'_\infty W(x, x_k). \]  (3.37)

Substituting (3.37) into (3.36) for \( Q(x, x_k) \), and assuming \( x \neq x_k \) then yields

\[
W(x, x_k) \left( g_h(x) \left( q_\infty(V_r(x)) + q'_\infty(V_r(x))v_h(x) \right) + g_{Cl}(x) \right) = G_a \frac{d^2W}{dx^2}(x, x_k) \quad (3.38)
\]

which, since \( g_{Cl}(x) \) is assumed known, gives us a way to find

\[
F(x; k) \equiv g_h(x) \left( q_\infty(V_r(x)) + q'_\infty(V_r(x))(V_r(x) - V_h) \right) \quad \text{for } k = 1, 2, \ldots N_k. \quad (3.39)
\]

In particular, for each stimulus location \( x_k \), \( F(x; k) \) can be computed from

\[
F(x; k) = G_a W_{xx}(x, x_k)/W(x, x_k) - g_{Cl}(x), \quad (3.40)
\]

and using the symmetry of \( W(x, x_k) \), and since \( g_{Cl} \) is assumed known, \( F \) can be determined away from the recording site \( (x = 0) \) at say \( x_k \), via

\[
F(x_k; k) = G_a W_{xhx_h}(x = 0, x_k)/W(x = 0, x_k) - g_{Cl}(x_k). \quad (3.41)
\]

Finally then, notice that at each stimulus location \( x_k \), (3.34) and (3.39) are two equations, each with two unknowns, namely \( g_h(x) \) and \( V_r(x) \). Now substitute

\[
g_h(x) = F(x; k)/\left( q_\infty(V_r(x)) + q'_\infty(V_r(x))(V_r(x) - V_h) \right) \quad (3.42)
\]

into (3.34) to obtain the following BVP:

\[
G_a \frac{d^2V_r}{dx^2} = g_{Cl}(x)(V_r - V_{Cl}) + \frac{F(x; k)q_\infty(V_r)(V_r - V_h)}{q_\infty(V_r) + q'_\infty(V_r)(V_r - V_h)}, \quad \frac{dV_r(0)}{dx} = \frac{dV_r(\ell)}{dx} = 0. \quad (3.43)
\]
The BVP of (3.43) can (hopefully!) be solved to recover \( V_r(x) \) for \( x \in [0, \ell] \) using MATLAB’s \texttt{bvp4c} routine, where \( g_{Cl} \) and \( F \) are first approximated with splines using the “computable” values at each of the stimulus locations. Furthermore, to make use of MATLAB’s \texttt{bvp4c} routine, define \( y = (u,v)^T = (V_r,v)^T \) and rewrite (3.43) as

\[
\begin{align*}
\frac{du}{dx} &= v \\
\frac{dv}{dx} &= \frac{1}{G_a} \left( g_{Cl}(x)(u - V_{Cl}) + \frac{F(x) q_{\infty}(u)(u - V_h)}{q_{\infty}(u) + q_{\infty}'(u)(u - V_h)} \right)
\end{align*}
\] (3.44)

subject to \( v(0) = v(\ell) = 0 \). (See \texttt{vr4bvp.m} for an implementation of (3.44).) The rest potential \( V_r(x) \) together with (3.42) then finally reveals \( g_h(x) \).

The entire procedure to recover the \( h \) conductances along an active cable can then be summarized as in Algorithm 2.

\begin{algorithm}
\caption{Method of moments for active cable.}
1: pharmacologically block \( h \)-channel
2: determine \( g_{Cl}(x_k) \) using algorithm for passive cable (Algorithm 1)
3: wait for drug to wear off
4: \textbf{for} \( k = 1 \) to \( N \) \textbf{do}
5: \hspace{1em} light up \( k \)th facet
6: \hspace{1em} record neuronal response at \( x = x_{rec} \): \( v(x_{rec}, t; k) \)
7: \hspace{1em} compute moment \( M(x_{rec}, x_k) = \int_0^\infty v(x_{rec}, t; k) dt \)
8: \textbf{end for}
9: compute \( M_{x_k x_k}(x_{rec}, x_k) \)
10: solve a BVP to get rest potential \( v_r \)
11: recover \( g_h(x_k) \) at each \( x_k \) from \( M(x, x_k), M_{x_k x_k}(x, x_k) \) and \( v_r \)
\end{algorithm}
Chapter 4

Results

“An experiment is a question which science poses to Nature, and a measurement is the recording of Nature’s answer.”

Max Planck (1858–1947)

The conductance recovery results for several different cables are presented in this chapter. In particular, examples are considered where the conductances are (i) uniform, (ii) smoothly varying, (iii) discontinuous, and (iv) chosen such that the method fails. However, before considering the recovery of conductances, section 4.1 illustrates and motivates some of the simulation choices for the results that follow.

4.1 Simulation parameters and slow $I_h$ dynamics

In section 4.1.1 the most common simulation parameters are specified, of which the time step $dt$ is arguably the most important. In particular, it is demonstrated (experimentally) that by taking $dt$ sufficiently small, the simulated neuronal response closely approximates the true (theoretical) neuronal response. Thereafter some of the challenges encountered when dealing with an ionic channel with slow dynamics are presented in section 4.1.2, which further motivated some of the simulation decisions for the remainder of this chapter.
4.1.1 Simulation parameters

An example of a simulation specification is given in Listing 4.1. More specifically, \( \text{cab.rad} \) refers to the cable radius \( a \), and will always be assumed to be \( 10^{-4} \) cm. The cable length \( \ell \) (\text{cab.ell}) will be fixed at 0.1 cm, which will be divided into compartments of length \( dx = 10^{-3} \) cm. The simulation time step \( dt \) is set to \( 10^{-3} \) ms below, but it will occasionally be changed. Furthermore, the membrane capacitance will remain fixed at \( C_m = 0.8 \) \( \mu \text{F/cm}^2 \), and the axial resistivity will remain \( R_a = 0.3 \) \( \Omega \cdot \text{cm} \).

Listing 4.1: Typical simulation specification.

```matlab
% cable properties:
cab = struct('rad',1e-4,'ell',0.1,'dx',1e-3,'dt',1e-3,'Cm',0.8,'Ra',0.3)
% uniform channel conductances:
g = struct('Cl',1/15,'h',1)
% reversal potentials:
E = struct('Cl',-68,'h',-40)
% ion currents flowing through membrane:
I = 'gCl*(V-VCl) + gh*q*(V-Vh)'

xmid = cab.dx/2:cab.dx: cab.ell-cab.dx/2; % compartment midpoints
% specification of stimulus and additional simulation parameters:
tstim = 1; % stimulation time (ms)
t1 = tstim - cab.dt; % start of current injection

t2 = tstim + cab.dt; % end of current injection
stim = struct('tstim',tstim,'t1',t1,'t2',t2,'amp',1e-4,...
 ...'loc',[],'Tfin',40,'mloc',xmid(1),'type',1)
```

The conductances are stored in \( g \), and it is fairly simple to specify a nonuniform conductance as shown in Listing 4.2, where it will always be assumed that \( \text{numel}(g.x) = 1 \) for constant conductances, or \( \text{numel}(g.x) = \text{numel}(xmid) \). That is, every compartment must have an associated conductance.

Listing 4.2: Specifying a nonuniform conductance.

```matlab
% define nonuniform conductances:
g.h = linspace(0.2,8,numel(xmid)); g.h=g.h(:);
g.Cl = linspace(1/15,1,numel(xmid)); g.Cl=g.Cl(:);
```
Next, Listing 4.1 specifies the Nernst or reversal potentials associated with the leak \( E_{\text{Cl}} \), and hyperpolarization-activated \( h \)-channels \( E_{\text{h}} \). These reversal potentials will remain unchanged, and in Chapter 3 they were denoted by \( V_{\text{Cl}} \) and \( V_{\text{h}} \), respectively.

The sum of ionic currents is specified as \( I = g_{\text{Cl}}(V - V_{\text{Cl}}) + g_{\text{h}}q(V - V_{\text{h}}) \) for the active cable, and \( I = g_{\text{Cl}}(V - V_{\text{Cl}}) \) for the passive cable.

Finally, Listing 4.1 specifies the stimulus and simulation time. Recall the stimulus considered in Chapter 3:

\[
I_{\text{stim}}(x, t; k) = I_0 \delta(t - t_{\text{stim}}) \delta(x - x_k). \quad (4.1)
\]

The ideal localization in time \( \delta(t - t_{\text{stim}}) \) of the stimulus is approximated by specifying a current pulse starting just after \( t_{\text{stim}} \) and ending just before \( t_{\text{stim}} + 2 \). The amplitude of the stimulus is specified in \( \text{stim.amp} \), which will be fixed at \( I_0 = 10^{-4} \) µA.

A note on discretizing and localizing the stimulus

I discretize and approximate \( \delta(t - t_{\text{stim}}) \approx 1_{t_{\text{stim}}}/dt \),

so that numerical integration of \( f \) over all time by the trapezoidal rule yields

\[
\int_0^\infty f(t)dt \approx \frac{0 + f(t_{\text{stim}})}{2}dt + \frac{f(t_{\text{stim}}) + 0}{2}dt = f(t_{\text{stim}})dt = 1.
\]

Localization in space \( \delta(x - x_k) \) is achieved by associating current injection with a particular compartment, as described in section 3.3.2. Note that \( x_k \) should correspond to the midpoint of the associated compartment.
Indeed, by setting \( \text{stim.t1} = \text{tstim} - \text{cab.dt} \) and \( \text{stim.t2} = \text{tstim} + \text{cab.dt} \) as in Listing 4.1, my implementation ensures that \( I_{\text{stim}}(x,t;k) \) is nonzero only when \((j-1)dt = \text{tstim}\). As could be expected, \text{stim.loc} \) refers to the stimulus location, and should be set to a value corresponding to a compartment midpoint. In Listing 4.1, the stimulus location is left unspecified, since this will change frequently. The recording (or measurement) location is specified in \text{stim.mloc}, and is commonly set to \( \text{xmid}(1) \), which corresponds to the midpoint of the first compartment (that is, \( x \approx 0 \text{ cm} \)).

Finally, the duration of the simulation is specified by setting \( \text{stim.Tfin} \) which will usually be set to \( T_{\text{fin}} = 40 \text{ ms} \). Note that \( \text{stim.type} \) should always be set to 1, which indicates that (4.1) is used as the stimulus.\(^1\)

With the parameters specified in Listing 4.1, along with current injection at location \( x_k = 0.0545 \text{ cm} \), the quasi-active neuronal response shown in Figure 4.1 is obtained.

\[ \begin{align*} 
0 & \quad 0.02 & \quad 0.04 & \quad 0.06 & \quad 0.1 \\
\text{time (ms)} & \quad 0 & \quad 0.02 & \quad 0.04 & \quad 0.06 & \quad 0.08 & \quad 0.1 \\
\tilde{V} (\text{mV}) & \quad 0 & \quad 1 & \quad 2 & \quad 3 & \quad 4 & \quad 5 \\
x (\text{cm}) & \quad 0 & \quad 0.02 & \quad 0.04 & \quad 0.06 & \quad 0.08 & \quad 0.1 \\
\end{align*} \]

Figure 4.1: Neuronal response showing two cross sections. Quasi-active neuronal response for a fixed stimulus location \( x_k \), showing two cross sections: one for which the recording location is fixed at \( x = 0.0405 \text{ cm} \) (corresponding to what can be recorded in practice), and another for which time is fixed at \( t = 1.3 \text{ ms} \) (to obtain this curve in practice would require distributed recording electrodes along the length of the cable, which is impractical).

\(^1\)Other stimuli are indeed possible, but the current implementation does not always check the \text{stim.type} \) flag and assumes at various places that (4.1) is used.
Chapter 4 Results

The importance of choosing $dt$ sufficiently small is demonstrated in Figure 4.2. In particular, recall that the exact solution to the uniform quasi-active cable was given in (3.30). By setting $dt = 0.05$ ms in the quasi-active simulation, and by using $N = 150$ terms in the evaluation of the exact solution, we obtain the results shown in Figure 4.2(a) and Figure 4.2(b), in which the simulated response is very different from the true response. By reducing the time step down to $dt = 0.005$ ms, the simulated and exact solutions match very closely as shown in Figure 4.2(c) and Figure 4.2(d).

![Figure 4.2: Comparison of exact and simulated quasi-active neuronal response to a stimulus at $x_k = 0.0505$ cm, with different time steps $dt$. In (a) and (c) the recording location is set to $x = 0.0205$ cm, and in (b) and (d) the time is fixed at $t = 1.3$ ms. In each case $N = 150$ terms are used to approximate the exact solution given in (3.30).]
4.1.2 Slow $h$-channel dynamics

Some of the challenges that arise when dealing with an ionic channel with a large time constant (i.e., channels causing a slowly decaying response) are presented here.

**Note:** the following results can be generated by running `sim8.m`.

Recall that the dynamics of the hyperpolarization-activated $h$-channel is at least partially characterized by a voltage-dependent gating variable $q$ with an associated steady state (or equilibrium) functional $q_\infty(V)$, and a rate functional (or time “constant”) $\tau_q(V)$, whose expressions are given in (3.8) and (3.9), respectively. These functions are shown in Figure 4.3.

![Figure 4.3: Hyperpolarization-activated $h$-channel dynamics defined in (3.8) and (3.9).](image)

It is not uncommon (at least in mammals) to observe $\tau_q$ on the order of hundreds of milliseconds.\(^2\) By increasing $\tau_q$ of (3.9) by a factor of 100—which is still in the plausible physical range for $\tau_q$—and by also considering a leak current with $g_{Cl} = 1/15$ mS/cm\(^2\)

---

\(^2\)I need to find a reference to justify this claim, or I need to modify the claim itself.
(refer to sim8.m for a full specification of all the simulation parameters), we obtain a resting potential \( V_r \approx -52.2 \text{ mV} \), which leads to a time constant of \( \tau_q(V_r) \approx 212 \).

Applying a small current injection then leads to the response shown in Figure 4.4. In Figure 4.4(a) it appears as though the cable is depolarized slightly after stimulation, whereafter the membrane potential decays (monotonically!) back to rest. Figure 4.4(b) further supports this observation, where the time window of observation has been increased to 100 ms.

Figure 4.4: Very small but persistent oscillatory behavior due to large time constants. A large time constant, \( \tau_q \gg 1 \) leads to very small (essentially unobservable) oscillatory behavior which ultimately has a significant contribution to the moment computation. Here \( \tau_q \approx 210 \), \( x = 0.0495 \text{ cm} \), \( x_k = 0.0245 \text{ cm} \), and \( dt = 0.001 \).
Indeed, one might be tempted to conclude that when numerically approximating the moments, truncating the response at say 20 ms would be sufficient, since the response is “clearly” back to rest after such a time. However, upon closer inspection, Figure 4.4(c) reveals that the membrane potential does not in fact decrease monotonically back to rest, but it in fact overshoots the rest potential, and it keeps on oscillating like this for quite some time (see Figure 4.4(d) where further oscillations are visible).

The important (and somewhat unexpected) thing about this very small but persistent oscillation is that it contributes significantly to the value of the moment, so that truncating the response too early leads to large errors in the numerical moment approximations.

As a concrete example, consider the uniform quasi-active cable whose response is shown in Figure 4.4, and recall the exact quasi-active potential given in (3.30) as

\[
\tilde{V}(x, t) = \sum_{n=0}^{\infty} w_{2,n}(x) \left( K_{n,0} \exp \left( (t - t_{\text{stim}}) \zeta_{n,0} \right) + K_{n,1} \exp \left( (t - t_{\text{stim}}) \zeta_{n,1} \right) \right), \quad t > t_{\text{stim}},
\]

which is then approximated by partial sums:

\[
v(x, t, N) = \begin{cases} 
0 & t \leq t_{\text{stim}} \\
\sum_{n=0}^{N} w_{2,n}(x) \left( K_{n,0} \exp \left( (t - t_{\text{stim}}) \zeta_{n,0} \right) + K_{n,1} \exp \left( (t - t_{\text{stim}}) \zeta_{n,1} \right) \right) & t > t_{\text{stim}}
\end{cases}
\]

(4.2)

so that integration over all time leads to

\[
\int_{0}^{\infty} v(x, t, N) dt = \int_{t_{\text{stim}}}^{\infty} \sum_{n=0}^{N} w_{2,n}(x) \left( K_{n,0} \exp \left( (t - t_{\text{stim}}) \zeta_{n,0} \right) + K_{n,1} \exp \left( (t - t_{\text{stim}}) \zeta_{n,1} \right) \right) dt
\]

\[
= \sum_{n=0}^{N} w_{2,n}(x) \left( K_{n,0} \int_{t_{\text{stim}}}^{\infty} \exp \left( (t - t_{\text{stim}}) \zeta_{n,0} \right) dt + K_{n,1} \int_{t_{\text{stim}}}^{\infty} \exp \left( (t - t_{\text{stim}}) \zeta_{n,1} \right) dt \right)
\]

\[
= - \sum_{n=0}^{N} w_{2,n}(x) \left( \frac{K_{n,0}}{\zeta_{n,0}} + \frac{K_{n,1}}{\zeta_{n,1}} \right). \tag{4.3}
\]
Figure 4.5 now shows the results obtained by truncating the response after 100 ms. The “quadrature” curve corresponds to applying the trapezoidal rule to the $N$-term expansion of (4.2), whereas the “analytic” curve corresponds to the analytic integration of the $N$-term quasi-active expansion given in (4.3). Notice the discrepancy! The numerical quadrature approximation to the moment is almost double the true moment! Furthermore, the magnitude of the oscillatory tail segment is so small that it will be impossible to resolve in practice (it is on the order of several nanovolts). Besides, it is impractical to record for such a long period anyway. Instead, we may choose to record until the response appears to be back at rest, after which we can add in the contribution from the tail segment analytically from known channel dynamics.

![Figure 4.5: Overestimation of moments by quadrature applied to truncated response. Here the response was truncated after $T_{\text{fin}} = 100$ ms, with recording location $x = 0.0495$ cm, stimulus location $x_k = 0.0245$ cm, and time step $dt = 0.001$ ms.](image)

Notice also that the analytic moment approximations converge fairly rapidly to the true moment value as the number of terms, $N$, is increased.
Figure 4.6 shows the neuronal responses of three cables, each with a different time constant $\tau_q$. More specifically, the three time constants correspond to that given in (3.9), multiplied by factors of 1, 10 and 1000, respectively; and the responses in Figure 4.6 were obtained by setting $g_{Cl} = 1$ mS/cm$^2$.

![Figure 4.6: Transient neuronal responses for different time constants $\tau_q$.](image)

Notice that even though the “faster” channels (corresponding to smaller time constants) have larger overshoots than their slower counterparts, they return to rest much more rapidly—this is especially clear from Figure 4.6(b).

When $\tau_q$ is on the order of several milliseconds, truncating the neuronal response after say 40 ms seems to lead to sufficiently accurate estimates of the moments so that near-perfect recovery of the ionic conductances can be obtained (see e.g., section 4.2.1).

Indeed, Figure 4.7 shows (for a slightly different set of simulation parameters as before) the convergence to the true moment of the numerical quadrature approximations corresponding to the three time constants considered previously, with increasing truncation time $T_{\text{fin}}$. When $\tau_q \approx 5$ ms, a recording time of only 30 ms seems to be sufficient, but when $\tau_q \approx 50$ ms, even after 100 ms the moment approximation is not
sufficiently accurate. Even worse, when $\tau_q \approx 550$ ms, the moment approximation is almost three times larger than the true moment, even after 100 ms.

![Numerical quadrature approximations](image)

Figure 4.7: Numerical quadrature approximations to the true moment as a function of truncation time $T_{\text{fin}}$, for different time constants, $\tau_q$.

For the remainder of this chapter I will consider only “fast” $h$-channels with $\tau_q$ defined as in (3.9), and with response truncation at 40 ms.

### 4.2 Recovery of leak conductances in passive cables

The recovery of leak conductances for passive cables is considered here, with section 4.2.1 presenting recovery results for a uniform passive cable, and section 4.2.3 that of two nonuniform passive cables. Furthermore, section 4.2.3 illustrates how the finite-duration numerical quadrature approximation to the moments approach the true moment as the truncation (or simulation) time is increased.
4.2.1 Uniform passive cable

Note: the following results can be generated by running `sim1.m`.

Consider the simulation summarized in Listing 4.3, where the only changes from Listing 4.1 are that the $h$-channel has been removed to arrive at a purely passive cable, and that the recording location has been changed to coincide with the midpoint of the $i = 20$th compartment. That is, $x = (i - 1/2)dx = 19.5 \times dx = 0.0195\, \text{cm}$.

Listing 4.3: Uniform passive cable simulation specification.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><code>cab</code></td>
<td><code>struct('rad',1e-4,'ell',0.1,'dx',1e-3,'dt',1e-3,'Cm',0.8,'Ra',0.3)</code></td>
</tr>
<tr>
<td><code>g</code></td>
<td><code>struct('Cl',0.2,'h',0)</code></td>
</tr>
<tr>
<td><code>E</code></td>
<td><code>struct('Cl',-68,'h',-40)</code></td>
</tr>
<tr>
<td><code>I</code></td>
<td><code>'gCl*(V-VCl)'</code></td>
</tr>
<tr>
<td><code>rlocID = 20;</code></td>
<td>% record at the midpoint of the 20th compartment</td>
</tr>
<tr>
<td><code>rloc = xmid(rlocID);</code></td>
<td>% define the recording location.</td>
</tr>
<tr>
<td><code>stim.mloc = rloc;</code></td>
<td>% update recording (measurement) location</td>
</tr>
</tbody>
</table>

From the simulation parameters it follows that the cable is discretized into $N_x = 99$ compartments. The stimulus is then applied, in turn, to the midpoint of each compartment (except at the recording site), and the response is recorded at the recording location for a duration of $T_{\text{fin}} = 40\, \text{ms}$ with a time resolution of $1\, \mu\text{sec}$. The simulated response (with the stimulus fixed at $x_k = 0.0445\, \text{cm}$) is shown in Figure 4.8.

![Simulated passive cable response for a fixed stimulus location.](image)

Figure 4.8: Simulated passive cable response for a fixed stimulus location.
For each stimulus location (or equivalently, for each compartment except for the recording compartment) the neuronal response is simulated on the full space-time grid as described in section 3.3.2. However, only the trace corresponding to the recording location is stored (see again Figure 4.8, where the response on the entire space-time grid is shown, but where only the blue curve in time at the recording location will be stored). The collection of recorded traces (one for each stimulus location) then forms another surface, shown in Figure 4.9, where it should now be clear that it must not be interpreted as a neuronal response, but rather as recorded time slices for a collection of \( N_x - 1 = 98 \) neuronal responses. The \( x \)-axis is therefore the *stimulus location*.

![Figure 4.9: Collection of \( N_x - 1 = 98 \) recorded traces for a uniform passive cable.](image)

Although not strictly necessary for the recovery of leak conductances in passive cables, it might be a good idea to briefly pause on the rest potential of the passive cable, since the rest potential will play an important part in the recovery of conductances in active cables later in this chapter. Recall the passive cable equation of (3.2), which in
the absence of stimuli is simply given as

\[ C_m \frac{\partial V(x,t)}{\partial t} = G_a \frac{\partial^2 V}{\partial x^2} - g_{Cl}(x)(V - V_{Cl}), \quad \frac{\partial V}{\partial x}(0,t) = \frac{\partial V}{\partial x}(\ell,t) = 0, \quad t \geq 0, \]

from which it is easy to see that \( V = V_{Cl} \) is a solution for any \( g_{Cl}(x) \). Indeed, the steady-state current \( I^{ss}(V) = g_{Cl}(x)(V + V_{Cl}) \) is shown in Figure 4.10, from which it is clear that \( I^{ss}(V) = 0 \) only when \( V = -68 \text{ mV} \), which is exactly \( V_{Cl} \), as expected.

Figure 4.10: Rest potential and steady state current for a uniform passive cable.

Next, each recorded trace in Figure 4.9 is numerically integrated (I simply use MATLAB’s \texttt{trapz} command) to obtain the approximate moments shown in Figure 4.11. From the moments of Figure 4.11, the second spatial derivative is then determined numerically, using a simple finite difference scheme,\(^3\) and the results are presented in Figure 4.12, along with the successful recovery of the leak conductance using (3.32).

\(^3\)Using a simple finite difference scheme can be very bad e.g., whenever there is some noise in the data. I will have to consider smarter implementations or approaches in the near future.
Chapter 4  Results

Figure 4.11: Moments for a uniform passive cable, recording at $x = 0.0195$ cm.

The red crosses in Figure 4.12 correspond to the recording location. That means that a stimulus was never applied there, and hence there is no recorded data or computed moment for $x_k = x$. Note however that except for possible issues with computing the second spatial derivative, (3.32) specifies a pointwise recovery of $g_{Cl}$, so that a missing isolated data point should not matter that much.

Figure 4.12: Recovery results for uniform passive cable, recording at $x = 0.0195$ cm.
4.2.2 Nonuniform passive cable

Note: the following results can be generated by running sim2.m.

Here the simulation parameters remain unchanged from that presented in Listing 4.4, except for the leak conductance, which is made nonuniform as follows:

Listing 4.4: Nonuniform passive cable leak conductance specification.

```
g.Cl = 0.2;
g.Cl = ones(numel(xmid),1)*g.Cl;
g.Cl(20:30) = 3*g.Cl(20:30);
```

That is, the underlying leak conductance is

\[
g_{\text{Cl}}(x) = \begin{cases} 
  0.6, & 0.0195 \leq x \leq 0.0295; \\
  0.2, & \text{otherwise}.
\end{cases}
\]

The rest potential remains constant and unchanged, and the recorded responses look very similar to before, so that the only remaining interesting part of this simulation is to see if the nonuniform (discontinuous even) conductance can be recovered successfully. From Figure 4.13, it is clear that the conductance was successfully recovered.

Figure 4.13: Moments and recovery for nonuniform passive cable.
As another somewhat arbitrary example (found in sim3.m), consider the nonuniform leak conductance

\[
g_{Cl}(x) = \begin{cases} 
0.2, & 0 \leq x < 0.029 \\
0.6, & 0.029 \leq x < 0.035 \\
1, & 0.035 \leq x < 0.049 \\
2x - 0.9, & 0.049 \leq x < 0.1
\end{cases}
\]

which leads to the moments, \( M(x,x_k) \), second spatial derivative \( M''(x,x_k) \) and near-perfect recovery presented in Figure 4.14.

\[x \times 10^4\]
\[M(x,x_k) d^2M(x,x_k) dx_k^2\]
\[g_{Cl} \text{ (mS/cm}^2)\]

(a) Moments and 2nd spatial derivative. (b) Leak conductance recovery

Figure 4.14: Moments and recovery for another nonuniform passive cable.

4.2.3 Convergence of approximate moments as \( T_{\text{fin}} \to \infty \)

The recovery results presented so far seem pretty good, and these were obtained using \( T_{\text{fin}} = 40 \) ms. It was previously argued that truncating prematurely could lead to overestimates of the true moments. However, when dealing with the passive cable, overshoot and undershoot should never occur. As a consequence, the finite-duration numerical quadrature moment approximations (henceforth denoted by \( \hat{M}(x,x_k) \)) will
always underestimate the true moments. This is illustrated in Figure 4.15, which shows \( \hat{M}(x, x_k) \) as a function of the truncation time, \( T_{\text{fin}} \). Notice further that the moment approximations increase monotonically as \( T_{\text{fin}} \) is increased, and that after 40 ms the difference between the true and approximate moments is small (see Figure 4.16).
4.3 Recovery of conductances in active cables

The task of recovering the hyperpolarization-activated $h$-channel conductances, $g_h(x)$, in active cables is considered here. However, it will be assumed throughout that the leak conductances $g_{Cl}(x)$ are known, since experimentally these would be determined before proceeding to the recovery of $g_h(x)$.

The recovery of $g_h(x)$ is first considered for a uniform active cable (section 4.3.1), followed by a nonuniform active cable (section 4.3.2). Finally, it is shown that the solution to the BVP of (3.43) is not unique (section 4.3.3) which means that, at least for now, $g_h(x)$ cannot always be recovered uniquely.

4.3.1 Uniform active cable

Note: the following results can be generated by running sim4.m.

Consider the simulation summarized in Listing 4.5, where the $h$-channel has been added to the passive cables considered previously, and where the recording location has been set to coincide with the midpoint of the 1st compartment. That is, $x = 0.0005$ cm.

Listing 4.5: Uniform active cable simulation specification.

```matlab
cab = struct('rad',1e-4,'ell',0.1,'dx',1e-3,'dt',1e-3,'Cm',0.8,'Ra',0.3)
g = struct('Cl',0.15,'h',1.5)
E = struct('Cl',-68,'h',-40)
I = 'gCl*(V-VCl) + gh*q*(V-Vh)'
rlocID = 1; % record at the midpoint of the 1st compartment
rloc = xmid(rlocID); % define the recording location.
stim.mloc = rloc; % update recording (measurement) location
```

Note that with constant conductances as specified in Listing 4.5, the rest potential for the active cable of (3.7) is also expected to be constant. And indeed, from Figure 4.17 it can be seen that the rest potential for this particular set of simulation parameters is about -54 mV.
The recorded traces for the uniform active cable are shown in Figure 4.18(a), but the recovery results are not shown, since the constant conductance case is rather uninteresting. Suffice it to say that for this example, recovery was near-perfect as with the passive cable examples considered earlier.

(a) Constant conductances for active cable.  (b) Constant rest potential for active cable.

Figure 4.17: Left: constant conductances, right: $I^{ss}$ to determine $V_r$.

(a) Quasi-active neuronal recordings.  (b) Moments for uniform active cable.

Figure 4.18: Neuronal response recordings and associated moments for a uniform quasi-active cable.
4.3.2 Nonuniform active cable

Note: the following results can be generated by running \texttt{sim5.m}.

Consider the nonuniform quasi-active cable specified by Listing 4.5 in addition to the nonuniform conductances defined in Listing 4.6. In particular, \( g_{Cl}(x) = 0.3 \) is constant, but now \( g_h(x) \) is defined by

\[
g_h(x) = \begin{cases} 
0.2 + 14x, & 0.03 \leq x \leq 0.04 \\
0.1 + 0.7x, & \text{otherwise}
\end{cases}
\]

Listing 4.6: Nonuniform active cable conductance specification.

```matlab
% define uniform conductances:
g.C1 = linspace(0,0.3,numel(xmid)); g.C1 = g.C1(:);
g.h = linspace(0.1,0.8,numel(xmid)); g.h = g.h(:);
g.h(30:40) = 2*g.h(30:40);
```

The spatial variation of \( g_h \) causes the rest potential to be spatially varying too, as shown in Figure 4.19(a), while Figure 4.19(b) shows that this is indeed a resting state.

![Figure 4.19: Rest potential for nonuniform active cable.](image)

(a) Spatially-varying rest potential. (b) Balance of ion currents and diffusion term.
The conductances and the resulting moments are shown in Figure 4.20, which we use to compute the pointwise estimates of \( F(x; k) \), given in (3.40), and these are shown in Figure 4.21.

(a) Spatially-varying conductances.  (b) Moments for nonuniform quasi-active cable.

Figure 4.20: Conductances and moments for nonuniform quasi-active cable.

The pointwise estimates to \( F(x; k) \) are then approximated either by piecewise linear interpolants, splines, or something similar, because the solution to the BVP assumes knowledge of \( F(x; k) \) at all \( x \in [0, 1] \), and not only at a number of discrete points. The same is true for \( g_{\text{Cl}} \), which is assumed to be fully known.
The continuous approximations to \( g_{\text{Cl}}(x) \) and \( F(x; k) \) are then used, along with knowledge of \( q_\infty(V) \) and \( q'_\infty(V) \) to solve (3.43) for the rest potential, \( V_r \).

Figure 4.22: Solution from BVP. Left: rest potential. Right: conductance recovery

Figure 4.22(a) shows the successful recovery of the rest potential by solving the BVP, with the resulting near-perfect \( h \)-channel conductance recovery shown in Figure 4.22(b). Unfortunately things don’t always work as smoothly, as the next section will show.

### 4.3.3 Non-uniqueness of solutions to the BVP

\[ \text{Note: the following results can be generated by running } \text{sim6.m.} \]

Unfortunately the solution to the BVP given in (3.43) is not guaranteed to be unique, and moreover, it is not even clear whether a solution necessarily always exists. Consequently the rest potential \( V_r \) cannot not be uniquely recovered, which in turn means that \( g_h \) also cannot be uniquely recovered. At least not without some additional constraints or clever workaround.

Indeed, to demonstrate the non-uniqueness of the solution to the BVP, consider the
cable described in Listing 4.5, with nonuniform conductances as given in Listing 4.7, as shown in Figure 4.23(a). Note that $g_h$ is much larger than before, and it is also much larger than $g_{Cl}$.

Listing 4.7: Nonuniform active cable conductance specification.

```matlab
% define uniform conductances:
g.Cl = linspace(0.1,0.5,numel(xmid)).^2; g.Cl = g.Cl(:);
g.h = linspace(0.1,3,numel(xmid)).^2; g.h = g.h(:);
```

For this set of conductances, the rest potential that is obtained from solving the BVP is shown in Figure 4.23(b), which almost looks like a simple translation of the true rest potential. To convince yourself that the incorrect rest potential is in fact a solution to the BVP, consider the results presented in Figure 4.24. In particular, Figure 4.24(a) shows the Right Hand Side (RHS) and Left Hand Side (LHS) of (3.43) for the true rest potential, from which it is clear that the BVP is satisfied at least on the interior of the domain (we can easily show that the Neumann boundary conditions are satisfied too). However, the incorrect rest potential also satisfies the BVP on the interior of the domain, as can easily be seen from Figure 4.23(b).
The resulting moments and conductance recovery are shown in Figure 4.25, from which it is clear the conductance recovery failed dramatically. Not only is the recovered conductance much larger in magnitude, but it is also negative! The fact that it failed in such a dramatic manner is perhaps a good thing, since it will make it easier to discard incorrect or nonphysical solutions. However, at this stage the diversity of possible solutions is poorly understood, and smarter ways to deal with the non-uniqueness will have to be sought.
The method of moments was successfully applied to the task of recovering spatially-varying ionic conductances in a simplified model of the LGMD neuron. In particular the method was demonstrated to work very well for passive cables, and to work well for quasi-active cables with hyperpolarization-activated $h$-channels, as long as the $h$ conductances are sufficiently small.

Unfortunately the method relies on the solution to a particular BVP whose solution is not guaranteed to be unique. Future work will include finding a way to constrain the solution of this BVP to the physical solution, as well as the extension of the simplified straight cable model to more realistic neuronal geometries.

The effects of adding recording noise to the system should also be investigated, and improvements will be made to the current naïve finite difference implementation of numerical differentiation.


dendrites from single and dual potential recordings. Mathematical biosciences,
190(1):9–37. (Cited on page 12.)

membrane parameters: comparison of optimization and peeling methods. IEEE
transactions on biomedical engineering, 33(12):1188–96. (Cited on page 11.)

for the analysis of neuron passive electrical data which uses integrals of voltage

technology books. Elsevier Science. (Cited on pages 20, 21, 22, 24, 25, 27 and 37.)

by a wide-field, motion-sensitive neuron. The Journal of neuroscience : the official
journal of the Society for Neuroscience, 19(3):1122–41. (Cited on page 7.)


Izhikevich, E. M. (2007). Dynamical systems in neuroscience: the geometry of ex-
citability and bursting. The MIT press. (Cited on pages 8 and 16.)


**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVP</td>
<td>Boundary Value Problem</td>
</tr>
<tr>
<td>DCMD</td>
<td>Descending Contralateral Movement Detector</td>
</tr>
<tr>
<td>LGMD</td>
<td>Lobula Giant Movement Detector</td>
</tr>
<tr>
<td>LHS</td>
<td>Left Hand Side</td>
</tr>
<tr>
<td>PDE</td>
<td>Partial Differential Equation</td>
</tr>
<tr>
<td>RHS</td>
<td>Right Hand Side</td>
</tr>
<tr>
<td>SIZ</td>
<td>Spike Initiation Zone</td>
</tr>
</tbody>
</table>