INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.
The Inverse Problem of Neuron Identification

by

Lin Ji

A Thesis Submitted
in Partial Fulfillment of the
Requirements for the Degree
Doctor of Philosophy

APPROVED, THESIS COMMITTEE:

Steven J. Cox, Professor, Chairman
Computational and Applied Mathematics

William Symes, Professor
Computational and Applied Mathematics

Liliana Borcea, Assistant Professor
Computational and Applied Mathematics

Robert Hardt, Professor
Mathematics

Houston, Texas
April, 2000
Dedicated to my wife, Ye Ying,
for
her forever love and support.
Abstract

The Inverse Problem of Neuron Identification

by

Lin Ji

Depending on the state of neuron membrane, the inverse problem of neuron identification is divided into two categories: the passive neuron identification and the active neuron identification. In the first category, we provided a more efficient way to recover neuron parameters than the traditional approach. By exploring the impedance function meticulously, our method reveals a clean and analytical relation between the electrical properties of neurons and their response to sub-threshold current stimulation.

Mathematical equations like the Hodgkin-Huxley equations and the Fitzhugh-Nagumo equations that model active neurons have been established for many years. However, the inverse problem in this category has barely started. Our research in this direction attempts to establish a proper formulation of the inverse problem and to investigate possible mathematical techniques that are needed to solve it. For the relatively simple Fitzhugh-Nagumo equations, we successfully reconstructed the nonlinear membrane conductance function and the coefficients of the recovering variable. The method is then extended to a more realistic neuron model, the Morris-Lecar model. We provide a computational strategy for systematically recovering the nonlinearity of both the calcium and the potassium channels.
Acknowledgments

I am so glad to have this opportunity to thank so many people who helped me in this way or another to accomplish my thesis work.

I first thank my advisor, Steve Cox, not only for those great advice which I believe will benefit the rest of my research career but also for his understanding and trust in my hard time. I cannot tell how important his encouragement is to the success of my thesis research but I know in my heart it is the source of my inspiration and my power. Thanks again, Dr. Cox, for being my advisor.

I wish to thank William Symes and Dan Sorensen for the wonderful classes I took from them. The knowledge and especially the way of thinking I learned from these classes constitutes the solid foundation for my research. I am also thankful and proud for their appreciation of my talent and my work.

I would also like Liliana Borcea and Robert Hardt to accept my thanks for their time being my thesis committee members. Life is beautiful because of their kindness and their always active cooperation.

I thank Genetha Gray who checked my English writing in such a detail that I was really impressed. I hope you understand what it means to an international student.

Finally, special thanks go from my heart to Michael Pearlman who, as our department computer system administrator, solved so many technical problems I encountered in my computation and in my thesis writing, to Daria Lawrence who did such wonderful secretary work to keep us aware of various deadline and to put the appropriate paper-work in our mailboxes always on time.
Contents

Abstract iii
Acknowledgments iv
List of Tables vii
List of Illustrations viii

1 Introduction 1

2 Passive Neuron Identification 13
  2.1 Literature Review 13
  2.2 The Single Compartment Case 19
  2.3 The Distributed Case 25
  2.4 Stability with $1.5 < L < 3.0$ 39
  2.5 A Comparison with the Constrained Inverse Algorithm of Holmes and Rall 43
  2.6 The Transfer Function Approach 47

3 Active Neuron Identification 52
  3.1 Literature Review 52
  3.2 The Fitzhugh-Nagumo System 63
  3.3 The Morris-Lecar Model 82
    3.3.1 Calcium channel identification 85
    3.3.2 Potassium channel identification 90

4 Future Directions 110
Bibliography
Tables

3.1 An example set of parameter values for Morris-Lecar Model . . . . . 87
Illustrations

1.1 The voltage response of neurons to sub-threshold (Left) and sup-threshold (Right) current stimulation. Notice the difference in the magnitude of response. ...................................................... 2

1.2 A schematic representation of a typical neuron and the series of $RCG$ circuits that models it. We ignore the dendrites and the telodendria in the model. ................................................................. 3

1.3 Electrical circuit that models a small patch of excited nerve membrane. . . 7

1.4 A typical action potential (Up, $mv$) and the time course of membrane conductance (Down, $mS/cm^2$) to sodium ($g_{Na}$) and potassium ($g_K$) respectively. The resting state membrane potential is adjusted to be zero. 8

1.5 The function $f(v)$ which is used in Fitzhugh-Nagumo’s equations to describe the ionic current flow across the membrane. ................................. 11

2.1 A simple circuit with only one $RCG$ compartment of unit length. ...... 20

2.2 The graph of the function $F$ defined by (2.30). Notice the narrow function value range and the part of curve with relatively steep slope. ............... 30

2.3 Graph of the functions $f_0(L)$ (Up) and $f_1(L)$ (Down). ..................... 36

2.4 Graph of the functions: (a) $\frac{F'(L)}{F_C(L)}$; (b) $\frac{F''(L)}{F_C(L)}$; (c) $\frac{F_C(L)}{F_C(L)}$ and (d) $\frac{F_C(L)}{F_C(L)}$. .... 37

2.5 Graph of the function $F'(L)$. ......................................................... 38

2.6 Relative error in the recovered parameters $R$, $C$, $G$, $C_s$, $G_s$ and $L$. 41
2.7 The input current, $i_0(t)$, and the voltage response, $v_0(t)$, in together with the estimated error in the original response data (solid line) and in the recovered response (dash-dot line) computed with the recovered parameter values. The error in the original data is introduced by forwardly solving (2.19) for various $dt$. ........................................ 42

2.8 Relative error in the recovered parameters $R_{md}, R_{ms}, C_m$ and $A_s$. $A_D$ is supposed to be known. .................................................. 43

2.9 The function $F_\sigma(L)$ defined by (2.51) with $\sigma = A_s/A_D = 0.01, 0.1, 0.2$ and 0.5. The shapes of these curves imply it is stable to solve (2.50) for $L$ in most situation. .................................................. 45

2.10 Relative error in the recovered parameters $R_{md}, R_{ms}, C_m$ and $L$ when $A_s$ and $A_D$ are known. Solid line represents our results and star is for Holmes and Rall's. .................................................. 47

2.11 The input current, $i_0(t)$, and the voltage response, $v_0(t)$, in together with the estimated error in the original response data (solid line) and in the recovered response (dash-dot line) computed with recovered parameter values for various $dt$. ........................................ 48

2.12 The function $f_u(L, \rho) \equiv \frac{\cosh(L)}{\cosh((1-\rho)L)}$ for $\rho = 0.2, 0.5, 0.8, 1.0$. ........................................... 49

2.13 Relative error in the recovered parameters $R, C, G, C_s, G_s$ and $L$ when the voltage responses, $v_0(t)$ and $v(X, t)$ at $X = \frac{4}{15} L$, are both known. . . . 50
3.1 A schematic diagram of the two-wire voltage-clamp experiments on the squid axon. One wire is used for monitoring the membrane potential and the other for passing current. The voltage clamp amplifier injects or withdraws charges from the interior of the squid axon in order to hold the membrane voltage constant. Voltage is clamped at the command voltage, $V_C$. Reproduced from Figure 6.1 in [36].

3.2 Currents measured with voltage clamp of squid axon. Membrane potential was held at $-60\ mV$ and then stepped (at $0\ msec$) to various potentials (shown at the right of each trace) for $8\ msec$ before stepping back to $-60\ mV$. Reproduced from Figure 6.2 in [36].

3.3 Separation of membrane current (solid trace) into $N_a^+$ (dashed trace) and $K^+$ (dotted trace) currents. $I_K$ is obtained in the presence of TTX or when $[N_a^+]_{out} = 0$; $I_{Na}$ is obtained in the presence of TEA. The voltage is stepped from $-60\ mV$ to $0\ mV$ for $8\ msec$. Reproduced from Figure 6.4 in [36].

3.4 Time course of $g_K$ (dashed traces) and $g_{Na}$ (solid traces) at various voltages ($V_C$) obtained from $I_K$ and $I_{Na}$ traces, according to Ohm’s law. Reproduced from Figure 6.7 in [36].

3.5 Unitary currents (upper 8 traces) and the ensemble average of unitary currents (lowest trace) of a $N_a^+$ (A) and $K^+$ (B) channel. The membrane voltage is stepped from $V_H = -80\ mV$ to $V_C = -30\ mV$ for (A) and from $V_H = -100\ mV$ to $0\ mV$ for (B). Compare it to Fig. 3.3 and Fig. 3.4 (Left). Reproduced from Figure 8.5 in [36].

3.6 The recovered parameter values for $b$ and $\gamma$ from (3.35) as a function of $s$. I, II, III and IV correspond the voltage response data I, II, III and IV in Fig. 3.7 respectively.
3.7 The voltage response, $v_0(t)$, of the FitzHugh-Nagumo system to input current, $i_0(t) = -0.008 \left[ \sin\left(\frac{t}{8} - \frac{\pi}{2}\right) + 1 \right]$. Computed with various step size.
I: $dx = 0.025$; II: $dx = 0.1$; III: $dx = 0.2$ and IV: $dx = 0.5$.

3.8 The first derivative of the parameters $b$ (Left) and $\gamma$ (Right) as a function of $s$. Computed by finite difference.

3.9 Relative error in the parameters $b$ and $\gamma$ that are recovered from noisy voltage responses. The error in the voltage response is introduced by varying the spatial step size $dx (= 0.025, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.5)$ in the forward solver.

3.10 The voltage response of the FitzHugh-Nagumo system to input current,

$$i_0(t) = 0.1\left[ \sin\left(\frac{t}{8} - \frac{\pi}{2}\right) + 1 \right].$$

3.11 The voltage response of the FitzHugh-Nagumo system to input current,

$$i_0(t) = -0.22\left[ \sin\left(\frac{t}{8} - \frac{\pi}{2}\right) + 1 \right].$$

3.12 The iterative sequence of functions, $\{\Pi[f_n]\}$ for recovering $f(v) = v(v - 0.2)(1 - v)$ where $\Pi$ is defined by (3.37). Shown are functions recovered after 1, 3, 6 and 10 iterations.

3.13 Error in the recovered $f$ (computed by (3.42)) as a function of error in the voltage response data (computed by (3.41)). The error in the voltage response data is introduced by varying the spatial step size, $dx$, in the forward solver.

3.14 The input current, $i_0(t) = 0.1\left[ \sin\left(\frac{t}{8} - \frac{\pi}{2}\right) + 1 \right]$, and the voltage response, $v_0(t)$. I: computed with $dx = 0.05$ (exact data); II: computed with $dx = 0.4$.

3.15 The recovered function $f$ (-x-x-line) by using the voltage response data II shown in Fig. 3.14.

3.16 Error in the recovered parameters $b$ and $\gamma$ by algorithm 2. The exact values are $b = 0.006$ and $\gamma = 0$. The function $f = v(v - 0.2)(1 - v)$.
3.17 The recovered function $f$ by using inexact parameters $b = 0.007$ (exact value: 0.006) and $\gamma = 0.0006$ (exact value: 0).

3.18 The voltage response, $v_0(t)$, of the Morris-Lecar system (3.44) to input current $i_0(t) = 6[\sin\left(\frac{t}{2} - \frac{x}{2}\right) + 1]$. I: computed with $dx = 0.05$ (considered exact data); II: computed with $dx = 0.075$.

3.19 The iterative sequence for recovering the function, $f$, as defined in (3.52). The exact voltage response (I) shown in Fig. 3.18 is employed in the computation.

3.20 The recovered $m_\infty$ function as defined by (3.46). I: recovered from the exact data shown in Fig. 3.18; II: recovered from the inexact data shown in Fig. 3.18.

3.21 The recovered $f$ function as defined by (3.52). I: recovered from the exact data shown in Fig. 3.18; II: recovered from the inexact data shown in Fig. 3.18.

3.22 Relative error in the recovered parameters $G_{Ca}$, $E_{Ca}$, $E_1$ and $E_2$ by least-square fitting (3.52) to the limit function of the iterations (Ref. Fig. 3.19). The exact values of these parameters are: $G_{Ca} = 1.1 \text{ mS/cm}^2$, $E_{Ca} = 100 \text{ mV}$, $E_1 = -1 \text{ mV}$ and $E_2 = 15 \text{ mV}$. The corresponding error in the voltage response data, $v_0(t)$, are shown in Fig. 3.23. The sign of error indicates over-estimating (+) or under-estimating (-).

3.23 The error in the voltage response data, $v_0(t)$, produced by varying the spatial step size $dx (= 0.025, 0.05, 0.075, 0.1)$ in the forward solver. The response data computed with $dx = 0.05$ is considered exact. The sign of error indicates over-shooting (+) or under-shooting (-) the exact response.
3.24 The function $v'_0(t) - v^{(n)}_t(0,t)$ computed by finite difference and cubic-spline technique where $v_0(t)$ is the "exact" response data we record in the beginning and $v^{(n)}_t(0,t)$ is the intermediate response data shown in Fig. 3.26. It is computed during the iterations. I: $n = 5$; II: $n = 20$; III: $n = 25$. .......................... 95

3.25 The iterative sequence \{u^{(n+1)} \equiv \Pi[u^{(n)}_\infty]\} where $\Pi$ is defined by (3.61)-(3.62). The derivatives involved in (3.61)-(3.62) are computed by finite difference. Compare it to Fig. 3.27. .......................... 95

3.26 The voltage response of the Morris-Lecar system (3.59)-(3.60) with $C_{a^+}$ removed or $C_{a^{++}}$ channel blocked. Shown are the responses of the system in which the $u_\infty$ function is recovered after I: 5; II: 20 and III: 25 iterations respectively. .......................... 96

3.27 The iterative sequence \{u^{(n+1)} \equiv \Pi[u^{(n)}_\infty]\} where the derivative involved is computed by cubic-spline technique in this case. Compare it to Fig. 3.25. .......................... 96

3.28 The recovered parameters $G_K$, $E_3$ and $E_4$ by least-square fitting

$$u_\infty(v) = \frac{1}{2} G_K \left[ 1 + \tanh\left( \frac{v-E_3}{E_4} \right) \right]$$

to the limit of the sequence \{u^{(n+1)}_{\infty} \equiv \Pi[u^{(n)}_\infty]\}. Shown are the relative error in $G_K$ and $E_4$ and the recovered value of $E_3$. The exact value for each parameter is:

$G_K = 2.0 \text{ mS/cm}^2$, $E_3 = 0 \text{ mv}$ and $E_4 = 30 \text{ mv}$. The corresponding error in the voltage response data is introduced by varying the spatial step size, $dx$ ($= 0.025, 0.05, 0.075, 0.1$). The response data computed with $dx = 0.05$ is considered the virtually exact data and the sign of error indicates over-estimating (+) or under-estimating (-). .......................... 98
3.29 The input current, \( i_0(t) = 10[\sin(\frac{t}{2} - \frac{\pi}{2}) + 1] \), and the voltage response, \( v_0(t) \), for recovering the time constant function \( \tau_w \) in the \( C_a^{++} \) free system (3.59)-(3.60). Notice the duration of the input current (12 ms) and compare it to Fig. 3.33.  

3.30 The iterative sequence for recovering \( \tau_w \). Left: no initial time period is ignored in the computation of the map (3.64); Right: some initial time period is ignored due to singularity at \( t = 0 \). The function value over that time period is obtained by extrapolation.

3.31 The iterative sequence of functions for recovering \( \tau_w \): the initial A. 1.3 ms; B. 2.2 ms and C. 3.0 ms are ignored. The duration of the input current is 12 ms (Ref. Fig. 3.29 and Fig. 3.32). The voltage response data, \( v_0(t) \), is computed with \( dx = 0.025 \) and is considered inexact in this case.

3.32 I: the intermediate function \( \bar{u}(t) \) as defined by (3.61) and II: the derivative of \( \bar{u}(t) \). It can be used to monitor the choice of time period ignored initially to avoid singularity at \( t = 0 \) in the map (3.64) (Ref. Fig. 3.31).

3.33 The input current, \( i_0(t) = 15[\sin(\frac{t}{10} - \frac{\pi}{2}) + 1] \), and the voltage response, \( v_0(t) \), for recovering \( \tau_w \). Notice the duration of the current (65 ms) and compare it to Fig. 3.29.

3.34 The recovered \( \tau_w(v) \) after 25 iterations. The voltage response data, \( v_0(t) \), shown in Fig. 3.33 is used for the reconstruction. Compare it to Fig. 3.30.

3.35 Relative error in the recovered parameters \( \Lambda_w \) and \( E_4 \). \( E_3 \) is shown directly by its recovered values. The exact values of the three parameters are \( \Lambda_w = 0.2 \text{ ms}^{-1} \), \( E_3 = 0 \text{ mv} \) and \( E_4 = 30 \text{ mv} \). The sign of the error indicates over-estimating (+) or under-estimating (-).
3.36 The three input currents and their corresponding voltage responses for recovering both $u_\infty$ and $\tau_w$. I: $i_0(t) = 16[\sin\left(\frac{t}{10} - \frac{\tau}{2}\right) + 1]$; II: $i_0(t) = 16[\sin\left(\frac{t}{5} - \frac{\tau}{2}\right) + 1]$ and III: $i_0(t) = 16[\sin\left(\frac{t}{5} - \frac{\tau}{2}\right) + 1]$. The voltage responses are computed with $dx = 0.05$ and is considered exact. Notice the duration of the input currents (about $40 ms$) and compare it to Fig. 3.38.

3.37 The recovered $u_\infty$ and $\tau_w$ after one iteration of the map (3.67). The big oscillation in $\tau_w$ indicates the computational error caused by the inappropriate choice of input currents in Fig. 3.36. Compare it to Fig. 3.39.

3.38 The three input currents and their corresponding voltage responses for recovering both $u_\infty$ and $\tau_w$. I: $i_0(t) = 16[\sin\left(\frac{t}{30} - \frac{\tau}{2}\right) + 1]$; II: $i_0(t) = 16[\sin\left(\frac{t}{30} - \frac{\tau}{2}\right) + 1]$ and III: $i_0(t) = 16[\sin\left(\frac{t}{30} - \frac{\tau}{2}\right) + 1]$. The solid-line curve represents the exact voltage response computed with $dx = 0.05$ while the dash-dot-line curve represents the inexact voltage response computed with $dx = 0.075$. Notice that the duration of the input currents in this case is about $200 ms$ which is much longer than that in Fig. 3.36.

3.39 The iterative sequence as defined by the map (3.67) for recovering both $u_\infty$ and $\tau_w$. It is computed by using the exact voltage response data shown in Fig. 3.38. Compare it to Fig. 3.37.

3.40 The iterative sequence as defined by the map (3.67) for recovering both $u_\infty$ and $\tau_w$. The voltage response data in this case is computed with $dx = 0.075$ and is inexact.

3.11 Relative error in the parameters $G_K$, $\Lambda_w$ and $E_4$ that are recovered from noisy voltage responses. $E_3$ is shown by its recovered value. The exact values for these parameters are $G_K = 2.0 mS/cm^2$, $\Lambda_w = 0.2 msec^{-1}$, $E_3 = 0 mv$ and $E_4 = 30 mv$. The error in the voltage response data is introduced by varying the spatial step size, $dx$, in the forward solver.
Chapter 1

Introduction

The classical neuron identification problem is to find the so-called electrical cell constants, the best known of which are the membrane resistivity ($R_m$, expressed in $\Omega cm^2$), the membrane capacity ($C_m$, expressed in $\mu F/cm^2$), and the resistivity of the axoplasm ($R_a$, expressed in $\Omega cm$). Unfortunately, a direct measurement of these cell constants is generally not possible. Therefore we look to the indirect impedance measurements which has become a standard practice in bioengineering literature ([61], [19], [20]) since World War II. In the context of our paper, it is to measure the soma membrane potential, $v_0(t)$ (evaluated as intra-cellular potential minus extracellular potential), after injecting a small current, $i_0(t)$, into the soma (cell body). Such experiment was made possible as early as in 1950s with the invention of the glass micro-electrode.

In this paper, we will call the recorded data, $i_0(t)$ and $v_0(t)$ the impedance data. We hope that some neuron properties like the above three cell constants can be recovered by decoding the impedance data. To achieve this goal, however we must first understand how neurons respond to stimulation.

We will first focus on the behavior of neurons in passive mode by which we mean the stimulation is not strong enough (at sub-threshold level) to cause an energy-lossless propagated voltage pulse (see Fig. 1.1). The reason is two-fold. First, passive mode voltage response has already contained much information in order to determine the electrotonic parameters of a neuron. Second, in passive mode, the conductance of the membrane of nerve fiber can be considered constant (does not change with time and voltage). This assumption of constant conductance will give us a linear diffusion
equation which is relatively easy to analyze. In fact, neuron identification research in the past 40 years was almost all limited to neurons in this mode.

If we further assume axial symmetry of the nerve fiber and zero potential of the extracellular medium, a single axon with soma lumped in can be modeled in passive mode by the one dimensional electrical circuit depicted in Fig. 1.2 where \( R(x) \) is the axoplasmic resistance per unit length (\( \Omega/cm \)), \( C(x) \) is the membrane capacitance of nerve fiber per unit length (\( \mu F/cm \)) and \( G(x) \) is the membrane conductance of nerve fiber per unit length (\( 1/k \Omega cm \)). By Ohm’s law and Kirchoff’s law, the membrane potential, \( v \), defined by intra-cellular potential minus extra-cellular potential and the longitudinal current, \( i \), flowing along the axis satisfy

\[
i(x,t) = - \frac{1}{R \delta x} (v(x + \delta x, t) - v(x, t)) \quad (1.1)
\]

\[
i(x, t) - i(x + \delta x, t) = C \delta x \frac{\partial v}{\partial t} (x + \delta x, t) + v(x + \delta x, t) G \delta x \quad (1.2)
\]
Figure 1.2. A schematic representation of a typical neuron and the series of RCG circuits that models it. We ignore the dendrites and the telodendria in the model.

where $\delta x$ is the length of a small segment of axon.

Letting $\delta x \to 0$, we arrive at what we called the cable equation

$$v_x(x, t) = -Ri(x, t) \quad 0 < x < \ell, \quad t > 0 \quad (1.3)$$

$$i_x(x, t) = -Cv_t(x, t) - Gv(x, t)$$

or in terms of $v(x, t)$ only

$$Cv_t(x, t) = \left(\frac{1}{R}v_x\right)_x(x, t) - Gv(x, t) \quad 0 < x < \ell, \quad t > 0 \quad (1.4)$$

where $\ell$ is the length of the axon. In relating to those electrotic parameters $R_m$, $C_m$ and $R_a$ we defined in the beginning, we have

$$R = \frac{4R_a}{\pi d^2}, \quad C = C_m\pi d \quad \text{and} \quad G = \frac{\pi d}{R_m} \quad (1.5)$$
where $d$ is the diameter (cm) of the nerve fiber. By injecting current into the soma and assuming the other end of the axon is sealed (no longitudinal current flow), we are interested in the following initial and boundary condition:

\begin{align}
v(x, 0) &= 0 \quad (1.6) \\
v_x(0, t) &= -Ri_0(t) + RC_s \nu_t(0, t) + RG_s \nu(0, t) \quad (1.7) \\
v_x(\ell, t) &= 0 \quad (1.8)
\end{align}

where $C_s$ is the soma membrane capacitance ($\mu F$) and $G_s$ is the soma membrane conductance ($1/k\Omega$). In this paper, we will call the quintuple, \{R, C, G, C_s, G_s\} our cable parameters.

Eqn. (1.4) with initial and boundary conditions (1.6)-(1.8) is called the somatic shunt model of the passive neuron. The meaning of somatic shunt will become clear later as we discuss this model. With the impedance data recorded at the soma, the passive neuron identification problem we will study in this paper is then to determine $R$, $C$, $G$, $C_s$ and $G_s$ by analyzing $\nu(0, t) = \nu_0(t)$ and $i_0(t)$.

When the stimulation exceeds the threshold value, the situation becomes quite complicated. In this case, not only can we observe a dramatic increase in the magnitude of the voltage response but the created voltage pulse is propagated down the axon without losing energy (see Fig. 1.1). This is a remarkable nonlinear phenomena. The theory that can explain it was set up in 1950s by the physiologists, Hodgkin, Huxley and Katz. According to their theory, the conductance of neuron membrane in active mode is not static any more. Rather, it depends on the membrane potential, $v$, and is a function of time during the action potential period. Further more, we can not even express the current that flows across the membrane simply as $I = Gv$ in the traditional sense where $G$ is alway nonnegative. The current flow should now be viewed as a mixture of various charged ion species. And the driving force for the
current does not only come from the membrane potential, but it also comes from the concentration gradient of those ion species. To measure the electrical force caused by a concentration gradient, the Nernst equilibrium potential is used. If we suppose \([ion]_o\) and \([ion]_i\) are the concentrations of some ion species outside and inside the nerve cell respectively, the Nernst potential is calculated by

\[
E_{ion} = \frac{RT}{FZ_{ion}} \ln \frac{[ion]_o}{[ion]_i}
\]  

(1.9)

where the sign of \(E_{ion}\) is defined in the sense internal potential minus external potential, \(R\) denotes the gas constant (1.987 cal/mol·°K) here, \(T\) the absolute temperature (°K), \(F\) the Faraday constant (9.648 \times 10^4 sec·A/mol) and \(Z_{ion}\) the valence of the ion.

Two ion species are considered to be of the most importance to the generation and propagation of the nerve impulse. They are the sodium ion (\(N_a^+\)) and the potassium ion (\(K^+\)). The concentration of potassium ions in the intracellular fluid of nerve cells is much higher than in the extracellular environment. And for sodium, the situation is just reversed. The typical value of the Nernst potential is about \(-75mV\) for potassium and \(+55mV\) for sodium as calculated by (1.9) in normal condition.

Based on their experiments, one important observation by Hodgkin and Huxley is that the permeability of neuron membrane to different ion species demonstrates different dynamic behavior during the activity. In fact, it was suggested that there are various kinds of ion channels embedded in the neuron membrane. Each of these ion channels can only allow a specific ion species to pass through. If we denote \(g_{N_a}\) as the membrane conductance to \(N_a^+\) and \(g_K\) as the membrane conductance to \(K^+\), the ionic current that flows across the membrane can now be written as

\[
I = g_{N_a}(x,t,v)(v - E_{N_a}) + g_K(x,t,v)(v - E_K) + I_L
\]
where \( E_{Na} \) and \( E_K \) represent the Nernst potential for sodium and potassium respectively and \( I_L \) accounts for any leakage current caused by ions passing through channels which do not change during activity. If we denote \( G_L \) as the leakage conductance and \( E_L \) the corresponding equilibrium potential, \( I_L \) would be a linear function in \( v \)

\[
I_L = G_L(v - E_L)
\]

Usually, \( I_L \) is small and can be disregarded in a preliminary description.

With these concepts in mind, we can model a small patch of neuron membrane by the electrical circuit depicted in Fig. 1.3. and put them in series to model the entire axon. Now we can explain how an action potential is generated and propagated along the axon based on the Hodgkin-Huxley theory.

At resting state, membrane potentials of about \(-70mV\) have been observed in intact squid axons with natural circulation. Since \( E_{Na} = 55mV \) and \( E_K = -75mV \), \( Na^+ \) has the tendency to move into the cell while \( K^+ \) has the tendency to move out of the cell. However, at resting state, both the sodium conductance and the potassium conductance are almost zero and a balance is kept between the ions that move in and the ions that move out. The peace is destroyed, however, when the soma is stimulated so that the membrane potential increases above the threshold level (a typical value is \(-55mV\)). When this happens, there will be a dramatic increase in the permeability of sodium channel while the response of potassium channel is somehow slower. The result is an influx of sodium ions which shoots the voltage towards the sodium equilibrium potential \( E_{Na}(+55mV) \). The membrane potential, however, can never reach \( E_{Na} \) because of the inactivation of sodium channel at a high voltage and the delayed wake up of potassium channel. The decrease of \( Na^+ \) influx and the increase of \( K^+ \) efflux will eventually bring down the voltage to resting state. In Fig. 1.4, we draw out the curve of a typical action potential and the time course of \( g_{Na} \) and \( g_K \).
Figure 1.3 Electrical circuit that models a small patch of excited nerve membrane.

When an action potential is fired at one point of the nerve fiber, it will also raise the membrane potential of neighboring nerve fiber segments through the axial current flowing along the axon and cause a cascading firing of voltage pulse all the way down to the end of the nerve fiber. The energy will never decay during the entire course of propagation because of the continuous energy supplement brought in by inward $Na^+$ current.

To quantitatively describe how the membrane conductance changes, however, is not so easy because of the tiny size of nerve fibers (0.1$\mu$m to 100$\mu$m in diameter). In Hodgkin and Huxley’s research, they chose the giant squid axon (500$\mu$m in diameter) as their target. By applying techniques such as space clamping, voltage clamping and introducing certain chemical agents to block a specific ion channel ([28], Vol.2 of [66] and [3]), they collected a large amount of experimental data about the properties of those imagined ion channels and came up with a set of ordinary differential equations which conforms to the dynamic behavior of $g_{Na}(t, v)$ and $g_{K}(t, v)$ as recorded in experiment. In Hodgkin-Huxley’s theory,

$$g_{Na} = G_{Na} m^3 h \quad \text{and} \quad g_{K} = G_{K} n^4$$
**Figure 1.4** A typical action potential (Up, $mv$) and the time course of membrane conductance (Down, $mS/cm^2$) to sodium ($g_{Na}$) and potassium ($g_K$) respectively. The resting state membrane potential is adjusted to be zero.

where $G_{Na}$ and $G_K$ are the maximum membrane conductance for sodium and potassium respectively. The variables $m$ and $h$ are called the activation and inactivation variables for sodium and $n$ is the potassium activation variable. They are unit-less variables and take values between 0 and 1.

After incorporating cable equation (1.4), the complete set of Hodgkin-Huxley equations takes the form

\begin{align*}
Cv_t &= \frac{1}{R} v_{xx} + G_{Na} m^3 h (E_{Na} - v) + G_K n^4 (E_K - v) + G_L (E_L - v) \\
 m_t &= \alpha_m (1 - m) - \beta_m m \\
 h_t &= \alpha_h (1 - h) - \beta_h h \\
 n_t &= \alpha_n (1 - n) - \beta_n n
\end{align*}  

(1.10) (1.11) (1.12) (1.13)
where the coefficients in (1.11)-(1.13) depend on voltage as follows

\[
\alpha_m(v) = \frac{25 - v}{10 (e^{(25-v)/10} - 1)} \quad (1.14)
\]
\[
\beta_m(v) = 4e^{-v/18} \quad (1.15)
\]
\[
\alpha_h(v) = \frac{7}{100}e^{-v/20} \quad (1.16)
\]
\[
\beta_h(v) = \frac{1}{e^{(30-v)/10} + 1} \quad (1.17)
\]
\[
\alpha_n(v) = \frac{10 - v}{100 (e^{(10-v)/10} - 1)} \quad (1.18)
\]
\[
\beta_n(v) = \frac{1}{8}e^{-v/80} \quad (1.19)
\]

Although numerical results from solving eqns. (1.10)-(1.13) fit experimental data collected on squid axons quite well, the Hodgkin-Huxley equations are empirical in the sense that those fancy variables \( m, h, n \) and those delicate \( \alpha, \beta \) coefficients are fabricated to suit data samples from experiments. When it comes to simulate a new kind of neuron, eqns. (1.10)-(1.13) will fail if we don't adjust those coefficient (1.14)-(1.19) and the power raised to \( m, h \) and \( n \) accordingly. Sometimes, we may have to introduce new ion channels and design new activation or inactivation variables and the corresponding \( \alpha, \beta \) coefficients ([32], [59], [60]). A good example of a more complicated Hodgkin-Huxley type of equations can be found in G.W. Beeler and H.Reuter ([4]) where a slow inward current primarily carried by calcium ions and a voltage- and time-dependent outward current primarily carried by potassium ions were introduced to model mammalian ventricular myocardial fibers. Although there are a few more Hodgkin-Huxley type of equations available ([6], [5] and [22]), to model any kind of nerve fiber by Hodgkin-Huxley's methodology is not an easy work if not impossible. Many nerve fibers are much smaller than the giant squid axon in diameter. Techniques like space clamping and voltage clamping are difficult to implement on these nerve fibers although some new optical recording technique like the acousto-
optic random-access laser scanning microscopy (P. Saggau [56]) may improve the situation. Therefore, it would be of great help if we can deduce something about the active membrane conductance from the impedance data, \(i_0(t)\) and \(v_0(t)\), we record at the soma. Compared to those experimental techniques that Hodgkin and Huxley used to determine those \(\alpha\) and \(\beta\) coefficients, recording voltage response at the soma is much simpler and easier. In the light of new optical recording techniques ([56], [57] and [2]), we may also assume knowledge of the voltage response, \(v(x, t)\), at some other site along the fiber. By injecting some voltage-sensitive dyes into the cell body, membrane potential change can be detected by measuring the fluorescence change of the target. This optical recording technique is much less invasive than the classical microelectrode which has to be inserted into the cell and it brings down the size limitation to a new level.

The Hodgkin-Huxley equations are usually considered too complicated for mathematical analysis ([40]). Even for numerical simulation, it is time consuming if we want to solve it on various initial and boundary conditions ([63]). In fact, little analytical work ([14], [15], [16], [9]) has been done on the Hodgkin-Huxley equations directly. Instead, another mathematical model which in some sense also arises from Hodgkin-Huxley's theory is being widely studied ([38], [45], [42], [64] and [7]). It is called the Fitzhugh-Nagumo model and has its origins in the works of Fitzhugh ([18]) and Nagumo, Arimoto and Yoshizawa ([43]).

Instead of inquiring on the detailed property of each ion channel and distinguishing between different ion species, the Fitzhugh-Nagumo equations attempt to capture the main nonlinear feature of the H-H model by simplifying the sodium current flow into one function \(f\) and by approximating the slow potassium gating variable \(n\) by the recovering variable \(w\) ([66]). In their universal form, the Fitzhugh-Nagumo equations
are

\[ \begin{align*}
    v_t &= v_{xx} + f(v) - w \\
    w_t &= bv - \gamma w
\end{align*} \quad (1.20)
\]

where \( b \) and \( \gamma \) are positive constants, \( f(v) \) is a function with the following properties

\[
f(v) \begin{cases} 
    < 0, & v \in (0, a) \\
    > 0, & v \in (a, 1)
\end{cases}
\]

\[
f'(0) < 0, \quad f'(1) < 0
\]

\[
f(0) = f(1) = 0
\]

\[
f_0^1 f(v) \, dv > 0
\]

The general shape of the function, \( f(v) \), is shown in Fig. 1.5. In Fitzhugh and

**Figure 1.5** The function \( f(v) \) which is used in Fitzhugh-Nagumo's equations to describe the ionic current flow across the membrane.
Nagumo’s original work, the cubic

$$f(v) = v(1 - v)(v - a), \quad 0 < a < 1$$

(1.23)

is used for the study of threshold effect and traveling-wave solutions.

In spite of the simplicity of appearance, Fitzhugh-Nagumo system does exhibit many of the nonlinear features as shown both in experiments on real neuron and in numerical simulation of Hodgkin-Huxley equations ([10] and [39]). Unlike Hodgkin-Huxley equations which have a strong connection to the type of neuron they simulate, we believe Fitzhugh-Nagumo system has more flexibility in simulating various kinds of neurons. For the purpose of neuron identification, we will use this model as the starting point for the recovering of the dynamic feature of neuron membrane during action potential period. More precisely, we will answer the question: can we uniquely determine the two positive constants $b$ and $\gamma$ and reconstruct the function $f(v)$ from our measured impedance data, $i_a(t)$, $v_0(t)$ and possibly $v(x, t)$ at $x$? We will also establish some numerical algorithm for our inverse problem with stability analysis if a unique solution exists.
Chapter 2

Passive Neuron Identification

As we discussed in the introduction, neuron identification can be put into two categories. One is to identify passive neuron. The other is to identify active neuron. This chapter is dedicated to passive neuron identification. We start with a review of past and current research in this arena.

2.1 Literature Review

In the most general situation where $R$, $C$ and $G$ are arbitrary functions of space, $x$, little work has been done even to address the inverse problem. One special yet common nonuniform case is to let $G$ vary with $x$ while assuming $R$ and $C$ known constants. This assumption is physically reasonable because of the nonuniform density of ion channels on the fiber surface. The question is whether knowledge of $v(x_j, t)$ at one or more $x_j$ indeed uniquely determine the function $G(x)$. Two approaches are proposed to solve the problem based on the work of Pierce ([48]) and the work of Isakov ([33]).

Following the line of Pierce's work, one can transform the inverse parabolic problem to an inverse spectral problem which is completely solvable by the methods of Pöschel and Trubowitz ([49]). The second approach, following Isakov's work, is to transform the inverse parabolic problem to an inverse hyperbolic problem. This transformed problem, like the inverse spectral problem, has a unique stable solution. However, the transformations in both methods are not stable. Additional data or constraints are required in order to stabilize the transformation.

In the uniform case when $R(x)$, $C(x)$ and $G(x)$ are all supposed to be constants, there is a rich literature ([53], [8], [31], [67], [11], [12], [52], [34], [65] and [62]) of
work primarily motivated and carried out by physiologists. The original work should be accredited to W. Rall ([52]). He first studied the inverse problem based on the cable equation (1.4) in 1960s. However, in Rall’s initial model, the soma membrane time constant \( \tau_s = C_s/G_s \) was considered to be the same as the time constant of the dendrite membrane, \( \tau = C/G \). In fact, the boundary condition

\[
v_x(0, t) = -Ri_0(t)
\]

was presumed instead of (1.7). In other words, the soma was treated as an integrated part of the axon. This assumption was later found to be in conflict with experimental data collected from living neurons. Therefore, the somatic shunting effect was taken into account by Durand ([12]). In their more general model, \( \tau_s \) was allowed to differ from \( \tau \).

You may not be surprised that cable equation (1.4) can be solved analytically using the classical separation of variables method or by Green’s function approach ([50], [51], [13]). The general solution takes the form,

\[
v(x, t) = h(x) + \sum_{i=0}^{\infty} h_i(x)e^{-t/\tau_i}
\]

where \( \tau_1 > \tau_2 > \cdots > \tau_n > \cdots \) are equalization time constants whose values depend on the cable parameters \( \{R, C, G, C_s, G_s\} \). The forms of the functions \( h_i(x)(i = 0, 1, \cdots) \) vary according to the existing boundary conditions we admit. Letting \( x = 0 \) and \( C_i = h_i(0)(i = 0, 1, \cdots) \), we get the following expression for \( v_0(t) \),

\[
v_0(t) = h(0) + \sum_{i=0}^{\infty} C_i e^{-t/\tau_i}
\]

where \( \{C_i\}_{i=0}^{\infty} \) are also functions of cable parameters \( \{R, C, G, C_s, G_s\} \). In the case of current clamp, \( h(0) = I_0R_N \) where \( I_0 \) is the clamping current and \( R_N \) is the input resistance. Since high-order terms \( \{C_i e^{-t/\tau_i}\}_{i=2,3,\cdots} \) in (2.3) usually decays very fast,
$v_0(t)$ can be approximated by

$$v_0(t) \approx h(0) + C_0 e^{-t/\tau_0} + C_1 e^{-t/\tau_1}$$

(2.4)

a short time, say 0.5 msec (during this time range, values of voltage response is not available due to bandwidth limitation) after we stimulate the soma.

Traditional approaches to the passive neuron identification problem take advantage of expression (2.4). They first estimate $R_N$, $C_0$, $\tau_0$, $C_1$ and $\tau_1$ by either the peeling method introduced by W. Rall ([52]) or by some optimization scheme ([11]). In Rall's peeling method, the difference between the time constants $\tau_0$ and $\tau_1$ is utilized to expose the corresponding exponential term one by one. At a faster decaying rate, $C_1 e^{-t/\tau_1}$ can be removed (peeled off) after a certain period of time while $C_0 e^{-t/\tau_0}$ still remains in effect. With only one exponential term left, it is a piece of cake to extract $C_0$ and $\tau_0$. $C_1$ and $\tau_1$ can be obtained in the same way after subtracting $C_0 e^{\tau_0}$ from $v_0(t)$. Although Rall's peeling method is simple and fast to implement, it requires the time constants $\tau_0$ and $\tau_1$ to be apart from each other. The accuracy is limited in the case where $\tau_0$ is close to $\tau_1$. So comes the optimization method in which the error between (2.4) and the recorded data $v_0(t)$ is minimized in the least-square sense over those coefficients $\{C_i, \tau_i\}_{i=0}^1$ as a whole. Certainly, we don't need $\tau_0$ and $\tau_1$ to stay away from each other any more.

With $R_N$ and $\{C_i, \tau_i\}_{i=0}^1$ in hand, cable parameters are then expected to be recovered from their analytical relation to $R_N$, $C_0$, $\tau_0$, $C_1$ and $\tau_1$. Since this relation depends on the boundary conditions, in some simple case, it can be solved explicitly ([52]). While in the somatic shunt situation, the relation is so complicated and implicit that another optimization process is needed.

Moreover, this last step comes with no guarantee. The optimization searching procedure is sensitive to errors in recorded data with somatic shunt taken into account.
This non-robust behavior was investigated systematically by J.A. White, P.B. Manis and E.D. Young ([67]). In their paper, instability of the inverse process was justified by the existence of some quite different cable parameters that could all give you very small error in fitting $C_0$ and $C_1$. However, the computation of these candidate parameters is nothing more than blindly solving for the contour (level sets) of the error function in fitting $C_0$ and $C_1$.

The most recent work along this traditional line on passive neuron identification is from Holmes and Rall ([29], [30] and [31]). They have come up with an algorithm called the inverse compartmental computation. Since their inverse algorithm represents the state of the art work in this area, we want to discuss it in some detail. Before we do that, however, we have to introduce the set of parameters Holmes and Rall use to describe a neuron in their paper. Some of these parameters are the same as what we defined in our introduction. Some use different notation. Some are new geometric parameters. We duplicate all of them down here without any change in order to keep the integrity of their parameters

- $rfl$: resistivity free length. $rfl = 2\ell/d^{1/2}$ where $\ell$ is the length of the axon and $d$ is the diameter of the axon.
- $A_s \text{ (}\mu cm^2\text{)}$: soma membrane area.
- $A_D \text{ (}\mu cm^2\text{)}$: dendrite membrane area, $A_D = \pi d\ell$
- $R_{md} \text{ (}\Omega cm^2\text{)}$: the dendrite membrane resistivity (same as $R_m$).
- $R_{ms} \text{ (}\Omega cm^2\text{)}$: the soma membrane resistivity.
- $R_i \text{ (}\Omega cm\text{)}$: intra-cellular resistivity (same as axoplasm resistivity, $R_a$).
- $C_m \text{ (}\mu F/cm^2\text{)}$: the membrane capacity.
- $L$: the electrotonic length, $L = \sqrt{R_i/R_{md}}rfl$. 
Although these parameters may reflect the interest of physiologists mostly, they are excessive in representing the equivalent cylinder model of passive neurons. We believe our cable parameters \( \{ R, C, G, C_s, G_s \} \) are compact and are more convenient to manipulate from the mathematical point of view and the two sets of parameters can transform to each other easily when certain geometric information is given.

Generally speaking, Holmes and Rall's approach is purely numerical and involves expensive computation. The first step of their inverse computation is to estimate 4 constants, \( R_N, \tau_0, C_0 \) and \( \tau_{vcl} \) (voltage-clamp time constant) by peeling or optimization method as usual. Here, \( \tau_{vcl} \) is used to replace \( C_1 \) and \( \tau_1 \) because of the difficulty in obtaining accurate values of \( C_1 \) and \( \tau_1 \). To obtain \( \tau_{vcl} \), however, an extra experiment is needed to record the voltage-clamp current response. In respect to cable equation (1.4), we are asking for the Dirichlet boundary condition

\[
v(0, t) = v_0 \quad (2.5)
\]

Once values for \( R_N, \tau_0, C_0 \) and \( \tau_{vcl} \) are obtained, they are considered to be known parameters. Then, the Newton-Raphson algorithm (an optimization scheme) is used to solve the following system of nonlinear equations

\[
\begin{align*}
\tau_0 &= \tilde{\tau}_0(R_{md}, R_{ms}, C_m, L, A_s, A_D) \\
C_0 &= \tilde{C}_0(R_{md}, R_{ms}, C_m, L, A_s, A_D) \\
R_N &= \tilde{R}_N(R_{md}, R_{ms}, C_m, L, A_s, A_D) \\
\tau_{vcl} &= \tilde{\tau}_{vcl}(R_{md}, R_{ms}, C_m, L, A_s, A_D)
\end{align*}
\quad (2.6)
\]

where \( \tilde{\tau}_0, \tilde{C}_0, \tilde{R}_N \) and \( \tilde{\tau}_{vcl} \) are estimates of known parameters \( \tau_0, C_0, R_N \) and \( \tau_{vcl} \) based on the given values of \( R_{md}, R_{ms}, C_m, L, A_s \) and \( A_D \).
However, the right hand side of (2.6) are implicit functions. Thus, values of $\bar{\tau}_0$, $\bar{C}_0$, $\bar{R}_N$ and $\bar{R}_{vcl}$ are computed not by some explicit relation but by forward computation of (1.4). More precisely, $\bar{v}(0, t)$ under current clamp and $\bar{I}_0(t)$ under voltage clamp are first obtained using a numerical forward solver of (1.4). Then, $\bar{\tau}_0$, $\bar{C}_0$, $\bar{R}_N$ and $\bar{R}_{vcl}$ are estimated from $\bar{v}(0, t)$ and $\bar{I}_0(t)$ by peeling or optimization method.

Their algorithm is called inverse compartmental computation because to numerically solve (1.4), the dendrite must be discretized first into many small compartments in order to approximate a continuous dendrite membrane. Although Holmes and Rall ([31]) claim that their algorithm is applicable to a large variety of neurons, they do not provide any theory in their paper to guarantee the uniqueness of the inverse procedure. Additionally, this inverse algorithm is computationally too expensive. Calculating both the current-clamp voltage response, $\bar{v}(0, t)$, and the voltage-clamp current response, $\bar{I}_0(t)$, requires two forward solves of (1.4), one with Neumann type boundary condition (1.7) and the other with Dirichlet boundary condition (2.5), at each updating step of Newton-Raphson algorithm. Moreover, in a trial of the algorithm on Matlab, different initial values gave us different solutions.

The sensitivity problem also arises when the unknown parameters are not constrained to certain extent. In fact, Holmes and Rall ([31]) themselves only obtained relatively stable solutions when both $A_s$ and $A_D$ were known. If only one of them or $C_m$ is known, the inverse procedure was considered to be too sensitive to converge. However, this is not true in any case. As we will show later, neurons with electrotonic length $L$ between 1.5 and 3 can be identified with certain stability even if only $A_s$ or $C_m$ is known.

A review of these past inverse algorithms on passive neuron identification suggests the following questions: what are the maximum set of parameters that can be uniquely determined by transient response at soma? How ill-posed is the inverse problem?
What information other than impedance data, \( i_0(t) \) and \( v_0(t) \), is needed to stabilize the inverse procedure? How much error in the recorded impedance data can be tolerated?

These questions are addressed in the papers reviewed above only through the authors' experimental and numerical experience. However, the mystery of the relation between parameters that describe a neuron and the neuron's response to a current stimulation still remains. A theoretically complete answer to these questions will certainly provide better guidance in designing algorithms for neuron identification.

In 1997, a new approach was introduced by S.J. Cox ([8]) to attack the passive neuron identification problem. Instead of looking at the time domain solution, \( v_0(t) \), directly, Cox ([8]) focuses on the Laplace transform of \( v_0(t) \), denoted \( \hat{v}_0(s) \), and the corresponding input impedance, \( z_0(s) = \frac{\hat{v}_0(s)}{\hat{i}_0(s)} \), where \( \hat{i}_0(s) \) is the Laplace transform of the input current \( i_0(t) \), at the soma.

The rest of this chapter explores Cox ([8])'s idea and extends it to the more complicated somatic shunt model of passive neuron with \( R, C \) and \( G \) being assumed to be constants.

### 2.2 The Single Compartment Case

Before studying the cable equation (1.4) with initial and boundary condition (1.6)-(1.8), we examined the circuit depicted in Fig. 2.1. Although this circuit can not be used to model any realistic neuron, it gives you an idea why the information about soma membrane potential alone is not enough to determine the whole circuit.

Balancing currents at each nodes of the circuit in Fig. 2.1 gives us the following equations,

\[
C_s v_0'(t) + G_s v_0(t) + (v_0(t) - v_1(t))/R = i_0(t)
\] (2.7)
Figure 2.1 A simple circuit with only one RCG compartment of unit length.

\[
\frac{(v_0(t) - v_1(t))}{R} = Cv'_1(t) + Gv_1(t).
\]  

(2.8)

Solving (2.7) for \(v_1\) and substituting it into (2.8) brings

\[
x_1i_0' + x_2i_0 = x_3v_0'' + x_4v_0' + x_5v_0
\]  

(2.9)

where

\[
x_1 = RC
\]

\[
x_2 = RG + 1
\]

\[
x_3 = RCC_s
\]

\[
x_4 = C + C_s + RG_sC + RGC_s
\]

\[
x_5 = G + G_s + RGG_s
\]  

(2.10)

Obviously, \(x_i > 0\) for \(i = 1, \ldots, 5\) and \(v_0\) depends only on the relative values of the quintuple \(\{x_1, x_2, \ldots, x_5\}\) i.e., multiplying each by a scalar \(\alpha\) results in the same differential equation. We exploit this freedom in our construction of two distinct quintuples of circuit parameters, \(\{R, C, G, C_s, G_s\}\), that produce identical soma potentials. We are assisted in this by the fact that one may invert the above transformation \((2.10)\).
Namely, with \( \mathbf{x} \) denoting the vector \([x_1, x_2, \cdots, x_5]^T\), we find

\[
R(\mathbf{x}) = \frac{x_1^2}{x_1 x_2 x_4 - x_1^2 x_5 - x_2^2 x_3} \\
C(\mathbf{x}) = x_2 x_4 - x_1 x_5 - x_2^2 x_3 / x_1 \\
G(\mathbf{x}) = \frac{x_2 - 1}{x_1} (x_2 x_4 - x_1 x_5 - x_2^2 x_3 / x_1) \\
C_s(\mathbf{x}) = x_3 / x_1 \\
G_s(\mathbf{x}) = x_5 - \frac{x_2 - 1}{x_1} (x_4 - x_2 x_3 / x_1) \tag{2.11}
\]

As a concrete instance, we note that

\[
R = 0.1 (k\Omega), \quad C = 2(\mu F), \quad G = 10(\frac{1}{k\Omega}) \\
C_s = 0.4(\mu F) \quad \text{and} \quad G_s = 2(\frac{1}{k\Omega})
\]

corresponds to

\[
x_1 = 0.2, \quad x_2 = 2.0, \quad x_3 = 0.08, \quad x_4 = 3.2 \quad \text{and} \quad x_5 = 14
\]

Now substituting \( \alpha \mathbf{x} \) into (2.11) will lead to a new quintuple of circuit parameters that produces the same voltage response, \( v_0(t) \), to a given current input, \( i_0(t) \). Direct calculation however has shown that in order for each of these parameters to remain positive \( \alpha \) must lie between 1/2 and 6/5. For example, with \( \alpha = 3/4 \) we arrive at

\[
\tilde{R} = 2/15 \ (k\Omega), \quad \tilde{C} = 9/8 \ (\mu F), \quad \tilde{G} = 4.5 \ (\frac{1}{k\Omega}) \\
\tilde{C}_s = 0.4 \ (\mu F) \quad \text{and} \quad \tilde{G}_s = 3.75 \ (\frac{1}{k\Omega})
\]

We can actually compute the 1-dimensional solution manifold in the space \( \mathbb{R}^5 \) of the five cable parameters when the impedance measurements, \( i_0(t) \) and \( v_0(t) \), are given. Assuming the circuit is quiet initially, i.e., \( v_0(0) = 0 \) and taking the Laplace transform of (2.9), we obtain the input impedance

\[
z_0(s) \equiv \frac{\hat{v}_0(s)}{\hat{i}_0(s)} = \frac{x_1 s + x_2}{x_3 s^2 + x_4 s + x_5} \tag{2.12}
\]
for the circuit. Now expressing (2.12) as

\[ x_3z_0(s)s^2 + (x_4z_0(s) - x_1)s + x_5z_0(s) - x_2 = 0 \]  

(2.13)

taking derivative with respect to \( s \) up to the fourth order and evaluating at \( s = 0 \), we get a linear system of equations

\[ Mx = 0 \]  

(2.14)

where

\[ M = \begin{pmatrix}
0 & -1 & 0 & 0 & z_0 \\
-1 & 0 & 0 & z_0 & z_0' \\
0 & 0 & 2z_0 & 2z_0' & z_0'' \\
0 & 0 & 6z_0' & 3z_0'' & z_0^{(3)} \\
0 & 0 & 12z_0'' & 4z_0^{(3)} & z_0^{(4)}
\end{pmatrix} \]

and \( z_0^{(i)} \) is the \( i \)-th derivative of \( z_0(s) \) evaluated at \( s = 0 \).

Clearly, (2.14) does not only have \( 0 \) vector solution if \( \{z_0^{(i)}\}_{i=0}^4 \) is calculated from real impedance data. The null space is at least one dimensional and it is exactly one dimensional as a matter of fact. To prove it, we apply Gaussian elimination to \( M \) and obtain the echelon form of \( M \).

\[ \hat{M} = \begin{pmatrix}
-1 & 0 & 0 & z_0 & z_0' \\
0 & -1 & 0 & 0 & z_0 \\
0 & 0 & 2z_0 & 2z_0' & z_0'' \\
0 & 0 & 0 & u & v \\
0 & 0 & 0 & 0 & w
\end{pmatrix} \]

where \( u = 3z_0'' - 6z_0'^2/z_0 \), \( v = z_0^{(3)} - 3z_0'z_0''/z_0 \) and

\[ w = z_0^{(4)} - 6z_0'^2/z_0 - \frac{(4z_0^{(3)} - 12z_0''z_0'^2/z_0)(z_0^{(3)} - 3z_0'z_0''/z_0)}{3z_0'' - 6z_0'^2/z_0} \]
Looking at $\hat{M}$, we have no reason to expect any of the diagonal elements necessarily to be zero if the impedance data $\{z_0^{(i)}\}_{i=0}^4$ are arbitrary numbers. However, they are not. They are determined by the circuit.

Taking derivative of the two sides of (2.12) and evaluating at $s = 0$, we get,

$$
\begin{align*}
    z_0 & = \frac{x_2}{x_5} \\
    z'_0 & = \frac{x_1}{x_5} - \frac{x_2 x_4}{x_5^2} \\
    z''_0 & = -\frac{2x_1 x_4}{x_5^2} + \frac{2x_2 x_4^2}{x_5^3} - \frac{2x_2 x_3}{x_5^2} \\
    z^{(3)}_0 & = \frac{6x_1 x_4^2}{x_5^3} - \frac{6x_1 x_3}{x_5^2} - \frac{6x_2 x_4^3}{x_5^4} + \frac{12x_2 x_3 x_4}{x_5^3} \\
    z^{(4)}_0 & = -\frac{24x_1 x_4^3}{x_5^4} + \frac{48x_1 x_3 x_4}{x_5^3} - \frac{12x_2 x_4^4}{x_5^5} - \frac{72x_2 x_3 x_4^2}{x_5^4} + \frac{24x_2 x_3^2}{x_5^3}
\end{align*}
$$

(2.15)

Substituting (2.15) into the diagonal elements of $\hat{M}$, we have $z_0 = x_2/x_5 > 0$ and $z_0 u = 3z_0 z''_0 - 6z'_0 = \frac{6x_2^2}{Rx_3} > 0$. As to the last diagonal element $w$, with the assistance of Matlab’s symbolic toolkit, we’ve got $w = 0$ which means the null space of $M$ is indeed one dimensional. The general solution to (2.14) can now be written as

$$
\mathbf{x} = \alpha \left( \begin{array}{c}
    z'_0 - \frac{z_0 u}{u} \\
    z_0 \\
    \frac{z'_0 u}{z_0 u} - \frac{z''_0}{2z_0} \\
    -\frac{v}{u} \\
    1
\end{array} \right)
$$

(2.16)

Substituting the general solution (2.16) into (2.11) and enforcing positivity on those circuit parameters, we obtain the one-dimensional manifold in the parameter space of $\{R, C, G, C_s, G_s\}$.
\[ R = \frac{1}{\alpha} \frac{6(z'_0 - z_0 u)^2}{z_0 u} \]

\[ C = \frac{\alpha^2}{6} \frac{z_0^2 u^2}{u z_0 z_1 - v z_0^2} \]

\[ G = \frac{\alpha(\alpha z_0 - 1)z_0 u}{6(z'_0 - z_0 u)^2} \]

\[ C_s = \frac{2z'_0 v - z'_0 u}{2z_0 z'_0 u - 2z_0^2 v} \]

\[ G_s = \frac{1}{z_0 - \frac{\alpha z_0 - 1}{6(z'_0 u - z_0 v)^2}} \]

with \( \frac{1}{z_0} < \alpha < \frac{z_0 u^3 + 6(z'_0 u - z_0 v)^2}{z_0 u^3} \).

To understand how such non-uniqueness phenomenon occurs, let us examine the circuit in Fig. 2.1 again. The input current \( i_0(t) \) divides into three branches after injection. One branch flows into \( G_s \), another into \( C_s \) and the third into the \( RCG \) compartment. If we denote the current that flows through \( G_s \) as \( i_{G_s}(t) \), then

\[ v_0(t) = \frac{i_{G_s}(t)}{G_s} \]

In order to get a new set of parameters, \( \{R, C, G, C_s, G_s\} \), while keeping \( v_0(t) \) unchanged, we can go through the following procedure: first, reduce \( G_s \) to a new fixed value and then adjust the values of \( R, C, G \) and \( C_s \) accordingly. If we can also reduce \( i_{G_s}(t) \) somehow, it appears that \( v_0(t) \) would remain unchanged. However, a closer look reveals that it is quite unlikely that \( v_0(t) \) can keep untouched because \( i_{G_s}(t) \) must be reduced by the same factor at all times. Since the relation between \( i_{G_s}(t) \) and \( \{R, C, G, C_s, G_s\} \) is nonlinear, it is not obvious that this is possible. Amazingly though, this can be done as is shown by the above example.

What happens if we add one more \( RCG \) compartment, with the same parameter values, to the circuit in Fig. 2.1? Following the same procedure as before, we get a
similar expression for \( z_0(s) \):

\[
z_0(s) = \frac{x_1s^2 + x_2s + x_3}{x_4s^3 + x_5s^2 + x_6s + x_7}
\]  

(2.17)

where \( x_1, x_2, \ldots, x_7 \) are functions of \( R, C, G, C_s, G_s \) as in (2.10) (The expression, however, are too complicated to be included here). Although we can still multiply \( x \) by a scalar \( \alpha \) without altering \( z_0(s) \), a scalar \( \alpha \) such that \( \alpha x \) gives us a positive set of parameters, \( \{R, C, G, C_s, G_s\} \) does not exist. Physically speaking, we are expanding the complexity of the circuit without adding in new adjustable parameters in accordance.

This added uniqueness is a desirable property of the inverse problem. However, some other problem still remains. Although the above parameter adjustment scheme no longer produces an identical \( v_0(t) \), it may generate a whole bunch of \( v_0(t) \) which is very close to one another. In other words, the inverse problem of identifying \( \{R, C, G, C_s, G_s\} \) becomes highly sensitive to error in the measured \( v_0(t) \).

Adding even more \( RCG \) compartments to the circuit in Fig. 2.1 appears to benefit the stability of inverse problem. It will also eventually model a real neuron. Can we now expect the inverse problem of passive neuron identification to be stable? The answer depends on the value of the electrotonic length, \( L \), as we will see in the next section.

### 2.3 The Distributed Case

Now, let's embark on the study of our somatic shunt model for a real neuron. Since \( \{R, C, G\} \) are assumed to be constants in our model, Eqn. (1.4) can be normalized in \( x \) by incorporating geometric information into electrical parameters. Our purpose is to obtain a geometry free system. To achieve this goal, from now on we will use \( R \) to denote the total axoplasm resistance of the entire dendrite (instead of the axoplasm resistance per unit length), \( C \) the total dendrite membrane capacitance and \( G \) the
total dendrite membrane conductance. In terms of those neuron parameters used by Holmes and Rall ([31]), we now have

$$R = \frac{4R_i \ell}{\pi d^2}, \quad C = C_m A_D \quad \text{and} \quad G = A_D/R_{md}$$

(2.18)

instead of (1.5) defined in the introduction and the electrotonic length $L$ equals $\sqrt{RG}$. After making the change of variable

$$X = \sqrt{R \frac{E}{G}} \frac{t}{\ell}$$

the cable equation (1.4) becomes

$$Cv_t(X,t) = Gv_{XX}(X,t) - Gv(X,t) \quad 0 < X < L, \quad t > 0$$

(2.19)

and the initial and boundary condition (1.6)-(1.8) become

$$v_X(0,t) = -\frac{L}{G} (i_0(t) - C_s v_t(0,t) - G_s v(0,t))$$

$$v_X(L,t) = 0$$

$$v(X,0) = 0$$

(2.20)

Notice that all geometric parameters have disappeared from (2.19) and (2.20). The absence of an explicit form of geometric parameters has important implication. Specifically, it tells us we can not recover both the geometric and the electric properties of a neuron if there is no constraint and if the impedance data, $i_0(t)$ and $v_0(t)$, are the only available data.

There are a total of five independent parameters, $\{L, C, G, C_s, G_s\}$ in (2.19) and (2.20). We claim that these five parameters and those that can be completely determined by them are the only recoverable parameters when $i_0(t)$ and $v_0(t)$ are all the information we have.
Taking the Laplace transform of (2.19) and (2.20), denoting the Laplace transform of \( v(X, t) \) as \( \hat{v}(X, s) \), we obtain

\[
\hat{v}_{XX}(X, s) = \left( \frac{C}{G} s + 1 \right) \hat{v}(X, s) \quad 0 < X < L, \quad \text{Re}(s) > -1/\tau_0 \tag{2.21}
\]

and

\[
\hat{v}_X(0, s) = -\frac{L}{G} \hat{i}_0(s) + \frac{L}{G} (C_s s + G_s) \hat{v}_0(s)
\]

\[
\hat{v}_X(L, s) = 0
\]

(2.22)

where \( \tau_0 \) is the largest equalization time constant in (2.3).

The Solution to (2.21) and (2.22) is

\[
\hat{v}(X, s) = \frac{\left[ \frac{L}{G} \hat{i}_0(s) - \frac{L}{G} (C_s s + G_s) \hat{v}_0(s) \right] \cosh(\sqrt{\frac{C}{G} s + 1}(L - X))}{\sqrt{\frac{C}{G} s + 1} \sinh(\sqrt{\frac{C}{G} s + 1}L)} \tag{2.23}
\]

Evaluating (2.23) at \( X = 0 \), we find

\[
\hat{v}_0(s) = \frac{\hat{i}_0(s) \frac{L}{G} \cosh(\sqrt{\frac{C}{G} s + 1}L)}{\frac{L}{G} (C_s s + G_s) \cosh(\sqrt{\frac{C}{G} s + 1}L) + \sqrt{\frac{C}{G} s + 1} \sinh(\sqrt{\frac{C}{G} s + 1}L)} \tag{2.24}
\]

Dividing (2.24) by \( \hat{i}_0(s) \), we get the input impedance.

\[
z_0(s) = \frac{L \cosh(\sqrt{\frac{C}{G} s + 1}L)}{\frac{L}{G} (C_s s + G_s) \cosh(\sqrt{\frac{C}{G} s + 1}L) + \sqrt{\frac{C}{G} s + 1} \sinh(\sqrt{\frac{C}{G} s + 1}L)} \tag{2.25}
\]

One important observation should be made before we continue. The impedance function \( z_0(s) \) has meaning in our context only when \( \text{Re}(s) > \sigma = -1/\tau_0 \). In other words \( \text{Re}(s) \) must be greater than the largest zero of the denominator of \( z_0(s) \) on the real axis. It can be proven that \( \sigma \) is always less than 0. Therefore, \( z_0(s) \) is always analytic at \( s = 0 \). In fact, \( z_0(s) \) is analytic in the entire half plane \( \text{Re}(s) > \sigma \) and it has no zeros in this half plane.

Now, proceeding with Cox ([8])'s idea, we hope to recover the five independent cable parameters, \( L, C, G, C_s \) and \( G_s \) from the five impedance data \( z_0(0), z'_0(0), \)
$z''_0(0)$, $z^{(3)}_0(0)$ and $z^{(4)}_0(0)$. Instinctively, it appears that we want to take the derivative of $z_0(s)$ up to the 4th order and evaluate it at $s = 0$. However, this turns out to be a daunting task even with the aid of the matlab symbolic tool. Instead, we take on the reciprocal, $w(s) = 1/z_0(s)$ which is called the input admittance. The form of $w(s)$ is much simpler and is tractable:

$$w(s) = \frac{i_0(s)}{v_0(s)} = C_s s + G_s + \frac{G}{L}\sqrt{\frac{C}{G}} s + 1 \tanh\left(\sqrt{\frac{C}{G}} s + 1L\right) \quad (2.26)$$

Thus, we will work with $\{w^{(i)}(0)\}_{i=0}^{4}$ instead of $\{z^{(i)}(0)\}_{i=0}^{4}$ where $i$ denote the $i$-th derivative. We will call $\{w^{(i)}(0)\}_{i=0}^{4}$ our admittance data.

Taking the derivative of (2.26) up to the 4th order and evaluating it at $s = 0$, we get

$$w(0) = G_s + G f_0(L)$$

$$w'(0) = C_s + C f_1(L)$$

$$w''(0) = \frac{C^2}{G} f_2(L) \quad (2.27)$$

$$w^{(3)}(0) = \frac{C^3}{G^2} f_3(L)$$

$$w^{(4)}(0) = \frac{C^4}{G^3} f_4(L)$$
where

\[
\begin{align*}
    f_0(L) &= \frac{\sinh(L)}{L \cosh(L)} \\
    f_1(L) &= \frac{\sinh(L)}{2L \cosh(L)} + \frac{1}{2 \cosh^2(L)} \\
    f_2(L) &= -\frac{\sinh(L)}{4L \cosh(L)} - \frac{L \sinh(L)}{2 \cosh^3(L)} + \frac{1}{4 \cosh^2(L)} \\
    f_3(L) &= \frac{3 \sinh(L)}{8L \cosh(L)} - \left( \frac{3}{8} - \frac{L^2}{2} \right) \frac{1}{\cosh^2(L)} - \frac{3L^2}{4 \cosh^3(L)} \\
    f_4(L) &= -\frac{15 \sinh(L)}{16L \cosh(L)} + \left( \frac{3}{8} - \frac{L^2}{2} \right) \frac{L \sinh(L)}{\cosh^3(L)} + \\
    &\quad + \frac{3L^3 \sinh(L)}{2 \cosh^5(L)} + \left( \frac{15}{16} - \frac{L^2}{2} \right) \frac{1}{\cosh^2(L)} + \frac{3L^2}{4 \cosh^4(L)} 
\end{align*}
\]

(2.28)

It is not difficult to get rid of \(C\) and \(G\) from the last three equations of (2.27) to get a single equation in \(L\) as

\[
\frac{w^{(4)}(0)w''(0)}{(w^{(3)}(0))^2} = \frac{f_4(L)f_2(L)}{f_3^2(L)} \tag{2.29}
\]

The left hand side of (2.29) is known from admittance data. It is relatively easy to solve a single nonlinear equation in the form of (2.29) if the function

\[
F(L) = \frac{f_4(L)f_2(L)}{f_3^2(L)} \tag{2.30}
\]

is well behaved.

The graph of \(F\) is shown in Fig. 2.2. Notice that the function is monotonically increasing when the value of \(F(L)\) is less than 5/3 or when \(0 < L < 3.2\). This feature of \(F(L)\) leads to the following proposition:

**Proposition 2.1** If the Input Admittance Data \(\{w^{(k)}(0)\}\) satisfies

\[
\frac{85}{63} < \frac{w^{(4)}(0)w''(0)}{(w^{(3)}(0))^2} < \frac{5}{3} \tag{2.31}
\]

then it uniquely determines the quintuple \(\{L, C, G, C_s, G_s\}\) of cable parameters.
Figure 2.2  The graph of the function $F$ defined by (2.30). Notice the narrow function value range and the part of curve with relatively steep slope.

Proof  Since $L$ is uniquely determined, as seen from the curve of $F(L)$, it remains only to find $C$, $G$, $C_s$ and $G_s$.

Solving (2.27) we will get

\[
C = \frac{w''(0)^2 f_3(L)}{w^{(3)}(0) f_2^2(L)}
\]

\[
G = \frac{w''(0)^3 f_2^3(L)}{w^{(3)}(0)^2 f_2^3(L)}
\]

\[
C_s = w'(0) - \frac{w''(0)^2 f_3(L)f_1(L)}{w^{(3)}(0) f_2^2(L)}
\]

\[
G_s = w(0) - \frac{w''(0)^3 f_2^3(L)f_0(L)}{w^{(3)}(0)^2 f_2^3(L)}
\]
What does proposition 2.1 tell us about parameters $R_{md}$, $R_{ms}$, $C_m$, $L$, $A_s$ and $A_D$? First of all, none of them can be uniquely determined if all of them are unknown. Second, all of them can be uniquely determined if either $C_m$ or $A_s$ or $A_D$ is known.

Proposition 2.1 suggests the following algorithm for identifying cable parameters, \( \{R, C, G, C_s, G_s\} \).

**Algorithm 1**  
*the inverse admittance algorithm.*

**I.** Inject $i_0(t)$ at $x = 0$ and record $v_0(t)$

**II.** Compute $w(0), w'(0), w''(0), w^{(3)}(0)$ and $w^{(4)}(0)$.

**III.** Solve (2.29) for $L$.

**IV.** Compute $C, G, C_s$ and $G_s$ by (2.32) and $R = L^2/G$.

This algorithm is computationally efficient. We only need to solve one nonlinear equation (2.29) and the computation of the admittance data \( \{w^{(i)}(0)\}_{i=0}^4 \) involves only five integrations.

Suppose $\hat{u}(s)$ is the Laplace transform of a function $u(t)$ which decays exponentially,

\[
\hat{u}(s) = \int_0^\infty u(t)e^{-st}dt
\]  

(i.e. \( \hat{u}(s) = \int_0^\infty u(t)e^{-st}dt \)) (2.33)

then the $k$th derivative of $\hat{u}(s)$ is given by

\[
\hat{u}^{(k)}(s) = (-1)^k \int_0^\infty t^k u(t)e^{-st}dt
\]  

(2.34)

Defining the $k$th moment([1]) of $u$ by

\[
M_k(u) = \int_0^\infty t^k u(t)dt
\]  

(2.35)

and following the rule of quotient derivative, we obtain the formula for computing the admittance data:
\[ w(0) = \frac{M_0(i_0)}{M_0(v_0)} \]
\[ w'(0) = \frac{-M_1(i_0) + M_1(v_0) w(0)}{M_0(v_0)} \]
\[ w''(0) = \frac{M_2(i_0) + 2M_1(v_0) w'(0) - M_2(v_0) w(0)}{M_0(v_0)} \]
\[ w^{(3)}(0) = \frac{-M_3(i_0) + 3M_1(v_0) w''(0) - 3M_2(v_0) w'(0) + M_3(v_0) w(0)}{M_0(v_0)} \]
\[ w^{(4)}(0) = \frac{M_4(i_0) + 4M_1(v_0) w^{(3)}(0) - 6M_2(v_0) w''(0)}{M_0(v_0)} \]
\[ + \frac{4M_3(v_0) w'(0) - M_4(v_0) w(0)}{M_0(v_0)} \]  

(2.36)

The other computations are merely pairs of function evaluations.

To analyze the stability of the inverse procedure, let us define the maximum error in the computed moments as

\[ \epsilon = \max \left\{ \frac{|\hat{M}_k(i_0) - M_k(i_0)|}{M_k(i_0)}, \frac{|\hat{M}_k(v_0) - M_k(v_0)|}{M_k(v_0)} : 0 \leq k \leq 4 \right\} \]  

(2.37)

and assume the input current \( i_0(t) \geq 0 \) for \( t \geq 0 \). Under this assumption, the voltage response \( v_0(t) \) is also nonnegative for \( t \geq 0 \). This fact can be easily proved by (2.24).

When \( i_0(t) \) and \( v_0(t) \) are nonnegative, their moments are all positive. With these facts, we have the following stability proposition:

**Proposition 2.2** Suppose \( \{w^{(k)}(0)\}_{k=0}^{4} \) and \( \{\hat{w}^{(k)}(0)\}_{k=0}^{4} \) are the exact and computed admittance data respectively. If both of them satisfy condition (2.31) and \( \epsilon \) is sufficiently small, then there exists a constant \( K_P > 0 \) for each cable parameter such that

\[ \left| \frac{\hat{P} - P}{P} \right| \leq K_P \epsilon \]
where $P$ represents each cable parameter from the quintuple $(L, C, G, C_s, G_s)$.

Furthermore, for the electrotonic length $L$, the constant $K_L$ is on the order of $O\left(\frac{1}{LF'(L)}\right)$.

**Proof** First, we examine the error in the computed admittance data $\{\hat{w}^{(k)}(0)\}_{k=0}^{4}$.

Applying the mean-value theorem to $w(0)$ in (2.36), we obtain

\[ |\hat{w}(0) - w(0)| = \frac{\partial(w(0))}{\partial(M_0(i_0))}(\eta_1)|\hat{M}_0(i_0) - M_0(i_0)| + \frac{\partial(w(0))}{\partial(M_0(v_0))}(\eta_2)|\hat{M}_0(v_0) - M_0(v_0)| \]

\[ = \frac{M_0(i_0)}{\eta_2} \frac{\hat{M}_0(i_0) - M_0(i_0)}{M_0(i_0)} + \frac{\eta_1 M_0(v_0)}{\eta_2^2} \frac{\hat{M}_0(v_0) - M_0(v_0)}{M_0(v_0)} \]

where $\eta_1 \in (M_0(i_0)(1 - \epsilon), M_0(i_0)(1 + \epsilon))$ and $\eta_2 \in (M_0(v_0)(1 - \epsilon), M_0(v_0)(1 + \epsilon))$.

When $\epsilon$ is small enough, say $\epsilon < \frac{1}{4}$, we have

\[ |\hat{w}(0) - w(0)| \leq K_0 \epsilon \]

where $K_0 = \frac{32}{9} \frac{M_0(i_0)}{M_0(v_0)} = O(w(0))$

Now applying mean-value theorem to $w^{(j)}(0)(1 \leq j \leq 4)$ we obtain

\[ |\hat{w}^{(j)}(0) - w^{(j)}(0)| \leq K_j \epsilon, \quad 1 \leq j \leq 4 \]
where

\[
K_1 = \frac{32}{9M_0(v_0)} \left( M_1(i_0) + M_1(v_0)(|w(0)| + \epsilon_0 + \frac{15}{32}K_0) \right)
\]

\[
K_2 = \frac{32}{9M_0(v_0)} \left( M_2(i_0) + 2M_1(v_0)(|w'(0)| + \epsilon_1 + \frac{15}{32}K_1) + 
M_2(v_0)(|w(0)| + \epsilon_0 + \frac{15}{32}K_0) \right)
\]

\[
K_3 = \frac{32}{9M_0(v_0)} \left( M_3(i_0) + 3M_1(v_0)(|w''(0)| + \epsilon_2 + \frac{15}{32}K_2) + 
3M_2(v_0)(|w'(0)| + \epsilon_1 + \frac{15}{32}K_1) + M_3(v_0)(|w(0)| + \epsilon_0 + \frac{15}{32}K_0) \right)
\]

\[
K_4 = \frac{32}{9M_0(v_0)} \left( M_4(i_0) + 4M_1(v_0)(|w^{(3)}(0)| + \epsilon_3 + \frac{15}{32}K_3) + 
+ 6M_2(v_0)(|w''(0)| + \epsilon_2 + \frac{15}{32}K_2) + 
M_3(v_0)(|w'(0)| + \epsilon_1 + \frac{15}{32}K_1) + M_4(v_0)(|w(0)| + \epsilon_0 + \frac{15}{32}K_0) \right)
\]

(2.38)

and \( \epsilon_j = K_j \epsilon, 0 \leq j \leq 4 \).

Since \( K_0 = O(w(0)) \) and \( \epsilon_0 = K_0 \epsilon \leq O(w(0)) \) when \( \epsilon < 1 \), we know that

\[
K_1 = \frac{32}{9M_0(v_0)} (M_1(i_0) + M_1(v_0)|O(w(0))|)
\]

(2.39)

Comparing (2.39) with the expression for \( w'(0) \) in (2.36), we find \( K_1 = O(w'(0)) \).

Applying the same arguments to \( K_j (2 \leq j \leq 4) \) iteratively, we obtain

\[
K_j = O(w^{(j)}(0)), \quad 0 \leq j \leq 4
\]

(2.40)

To estimate the error in the recovered electronic length, \( \hat{L} \), we first observe from

\[
F(L) = \frac{w''(0)w^{(4)}(0)}{w^{(3)}(0)^2}
\]

(2.41)

and (2.31) that \( w^{(3)} \neq 0 \). If we choose \( \epsilon \) small enough s.t. \( \epsilon \leq \frac{|w^{(3)}(0)|}{4K_3} \), then

\[
\epsilon_3 = K_3 \epsilon \leq \frac{1}{4}|w^{(3)}(0)|
\]

(2.42)
Now applying mean-value theorem to (2.41) and noticing (2.40) and (2.31), we obtain

$$|F(\hat{L}) - F(L)| \leq K_F \epsilon$$  \hspace{1cm} (2.43)

where

$$K_F = \frac{16}{9} \left| O\left( \frac{w^{(4)}(0)w''(0)}{w^{(3)}(0)^2} \right) \right| = O(1)$$  \hspace{1cm} (2.44)

On the other hand,

$$|F(\hat{L}) - F(L)| = |F'(\xi)||\hat{L} - L|$$  \hspace{1cm} (2.45)

where $\xi$ is a value between $L$ and $\hat{L}$.

(2.43) and (2.45) give us

$$\left| \frac{\hat{L} - L}{L} \right| = \frac{|F(\hat{L}) - F(L)|}{L|F'(\xi)|} \leq K_L \epsilon$$

where

$$K_L = \frac{K_F}{L \min \{ F'(\xi) : \xi \in [L, \hat{L}] \}} = O\left( \frac{1}{LF'(L)} \right)$$  \hspace{1cm} (2.46)

Finally, to obtain the error in all the other recovered cable parameters, we define

$$F_C(L) = \frac{f_3(L)}{f_3^2(L)}, \quad F_G(L) = -\frac{f_2(L)}{f_3(L)}$$

$$F_{C_s}(L) = \frac{f_3(L)f_1(L)}{f_3^2(L)}, \quad F_{G_s}(L) = -\frac{f_2(L)f_6(L)}{f_3^2(L)}$$

and apply mean-value theorem to (2.32). Noticing (2.40) and (2.42) we get

$$\left| \frac{\hat{C} - C}{C} \right| \leq K_C \epsilon$$

$$\left| \frac{\hat{G} - G}{G} \right| \leq K_G \epsilon$$

$$\left| \frac{\hat{C_s} - C_s}{C_s} \right| \leq K_{C_s} \epsilon$$

$$\left| \frac{\hat{G_s} - G_s}{G_s} \right| \leq K_{G_s} \epsilon$$
where

\[
K_C = \frac{1}{C} \left| \frac{w''(0)^2}{w^{(3)}(0)} F_C(L) \right| \left( 1 + K_L \frac{F_C'(L)}{F_C(L)} \right) O(1)
\]

\[
K_G = \frac{1}{G} \left| \frac{w''(0)^3}{w^{(3)}(0)^2} F_G(L) \right| \left( 1 + K_L \frac{F_G'(L)}{F_G(L)} \right) O(1)
\]

\[
K_{C_s} = \left[ \frac{1}{C_s} \left| \frac{w''(0)^2}{w^{(3)}(0)} F_C(L) \right| \left( f_1(L) + K_L \frac{F_C'(L)}{F_C(L)} \right) + \frac{|w'(0)|}{C_s} \right] O(1)
\]

\[
K_{G_s} = \left[ \frac{1}{G_s} \left| \frac{w''(0)^3}{w^{(3)}(0)^2} F_G(L) \right| \left( f_0(L) + K_L \frac{F_G'(L)}{F_G(L)} \right) + \frac{|w(0)|}{G_s} \right] O(1)
\]

**Figure 2.3** Graph of the functions \( f_0(L) \) (Up) and \( f_1(L) \) (Down).
Observing from Fig. 2.3 that $|f_0(L)| \leq 1$, $|f_1(L)| \leq 1$ and also noticing (2.32), we have

$$
K_C = K_L \left| \frac{F'_C(L)}{F_C(L)} \right| O(1)
$$

$$
K_G = K_L \left| \frac{F'_G(L)}{F_G(L)} \right| O(1)
$$

$$
K_{C_s} = \left( K_L \frac{C}{C_s} \left| \frac{F'_{C_s}(L)}{F_C(L)} \right| + \frac{|w'(0)|}{C_s} \right) O(1)
$$

$$
K_{G_s} = \left( K_L \frac{G}{G_s} \left| \frac{F'_{G_s}(L)}{F_G(L)} \right| + \frac{|w(0)|}{G_s} \right) O(1)
$$

Figure 2.4 Graph of the functions: (a) $\frac{F'_C(L)}{F_C(L)}$; (b) $\frac{F'_G(L)}{F_G(L)}$; (c) $\frac{F'_{C_s}(L)}{F_C(L)}$ and (d) $\frac{F'_{G_s}(L)}{F_G(L)}$. 
In Fig. 2.4, we also plotted the ratios of $\frac{F_C'(L)}{F_C(L)}$, $\frac{F_G'(L)}{F_G(L)}$, $\frac{F_C''(L)}{F_C(L)}$ and $\frac{F_G''(L)}{F_G(L)}$. From these curves, we obtain the final estimation of those $K$-constants

$$K_C = K_L O(1) \quad \text{and} \quad K_{C_s} = \left( K_L \frac{C}{C_s} + \frac{|w'(0)|}{C_s} \right) O(1)$$

and when $L$ stays away from zero,

$$K_G = K_L O(1) \quad \text{and} \quad K_{G_s} = \left( K_L \frac{G}{G_s} + \frac{|w(0)|}{G_s} \right) O(1)$$

When $L$ approaches zero, both $\frac{F_C'(L)}{F_C(L)}$ and $\frac{F_G'(L)}{F_G(L)}$ are on the order of $O(1/L)$.

\[\square\]

**Figure 2.5** Graph of the function $F'(L)$.

Since $L$ is the key parameter in determining all the other cable parameters, the number $K_L$ can be regarded as the condition number of our inverse problem. Since it is on the order of $\frac{1}{L F'(L)}$, we plotted $F'(L)$ in Fig. 2.5. It can be proved that
\( F'(L) = O(L) \) as \( L \) approaches zero. Hence \( K_L \) can be very large when \( L \) is close to zero. Even at \( L = 1.0 \), the derivative of \( F(L) \) is as small as 0.05 which renders \( K_L \) to be as large as 20. This explains why it is sensitive to recover all cable parameters from only knowledge about the soma membrane potential.

### 2.4 Stability with \( 1.5 < L < 3.0 \)

The value of \( L \) between 1.5 and 3.0 produces a relatively stable region for recovering cable parameters as suggested by the \( F \)-function. In many cases, this is a normal range of electrotonic length ([52], [30]). In this section, we will present a numerical experiment that carries out the inverse admittance algorithm provided in the previous section. The results show that if the measured impedance data is accurate enough, all cable parameters can be identified to a fairly decent accuracy. Furthermore, if either \( C_m \) or \( A_s \) is known, \( R_{md}, R_{ms}, C_m, A_s \) and \( A_D \) can also be identified.

Our voltage response data, \( v_0(t) \) comes from forwardly solving (2.19) with initial and boundary condition (2.20). We introduce a regular partition of space–time. More precisely, for some final time, \( T \), and natural numbers \( n \) and \( m \) we define \( dX \equiv L/n \) and \( dt \equiv T/m \) and write

\[
0 = X_0 < X_1 < \cdots < X_n = L, \quad X_j = dX + X_{j-1}
\]

\[
0 = t_0 < t_1 < \cdots < t_m = T, \quad t_k = dt + t_{k-1}
\]

Denoting \( V(j,k) = v(X_j, t_k) \) and \( I_0(k) = i_0(t_k) \) we discretize (2.19) and (2.20) via Finite–Differences in space

\[
v_X(X_j, t_k) \approx \frac{v(X_{j+1}, t_k) - v(X_j, t_k)}{dX}
\]

\[
v_{XX}(X_j, t_k) \approx \frac{v(X_{j+1}, t_k) - 2v(X_j, t_k) + v(X_{j-1}, t_k)}{dX^2}
\]
and in time

\[ v_t(X_j, t_k) \approx \frac{v(X_j, t_k) - v(X_j, t_{k-1})}{dt} \]

We employ a Backward Euler scheme to proceed (in time) from \( V(\cdot, k - 1) \) to \( V(\cdot, k) \). More precisely, for each \( k \) we solve the linear system

\[ AV(\cdot, k) = V(\cdot, k - 1) + (dt/C_s)I_0(k)e_1 \]  

(2.47)

where \( e_1 \) is the \( n \)-component vector that is zero save the one in its first component and

\[
A = 
\begin{pmatrix}
\beta_0 & -\alpha_1 \\
-\alpha & \beta & -\alpha \\
-\alpha & \beta & -\alpha \\
-\alpha & \beta & -\alpha
\end{pmatrix}
\]

where \( \alpha_1 = \frac{G_s}{C_s} \frac{dt}{dX}, \beta_0 = 1 + \alpha_1 + \frac{G_s}{C_s} dt, \alpha = \frac{G_s}{C_s} \frac{dt}{dX^2} \) and \( \beta = 1 + 2\alpha + \frac{G_s}{C_s} dt \).

The pseudo neuron we simulated is given by the following parameters,

\[ R_{md} = 14.97 \; (k\Omega cm^2), \quad R_{ms} = 1.272 \; (k\Omega cm^2), \quad C_m = 1.0 \; (\mu F/cm^2) \]
\[ A_s = 5.000 \; (\mu m^2), \quad A_D = 49.961 \; (\mu m^2) \quad \text{and} \quad L = 1.96 \]

which give us

\[ R = 115.11 \; (M\Omega), \quad C = 4.996 \times 10^{-4} \; (\mu F), \quad G = 3.34 \times 10^{-5} \; (\frac{1}{k\Omega}) \]
\[ C_s = 5.0 \times 10^{-5} \; (\mu F) \quad \text{and} \quad G_s = 3.93 \times 10^{-5} \; (\frac{1}{k\Omega}) \]

By varying the time step, \( dt \), we were able to get voltage responses of different accuracies. Once we obtained \( i_0(t) \) and \( v_0(t) \), the admittance data \( \{w_0^{(i)}\}_{i=0}^4 \) was computed by (2.36).
The next step was to solve (2.29) for electrotonic length, $L$. Once we had $L$, the other cable parameters were easy to calculate using (2.32).

The relative error in the recovered cable parameters for various time steps, $dt$, is plotted in Fig. 2.6. The relative error is defined in the form

$$\frac{|P_e - P_a|}{|P_e|}$$ (2.48)

where $P_e$ is the exact value for parameter $P$ and $P_a$ is the approximate value for $P$.

![Graphs showing relative error in recovered parameters](image)

**Figure 2.6** Relative error in the recovered parameters $R, C, G, C_s, G_s$ and $L$.

To get an idea how much error is introduced in the response data, $v_0(t)$, by the forward solver of (2.19), we compared our response data, $v_0(t)$, computed with $dt = 0.01, 0.05, 0.1, 0.5$ to the response data computed with $dt = 0.001$ and plotted the difference in Fig. 2.7(solid line). In Fig. 2.7(dash-dot line), we also plotted the difference between the recovered response computed with our recovered parameter
values and the original response data. As you can see, the two differences are on the same magnitude. This fact implies we can hardly do anything more to improve the accuracy as shown in Fig. 2.6.

Figure 2.7  The input current, \( i_0(t) \), and the voltage response, \( v_0(t) \), in together with the estimated error in the original response data(solid line) and in the recovered response(dash-dot line) computed with the recovered parameter values. The error in the original data is introduced by forwardly solving (2.19) for various \( dt \).

The estimated error in the computed moments as defined by (2.37) for \( dt = 0.01, 0.05, 0.1, 0.5 \) are 0.00178, 0.0066, 0.0126 and 0.0729 respectively. If we examine the relative error in the recovered \( L \) (Fig. 2.6), we find the error in the moments is exaggerated by about 10 times. Since the derivative of \( F(L) \) at \( L = 1.96 \) is about 0.146, the exaggeration factor is in agreement with \( O(\frac{1}{F'(1.96)}) \) as we discussed in proposition 2.2.
If we want to recover $R_{md}$, $R_{ms}$, $C_m$, $A_s$ and $A_D$, we must know either $C_m$ or $A_s$ or $A_D$ as we claimed before. In Fig. 2.8, we plot the relative error in recovered $R_{md}$, $R_{ms}$, $C_m$ and $A_s$ when $A_D$ is known.

![Graphs showing relative error in recovered parameters](image)

**Figure 2.8** Relative error in the recovered parameters $R_{md}$, $R_{ms}$, $C_m$ and $A_s$. $A_D$ is supposed to be known.

### 2.5 A Comparison with the Constrained Inverse Algorithm of Holmes and Rall

In order to identify the cable parameters uniquely and in a stable manner, especially when the electrical length $0 < L < 1.5$, we must have more information than just the voltage response of the neuron at the soma end. The extra information could be some kind of constraints on the parameters.
Holmes and Rall ([31]) suggest that the soma membrane area, \( A_s \), and the dendrite membrane area, \( A_D \), can be measured and the membrane capacitance per unit area, \( C_m \) \((\mu F/cm^2)\), can be assumed to be the same. This extra information, enables them to identify \( R_{md}, R_{ms}, C_m \) and \( L \).

In comparison, the information about \( A_s \) and \( A_D \) when used in our scheme results in

\[
C_s = C_m A_s \quad \quad \quad (2.49)
\]

\[
C = C_m A_D
\]

Substituting (2.49) into (2.27), defining \( \sigma = A_s/A_D \) and doing some algebraic manipulation yields

\[
\frac{w'(0)w^{(3)}(0)}{w''(0)^2} = \frac{(\sigma + f_1(L))f_3(L)}{f_2^2(L)} \quad (2.50)
\]

Notice that (2.50) does not involve impedance data \( w^{(4)}(0) \) and has only one unknown, \( L \). Defining

\[
F_\sigma(L) \equiv \frac{(\sigma + f_1(L))f_3(L)}{f_2^2(L)} \quad (2.51)
\]

and drawing the curve of \( F_\sigma(L) \) for different values of \( \sigma = A_s/A_D \), as in Fig. 2.9, illustrates that \( F_\sigma(L) \) is a nice monotonic function except for \( 3 < L < 6 \) in which case it flattens out when \( A_s/A_D = 0.01 \).

Solving (2.50) for \( L \) and substituting it into the first three equations of (2.27) with \( \sigma = C_s/C \), we get

\[
C = \frac{w'(0)}{\sigma + f_1(L)}
\]

\[
G = \frac{C^2 f_2(L)}{w''(0)}
\]

(2.52)

\[
C_s = C \sigma
\]

\[
G_s = w(0) - Gf_0(L)
\]
Figure 2.9 The function $F_\sigma(L)$ defined by (2.51) with $\sigma = A_s/A_D = 0.01, 0.1, 0.2$ and 0.5. The shapes of these curves imply it is stable to solve (2.50) for $L$ in most situation.

The systems of equations in (2.50) and (2.52) suggest a nice inverse procedure. Once $C$, $G$, $C_s$ and $G_s$ are estimated, it is easy to calculate $R_{md}$, $R_{ms}$ and $C_m$ with $A_s$ and $A_D$ known. We obtain

$$R_{md} = A_D/G, \quad R_{ms} = A_s/G_s \quad \text{and} \quad C_m = C/A_D = C_s/A_s$$

In our experiment, we made a direct comparison between the Holmes and Rall algorithms and ours. Since there are no concrete results published in the Holmes and Rall paper, we performed their inverse compartmental computation together with our own algorithm.
The following parameters are used to simulate a hypothetical neuron

\[ R_{md} = 29.94 \, (k\Omega \text{cm}^2), \quad R_{ms} = 2.545 \, (k\Omega \text{cm}^2), \quad C_m = 0.5 \, (\mu F/cm^2) \]
\[ A_s = 6,000 \, (\mu m^2), \quad A_D = 99,921 \, (\mu m^2) \quad \text{and} \quad L = 1.06 \] (2.53)

which give us

\[ R = 33.67 \, (M\Omega), \quad C = 4.996 \times 10^{-4} \, (\mu F), \quad G = 3.34 \times 10^{-5} \, (\frac{1}{k\Omega}) \]
\[ C_s = 3.0 \times 10^{-5} \, (\mu F) \quad \text{and} \quad G_s = 4.72 \times 10^{-5} \, (\frac{1}{k\Omega}) \] (2.54)

The response data is also generated by solving (2.47) with different time steps, \( dt \), and the number of compartments used to approximate a real neuron is represented by \( n \). We chose \( n = 75 \) for all our forward computation and chose the initial values for \( R_{md}, R_{ms}, C_m \) and \( L \) in the Holmes and Rall algorithm to be the recovered values from our algorithm to see if our values can be improved.

The relative error as defined by (2.48) for each recovered parameter from both algorithms are plotted in Fig. 2.10. Observe that there is no improvement achieved by Holmes and Rall's inverse computation.

Again, we claim the relative error depicted in Fig. 2.10 is the best we could have as suggested by Fig. 2.11 in which we can see the error in recovered response (dash-dot line) computed with the recovered parameter values is on the same magnitude as the estimated error in the original response data(solid line) computed with \( dt = 0.01, 0.05, 0.1, 0.5 \).

The estimated error in the computed moments as defined by (2.37) for \( dt = 0.01, 0.05, 0.1, 0.5 \) are 0.0016, 0.0055, 0.0104 and 0.0605 respectively. If we examine the relative error in the recovered \( L \) (Fig. 2.10), we find the error in the moments is exaggerated by about 5 times. If we notice that the electrical length \( L \) is 1.06 in this case and \( F'(1.06) \approx 0.05 \), we know that the stability has been greatly improved with the knowledge of \( \sigma = A_s/A_D \).
Figure 2.10  Relative error in the recovered parameters $R_{md}$, $R_{ms}$, $C_m$ and $L$ when $A_s$ and $A_D$ are known. Solid line represents our results and star is for Holmes and Rall’s.

2.6 The Transfer Function Approach

The other possible source of information is the voltage response, $v(X, t)$, at some other site, $X$, along the fibre. The recording of this information is feasible because of the new optical recording techniques ([56], [57] and [2]) and the dual recording work by Johnston ([35]). If the response data, $v(X, t)$, at $X = \rho L$ ($0 < \rho \leq 1$) can be measured, the stability of the inverse procedure will be greatly improved.

Denote the Laplace transform of $v(X, t)$ as $\hat{v}(X, s)$. It is not hard to derive the expression of $\hat{v}(X, s)$ from (2.23) and (2.24)

$$
\hat{v}(X, s) = \frac{\hat{i}_0(s) \frac{L}{C} \cosh(\sqrt{\frac{C}{G}}s + 1(L - X))}{\frac{L}{C}(C_s + G_s) \cosh(\sqrt{\frac{C}{G}}s + 1L) + \sqrt{\frac{C}{G}}s + 1 \sinh(\sqrt{\frac{C}{G}}s + 1L)}
$$
Figure 2.11  The input current, \( i_0(t) \), and the voltage response, \( v_0(t) \), in together with the estimated error in the original response data(solid line) and in the recovered response(dash-dot line) computed with recovered parameter values for various \( dt \).

Defining the transfer function as

\[
    u(s) \equiv \frac{\dot{v}_0(s)}{\dot{v}(X, s)} = \frac{\cosh\left(\sqrt{\frac{C}{G}} s + 1L\right)}{\cosh\left(\sqrt{\frac{C}{G}} s + 1(L - X)\right)}
\]  

(2.56)

and noticing that \( X = \rho L \) \((0 < \rho \leq 1)\), we get

\[
    u(0) = \frac{\cosh(L)}{\cosh((1 - \rho)L)}
\]

\[
    u'(0) = \frac{C}{G} f_{du}(L, \rho)
\]  

(2.57)

where

\[
    f_{du}(L, \rho) = \frac{1}{2} \left( \frac{L \sinh(L)}{\cosh((1 - \rho)L)} - \frac{\cosh(L) \sinh((1 - \rho)L)}{\cosh^2((1 - \rho)L)} (1 - \rho)L \right)
\]  

(2.58)

after taking the derivative of \( u(s) \) and evaluating it at \( s = 0 \).
Figure 2.12 The function $f_u(L, \rho) \equiv \frac{\cosh(L)}{\cosh((1-\rho)L)}$ for $\rho = 0.2, 0.5, 0.8, 1.0$.

System (2.57) provides additional information needed to solve for cable parameters. In fact, $L$ is now easily obtained from the 1st equation of (2.57) and sensitivity will not be a problem since the function

$$f_u(L, \rho) \equiv \frac{\cosh(L)}{\cosh((1-\rho)L)}$$  \hspace{1cm} (2.59)

is a nice monotone function. See Fig. 2.12.
Figure 2.13  Relative error in the recovered parameters $R$, $C$, $G$, $C_s$, $G_s$ and $L$ when the voltage responses, $v_0(t)$ and $v(X,t)$ at $X = \frac{1}{15}L$, are both known.

Combining (2.57) and the first three equations of (2.27) yields

$$
C = \frac{w''(0) f_{du}(L, \rho)}{u'(0) f_2(L)} \\
G = C \frac{f_{du}(L, \rho)}{u'(0)} \\
C_s = w'(0) - Cf_1(L) \\
G_s = w(0) - Gf_0(L)
$$

(2.60)

Notice that the impedance data $w^{(3)}(0)$ and $w^{(4)}(0)$ are no longer needed in (2.60).

A numerical experiment is also carried out to test the stability of solving (2.57) and (2.60) with $X = \frac{1}{15}L$ (i.e. $\rho = \frac{1}{15}$). The same synthetic neuron as in (2.54) is used in the experiment again. The relative error in each recovered parameter is plotted in Fig. 2.13. The high accuracy in all recovered parameters except $C_s$ indicates the
inverse procedure is much more stabilized when we add in the response data at the sealed end of the dendrite. The large error in recovered $C_s$ can be explained by the 3rd equation in (2.60). That equation for $C_s$ involves subtraction of two numbers close to each other. From the physical point of view, the soma membrane capacitance, $C_s$, is too small compared to the dendrite membrane capacitance, $C$ in this case. Thus, change in $C_s$ has little effect on the response of the whole neuron.
Chapter 3

Active Neuron Identification

3.1 Literature Review

Within the Hodgkin-Huxley formalism, the concept of ion channels (e.g. \( N_a^+ \) and \( K^+ \) channel) and their corresponding gating variables (e.g. \( m, h \) for \( N_a^+ \) and \( n \) for \( K^+ \)) plays a central role in describing the nonlinear feature of neuron membrane. Great effort has been devoted to finding the maximum conductance (e.g. \( G_N \) and \( G_K \)) of each ion channel and to obtaining the kinetics, i.e., the \( \alpha \) and \( \beta \) coefficient functions for ion channels.

The voltage-clamp experiment is the classic yet effective way to quantitatively study the nonlinear properties of ion conductances. It was originally performed by Hodgkin and Huxley on the squid giant axon ([23], [24], [25], [26], [27]), and it constitutes the experimental foundation for their ion-channel theory. The experiment, however, is technically difficult when the fiber diameter is small and especially when dealing with neurons that have branching dendrites. Therefore, our inverse problem research seeks alternate ways of identifying neuron membrane conductances. We especially want to deduce something by simply analyzing the voltage response data, \( v_0(t) \). Since the voltage-clamp experiment has its own insuperable credit, our new method is not meant to replace it completely but rather to stand as a supplement to the arsenal.

Before we rush into the discussion of our approach, we would like to review voltage-clamp experiments so that the merits of both methods can be better appreciated ([36]). The experiment usually involves inserting two electrodes into the
Figure 3.1 A schematic diagram of the two-wire voltage-clamp experiments on the squid axon. One wire is used for monitoring the membrane potential and the other for passing current. The voltage clamp amplifier injects or withdraws charges from the interior of the squid axon in order to hold the membrane voltage constant. Voltage is clamped at the command voltage, $V_C$. Reproduced from Figure 6.1 in [36].

axon, one for recording the transmembrane voltage and the other for passing current into the axon to keep the transmembrane voltage constant (or clamped). The basic circuitry of the voltage-clamp experiment is shown in Fig. 3.1.

Under voltage-clamp conditions, the ion currents flowing across the membrane can be measured as a function of time. Fig. 3.2 shows the current records of the squid axon when the voltage is changed from a holding voltage ($V_H$) to a command voltage ($V_C$) of various levels. The current consists of an early transient inward current and a late steady outward current.

It can be shown experimentally that the two currents are carried mainly by two separate ions through two separate conductances, the $N_a^+$ and $K^+$ ion conductances respectively (leak current is ignored here). If the extracellular $N_a^+$ is removed, which eliminates the driving force of the inward $N_a^+$ flux or if tetrodotoxin (TTX), which
Figure 3.2 Currents measured with voltage clamp of squid axon. Membrane potential was held at \(-60\) mv and then stepped (at 0 msec) to various potentials (shown at the right of each trace) for 8 msec before stepping back to \(-60\) mv. Reproduced from Figure 6.2 in [36].

blocks \(N_a^+\) channels, is added, one can eliminate the early transient inward current mediated by \(N_a^+\) channels. On the other hand, the removal of intracellular \(K^+\) or addition of tetraethylammonium (TEA), which blocks \(K^+\) channels, can eliminate the late outward current mediated by \(K^+\) channels. The separation of these two currents is illustrated in Fig. 3.3.

The main reasons for performing the voltage-clamp experiment, as we understand, is to simplify the corresponding mathematical model and make the mathematical analysis of experimental data easier. Precisely speaking, there are three advantages for voltage-clamping the axon.
Figure 3.3 Separation of membrane current (solid trace) into $N_a^+$ (dashed trace) and $K^+$ (dotted trace) currents. $I_K$ is obtained in the presence of TTX or when $[N_a^+]_{out} = 0$; $I_{Na}$ is obtained in the presence of TEA. The voltage is stepped from $-60 \text{mv}$ to $0 \text{mv}$ for $8 \text{msec}$. Reproduced from Figure 6.4 in [36].

1. By inserting two wire electrodes into the axon, one can space-clamp it so that the whole length of the axon is isopotential. In other words, the wire short-circuits the interior of the axon.

Mathematically, this means that the space derivatives are no longer needed in the equation. Therefore, the patch of neuron under the voltage-clamp can be simply modeled by an ordinary differential equation

$$I_m = C_m \frac{dv}{dt} + I_K + I_{Na} + I_L$$

(3.1)

where $I_m$ is the total membrane current, $C_m$ is the membrane capacitance, $I_K$ and $I_{Na}$ are currents carried by $K^+$ and $N_a^+$ respectively and $I_L$ is the leak current carried mainly by $Cl^-$ and other ions.

2. By keeping the voltage constant, the capacitive current can be eliminated.
Hence, $C_m \frac{dv}{dt} = 0$. Equation (3.1) is thus reduced to an algebraic equation. If we assume all the currents obey Ohm's law, we can write

$$I_m = g_K(v, t)(v - E_K) + g_{Na}(v, t)(v - E_{Na}) + g_L(v - E_L)$$

(3.2)

where $g_K(v, t)$ and $g_{Na}(v, t)$ are voltage and time dependent $K^+$ and $Na^+$ conductances respectively and $g_L$ is constant.

Since we can record $I_K(v, t)$ and $I_{Na}(v, t)$ separately, we can easily compute

$$g_K(v, t) = \frac{I_K(v, t)}{v - E_K} \quad \text{and} \quad g_{Na}(v, t) = \frac{I_{Na}(v, t)}{v - E_{Na}}$$

3. By keeping the voltage constant, the time dependent characteristics of ion conductances can be measured without the influence of voltage-dependent parameters.

Hodgkin and Huxley surmised that the $Na^+$ and $K^+$ conductances are controlled by gating particles. Thus $g_K$ and $g_{Na}$ can be written as products of gating variables and maximum conductances:

$$g_K(v, t) = Y_K(v, t)G_K \quad \text{and} \quad g_{Na}(v, t) = Y_{Na}(v, t)G_{Na}$$

where $Y_K$ and $Y_{Na}$ take values between 0 and 1, and $G_K$ and $G_{Na}$ are the maximum conductances.

From the time course of the measured $g_{Na}$ and $g_K$ (Fig. 3.4), Hodgkin and Huxley proposed that

$$Y_K(v, t) = n^4 \quad \text{and} \quad Y_{Na}(v, t) = m^3h$$

where the gating variables $n$, $m$ and $h$ follow first order kinetics (exponential time course) given by

$$\frac{dn}{dt} = (n_{\infty}(v) - n)/\tau_n(v) \quad n_{\infty} = \frac{\alpha_n}{\alpha_n + \beta_n}, \quad \tau_n = \frac{1}{\alpha_n + \beta_n};$$

(3.3)

$$\frac{dm}{dt} = (m_{\infty}(v) - m)/\tau_m(v) \quad m_{\infty} = \frac{\alpha_m}{\alpha_m + \beta_m}, \quad \tau_m = \frac{1}{\alpha_m + \beta_m};$$

(3.4)

$$\frac{dh}{dt} = (h_{\infty}(v) - h)/\tau_h(v) \quad h_{\infty} = \frac{\alpha_h}{\alpha_h + \beta_h}, \quad \tau_h = \frac{1}{\alpha_h + \beta_h}.$$

(3.5)
Figure 3.4  Time course of $g_K$ (dashed traces) and $g_{Na}$ (solid traces) at various voltages ($V_C$) obtained from $I_K$ and $I_{Na}$ traces, according to Ohm's law.
Reproduced from Figure 6.7 in [36].

Due to the voltage-clamp, equations (3.3)-(3.5) can be solved without worrying about voltage-dependency as follows

$$n(t) = n_0 + [(n_\infty(v) - n_0)(1 - e^{-t/\tau_n})]$$
$$m(t) = m_0 + [(m_\infty(v) - m_0)(1 - e^{-t/\tau_m})]$$
$$h(t) = h_0 + [(h_\infty(v) - h_0)(1 - e^{-t/\tau_h})]$$

The values of $n_\infty$ and $\tau_n$ at each clamped voltage can then be identified from a least-square fitting of the time course of $g_K$ at that clamped voltage. Similarly, the parameters for $N_a^+$ can be identified from a least-square fitting of the time course of $g_{Na}$. 
Then, the $\alpha$, $\beta$ coefficients can be calculated using the following relationships

\[
\alpha_n = n_\infty / \tau_n, \quad \beta_n = (1 - n_\infty) / \tau_n \\
\alpha_m = m_\infty / \tau_m, \quad \beta_m = (1 - m_\infty) / \tau_m \\
\alpha_h = h_\infty / \tau_h, \quad \beta_h = (1 - h_\infty) / \tau_h
\]

Hence, the empirical functions (1.14)-(1.19) presented in the introduction chapter are nothing more than the best fit to the calculated $\alpha$, $\beta$ curves ([68]).

It is worth noting that the ion channel behavior described by Hodgkin and Huxley is collective behavior or the behavior of the sum of many single channels of the same type. At the molecular level, all channels open and close in a random and abrupt fashion. In other words, the channels change between conductive and nonconductive states stochastically, with opening (or closing) probabilities controlled by transmembrane potential. Stochastic analysis of such single-channel behavior establishes the connection between the macroscopic behavior of a neuron and its microscopic structure.

The patch-clamp technique developed by Neher and Sakmann ([44], [58]) makes the recording of single-channel currents a reality. The ensemble average of unitary currents flowing through single channels of the same type (e.g. $N_a^+$, $K^+$ and $C_a^{2+}$) is similar to the whole-cell current recorded by Hodgkin and Huxley (Fig. 3.5). A good description of the patch-clamp technique and the stochastic theory of ion channels can be found in D. Johnston ([36]).

Our research on active neuron identification follows the deterministic approach taken by Hodgkin and Huxley on the macroscopic level. However, unlike Hodgkin and Huxley's voltage clamping experiment, we tend to seek power from advanced mathematical analysis instead of complicated experimental technique.

First, we want to have a review of some mathematical results that are obtained by mathematicians in their study of some similar inverse parabolic problems. These
Figure 3.5  Unitary currents (upper 8 traces) and the ensemble average of unitary currents (lowest trace) of a $N_a^+$ (A) and $K^+$ (B) channel. The membrane voltage is stepped from $V_H = -80 mV$ to $V_C = -30 mV$ for (A) and from $V_H = -100 mV$ to $0 mV$ for (B). Compare it to Fig. 3.3 and Fig. 3.4 (Left). Reproduced from Figure 8.5 in [36].

results may not be applied to our neuron identification problem directly because of the different data sets and requirements they assume, but their methodology has inspired and we believe will continue to inspire new ideas in our current and future research. We start with the work done by Isakov ([33]) who studied the general nonlinear parabolic equation

$$a_0(x, u) u_t - \Delta u + c(x, t, u) = 0$$  \hspace{1cm} (3.6)

in $Q \equiv \Omega \times (0, T)$ where $\Omega$ is a bounded domain in $\mathbb{R}^n$ with $C^2$-smooth boundary. Here, $a_0, c$ are real-valued $L^\infty$-functions on their corresponding domain, $a_0 > \epsilon > 0$. 
The initial condition

$$u = u_0 \quad \text{on } \Omega \times \{0\} \quad (3.7)$$

and the lateral boundary condition

$$u = g \quad \text{on } \partial \Omega \times (0, T) \quad (3.8)$$

are prescribed in Isakov's book. Setting $a_0(x, u) = 1$ and $c(x, t, u) = -f(u) + w(t, u)$ or $c(x, t, u) = G_N m^3 h(E_N - u) + G_K n^4 (E_K - u) + G_L (E_L - u)$, we can easily cast the Fitzhugh-Nagumo eqn. (1.20) or the H-H eqn. (1.10) into the form of (3.6). The bounded domain $\Omega$ is now the line segment $[0, \ell]$. In regard to the initial condition (3.7), it is simply $u_0 = 0$ for our problem. The Dirichlet boundary condition (3.8), however, is not what we are interested in. Instead, we are facing the Neumann type boundary condition (1.7) and (1.8) which are ruled by the way we collect our impedance measurement data. In addition, the following Neumann type of lateral data is considered as known by Isakov

$$a \nabla u \cdot \eta = h \quad \text{on } \Gamma \times (0, T) \quad (3.9)$$

where $\Gamma$ is a part of $\partial \Omega$ and $\eta$ is the normal vector to $\Gamma$. In our neuron identification problem, however, we have the following Dirichlet type of lateral data

$$v(0, t) = v_0(t), \quad 0 < t < T \quad (3.10)$$

recorded at the soma.

Keeping in mind these differences on the lateral data we could collect, we are ready to introduce Isakov's theorem. The proof of the theorem, however, requires the following restrictions on the coefficients $a_0(x, u)$ and $c(x, t, u)$

$$0 < a_0 \quad \text{on } \Omega \times \mathbb{R}, \quad 0 \leq \partial_u c, \quad c(x, t, 0) = 0$$

$$a_0, \partial_u a_0, \partial^2_u a_0, c, \partial_u c, \partial^2_u c \text{ are in } L^\infty(\Omega \times [-U, U]) \quad (3.11)$$
for any finite $U$. Besides, the lateral Dirichlet-to-Neumann map

$$\Lambda_l : g \mapsto h$$

alone seems to be inadequate for recovering $a_0(x, u)$ or $c(x, t, u)$ in general. Additional data at the final moment of time $T$, i.e.

$$u = u_T \quad \text{on} \quad \Omega \times \{T\}$$

is needed. In fact, the so-called complete Dirichlet-to-Neumann map

$$\Lambda : (g, u_0) \mapsto (h, u_T)$$

is required for the uniqueness theorem. With condition (3.11), the theorem says

**Theorem 3.1 (Isakov)** Assume that $a_0 = 1$. Then the complete Dirichlet-to-Neumann map $\Lambda : (g, u_0) \to (h, u_T)$ uniquely determines $c$ on $Q \times \mathbb{R}$.

Although theorem 3.1 provides us a quite strong conclusion, the condition $0 \leq \partial_u c$ in (3.11) is unlikely to be satisfied by the nonlinear term, $c(x, t, u) = -f(u) + w(t, u)$ or $G_{Na} m^3 h(E_{Na} - u) + G_K n^4 (E_K - u) + G_L (E_L - u)$. Worse than that, it does not make sense to stimulate every point along the nerve fiber at the same time. In other words, we can not prescribe an arbitrary initial data $u_0 = v(\cdot, 0)$ which is required for obtaining the complete Dirichlet-to-Neumann map $\Lambda$. Even we can do that, to collect the final data $u_T = v(\cdot, T)$ everywhere along the nerve fiber is not an easy work. Therefore, we hope to relax these requirements by assuming an equivalent cylinder model for the axon and by taking advantage of the special structure

$$c(x, t, u) = -f(u) + w(t, u)$$

or

$$c(x, t, u) = G_{Na} m^3 h(E_{Na} - u) + G_K n^4 (E_K - u) + G_L (E_L - u)$$
The work by Pilant and Rundell reflected this idea. Their fixed-point method proves to be quite effective and suitable to our problem. The reaction-diffusion equation Pilant and Rundell considered in their paper is the following

\begin{align}
    u_t - u_{xx} &= f(u) + \gamma(x,t), \quad x > 0, \ t > 0 \tag{3.13} \\
    u(x,0) &= u_0(x) \tag{3.14} \\
    u_x(0,t) &= -i_0(t) \tag{3.15}
\end{align}

where the unknown function, \( f(\cdot) \), is to be determined by overposing boundary data \( u(0,t) = \theta(t) \), \( t > 0 \).

Note that \( \theta(t) \) plays the role that the voltage response data, \( v_0(t) \), at \( x = 0 \) plays in our problem. The discussion is restricted to the space \( C^{0,\alpha}(D) \) with norm

\[ ||f||_{\alpha} = ||f||_{\infty} + \sup_{u_1, u_2 \in D} \frac{|f(u_1) - f(u_2)|}{|u_1 - u_2|^\alpha} \]

where \( 0 < \alpha \leq 1 \) is the Hölder exponent and \( D = [0,U] \). When \( \alpha = 1 \), the function is Lipschitz, usually the basic requirement for studying the existence, stability and regularity of solutions to an reaction-diffusion system like the Fitzhugh-Nagumo equations ([54], [21], [39]). The Lipschitz condition is also necessary in our inverse problem research on such system. In fact, it is crucial for the convergence of our algorithm in practice.

Because of the special structure \( c(x,t,u) = f(u) + \gamma(x,t) \), Pilant and Rundell were able to define the map

\[ \Pi : C^{0.1}(D) \hookrightarrow C^{0.1}(D) \]

for any given \( f^* \in C^{0.1}(D) \) via

\[ \Pi[f^*](\theta(t)) \equiv \theta'(t) - u_0^*(0,t) + f^*(u^*(0,t)) \tag{3.16} \]
where \( u^*(x,t) \) is the solution to (3.13)-(3.15) with \( f = f^* \) and \( \theta(t) \) is assumed to be monotonic. Pilant and Rundell then proved the equivalence between the inverse problem of recovering \( f \) and the problem of finding the fixed point of \( \Pi \). Under some additional conditions, they also proved the uniqueness of the fixed point and the contractness of the map. In this chapter, Pilant and Rundell’s fixed point method is explored and extended. Their proof is judged under the new framework.

### 3.2 The Fitzhugh-Nagumo System

We first consider the Fitzhugh-Nagumo equation

\[
\begin{align*}
v_t &= v_{xx} + f(v) - w \\
w_t &= bv - \gamma w
\end{align*}
\]

with initial and boundary conditions

\[
\begin{align*}
v(x,0) &= 0 & w(x,0) &= 0 \\
v_x(0,t) &= -i_0(t) \\
v_x(\ell,t) &= 0
\end{align*}
\]

Our goal is to recover the nonlinear conductance function \( f(v) \) and the parameters \( b \) and \( \gamma \) by decoding the voltage response, \( v_0(t) \), at \( x = 0 \) to current injection \( i_0(t) \). Since the reconstruction of \( f(v) \) requires knowledge of \( b \) and \( \gamma \), we will first discuss the identification of \( b \) and \( \gamma \). The key observation here is that \( f(v) \) can be linearized for small \( v \), especially when \( v < 0 \). The linearization is valid so long as we keep \( i_0(t) \) away from its threshold. Under this assumption, the system is actually in passive mode. Therefore, we can once again employ Cox’s ([8]) impedance function mechanism by taking the Laplace transform of the linearized Fitzhugh-Nagumo equation.
\[ v_t = v_{xx} - Gv - w \]  
\[ w_t = bv - \gamma w \]  

Applying the same initial and boundary conditions as in (3.19)-(3.21), we obtain

\[ \hat{v}_{xx} = (s + G + \frac{b}{s + \gamma})\hat{v} \]  

and

\[ \hat{v}_x(0, s) = -\hat{t}_0(s) \]  
\[ \hat{v}_x(\ell, s) = 0 \]  

Solving (3.24)-(3.26), we get the corresponding input impedance function

\[ z_0(s) = \frac{1}{\sqrt{s + G + \frac{b}{s + \gamma}}} \frac{\cosh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)}{\sinh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)} \]  

Taking the derivatives of \( z_0(s) \) up to the second order, we get

\[ z'_0(s) = \frac{\ell}{2} \frac{1 - \frac{b}{b + s + \gamma}}{s + G + \frac{b}{s + \gamma}} - \frac{\ell^2}{2} \frac{\cosh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)}{\sinh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)} \]  

and

\[ z''_0(s) = -\frac{3\ell}{4} \left( \frac{1 - \frac{b}{b + s + \gamma}}{s + G + \frac{b}{s + \gamma}(s + \gamma)} \right)^2 + \frac{\ell b}{(s + G + \frac{b}{s + \gamma})(s + \gamma)^3} \]

\[ + \left( \frac{3}{4} \frac{1 - \frac{b}{b + s + \gamma}}{(s + G + \frac{b}{s + \gamma})^{3/2}} - \frac{b}{(s + G + \frac{b}{s + \gamma})^{3/2}(s + \gamma)^3} - \frac{\ell^2}{2} \frac{1 - \frac{b}{b + s + \gamma}}{(s + G + \frac{b}{s + \gamma})^{3/2}} \right) \frac{\cosh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)}{\sinh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)} \]

\[ + \left( \frac{3\ell}{4} \frac{1 - \frac{b}{b + s + \gamma}}{(s + G + \frac{b}{s + \gamma})^{3/2}} - \frac{\ell b}{(s + G + \frac{b}{s + \gamma})(s + \gamma)^3} \right) \left( \frac{\cosh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)}{\sinh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)} \right)^2 \]  

\[ + \frac{\ell^2}{2} \frac{(1 - \frac{b}{b + s + \gamma})^2}{(s + G + \frac{b}{s + \gamma})^{3/2}} \left( \frac{\cosh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)}{\sinh(\sqrt{s + G + \frac{b}{s + \gamma}} \ell)} \right)^3 \]  

(3.29)
To guarantee positivity of $s + G + \frac{b}{s+\gamma}$, we only consider $s \geq 0$ (and $s \neq 0$ when $\gamma = 0$). Now, using the identities

\[ L \equiv \sqrt{s + G + \frac{b}{s+\gamma} \ell} \]
\[ \alpha \equiv 1 - \frac{b}{(s+\gamma)^2} \]
\[ \beta \equiv \frac{b}{(s+\gamma)^3} \]

(3.30)

eqn. (3.27)-(3.29) can be simplified to

\[ z_0(s) = \frac{\ell}{L} \frac{\cosh(L)}{\sinh(L)} \]
(3.31)

\[ z'_0(s) = \frac{\ell^3 \alpha}{2L^2} - \frac{\ell^3 \alpha \cosh(L)}{2L^3 \sinh(L)} - \frac{\ell^3 \alpha}{2L^2} \left( \frac{\cosh(L)}{\sinh(L)} \right)^2 \]
\[ = \left( \frac{\ell^3}{2L^2} - \frac{\ell^2}{2L^2} z(s) - \frac{\ell}{2} z^2(s) \right) \alpha \]
(3.32)

\[ z''_0(s) = -\frac{3\ell^5 \alpha^2}{4L^4} + \frac{\ell^3 \beta}{L^2} + \left( \frac{3\ell^5 \alpha^2}{4L^5} - \frac{\ell^3 \beta}{L^3} - \frac{\ell^5 \alpha^2}{2L^3} \right) \frac{\cosh(L)}{\sinh(L)} \]
\[ + \left( \frac{3\ell^5 \alpha^2}{4L^4} - \frac{\ell^3 \beta}{L^2} \right) \left( \frac{\cosh(L)}{\sinh(L)} \right)^2 + \frac{\ell^5 \alpha^2}{2L^3} \left( \frac{\cosh(L)}{\sinh(L)} \right)^3 \]
\[ = \frac{2z'(s)}{\alpha} \beta - \frac{3\ell^2 z'(s)}{2L^2} \alpha - \left( \frac{\ell^4 z(s)}{2L^2} - \frac{\ell^2 z^3(s)}{2} \right) \alpha^2 \]
(3.33)

Since the right-hand side of Eqn. (3.31) is a monotonic function in $L(L > 0)$, it can be easily solved when $z_0(s)$ is known. Once we have the value of $L$, $\alpha$ and $\beta$ can be obtained from (3.32) and (3.33) when $z'_0(s)$ and $z''_0(s)$ are known.

\[ \alpha = \frac{2L^2 z'_0(s)}{\ell^3 - \ell^2 z_0(s) - L^2 \ell z_0^2(s)} \]
(3.34)

\[ \beta = \frac{2L^2 z''_0(s) \alpha + 3\ell^2 z'_0(s) \alpha^2 + [\ell^2 z_0(s) - L^2 z_0^2(s)] \ell^2 z_0(s) \alpha^3}{4L^2 z'_0(s)} \]
Finally, we can calculate $b$ and $\gamma$ using (3.30)

$$\gamma = \frac{1 - \alpha}{\beta} - s$$

$$b = (1 - \alpha)(s + \gamma)^2$$  \hspace{1cm} (3.35)

Given the voltage response data, $v_0(t)$, and the input current, $i_0(t)$, the computation of the impedance data $\{z_0(s), z_0'(s), z_0''(s)\}$ is similar to the computation of admittance data in (2.36). If we denote

$$M_k(u, s) = \int_0^\infty t^k u(t) e^{-st} dt$$

as the k-th moment of $u$ at $s$, then

$$z_0(s) = \frac{M_0(v_0, s)}{M_0(i_0, s)}$$

$$z_0'(s) = -\frac{M_1(v_0, s) + z_0(s) M_1(i_0, s)}{M_0(i_0, s)}$$

$$z_0''(s) = \frac{M_2(v_0, s) - M_2(i_0, s) z_0(s) + 2 M_1(i_0, s) z_0'(s)}{M_0(i_0, s)}$$  \hspace{1cm} (3.36)

One advantage of our derivation is that we don't have to force $s = 0$ or any other particular value. Theoretically, every $s \geq 0$ (and $s \neq 0$ when $\gamma = 0$) should offer the same answer. However, in practice, since error in the experimental data is inevitable, our numerical simulation shows quite different recovered parameter values for different choices of $s$ (Fig. 3.6). And, as we can see from Fig. 3.6, the more accurate the recorded voltage response, $v_0(t)$, the closer the curve $b(s)$ (or $\gamma(s)$) is to a horizontal line. The question now becomes which $s$ should we trust?

There is no doubt some choices of $s$ inhibit the error in collected data, some magnify it. For example, if $s$ is too big, the tail of our recorded voltage response, $v_0(t)$, will be eliminated when we compute the impedance data $z_0(s)$. This is because
Figure 3.6  The recovered parameter values for $b$ and $\gamma$ from (3.35) as a function of $s$. I, II, III and IV correspond the voltage response data I, II, III and IV in Fig. 3.7 respectively.

Figure 3.7  The voltage response, $v_0(t)$, of the Fitzhugh-Nagumo system to input current, $i_0(t) = -0.008 \left[ \sin \left( \frac{t}{2} - \frac{T}{2} \right) + 1 \right]$. Computed with various step size. I: $dx = 0.025$; II: $dx = 0.1$; III: $dx = 0.2$ and IV: $dx = 0.5$. 
the integrand involves $e^{-st}$, a fast decreasing factor for large $t$. Typically, we choose $s$ to be less than $10/T$ where $T$ is the time span of the recorded voltage response. Additionally, if $s$ is chosen such that $s + \gamma$ is too small, $L$, $\alpha$ and $\beta$ as defined in (3.30) would blow up.

![Graphs](image)

**Figure 3.8** The first derivative of the parameters $b$ (Left) and $\gamma$ (Right) as a function of $s$. Computed by finite difference.

Unfortunately, it is difficult to give a mathematical criteria that strictly distinguishes a good $s$ from the bad one. However, a reasonable candidate for $s$ based on our numerical experiment, can be obtained by studying the derivatives of recovered $b$ and $\gamma$ as functions of $s$. The point $s_b$ (or $s_\gamma$) in Fig. 3.8, where $|b'(s)|$ approximates the first local minimum of $|b'(s)|$ for $s > 0$, indicates that the dramatic change in the recovered parameter $b$ (or $\gamma$) slows down. Therefore, $s_b$ (or $s_\gamma$) can be regarded as the starting point of good $s$. Since it is difficult to tell which choice of $s$ is better after
let \( s_b \) (or \( s_\gamma \)), we will simply choose \( b(s_b) \) and \( \gamma(s_\gamma) \). In summary, our discussion yields the algorithm

**Algorithm 2**  \textit{Recover b and }\gamma.

\textbf{I.} Inject a sub-threshold current \( i_0(t) \) into the soma and record the entire course of voltage response \( v_0(t) \).

\textbf{II.} Suppose the recording time range is up to \( T \). Let \( S = 10/T \) and \( ds = S/100 \).

\textbf{III.} For \( s = 10^{-1} : ds : S \), do the following

- Compute the impedance data \( \{z_0(s), z_0'(s), z_0''(s)\} \) by (3.36).

- Solve the Eqn. (3.31) for \( L \).

- Compute \( \alpha(s) \) and \( \beta(s) \) by (3.34).

- Compute \( b(s) \) and \( \gamma(s) \) by (3.35).

\textbf{IV.} Find \( s_b \) and \( s_\gamma \) from the \( b'(s) \) and \( \gamma'(s) \) curves. The values of \( b(s_b) \) and \( \gamma(s_\gamma) \) are the final recovered parameters.

We tested algorithm 2 for \( f(v) = v(v - 0.2)(1 - v), b = 0.01 \) and \( \gamma = 0.008 \). Our voltage response data \( v_0(t) \) comes from solving the forward problem (3.17)-(3.21) with

\[ i_0(t) = -0.008[\sin\left(\frac{t}{8} - \frac{\pi}{2}\right) + 1]. \]

By varying the spatial step size, \( dx \), we are able to obtain \( v_0(t) \) of different accuracies(Fig. 3.7). In Fig. 3.9, the relative errors

\[ \epsilon_b = \frac{|b - b_e|}{b_e}, \quad \epsilon_\gamma = \frac{|\gamma - \gamma_e|}{\gamma_e} \]

where \( b_e \) and \( \gamma_e \) denote the exact values of \( b \) and \( \gamma \) respectively are plotted against the relative error in voltage response

\[ \epsilon_v = \frac{\max_{0 \leq t \leq T} |v_0(t) - \tilde{v}_0(t)|}{\max_{0 \leq t \leq T} |\tilde{v}_0(t)|}. \]
The exact voltage response, denoted $\tilde{v}_0(t)$, is computed by solving the forward linearized system (3.22)-(3.23) with $dx = 0.025$.

![Graph](image)

**Figure 3.9** Relative error in the parameters $b$ and $\gamma$ that are recovered from noisy voltage responses. The error in the voltage response is introduced by varying the spatial step size $dx (= 0.025, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.5)$ in the forward solver.

Once $b$ and $\gamma$ are known, we can recover $f(v)$. Following the idea of Pilant and Rundell's fixed point method ([46], [47]), given $f^* \in C^{0,1}(D)$, we define the map

$$\Pi : C^{0,1}(D) \mapsto C^{0,1}(D)$$

such that

$$\Pi[f^*](v_0(t)) \equiv v_0'(t) - v_t^*(0, t) + w_0(t) - w^*(0, t) + f^*(v^*(0, t))$$  \hspace{1cm} (3.37)

where

$$w_0(t) = b \int_0^t e^{\gamma(t-\tau)} v_0(\tau) \, d\tau$$
and \((v^*, w^*)\) is the solution to (3.17)-(3.21) with \(f = f^*\). Since the definition of \(\Pi[f^*]\) is in the time domain, \(t\), we require that \(v_0(t)\) is monotonic in certain time span \(0 < t < T\) in order to have a function in voltage domain, \(v\). This can be achieved by injecting an appropriate current, \(i_0(t)\).

It is easy to verify that \(\Pi[f](0) = 0\). The following theorem allows us to transform the inverse problem of recovering \(f(v)\) into finding the fixed point of \(\Pi\) in \(C^{0,\alpha}\).

**Theorem 3.2** Given \(f^* \in C^{0,1}\), \(v^*(x, t)\) is a solution to (3.17)-(3.21) with \(v^*(0, t) = v_0(t)(0 \leq t < T)\) if and only if \(f^*\) is the fixed point of \(\Pi\).

**Proof** \(\implies\) If \(v^*\) is the solution with \(v^*(0, t) = v_0(t)\), then

\[
\begin{align*}
v'_0(t) &= v^*_t(0, t) \\
w_0(t) &= b \int_0^t e^{\gamma(\tau-t)} v_0(\tau) d\tau \\
&= b \int_0^t e^{\gamma(\tau-t)} v^*_t(0, \tau) d\tau \\
&= w^*(0, t)
\end{align*}
\]

From the definition of \(\Pi\) in (3.37), it is easy to see that

\[
\Pi[f^*](v) = f^*(v)
\]

for any \(v = v_0(t)(0 \leq t < T)\).

\(\impliedby\) if \(f^*\) is a fixed point of \(\Pi\) in (3.37), then we have

\[
f^*(v_0(t)) = v'_0(t) - v^*_t(0, t) + w_0(t) - w^*(0, t) + f^*(v^*(0, t))
\]

Setting \(\alpha(t) = v_0(t) - v^*(0, t)\), we obtain

\[
\alpha'(t) = f^*(v_0(t)) - f^*(v^*(0, t)) - (w_0(t) - w^*(0, t))
\]

\[
= f^*(v_0(t)) - f^*(v^*(0, t)) - b \int_0^t e^{\gamma(\tau-t)} \alpha(\tau) d\tau
\]
Since $f^*$ is Lipschitz, it follows that
\[ |\alpha'(t)| \leq B|\alpha(t)| + b \int_0^t |\alpha(\tau)| \, d\tau \]  
(3.38)

Integrating (3.38) from 0 to $t$, we get
\[
\left| \int_0^t \alpha'(\tau) \, d\tau \right| \leq \int_0^t |\alpha'(\tau)| \, d\tau \\
\leq B \int_0^t |\alpha(\tau)| \, d\tau + b \int_0^t \int_0^\tau |\alpha(\eta)| \, d\eta \, d\tau \\
\leq (B + bT) \int_0^t |\alpha(\tau)| \, d\tau
\]

for $0 < t < T$. Since $\alpha(0) = 0$, it follows from Gronwall's inequality that $\alpha(t) = 0$ for all $0 < t < T$, i.e. $v^*(x, t)$ is the solution to (3.17)-(3.21) with $v^*(0, t) = v_0(t)$.

\[ \Box \]

To find the fixed point of the map $\Pi$, we compute the iterative sequence $\{f_{n+1} \equiv \Pi[f_n]\}_{n=0}^\infty$. This sequence will converge if the map $\Pi$ is a contraction. Although our numerical experiments do exhibit a strongly convergent sequence for a widely varying set of initial functions, the mathematical proof turns out to be quite challenging. The proof found in Pilant and Rundell's original paper ([46]) is premature. Although they did provide a more detailed and careful proof in a later paper ([47]), some of their required assumptions do not apply to our problem. At the end of this section, we will give the general idea of their proof and discuss its limitation in predicting the global convergence observed in our numerical experiment. First, we present the main algorithm.

**Algorithm 3**  Reconstruct $f(v)$ with $b$ and $\gamma$ known.

I. Input a current $i_0(t)$ and record the entire monotonic part of the voltage response $\{v_0(t_k) : 0 = t_0 < t_1 < \cdots < t_m = T\}$.

II. Compute $w_0(t_k) = b \int_0^{t_k} e^{\gamma(\tau-t_k)} v_0(\tau) \, d\tau$, $k = 0, 1, \cdots, m$. 
III. choose the initial function $f_0(v)$ and set $n = 0$. Also, choose a set of sampling nodes, $0 = T_0 < T_1 < \cdots < T_M = T$, for the purpose of cubic spline interpolation.

IV. Solve the Fitzhugh-Nagumo equation with $f = f_n$ and denote the solution $(v^{(n)}(x, t), w^{(n)}(x, t))$.

V. Compute $y(t_k) \equiv \Pi[f_n(v_0(t_k)) \equiv v_0'(t_k) - v^{(n)}(0, t_k) + w_0(t_k) - w^{(n)}(0, t_k) + \left. c_n(v^{(n)}(0, t_k)) \right|_{k = 0, 1, \cdots, m}$.

VI. Interpolate $(v_0(T_0), y(T_0)), (v_0(T_1), y(T_1)), \cdots, (v_0(T_M), y(T_M))$ by cubic spline to get $f_{n+1}(v)$.

VII. Increase $n$ by 1 and repeat step IV-VII until $||f_{n+1} - f_n||_1$ is small enough.

**Note:** The cubic-spline is not only important for representing a general $C^2$ function. It also helps to smooth $\Pi[f_n]$ after each iteration, which is a critical technique for suppressing the numerical error that arises from computing the first derivative by finite differences. We give more detailed discussion of this issue when we extend the fixed-point method to a real neuron model.

The algorithm is tested on the nonlinear function $f(v) = v(v - 0.2)(1 - v)$ and using the known parameters $b = 0.006$, $\gamma = 0$ and $\ell = 10$. The voltage response data, $v_0(t)$, is collected by numerically solving the Fitzhugh-Nagumo equation (3.17)-(3.18).

To solve the Fitzhugh-Nagumo equation, we first partition the space as

$$0 = x_0 < x_1 < \cdots < x_n = \ell, \quad x_j = x_{j-1} + dx$$

where $dx = \ell/n$ and we discretize the equation (3.17)-(3.18) via finite-differences to get

$$v_x(x_j, t) \approx \frac{v(x_{j+1}, t) - v(x_j, t)}{dx}$$
\[ v_{xx}(x_j, t) \approx \frac{v(x_{j+1}, t) - 2v(x_j, t) + v(x_{j-1}, t)}{dx^2} \]

where \(0 \leq j \leq n\). Denoting \(V(j, t) = v(x_j, t)\) and \(W(j, t) = w(x_j, t)\) for \(1 \leq j \leq n\), we then proceed to solve the ordinary differential equations

\[
\frac{dV}{dt} = AV + F(V) - W + I_0 \tag{3.39}
\]
\[
\frac{dW}{dt} = BV - RW \tag{3.40}
\]

where \(I_0 = (-i_0(t)/dx, 0, \cdots, 0)^T\).

\[
A = \begin{pmatrix}
-1 & 1 & & & \\
1 & -2 & 1 & & \ \\
& 1 & -2 & 1 & \\
& & \cdots & \cdots & \cdots \\
1 & & -2 & 1 & \\
& & & 1 & -1
\end{pmatrix}, \quad F(V) = \begin{pmatrix}
f(V(1, t)) \\
f(V(2, t)) \\
\vdots \\
f(V(n, t))
\end{pmatrix}
\]

and

\[
B = \begin{pmatrix}
b \\
& b \\
& & \cdots \\
& & & b \\
& & & & b
\end{pmatrix}, \quad R = \begin{pmatrix}
\gamma \\
& \gamma \\
& & \gamma \\
& & & \gamma \\
& & & & \gamma
\end{pmatrix}
\]

Under the assumption of a quiet neuron at \(t = 0\), the initial condition would be \(V(\cdot, 0) \equiv 0\). Then, (3.39)-(3.40) can be solved using the existing Matlab ODE solver "ode15s".

In our numerical experiment, we choose the input current \(i_0(t) = 0.1(\sin(\frac{t}{8} - \frac{\pi}{2}) + 1)\) to recover \(f\) for \(v > 0\) (Fig. 3.10) and \(i_0(t) = -0.22(\sin(\frac{t}{8} - \frac{\pi}{2}) + 1)\) to recover \(f\) for
Figure 3.10  The voltage response of the FitzHugh-Nagumo system to input current, \( i_0(t) = 0.1 \left[ \sin \left( \frac{t}{8} - \frac{\pi}{2} \right) + 1 \right] \).

Figure 3.11  The voltage response of the FitzHugh-Nagumo system to input current, \( i_0(t) = -0.22 \left[ \sin \left( \frac{t}{8} - \frac{\pi}{2} \right) + 1 \right] \).
\( v < 0 \) (Fig. 3.11). We also choose \( dt = 0.25 \) as the recording time interval and \( T = 50 \) as the recording time length. The voltage response data, \( v_0(t) \), is then computed with \( dx = 0.5 \). The length of the neuron is set to be \( \ell = 10 \). For the first test of the algorithm, we choose the same space discretization \( dx = 0.5 \) to solve the Fitzhugh-Nagumo equations in step IV. In this sense, the data is regarded as exact (no noise). The result of running algorithm 3 for different initial functions \( f_0 \) are shown in Fig. 3.12. As you can see, the sequence converges after only 10 iterations and this convergence is independent of the choice of initial functions.

**Figure 3.12** The iterative sequence of functions, \( \{\Pi[f_n]\} \) for recovering \( f(v) = v(v - 0.2)(1 - v) \) where \( \Pi \) is defined by (3.37). Shown are functions recovered after 1, 3, 6 and 10 iterations.
To investigate the sensitivity of the inverse problem to error in the recorded data, \( v_0(t) \), we vary the space step size, \( dx \), in computing the original response data, \( v_0(t) \). The error in \( v_0(t) \) is then measured by

\[
\varepsilon_v = \frac{\max_{0 < t < T} |v_0(t) - \tilde{v}_0(t)|}{\max_{0 < t < T} |\tilde{v}_0(t)|} + \frac{\max_{0 < t < T} |v_0'(t) - \tilde{v}_0'(t)|}{\max_{0 < t < T} |\tilde{v}_0'(t)|}
\]  

(3.41)

where \( \tilde{v}_0(t) \) is the "exact" voltage response data. The distance between the reconstructed function \( f(v) \) and the target function \( \tilde{f} \) is measured by

\[
\varepsilon_f = \frac{||f - \tilde{f}||_\infty}{||f||_\infty}
\]

(3.42)

Figure 3.13  Error in the recovered \( f \) (computed by (3.42)) as a function of error in the voltage response data (computed by (3.41)). The error in the voltage response data is introduced by varying the spatial step size, \( dx \), in the forward solver.
Figure 3.14  The input current, \( i_0(t) = 0.1[\sin(\frac{t}{8} - \frac{\pi}{2}) + 1] \), and the voltage response, \( v_0(t) \). I: computed with \( dx = 0.05 \) (exact data); II: computed with \( dx = 0.4 \).

Figure 3.15  The recovered function \( f \) (-x-x- line) by using the voltage response data II shown in Fig. 3.14.
Figure 3.16 Error in the recovered parameters $b$ and $\gamma$ by algorithm 2. The exact values are $b = 0.006$ and $\gamma = 0$. The function $f = v(v - 0.2)(1 - v)$.

Figure 3.17 The recovered function $f$ by using inexact parameters $b = 0.007$ (exact value: 0.006) and $\gamma = 0.0006$ (exact value: 0).
The relationship between $\epsilon_f$ and $\epsilon_v$ that results from running algorithm 3 for $dx = 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4$ and $0.5$ is shown in Fig. 3.13. The response computed from $dx = 0.05$ is used as the "exact" data in the error computation. In all cases, $dx = 0.05$ in step IV. Fig. 3.14 and Fig. 3.15 illustrate the response curve, $v_0(t)$, and the corresponding recovered function, $f(v)$, for the case $dx = 0.4$ to show a direct comparison between the two errors.

Combining algorithm 3 and algorithm 2 in this section, we are able to reconstruct the whole Fitzhugh-Nagumo system (3.17)-(3.18) by analyzing the system's voltage response to input current at the soma. To get an idea how accurate the entire reconstruction is, we first run algorithm 2 on the example model

$$f(v) = v(v - 0.2)(1 - v) \quad \text{and} \quad b = 0.006, \quad \gamma = 0$$

to get $b$ and $\gamma$. The relative error in the recovered $b$ and the absolute error in the recovered $\gamma$ are plotted in Fig. 3.16. We then choose $b = 0.007, \gamma = 0.0006$ for the reconstruction of $f(v)$. The error in the recorded voltage response in this case is about 9%. The converging sequence to the target function that results from algorithm 3 is shown in Fig. 3.17. Due to the error in $b$ and $\gamma$, Fig. 3.17 shows a small gap between the limit of the sequence and the target function. However, this error is less than 10% and is approximately the same as the error in the voltage response.

To close this section, we would like to introduce the convergence theorem from Pilant and Rundell ([47]). For conformity, some of their notation has changed. To prove their theorem, Pilant and Rundell made the following assumptions on the data

**A1.** $u_0 \in C^{2,\alpha}[0, \infty)$,

$$i_0(t) = 0$$

$$\gamma(x, t) \in C^{0,\alpha}[0, \infty) \times C^{0,\alpha}[0, \infty).$$
A2. The function $\theta(t)$ is a monotone function whose derivative lies in $C^{0,\alpha}[0, \infty)$, and $\inf_{t \geq 0} |\theta'(t)| \geq \delta > 0$.

A3. $f \in B_E := \{||f||_\alpha \leq E\}$ for some constant $E$.

In addition, they defined and used the “Property S” of the target function $f$

**Property S:** Given functions $u, v \in C^{0,\alpha}$, we say a function $f \in C^{0,\alpha}$ has “Property S” if there exists a constant $C_S < \infty$ s.t.

$$||f \circ u - f \circ v||_\alpha \leq C_S ||u - v||_\alpha$$

Under assumptions A1-A3, the theorem concludes

**Theorem 3.3 (Pilant-Rundell)** If the fixed point $f$ of the map $\Pi$ has property S, then it is unique. Furthermore, the map is a contraction on $C^{0,\alpha}$, $\alpha < 1$ for $t \in [0, T_E]$ where $T_E$ is small enough.

A direct result of theorem 3.3 is

**Corollary 3.1** If the overposed data $\theta(t)$ arises from a Lipschitz function $f$ with property S, then the iterative sequence $\{f_{n+1} \equiv \Pi[f_n]\}$ converges strongly in $C^{\alpha}$, $\alpha < 1$, to the unique solution.

The proof of the theorem involves the *a priori estimate* for parabolic equations.

Noting that the map defined in (3.16) can be written in the equivalent form

$$\Pi[f](\theta(t)) = \theta'(t) - u_{xx}(0, t) - \gamma(0, t)$$

we have

$$\Pi[f^*] - \Pi[f] = u^*_{xx} - u_{xx}$$

$$= \int_0^t \int_0^\infty G_{xx}(0, y; t - \tau) [f^*(u^*(y, \tau)) - f(u(y, \tau))]\,dy\,d\tau$$
The main goal is then to estimate \( \|\Pi[f^*] - \Pi[f]\|_\alpha \) in terms of \( \|f^* - f\|_\alpha \) where \( f \) is the fixed point of \( \Pi \) and \( f^* \) is in a neighborhood of \( f \). The map is a contraction if there exists a constant \( \Lambda < 1 \) such that

\[
\|\Pi[f^*] - \Pi[f]\|_\alpha \leq \Lambda \|f^* - f\|_\alpha
\]

After a lengthy computation, Pilant and Rundell do come up with such a constant \( \Lambda \). The assumptions A1-A3 turn out to be essential and cannot be circumvented. Although the Fitzhugh-Nagumo equations appear to be quite similar to Pilant and Rundell’s equation (3.13), this proof, unfortunately, is not applicable because two of the fundamental assumptions are violated. First, the input current, \( i_0(t) \), is meant to be non-zero in our system in order to evoke a voltage response. Secondly, unlike in equation (3.13) where the external forcing term \( \gamma(x,t) \) can guarantee

\[
\inf_{t \geq 0} |\theta'(t)| \geq \delta > 0
\]

the voltage response, \( v_0(t) \), in our case always has a zero derivative at \( t = 0 \) as long as the input current \( i_0(t) \) is continuous at \( t = 0 \).

The other limitation of Pilant and Rundell’s proof is that the time span \([0, T_E]\) in theorem 3.3 has to be “small enough”. It is not clear from their paper how small it should be. On the other hand, our numerical experiment shows that the convergence occurs in a global sense. Therefore, we believe that there must be some other mechanism hidden in the system waiting to be explored.

### 3.3 The Morris-Lecar Model

It has been argued that the Fitzhugh-Nagumo system does not represent any real-life neuron. In this section, we shall extend Pilant and Rundell’s fixed point method to a realistic neuron model. The Morris-Lecar model ([41]) describes the conductance
system of the Barnacle muscle fiber. The system is established following the Hodgkin-Huxley theory and consists of two voltage dependent ion channels, the \( C_{a}^{++} \) and the \( K^{+} \) channels. In their original form, the equations are given as

\[
C_{m} v_{t} = \frac{d}{4R_{a}} v_{xx} - G_{C_{a}} m(v - E_{C_{a}}) - G_{K} w(v - E_{K}) - G_{L}(v - E_{L})
\]

\[
m_{t} = (m_{\infty}(v) - m)/\tau_{m}(v)
\]

\[
w_{t} = (w_{\infty}(v) - w)/\tau_{w}(v)
\]

However, voltage-clamping experiments on Barnacle muscle fiber show that the \( C_{a}^{++} \) currents responds to a voltage change much faster than the \( K^{+} \) currents and therefore can be assumed to always be in equilibrium for the time course we are considering. This assumption allows us to neglect the dynamics of \( C_{a}^{++} \) channel and to consider the two dimensional reduced version of the equations ([37]). There are different variations of the Morris-Lecar equations in usage. The one we chose for our inverse problem research is from the presentation in Rinzel and Ermentrout ([55])

\[
C_{m} v_{t} = \frac{d}{4R_{a}} v_{xx} - G_{C_{a}} m_{\infty}(v)(v - E_{C_{a}})
\]

\[-G_{K} w(v - E_{K}) - G_{L}(v - E_{L})\]  

(3.44)

\[
w_{t} = (w_{\infty}(v) - w)/\tau_{w}(v)
\]

(3.45)

where \( m_{\infty}(v) \) and \( w_{\infty}(v) \) are the steady state kinetic functions for \( C_{a}^{++} \) and \( K^{+} \) channels respectively and \( \tau_{w}(v) \) is the time constant for opening of \( K^{+} \) channels. In general, these functions take the following forms

\[
m_{\infty}(v) = \frac{1}{2} \left[ 1 + \tanh\left(\frac{v - E_{1}}{E_{2}}\right) \right]
\]

(3.46)

\[
w_{\infty}(v) = \frac{1}{2} \left[ 1 + \tanh\left(\frac{v - E_{3}}{E_{4}}\right) \right]
\]

(3.47)

\[
\tau_{w}(v) = \frac{1}{\Lambda_{w} \cosh\left(\frac{v - E_{3}}{2E_{4}}\right)}
\]

(3.48)
and are obtained mainly from analyzing voltage-clamp experimental data. The variables \( m \) and \( w \) are analogous to the variables \( m \) and \( n \) in Hodgkin-Huxley’s system (1.10)-(1.13). They can be viewed as the fraction of channels open at any given time or membrane potential. The physical meaning of the other parameters in (3.44) and in (3.46)-(3.48) are listed below:

- \( C_m \): the membrane capacitance (\( \mu F/cm^2 \)).
- \( G_{C_a}, G_K, G_L \): the maximum or instantaneous conductance for \( C_{a^{++}} \), \( K^+ \) channels and leakage respectively (\( mS/cm^2 \)).
- \( E_{C_a}, E_K, E_L \): the equilibrium potential for \( C_{a^{++}} \), \( K^+ \) and leakage respectively (\( mv \)).
- \( E_1 \): potential at which \( m_\infty = 0.5 \) (\( mv \))
- \( E_2 \): reciprocal of slope of voltage dependence of \( m_\infty \) (\( mv \)).
- \( E_3 \): potential at which \( w_\infty = 0.5 \) (\( mv \)).
- \( E_4 \): reciprocal of slope of voltage dependence of \( w_\infty \) (\( mv \)).
- \( \Lambda_w \): maximum rate constant for \( K^+ \) channel opening (\( ms^{-1} \)).

As before, the neuron is assumed to be undisturbed in the beginning and is subject to a current injection at \( x = 0 \). The initial and boundary conditions thus are

\[
\begin{align*}
v(x, 0) &= V_r \\
v_x(0, t) &= -\frac{d}{4R_a} i_0(t) \\
v_x(\ell, t) &= 0
\end{align*}
\]  

(3.49) (3.50) (3.51)

where \( \ell \) is the length of the muscle fiber, \( V_r \) is the resting membrane potential and \( W_r = w_\infty(V_r) \). In fact, \( (V_r, W_r) \) solves the equation

\[
G_{C_a} m_\infty(v)(v - E_{C_a}) + G_K w(v - E_K) + G_L(v - E_L) = 0
\]

\[
w_\infty(v) - w = 0
\]
in \((v, w)\) and represents the stable equilibrium point of the system.

### 3.3.1 Calcium channel identification

The ultimate goal of active neuron identification is to recover all the parameters in the system. However, it is usually not possible to identify them all at one time. If we define

\[
f(v) = G_{Ca} m_\infty(v)(v - E_{Ca})
\]

then the simplified Morris-Lecar system (3.44)-(3.45) looks very similar to the Fitzhugh-Nagumo equations. We therefore attempt to reconstruct the function \(f(v)\) first. Under the assumption that all the other parameters

\[
\{C_m, R_a, G_L, G_K, E_L, E_K, d, \ell\}
\]

are known, we can define the map

\[
\Pi : C^{0,1}(D) \rightarrow C^{0,1}(D)
\]

for which

\[
\Pi[f^*(v_0(t))] = f^*(v^*(0, t)) - C_m[v_0'(t) - v^*_t(0, t)] - G_L[v_0(t) - v^*(0, t)]
\]

\[
- G_K[w_0(t)(v_0(t) - E_K) - w^*(0, t)(v^*(0, t) - E_K)]
\]

where \(v_0(t) (0 < t < T)\) is the voltage response recorded at \(x = 0\) and \((v^*(x, t), w^*(x, t))\) is the solution to (3.44)-(3.45) with the same current stimulation as for \(v_0(t)\) and with \(f = f^*\). As is the case of Fitzhugh-Nagumo equations, since the function \(w_\infty\) and \(\tau_\infty\) are known, eqn. (3.45) can be solved analytically to obtain

\[
w_0(t) = e^{-\int_0^t h(\tau) d\tau} \int_0^t g(\tau) e^{\int_0^\tau h(\sigma) d\sigma} d\tau
\]

where

\[
g(t) = \frac{w_\infty(v_0(t))}{\tau_w(v_0(t))} \quad \text{and} \quad h(t) = \frac{1}{\tau_w(v_0(t))}
\]
Applying algorithm 3 with the map $\Pi$ defined in (3.53), we carried out a numerical simulation of the inverse procedure for the set of parameter values prescribed in Table 3.1 where the parameter values for $C_a^{++}$ are only used to numerically generate the response data and are assumed to be unknown everywhere else. To numerically solve the Morris-Lecar system (3.44)-(3.45) with initial and boundary conditions (3.49)-(3.51), we utilize the same procedure used in solving the FitzHugh-Nagumo equations. Precisely speaking, we solve the following ordinary differential equations after discretization

\[
\begin{align*}
\frac{dV}{dt} & = AV - F(V) - G_K W \circ (V - E_K) - G_L (V - E_L) + I_0 & (3.55) \\
\frac{dW}{dt} & = P(V, W)
\end{align*}
\]

where $I_0 = (-\frac{4R_n i_0(t)}{dx_d}, 0, \ldots, 0)^T$,

\[A = \frac{1}{RC} \begin{pmatrix} -1 & 1 \\ 1 & -2 & 1 \\ 1 & -2 & 1 \\ \vdots & \vdots & \vdots \\ 1 & -2 & 1 \\ 1 & -1 \end{pmatrix}, \quad F(V) = \begin{pmatrix} f(V(1, t)) \\ f(V(2, t)) \\ f(V(3, t)) \\ \vdots \\ f(V(n, t)) \end{pmatrix}
\]

and

\[P(V, W) = \begin{pmatrix} p(V(1, t), W(1, t)) \\ p(V(2, t), W(2, t)) \\ p(V(3, t), W(3, t)) \\ \vdots \\ p(V(n, t), W(n, t)) \end{pmatrix}, \quad p(v, w) = (w_\infty(v) - w)/\tau_w(v).
\]

The operator $\circ$ in (3.55) represents component wise vector product.
Table 3.1  An example set of parameter values for Morris-Lecar Model

<table>
<thead>
<tr>
<th>geometry</th>
<th>$K^+$ channel</th>
<th>$Ca^{++}$ channel</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d = 0.04\ cm$</td>
<td>$G_K = 2.0\ mS/cm^2$</td>
<td>$G_{Ca} = 1.1\ mS/cm^2$</td>
<td>$G_L = 0.5\ mS/cm^2$</td>
</tr>
<tr>
<td>$\ell = 5\ cm$</td>
<td>$E_K = -70\ mv$</td>
<td>$E_{Ca} = 100\ mv$</td>
<td>$E_L = -50\ mv$</td>
</tr>
<tr>
<td></td>
<td>$E_3 = 0$</td>
<td>$E_1 = -1\ mv$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E_4 = 30\ mv$</td>
<td>$E_2 = 15\ mv$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\Lambda_w = 0.2\ ms^{-1}$</td>
<td>$C_m = 1\ \mu F/cm^2$</td>
<td>$R_a = 0.03\ k\Omega cm$</td>
</tr>
</tbody>
</table>

As before, in our first trial of the algorithm, we chose the same $dx(=0.05)$ for both the computation of response data and the use of the intermediate solver in step IV. This will give us a virtually exact data set. The recording time interval is $dt = 0.1\ msec$. After running the algorithm with input current (Fig. 3.18)

$$i_0(t) = 6\left[\sin\left(\frac{t}{2} - \frac{\pi}{2}\right) + 1\right]$$

and initial function $f_0 \equiv 0$, we plotted the converging sequence in Fig. 3.19. As you can see, the limit function almost completely matches the target function, which is expected since the data is virtually exact.

Suppose we know a general function form that can best represent what ever function shape we recovered, then we could proceed to find the corresponding parameters in the general form (e.g. $G_{Ca}$, $E_{Ca}$, $E_1$ and $E_2$ in (3.52)). This is easily done by a least-square fitting if the function form we choose is appropriate. The parameter values we recovered from a least square fitting of the limit function in Fig. 3.19 are

$$G_{Ca} = 1.1144,\ E_{Ca} = 99.2036,\ E_1 = -0.9046\ and\ E_2 = 15.0304$$

These values are found to be very accurate in comparing to the exact values in Table 3.1. We therefore proceed to study the sensitivity of the whole inversion procedure. We are particularly interested in how much error can be tolerated in $v_0(t)$.
Figure 3.18 The voltage response, $v_0(t)$, of the Morris-Lecar system (3.44) to input current $i_0(t) = 6[\sin(\frac{t}{2} - \frac{\pi}{2}) + 1]$. I: computed with $dx = 0.05$ (considered exact data); II: computed with $dx = 0.075$.

Figure 3.19 The iterative sequence for recovering the function, $f$, as defined in (3.52). The exact voltage response (I) shown in Fig. 3.18 is employed in the computation.
Figure 3.20  The recovered $m_\infty$ function as defined by (3.46). I: recovered from the exact data shown in Fig. 3.18; II: recovered from the inexact data shown in Fig. 3.18.

Figure 3.21  The recovered $f$ function as defined by (3.52). I: recovered from the exact data shown in Fig. 3.18; II: recovered from the inexact data shown in Fig. 3.18.
We shall continue to assume the response data computed with $dx = 0.05$ the exact data which means we shall keep $dx = 0.05$ in step IV of algorithm 3 and to simulate the contaminated data by forwardly solving (3.44)-(3.45) with other step size. In Fig. 3.22, the relative error in each recovered parameter is plotted against the space step size used to compute the corresponding response data. We also plotted the error in the response data as a function of $dx$ in Fig. 3.23. As you can see, the error in all recovered parameters except $E_1$ are kept below 15% for a 6% error in $v_0(t)$. Although the error in $E_1$ could exceed 200%, this is in fact not such a bad result when we notice the magnitude of $E_1$ in this case is only 1 mV which is relatively small compared to the normal range of an action potential. Thus, even a 200% error in $E_1$ will have little effect on the final voltage response.

3.3.2 Potassium channel identification

To reconstruct the $K^+$ channel kinetic functions $w_\infty(v)$ and $\tau_w(v)$ without any knowledge of the $C_{a^+}$ channel, we must block the $C_{a^+}$ channel by introducing some chemical agent. Since the Barnacle muscle fiber is in the $C_{a^+}$ free solution, we can consider the following all $K^+$ system

$$C_m v_t = \frac{d}{4R} v_{xx} - G_K w(v - E_K) - G_L (v - E_L)$$  \hspace{1cm} (3.57)

$$w_t = (w_\infty(v) - w)/\tau_w(v)$$  \hspace{1cm} (3.58)

and try to recover the maximum potassium conductance $G_K$ and the kinetic functions $w_\infty$ and $\tau_w$. Ideally, we want to reconstruct $G_K$, $w_\infty$ and $\tau_w$ altogether by just analyzing the voltage response data $v_0(t)$. However, for the sake of mathematical analysis, we shall first study the inverse problem of identifying $G_K$ and $w_\infty$ when $\tau_w$ is known and then study the inverse problem of identifying $\tau_w$ when $G_K$ and $w_\infty$ are known. This may sound like a cyclic deduction which would be useless in practice if
Figure 3.22  Relative error in the recovered parameters $G_{Ca}$, $E_{Ca}$, $E_1$ and $E_2$ by least-square fitting (3.52) to the limit function of the iterations (Ref. Fig. 3.19).

The exact values of these parameters are: $G_{Ca} = 1.1$ $mS/cm^2$, $E_{Ca} = 100$ $mv$, $E_1 = -1$ $mv$ and $E_2 = 15$ $mv$. The corresponding error in the voltage response data, $v_0(t)$, are shown in Fig. 3.23. The sign of error indicates over-estimating (+) or under-estimating (-).

Figure 3.23  The error in the voltage response data, $v_0(t)$, produced by varying the spatial step size $dx$ (= 0.025, 0.05, 0.075, 0.1) in the forward solver. The response data computed with $dx = 0.05$ is considered exact. The sign of error indicates over-shooting (+) or under-shooting (-) the exact response.
we had to go back to voltage-clamping experiment in order to recover one of them first. But, we believe, theoretically, that such approach is essential especially when the amount of data required for recovering two unknown functions uniquely is unknown. Furthermore, it is important for any stability analysis.

Let \( u_\infty(v) = G_K w_\infty(v) \) and \( u(t) = G_K w(t) \). Then the equations (3.57)-(3.58) become

\[
C_m v_t = \frac{d}{4R_a} v_{xx} - u(v - E_K) - G_L(v - E_L)
\]

\[
u_t = (u_\infty(v) - u)/\tau_w(v)
\]

Since \( \lim_{v \to \infty} w_\infty(v) = 1 \), the reconstruction of \( u_\infty \) is equivalent to identifying both \( G_K \) and \( w_\infty \). Therefore, from now on, we shall focus on the two unknown functions \( u_\infty \) and \( \tau_w \). We will also assume that these two functions, together with the corresponding solutions to (3.59)-(3.60), are always regular enough. Typically, this assumption is satisfied when \( u_\infty, \tau_w \in C^{0,1}(D) \) ([54]).

First, consider the case in which \( \tau_w \) is known and we want to recover \( u_\infty \). Given \( u_\infty^*(v) \in C^{0,1}(D) \), suppose \( (v^*(x, t), u^*(x, t)) \) is the solution to (3.59)-(3.60) with \( u_\infty(v) = u_\infty^*(v) \). Then, we can define the map

\[
\Pi : C^{0,1}(D) \mapsto C^{0,1}(D)
\]

such that

\[
\tilde{u}(t) = \frac{u^*(0, t)v^*(0, t) - E_k}{v_0(t) - E_k} - \frac{C_m[v_0'(t) - v^*_K(0, t)] + G_L[v_0(t) - v^*(0, t)]}{v_0(t) - E_k}
\]

\[
\Pi[u_\infty^*](v_0(t)) = u_\infty^*(v^*_K(0, t)) + [\tilde{u}(t) - u^*(0, t)] + \tilde{u}_t \tau_w(v_0(t)) - u^*_K(0, t)\tau_w(v^*_K(0, t))
\]

As before, we hope the function we are trying to recover is the fixed point of the map \( \Pi \). This is guaranteed by the following theorem.
Theorem 3.4 Given \( u_\infty^*(v) \in C^{0,1} \), suppose \((v^*(x,t), u^*(x,t))\) is the solution to (3.59)-(3.60) with \( u_\infty = u_\infty^*(v) \), then \( u_\infty^* \) is the fixed point of \( \Pi \) if and only if \( v^*(0,t) = v_0(t)(0 \leq t < T) \).

Proof  \( \iff \) If \( v^* \) is the solution with \( v^*(0,t) = v_0(t) \), then

\[
v_0'(t) = v_t^*(0,t)
\]

From (3.61), we know

\[
\ddot{u}(t) = u^*(0,t)
\]

which implies

\[
\ddot{u}_t = u_t^*(0,t)
\]

From here and (3.62), it is easy to see that

\[
\Pi[u_\infty^*](v) = u_\infty^*(v)
\]

for any \( v = v_0(t)(0 \leq t < T) \).

\( \implies \) Now, suppose \( u_\infty^* \) is the fixed point of the map \( \Pi \). i.e.

\[
u_\infty^*(v_0(t)) = u_\infty^*(v^*(0,t)) +
(\ddot{u}(t) - u^*(0,t)) + \ddot{u}_t \tau_w(v_0(t)) - u_t^*(0,t) \tau_w(v^*(0,t)) \quad (3.63)
\]

Setting \( \alpha(t) = v_0(t) - v^*(0,t) \) and \( \beta(t) = \ddot{u} - u^*(0,t) \), we obtain from (3.61) and (3.63)

\[
C_m \alpha'(t) = -(G_L + \dddot{u}) \alpha(t) + (v^*(0,t) - E_K) \beta(t)
\]

\[
\tau_w(v_0(t)) \beta'(t) = u_\infty^*(v_0(t)) - u_\infty^*(v^*(0,t)) - \beta(t)
- u_t^*(0,t) \left[ \tau_w(v_0(t)) - \tau_w(v^*(0,t)) \right]
\]
Since $u_{\infty}^*, \tau_w \in C^{0,1}(D)$, it follows that
\[
\begin{pmatrix}
|\alpha'(t)| \\
|\beta'(t)|
\end{pmatrix} \leq A \begin{pmatrix}
|\alpha(t)| \\
|\beta(t)|
\end{pmatrix}
\]
where $A$ is a non-negative constant matrix. Since $\alpha(0) = 0$ and $\beta(0) = 0$, it follows from the Gronwall's inequality that $\alpha(t) \equiv 0$ for all $0 \leq t < T$, i.e. $v^*(x, t)$ is the solution to (3.59)-(3.60) with $v^*(0, t) = v_0(t)$.

\[\Box\]

Again, a numerical experiment is designed to test the convergence and stability of algorithm 3 with the map $\Pi$ now defined by (3.61)-(3.62). Before we can actually apply algorithm 3, there is one important issue which was previously ignored. The formation of the map $\Pi$ requires taking the derivative of the response data $v_0(t)$ in order to compute the intermediate function $\tilde{u}(t)$. The function $\tilde{u}(t)$ is differentiated again in (3.62). Serious problems may result if the derivative is computed by the 1st order finite difference scheme
\[v_0'(t_k) = \frac{v_0(t_{k+1}) - v_0(t_k)}{t_{k+1} - t_k}.
\]
In Fig. 3.24, this problem is illustrated by the plots of the function curves of $v_0'(t) - v_t^{(n)}(0, t)$ where $n$ is the number of iterations. As you can see, in the case of finite differences, the function curve oscillates dramatically and the oscillation worsens with more and more iterations. If we look at the corresponding function sequence $u_{\infty}^{(n)} \equiv \Pi[u_{\infty}^{(n-1)}]$ in Fig. 3.25, we notice the same oscillations locally. However, globally, the sequence still tends to converge to the target function. The two oscillations are actually enhancing one another iteration after iteration. Furthermore, note that the response data, $v_0(t)$, we used here is the virtually exact data (computed with $dx = 0.05$) without any kind of noise. The response curves $v_0(t)$ and $v^{(n)}(0, t)(n = 5, 20, 25)$ are also plotted in Fig. 3.26. Notice that these curves are smooth visually.
Figure 3.24 The function $v_0(t) - v_t^{(n)}(0, t)$ computed by finite difference and cubic-spline technique where $v_0(t)$ is the "exact" response data we record in the beginning and $v_t^{(n)}(0, t)$ is the intermediate response data shown in Fig. 3.26. It is computed during the iterations. I: $n = 5$; II: $n = 20$; III: $n = 25$.

Figure 3.25 The iterative sequence $\{u^{(n+1)}_\infty \equiv \Pi[u^{(n)}_\infty]\}$ where $\Pi$ is defined by (3.61)-(3.62). The derivatives involved in (3.61)-(3.62) are computed by finite difference. Compare it to Fig. 3.27.
Figure 3.26  The voltage response of the Morris-Lecar system (3.59)-(3.60) with $C_{a}^{++}$ removed or $C_{a}^{+}$ channel blocked. Shown are the responses of the system in which the $u_{\infty}$ function is recovered after I: 5; II: 20 and III: 25 iterations respectively.

Figure 3.27  The iterative sequence $\{u_{\infty}^{(n+1)} = \Pi[u_{\infty}^{(n)}]\}$ where the derivative involved is computed by cubic-spline technique in this case. Compare it to Fig. 3.25.
So, why is this not a problem in the case of Fitzhugh-Nagumo equations and in the recovering of $C_a^{++}$ kinetic function $m_{\infty}$ where finite difference is also used to compute the first derivative? How can we overcome the finite difference obstacle in the all $K^+$ M-L equations? The answer to both questions is cubic-spline interpolation.

In the case of Fitzhugh-Nagumo equations and in the case of recovering $m_{\infty}$ in the M-L equations when both $w_{\infty}$ and $\tau_w$ are known, the derivative $v'_0(t) - v^n_l(0, t)$ is used to compute $f_{n+1} = \Pi[f_n]$ directly in step V of algorithm 3. The function $f_{n+1}$ is then interpolated in step VI using cubic splines which act as an implicit filter for those local oscillations. In the case of all $K^+$ M-L equations, we still have cubic spline interpolation in step VI for recovering $u_{\infty}$, but it is simply not enough to smooth those oscillations. This is essentially because the map $\Pi$ defined in (3.61)-(3.62) now involves a further differentiation of $v'_0(t) - v^n_l(0, t)$. Therefore, instead of 1st order finite differences, we use cubic splines to interpolate $v_0(t)$ and $v^n_l(0, t)$. Once we have the cubic spline approximation, the first derivative of $v_0(t)$ and $v^n_l(0, t)$ will then be computed analytically. As you can see in Fig. 3.24, the function curve of $v'_0(t) - v^n_{l+1}(0, t)$ computed with cubic spline techniques is much smoother than the one resulting from finite difference. Moreover, it converges. The iterative sequence $u_{\infty}^{(n+1)} = \Pi[u_{\infty}^{(n)}]$ also converges rapidly to our target function as is shown in Fig. 3.27.

The maximum potassium conductance $G_K$ and the parameters $E_3$ and $E_4$ in (3.47) are recovered by least-square fitting. The parameter values, obtained by a least-square fitting of the reconstructed function shown in Fig. 3.27 are

$$G_K = 1.9952, \quad E_3 = -0.0277 \quad \text{and} \quad E_4 = 29.8064$$

which is very accurate as expected.

We then performed the same sensitivity test as was done in the case of $C_a^{++}$ channel identification. The error in each recovered parameter is shown in Fig. 3.28.
Figure 3.28  The recovered parameters $G_K$, $E_3$ and $E_4$ by least-square fitting $u_\infty(v) = \frac{1}{2}G_K \left[ 1 + \tanh(\frac{v-E_1}{E_4}) \right]$ to the limit of the sequence $\{u_\infty^{(n+1)} \equiv \Pi[u_\infty^{(n)}]\}$. Shown are the relative error in $G_K$ and $E_4$ and the recovered value of $E_3$. The exact value for each parameter is: $G_K = 2.0 \text{ mS/cm}^2$, $E_3 = 0 \text{ mv}$ and $E_4 = 30 \text{ mv}$. The corresponding error in the voltage response data is introduced by varying the spatial step size, $dx (= 0.025, 0.05, 0.075, 0.1)$. The response data computed with $dx = 0.05$ is considered the virtually exact data and the sign of error indicates over-estimating (+) or under-estimating (-).

Next, we consider the case in which $u_\infty$ is known and we want to recover $\tau_w$. Following the same idea as above, we suppose $(v^*(x,t), u^*(x,t))$ is the solution to (3.59)-(3.60) with $\tau_w(v) = \tau_w^*(v) \in C^{0,1}(D)$ and define the map

$$\Pi : C^{0,1}(D) \rightarrow C^{0,1}(D)$$

such that

$$\Pi[\tau_w^*](u_0(t)) = \frac{u_t^* \tau_w^*(v^*(0,t)) + [u_\infty(v_0(t)) - \tilde{u}] - [u_\infty(v^*(0,t)) - u^*]}{\tilde{u}_t} \quad (3.64)$$

where $\tilde{u}$ is the intermediate function computed by (3.61). Similarly, we can prove
Theorem 3.5 Given \( \tau^*_w(v) \in C^{0,1} \), suppose \((v^*(x,t), u^*(x,t))\) is the solution to (3.59)-(3.60) with \( \tau_w(v) = \tau^*_w(v) \). then \( \tau^*_w \) is the fixed point of \( \Pi \) if and only if \( v^*(0,t) = v_0(t)(0 \leq t < T) \).

Since the map \( \Pi \) defined in (3.64) involves division by \( \tilde{u}_t \), the numerical error that arises from calculating the numerator of (3.64) will be boosted if \( \tilde{u}_t \) is too small. This is the case when \( t \) is close to zero. The large oscillation seen in Fig. 3.30 (Left) when \( \nu \) is close to the resting membrane potential, \(-51 mV\), demonstrates these dangers. To prevent such errors in the early stage from propagating into the future iterations, we simply ignore data in the early time period and obtain the values of \( \Pi[\tau^*_w](v_0(t)) \) for that period through extrapolating the safely computed \( \Pi[\tau^*_w](v_0(t)) \) at later time. An appropriate length of the ignored time period can be chosen by studying the function curves of \( \tilde{u}(t) \) and \( \tilde{u}_t \) (Fig. 3.32) and also by observing any irregular change during the iteration (Fig. 3.31). The set of model parameters in Table 3.1 is used to numerically simulate the inverse procedure of identifying \( \tau_w \). As in the previous case, we assume the response data, \( v_0(t) \), computed with \( dx = 0.05 \), the virtually exact data and noisy data are computed by varying spatial step size \( dx (= 0.025, 0.075, 0.1) \). After the iterative function sequence converges to a limit for each data set, an optimization scheme is performed to recover the three key parameters, \( \Lambda_w, E_3 \) and \( E_4 \) in the function

\[
\tau_w(v) = \frac{1}{\Lambda_w \cosh \left( \frac{v - E_3}{2E_4} \right)}
\]

in the sense of least-square fitting. The relative error in each recovered parameter is plotted in Fig. 3.35.

In the case of exact data set (Fig. 3.30 (Right)), the limit function does not match the target function so well as in recovering \( u_\infty \). It indicates that the detailed shape of the time constant function does not have much effect on the system's voltage response.
Figure 3.29 The input current, $i_0(t) = 10[\sin(t/2 - \pi/2) + 1]$, and the voltage response, $v_0(t)$, for recovering the time constant function $\tau_w$ in the $C_{a}^{++}$ free system (3.59)-(3.60). Notice the duration of the input current (12 ms) and compare it to Fig. 3.33.

Figure 3.30 The iterative sequence for recovering $\tau_w$. Left: no initial time period is ignored in the computation of the map (3.64); Right: some initial time period is ignored due to singularity at $t = 0$. The function value over that time period is obtained by extrapolation.
Figure 3.31  The iterative sequence of functions for recovering $\tau_w$: the initial A. 1.3 ms; B. 2.2 ms and C. 3.0 ms are ignored. The duration of the input current is 12 ms (Ref. Fig. 3.29 and Fig. 3.32). The voltage response data, $v_0(t)$, is computed with $dx = 0.025$ and is considered inexact in this case.
Figure 3.32  I: the intermediate function $\tilde{u}(t)$ as defined by (3.61) and II: the derivative of $\tilde{u}(t)$. It can be used to monitor the choice of time period ignored initially to avoid singularity at $t = 0$ in the map (3.64) (Ref. Fig. 3.31).

to current injection. It is the magnitude (reflected by $\lambda_w$) of the time constant that is the most important factor in determining the behavior of the whole system.

The situation, however, can be made better (Fig. 3.34) if we choose a different current injection. The current we used in the previous experiment (Fig. 3.29) is

$$i_0(t) = 10[\sin\left(\frac{t}{2} - \frac{\pi}{2}\right) + 1]$$  \hspace{1cm} (3.65)

which has a duration of 12 $ms$ with peak value 20 $\mu A/cm^2$ (Fig. 3.29). If we opt for a current of

$$i_0(t) = 15[\sin\left(\frac{t}{10} - \frac{\pi}{2}\right) + 1]$$  \hspace{1cm} (3.66)

which has a longer duration of 65 $ms$ with peak value 30 $\mu A/cm^2$ (Fig. 3.33), the corresponding limit function (shown in Fig. 3.34) matches the target function much better than in Fig. 3.30. The reason is that the voltage response to current (3.66) has a smaller slope than the voltage response to current (3.65). Since the computation of
Figure 3.33  The input current, $i_0(t) = 15[\sin(\frac{t}{10} - \frac{\pi}{2}) + 1]$, and the voltage response, $v_0(t)$, for recovering $\tau_w$. Notice the duration of the current($65\, ms$) and compare it to Fig. 3.29.

Figure 3.34  The recovered $\tau_w(v)$ after 25 iterations. The voltage response data, $v_0(t)$, shown in Fig. 3.33 is used for the reconstruction. Compare it to Fig. 3.30.
the map $\Pi$ involves taking derivative of $v_0(t)$, the smaller the slope means less error particularly when the error will be divided by $\hat{u}_t$ in (3.64).

We are now ready to address the inverse problem of recovering both $u_\infty$ and $\tau_w$ concurrently. It should be obvious after our previous two case studies that a single recording set of voltage response data $v_0(t)$ is not adequate for recovering two unknown functions. We need a second current injection and a second recording trace of voltage response. We shall denote the two input currents by $i_0(t)$ and $j_0(t)$ and denote the corresponding voltage responses by $v_0(t; i_0)$ and $v_0(t; j_0)$. Given $u^*_\infty, \tau^*_w \in C^{0,1}$, we continue to assume $(v^*, u^*)$ the solution to (3.59)-(3.60) with $u_\infty = u^*_\infty$ and $\tau_w = \tau^*_w$. To distinguish the solutions between different input currents, we use the notation $(\cdot, \cdot; i_0)$ and $(\cdot, \cdot; j_0)$. Using the intermediate function $\tilde{u}$, computed again by
(3.61) for both voltage responses, we define the map

\[ \Pi : C^{0.1} \times C^{0.1} \longrightarrow C^{0.1} \times C^{0.1} \]

such that \( \Pi[u^*_\infty](\mu) \) and \( \Pi[\tau^*_w](\mu) \) solve

\[
\begin{pmatrix}
1 & -\tilde{u}_t(t; i_0) \\
1 & -\tilde{u}_t(t'; j_0)
\end{pmatrix}
\begin{bmatrix}
\Pi[u^*_\infty](\mu) \\
\Pi[\tau^*_w](\mu)
\end{bmatrix}
= \begin{bmatrix} b_1 \\ b_2 \end{bmatrix}
\]

(3.67)

where

\[
b_1 = [\tilde{u}(t; i_0) - u^*(0, t; i_0)] + u^*_\infty(v^*(0, t; i_0)) - u^*_t(0, t; i_0)\tau^*_w(v^*(0, t; i_0))
\]

\[
b_2 = [\tilde{u}(t'; j_0) - u^*(0, t'; j_0)] + u^*_\infty(v^*(0, t'; j_0)) - u^*_t(0, t'; j_0)\tau^*_w(v^*(0, t'; j_0))
\]

and \( \mu = v_0(t; i_0) = v_0(t'; j_0) \).

The system (3.67) is singular when \( \tilde{u}_t(t; i_0) = \tilde{u}_t(t'; j_0) \). Therefore, it is important to choose the input currents so that the numbers \( \tilde{u}_t(t; i_0) \) and \( \tilde{u}_t(t'; j_0) \) are sufficiently different. In our numerical experiments, we actually employed three different input currents (Fig. 3.36 and Fig. 3.38). Furthermore, the input currents should have a long enough duration so that the local oscillation would be under control in \( \{\tau^{(n)}_w\} \) as we discussed in the case of recovering \( \tau_w \) alone. In fact, if the duration of the input currents is too short (Fig. 3.36), the iterative sequence would not even converge (Fig. 3.37). With the right choice of input currents, the convergence of the iteration is quite promising (Fig. 3.39). In the case of \( u_\infty \), the limit matches the target function very well when the three data sets are exact. The recovered time-constant function \( \tau_w \) is not as good as \( u_\infty \) if viewed locally. This is expected as it also occurs in the recovery of \( \tau_w \) when \( u_\infty \) is known. Globally viewed, the reconstructed \( \tau_w \) still captures the bell shape of the target function. The sensitivity test of the algorithm for noisy data is performed as previously done. The converging sequence for \( dx = 0.075 \) plotted in Fig. 3.40 gives an idea of the relation between the error in
Figure 3.36  The three input currents and their corresponding voltage responses for recovering both $u_\infty$ and $\tau_w$. I: $i_0(t) = 16[\sin(\frac{1}{10} - \frac{x}{2}) + 1]$; II: $i_0(t) = 16[\sin(\frac{x}{3} - \frac{3x}{2}) + 1]$ and III: $i_0(t) = 16[\sin(\frac{x}{3} - \frac{3x}{2}) + 1]$. The voltage responses are computed with $dx = 0.05$ and is considered exact. Notice the duration of the input currents (about 40 ms) and compare it to Fig. 3.38.

Figure 3.37  The recovered $u_\infty$ and $\tau_w$ after one iteration of the map (3.67). The big oscillation in $\tau_w$ indicates the computational error caused by the inappropriate choice of input currents in Fig. 3.36. Compare it to Fig. 3.39.
Figure 3.38  The three input currents and their corresponding voltage responses for recovering both $u_\infty$ and $\tau_w$. I: $i_0(t) = 16[\sin(\frac{t}{50} - \frac{\pi}{2}) + 1]$; II: $i_0(t) = 16[\sin(\frac{t}{30} - \frac{\pi}{2}) + 1]$ and III: $i_0(t) = 16[\sin(\frac{t}{20} - \frac{\pi}{2}) + 1]$. The solid-line curve represents the exact voltage response computed with $dx = 0.05$ while the dash-dot-line curve represents the inexact voltage response computed with $dx = 0.075$. Notice that the duration of the input currents in this case is about $200 \text{ms}$ which is much longer than that in Fig. 3.36.

Figure 3.39  The iterative sequence as defined by the map (3.67) for recovering both $u_\infty$ and $\tau_w$. It is computed by using the exact voltage response data shown in Fig. 3.38. Compare it to Fig. 3.37.
response data and the error in recovered functions. We also recovered the parameter values of $G_K$, $\Lambda_w$, $E_3$ and $E_4$ by least-squares fitting. The relative error is shown in Fig. 3.41.

![Graphs showing iterative sequence](image)

**Figure 3.40** The iterative sequence as defined by the map (3.67) for recovering both $u_\infty$ and $\tau_w$. The voltage response data in this case is computed with $dx = 0.075$ and is inexact.

As before, the equivalence between finding the fixed point of the map $\Pi$ and recovering the unknown functions in the system from voltage response data is certified by a theorem

**Theorem 3.6** Given $u_\infty^*(v)$, $\tau_w^*(v) \in C^{0,1}$, suppose $(v^*(x,t), u^*(x,t))$ is the solution to (3.59)-(3.60) with $u_\infty = u_\infty^*(v)$ and $\tau_w(v) = \tau_w^*(v)$, then $(u_\infty^*, \tau_w^*)$ is the fixed point of $\Pi$ if and only if $v^*(0, t) = v_0(t) (0 \leq t < T)$. 
Figure 3.41  Relative error in the parameters $G_K$, $\Lambda_w$ and $E_4$ that are recovered from noisy voltage responses. $E_3$ is shown by its recovered value. The exact values for these parameters are $G_K = 2.0 \text{ mS/cm}^2$, $\Lambda_w = 0.2 \text{ msec}^{-1}$, $E_3 = 0 \text{ mV}$ and $E_4 = 30 \text{ mV}$. The error in the voltage response data is introduced by varying the spatial step size, $dx$, in the forward solver.
Chapter 4

Future Directions

The research on how to characterize nonuniform neuron even in the passive mode has just started. We still need more constructive work in order to address the inverse problem appropriately under various physically meaningful constraints. A nonuniform conductance $G$ with constant $R$ and $C$ is one of the possible ways to capture heterogeneities in a nerve fiber. The two attractive approaches to the corresponding inverse problem as suggested by the work of Pierce ([48]) and Isakov ([33]) remain to be stabilized before they can be applied in practice. There is no sign this is not a tough challenge both mathematically and numerically.

In the case of active neuron identification, a serious mathematical proof is missing in order to justify the correctness of the fixed-point method. We believe that a complete justification relies on a more profound understanding of the forward model especially the global behavior of the nonlinear system. It is also worthwhile to extend the method to more realistic neuron models and to test the algorithm on impedance data recorded from real neurons.
Bibliography


[19] S.E. Fox, Location of membrane conductance changes by analysis of the input Impedance of neurons. I. Theory, J. of Neurophys. 54 No.6 (1985): 1578-1593

[20] S.E. Fox, C.Y. Chan, Location of membrane conductance changes by analysis of the input Impedance of neurons. II. Implementation, J. of Neurophys. 54 No.6 (1985): 1594-1606


[34] M.B. Jackson, Cable analysis with the whole cell patch clamp. Theory and experiment, Biophys. J. 61 No.3 (1992): 756-766


