Modelling the Somatic Electrical Response of Hippocampal Pyramidal Neurons

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Abstract

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Abstract

A modelling study of hippocampal pyramidal neurons is described. This study is based on simulations using HIPPO, a program which simulates the somatic electrical activity of these cells. HIPPO is based on a) descriptions of eleven non-linear conductances that have been either reported for this class of cell in the literature or postulated in the present study, and b) an approximation of the electrotonic structure of the cell that is derived in this thesis, based on data for the linear properties of these cells.

HIPPO is used a) to integrate empirical data from a variety of sources on the electrical characteristics of this type of cell, b) to investigate the functional significance of the various elements that underly the electrical behavior, and c) to provide a tool for the electrophysiologist to supplement direct observation of these cells and provide a method of testing speculations regarding parameters that are not accessible.

The novel results of this thesis include:

- Simulation of a wide range of electrical behavior of hippocampal pyramidal cells by using descriptions of ionic conductances (channels) whose kinetic properties are developed from both limited voltage-clamp and current-clamp data and from the theory of single-barrier gating mechanisms. This result suggests that the single-barrier gating mechanism of the Hodgkin-Huxley model for ionic channels is empirically valid for a wide variety of currents in excitable cells.

- An estimation of the linear parameters of hippocampal pyramidal cells that suggest that the membrane resistivity, and thus the membrane time constant, is non-homogeneous.

- An estimation of dendritic membrane resistivity ($R_m$) and cytoplasmic resistivity ($R_i$) that is higher than generally considered, and the conclusion that the cell is more electrically compact than previously thought. This compactness implies that distal and proximal dendritic input have similar efficacies in generating a somatic response.

- A method for estimating the dimensions of the equivalent cable approximation to the dendritic tree based solely on histological data.
• Descriptions of three putative $Na^+$ currents ($I_{Na-trig}$, $I_{Na-rep}$, and $I_{Na-tail}$) that quantitatively reproduce the behavior generally ascribed to $Na^+$ currents in hippocampal pyramidal cells.

• Descriptions of two $Ca^{2+}$ currents ($I_Ca$ and $I_CaS$) and a system for regulating $Ca^{2+}$ inside the cell that qualitatively reproduces the data for $Ca^{2+}$-only behavior in hippocampal pyramidal cells.

• Descriptions of six $K^+$ currents (a delayed rectifier $K^+$ current – $I_{DR}$, a transient $K^+$ current – $I_A$, a $Ca^{2+}$-mediated $K^+$ current – $I_C$, a $Ca^{2+}$-mediated slow $K^+$ current – $I_{AHP}$, a muscarinic $K^+$ current – $I_M$, and an anomalous rectifier $K^+$ current – $I_Q$) that are consistent with the available data on these currents and that reproduce either quantitatively or qualitatively the behavior associated to each current during the electrical response of hippocampal pyramidal cells.

• Simulations demonstrating possible computational and/or pathologic roles for the model currents.

• The design of an interactive program that simulates hippocampal pyramidal cells with a variety of models of electrotonic structure and the inclusion of Hodgkin-Huxley-like non-linear conductances at various points in the cell.
Errata and Update to AI-TR 1161 - Winter 1990
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Errata

The author apologizes for the following errors, and would greatly appreciate notification of any further errors that are discovered by the reader.

Chapter 3, p. 47-48: In Equation 3.5, the right hand side is inverted, and in Equation 3.6 the denominator, L, should be a coefficient of the numerator. However, the final equation on the top of p. 48 is correct.

In several places calculation of somatic area is underestimated by a factor of 3. This changes some results quantitatively but not qualitatively. Some of these effects are as follows:

Chapter 3: The soma radius of the soma/short-cable geometry derived from the Brown et. al. data is incorrect: the correct radius is 42 μm (instead of 73 μm). However, this “reversed-engineered” value is still inconsistent with the actual cell geometry, as illustrated in Figure 3.6.

The estimated specific resistivity of the soma membrane in the model is incorrect; instead of 850Ωcm² it should be 2500Ωcm². Note, however, that this higher value is still significantly lower than the ≈ 40kΩcm² resistivity estimated for the dendritic cable, thus preserving the conclusions based on an inhomogeneous membrane resistivity.

The somatic (linear) resistance is correct, but the somatic capacitance is underestimated by a factor of 3. This means that the (resting) time constant of the soma should be 3 times longer, which in turn slightly affects some of the channel parameters (particularly those estimated on the basis of single spike waveforms). Values of channel \( \bar{g}_{\text{dens}} \), where given, are overestimated by a factor of 3, independent of the error accrued by the change in somatic \( \tau \) and capacitance. We have not attempted to refit channel parameters to the corrected model since the old parameters (as listed in the TR) work well and further tweaking is beyond the scope (and validity) of this project.

Chapter 6: The \( Ca^{++} \) system also has some (related) errors, and many of the parameters for this system are being revised. However, the basic behavior of the model’s \( Ca^{++} \) system is valid. In particular, the prediction of the co-localization of the \( I_C \) channels and \( Ca^{++} \) channels along with the random distribution of the \( I_{AHP} \) channels, with the result these two \( Ca^{++} \)-dependent \( K^+ \) channels see quite different changes in \( [Ca^{++}]_i \), still stands.

Chapters 5-7: Channel parameters listed in the tables should be double checked for the correct sign, specifically so that they are consistent with the figures for the particles’ \( \tau(V) \) and \( \text{inf}(V) \) (which are correct).

There are some bugs in the HIPPO listing. Because of these (which will not be fixed) and since our simulation work is now entirely done with the SURF-HIPPO system (see below), it is recommended that the HIPPO code not be used.

Update

Our simulation work has been transferred to another program, the SURF-HIPPO Neuron Circuit Simulator (based in part on the SURF circuit simulator, written by Don Webber, VLSI CAD Group at the University of California at Berkeley). This code is much more efficient and modular than the code listed in this TR. The numerical technique is adapted from that of Hines (“Efficient computation of branched nerve equations”, Int. J. Bio-Medical Computing (15), 1984, p69-76), with adaptive time steps. SURF-HIPPO allows ready construction of multiple cells, complicated dendritic trees in 3-space with distributed non-linearities, and synaptic contacts between cells. Stationary and moving two dimensional light input (for retinal simulations) is also provided. SURF-HIPPO is written in Common LISP and *LISP (which uses relaxation techniques to solve the matrix). One version, complete with extensive user interface (menus, 3-D graphics of dendritic trees, automatic plotting) runs in the Symbolics LISP Machine environment, another (currently without the extensive user interface) runs in the Sun environment. A Connection Machine (CM2) version is presently being debugged. SURF-HIPPO is not “public domain” in the sense that it is not supported (since it is under development), but inquiries are welcome.

An expanded version of Chapter 4 of this TR appears in:
Acknowledgments

I would like to thank the following people for their contribution to this Thesis:

Prof. Tomaso Poggio for his continued support and thought-provoking interjections on how this work may have relevance for understanding the computational mechanisms of the brain.

Prof. Paul Adams and Dr. Johan Storm for their invaluable collaboration in both the acquisition of new data that formed the foundation of the model, for their assistance in the critical reading of the literature that was referenced to build the model, for their critique of the putative features of the work, and for their constant and enthusiastic feedback with the result that this project reflected some symbiosis between experiment and theory.

Prof. Christof Koch for providing the initial impetus towards my studying the problem presented here, and for steering my work early on so as to avoid some of the pitfalls that await the unwary neural modeller.

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Chapter 1

INTRODUCTION

1.1 Modelling Neurons of the Central Nervous System

Understanding the brain is a multi-level task, incorporating perspectives from molecular biology to cognitive science and psychology. At some point in this hierarchy the single cell is encountered, and the view that all information processing in the brain derives from mechanisms on this level is generally accepted; i.e. it is correct to speak of a neuron processing signals, rather than the neuropil being the basic functional unit for computation.

The actual role of individual neurons in information processing is open to speculation. In some systems good arguments have been advanced in support of the handling of certain tasks by specific cells. In most structures in the central nervous system (CNS), however, the role of the single cell is not well defined. Typically, descriptions of information processing in the CNS refer to anatomical structures consisting of (at least) thousands of cells, and fail to assign roles to single cells.

Thus, an investigation into information processing on the level of the single neuron is important. Over the past decade quantitative data on CNS neurons has grown considerably, and interpretation of this data is now appropriate in order to establish the role of the neuron as it receives the multitudinous signals from the neural mesh. Utilization of systematic models is a method of addressing this problem. One of the models that is an appropriate vehicle for this task is named HIPPO.
1.2 The HIPPO Model of Hippocampal Pyramidal Cells

This thesis describes the development and application of the computer model, HIPPO. This model simulates the somatic electrical behavior of a stereotypical cortical integrating neuron, the mammalian hippocampal pyramidal cell (HPC). The development of HIPPO includes an estimation of the electrical structure for this cell, development of the numerical technique used in the model algorithm, integration of electrophysiological data into the model (particularly that describing the non-linear conductances reported for the HPC), and implementation of the model on a Symbolics 3600 LISP machine. The application of HIPPO includes an integration of sparse and conflicting data obtained from a variety of electrophysiological protocols. Applying HIPPO includes also testing of speculations regarding characteristics not accessible to in vivo or in vitro measurement.

As set forth this report, modelling a non-linear system as complex as the hippocampal pyramidal cell is problematic at best. The situation is complicated by both the numerous interdependencies of the mechanisms underlying electrical behavior in these neurons, and by the approximations and assumptions (e.g. the Hodgkin-Huxley model, ref. Chapter 4) that are required due to the present state of the data.

In light of these difficulties, this model is presented with the understanding that many of the putative mechanisms described could easily be incorrect in their details, but given the constraints imposed on the development of the model parameters (as defined throughout this Thesis), these descriptions are reasonable in that they are based on first principles and that they generate the desired behavior. At best, the descriptions will in some way reflect what is actually going on in these cells; at worst, the descriptions and the resulting behavior of the model will generate testable predictions and suggestions for postulating more accurate mechanisms.

1In fact, these interdependencies provide important and implicit constraints on the derivation of parameters, which in turn causes the selection of parameters to be less arbitrary than otherwise would be the case. These constraints are manifest in the cross-checking of overall model behavior, required whenever a subset of the model parameters is altered. This point will be reiterated several times in later chapters when strategies for developing various elements are reviewed.
1.3 Organization of Thesis

In this chapter Sections 1.4 through 1.7 will introduce the hippocampal pyramidal neuron and describe the motivations for modeling this cell. Some comments on the applied aspects of the program are also presented.

Chapter 2 contains a discussion of the strategy used herein in developing HIPPO and the basic structure of the model, outlining the geometry of the model and the type of circuit that it simulates. The development of HIPPO involves careful examination of the literature on hippocampal cells (and other neurons, as required) in conjunction with consultation with electrophysiologists. The techniques used by the electrophysiologist to measure the various components of the electrical behavior of a neuron are reviewed since these techniques guide the construction of the model from available data and the evaluation of any inconsistencies in that data. This chapter closes with a brief discussion of the network elements, in particular the electrochemical potentials that drive the electrical excitability of these neurons.

Chapter 3 covers the evaluation of the linear characteristics of the HPC. This analysis forms a basis for building the model of the pyramidal neuron, particularly since many of the non-linear parameters must be estimated from incomplete data. Estimating the characteristics of non-linearities in the cell is fruitless without a solid linear description to build on. Several approaches to this problem, as well as a critical review of the published data on the linear structure of the HPC, are presented. Finally, the linear parameters used for the present version of HIPPO are discussed.

The non-linear conductances in the model are all based on some variation of the classic Hodgkin and Huxley model ([21], [20], [22], [23]) of the Na$^+$ and K$^+$ conductances in the squid axon. This approach represents a major assumption in the HIPPO model, particularly since many of the non-linear conductances in HPC have not been conclusively demonstrated as being Hodgkin-Huxley-like conductances. However, in light of the paucity of data for these cells, this approach is a reasonable one, and in fact has been successful in reproducing many qualitative and quantitative aspects of HPC electrical behavior. Since the Hodgkin-Huxley model is of such basic importance to the HIPPO description, this model and the application of this model to putative HPC conductances are described in Chapter 4. In addition, the implications of the single-barrier gating interpretation of the Hodgkin-Huxley model are discussed in detail.

In the next three chapters the development of descriptions of the various non-linear currents is described, along with the simulated behavior of these
currents. In these chapters the behavior of the model is compared typically with data from cells obtained under conditions similar to those being simulated.

In Chapter 5, the three proposed Na$^+$ currents, $I_{Na-trig}$, $I_{Na-rep}$, and $I_{Na-tail}$, are presented and the HIPPO simulation of Na$^+$-only HPC behavior is shown.

In Chapter 6, the HIPPO description of the two Ca$^{2+}$ currents, $I_{Ca}$ and $I_{CaS}$, are presented with simulations of Ca$^{2+}$-only HPC behavior, as well as the HIPPO description of the dynamics of intracellular Ca$^{2+}$ and the factors that determine the concentration of Ca$^{2+}$ underneath the cell membrane. This latter component is important since two K$^+$ currents ($I_C$ and $I_{AHP}$) are presumably mediated by the concentration of intracellular Ca$^{2+}$, and the magnitude of $[Ca^{2+}]_{shell,1}$ (ref. Chapter 6) can significantly change the reversal potential for Ca$^{2+}$ ($E_{Ca}$).

In Chapter 7 the six K$^+$ currents in the model are presented. These currents, $I_{DR}$, $I_A$, $I_C$, $I_{AHP}$, $I_M$, and $I_Q$, display a wide range of activation/inactivation characteristics and thus modulate the HPC response in many different ways. The parameters used in the model for these currents are presented here, as well as various simulations demonstrating their behavior.

In Chapter 8 and Chapter 9 some selected simulations are presented of voltage clamp protocols and current clamp protocols, respectively. These simulations augment the ones that are presented in earlier chapters, and demonstrate the overall behavior of the model and how the model reproduces various data taken from cells. In contrast to the results presented in earlier chapters, the simulations discussed here represent speculative behavior of the HPC, given the HIPPO description of its electrical characteristics.

In Chapter 10 implications of the results obtained by the model are discussed, and the validity of both these results and the approach used in constructing HIPPO. Guidelines are also proposed regarding the application of HIPPO. In the final chapter, Chapter 11, some of the future applications of HIPPO are presented.

In Appendix A a sample simulation session is described, showing the interactive nature of the menu-driven HIPPO and the presentation of simulation results. Appendix B contains a description of the predictor-corrector algorithm used by HIPPO to solve the network equations. In Appendix C the structure of the HIPPO code will be described. Appendix D contains the software listing for HIPPO.
1.4 Hippocampal Pyramidal Neurons As A Stereotypical Cortical Integrating Neuron

The hippocampus is a part of the cerebral cortex. This structure carries and (presumably) processes signals projecting to and leaving from various regions of the neocortex. The hippocampus forms along the free medial edge of the temporal lobe of each cerebral hemisphere, extending from the several layers of neocortex, forming its characteristic spiral, which in turn consists of a single layer of pyramidal cells. Historically, the striking anatomy and connectivity of the hippocampus has made it one of the more studied areas of cortex. Although the classical role of the hippocampus as a major player in the so-called "limbic system" is now being re-evaluated, there is substantial evidence of various functional roles of this structure, including a putative role in mediating long-term memory.

The pyramidal neuron is the basic efferent cell of the cerebral cortex, integrating afferents from both intracortical and extracortical structures. The connectivity of a single pyramidal cell is typically very large, with hundreds to thousands of afferent connections. This input tends to be quite segregated, with distinct tracts originating from various structures making synapses with specific regions of the pyramidal cell's extensive dendritic tree. The pyramidal cell, as one of the major cell types in the cortex, is an important determinant of cortical function on the cellular level. The hippocampal pyramidal cell is representative of this class of neurons, and for these reasons and those set forth below, it is a cell of choice for investigations of central neuron characteristics.

The large body of knowledge for the hippocampus has been enhanced in recent years by the brain slice technique used for obtaining stable in vitro electrophysiological measurements with various micro-electrode techniques. In the slice technique, approximately 500 μm thick transverse slices of freshly excised hippocampus (typically rat or guinea pig) are maintained for several hours in small chambers filled with an appropriate oxygenated solution. Once set up in this manner, intracellular recordings from microelectrodes can be obtained for several hours. A related technique, which also has been developed recently, is the combination of patch clamp recording methods with pyramidal cells cultured from embryonic neurons. This technique, while clearly moving one more step away from the physiological environment, allows for higher quality measurements due to the improved electrical and mechanical characteristics of the patch electrode over the micro-electrode.
The hippocampal pyramidal cell has therefore been chosen as the target cell for the present study. To build this model, an attempt was made to evaluate a large sample of the literature, which is quite extensive. As an initial modelling study, this effort was successful in quantifying much of the behavior of this representative cell in the CNS, and in establishing the basic aspects of somatic HPC function. These results may be extended to other cells in the CNS, especially when more data on these cells becomes available.

1.5 Application of HIPPO

An important aspect for the application of the HIPPO model as a research tool is its flexibility. The structure of HIPPO allows straightforward testing of the sensitivity of the model to changes in various parameters. In particular, estimating a parameter which is based on low-confidence experimental data can require testing of values over a wide range. One cost of this flexibility is in the execution time of a given simulation protocol. For this reason, versions of HIPPO were developed which had a relatively fixed structure and simulation protocol but executed considerably faster. In some cases the use of these quick "customized" HIPPOs was effective in developing an intuitive sense of the behavior of the model, and presumably that of the cell. For example, voltage-clamp simulations of isopotential structures involve considerably less computation than that of voltage-clamp simulations of non-isopotential structures or current-clamp simulations in general. Yet, to a first approximation, much of the data in the literature can be effectively simulated with the simplified voltage-clamp protocol. Once initial estimates of simulation parameters have been tested on the simplified HIPPO, then the more general HIPPO can be used to examine more realistic structures.

1.6 The User Interface

A substantial effort was invested in the user interface of HIPPO. Input to the model is done via a menu hierarchy (ref. Appendix A) that allows efficient manipulation of relevant parameters and a subsequently rapid set-up for a given simulation. A limited degree of automated simulation execution is also provided. Output of HIPPO is both graphical and numerical. Manipulation of the output is straightforward and non-displayed parameters are easily accessible. The user interface design has a net result of being able to use HIPPO in an interactive, self-documenting fashion.
1.7 Previous Work

Much of the program design philosophy and the approaches used in estimating model parameters were inspired by an earlier model constructed by Prof. Christof Koch and Prof. Paul Adams for the bullfrog sympathetic ganglion cell [2].
Chapter 2

MODELLING STRATEGY AND THE ELEMENTS OF HIPPO

2.1 Introduction

The goal of the HIPPO model is to give a reasonable description of a non-linear time-varying multi-variable system. To achieve this, development of the model was accomplished in stages of increasing complexity along several degrees of freedom, including the geometry of the model cell and its non-linear, time-varying properties. Since many of the network components are non-linear, superposition does not hold in general. The resulting interdependence of the parameters was a considerable problem in constructing a valid description, especially since any change in a single parameter often meant that much of the model behavior had to be checked. Careful evaluation of experimental results was essential in order to prevent generation of false-positive solutions. This chapter will discuss the general development of the model, the structure of the modelled system and its elements.

2.2 Determining the Validity of the Model Results

A key consideration in the interpretation of the HIPPO results is in determining the validity of a given version of the model. There is no clear-cut
unique solution set for the model parameters. For example, many (non-
physiological) descriptions of the kinetics will yield reasonable behavior.

The basic approach considers an evaluation of as many parameters as
possible under orthogonal or nearly orthogonal simulation protocols, mim-
icking the electrophysiologist's technique. Particular attention is paid to
when experimental results reflect the overlapping of several kinetic mecha-
nisms, particularly when superposition does not hold (when superposition
does hold, then it may be exploited to extract the relevant parameters from
the total response). Whenever several non-linear elements contribute to the
model response the model is used iteratively to test different hypotheses for
the parameters in question.

Most of the HPC currents are present over a limited range of membrane
voltages. In the simplest case, involving a determination of the kinetics
of a system with two currents X1 and X2, when the activation ranges for
X1 and X2 are non-overlapping, then the voltage clamp protocol will have
no problem quantifying each current. In practice, however, there are few
currents that experience an exclusive range of activation, and therefore the
situation is more complicated.

While more than one current may be activated at a given voltage range,
different components may be distinguished if they have significantly different
time courses. For example, \( I_A \) and \( I_{DR} \) are activated over the same range.
Since \( I_A \) activates and inactivates much faster than \( I_{DR} \) over part of this
range, however, the two currents can be distinguished by their distinct time
courses in voltage clamp protocols (Segal and Barker, 1980).

Another technique to separate different currents is to exploit the phar-
mocological sensitivity of some currents. For example, \( Na^+ \) currents are
generally believed to be blocked by the puffer fish toxin, tetradoxin (TTX),
and that channels for other ions are largely unaffected by TTX. Thus, in
voltage clamp preparations TTX is commonly used to unmask currents that
might otherwise be swamped by larger \( Na^+ \) currents, with similar kinet-
ics. Other examples of selective blocking of currents include the use of
tetra-ethylammonium (TEA) to block some potassium currents (e.g. \( I_{DR} \)),
4-aminopyridine (4-AP) to block \( I_A \), and various \( Ca^{2+} \) blockers (e.g. \( Mn^+ \))
or \( Ca^{2+} \)-chelators to inhibit \( Ca^{2+} \) currents, and calcium-mediated currents
(\( I_C \) and \( I_{AHP} \)) (ref. Table 7.1).

\(^1\)The main exception is \( I_Q \), which is the only current activated at fairly hyperpolarized
potentials (Chapter 7). The leak current is superimposed on the \( Q \) current, but that may
be readily distinguished from the \( I_Q \).
2.3 Geometry Of Model

HIPPO simulates hippocampal pyramidal neurons with a compartmental model that incorporates several isopotential compartments connected together with resistors. The simplest morphology is a single compartmental, isopotential spherical model of the entire cell, i.e. no dendritic structure or axonal process. This structure can be extended with the addition of as many as five processes, which can be configured as four dendrites and one single compartment axon. Four of the processes are represented by an arbitrary number of lumped cylindrical segments, with each segment having its own set of linear and non-linear electrical parameters. The fifth process, when included, is represented by a single isopotential cylindrical compartment. Most simulations were run with a single dendrite and no axon, as illustrated in Figure 2.1.

The physical and electrical parameters for each of the compartments -
soma sphere and process cylinders - can be set uniquely for each compartment. For example, the soma can be set up with at most eleven non-linear currents, a particular membrane resistivity and capacitance, and a particular radius. A single dendrite might be added with ten segments, with eight configured as linear cables using the same linear parameters but distinct dimensions. The remaining two segments could have two non-linear conductances in addition to their linear properties, and one of the all-linear segments could have a synapse. In the present report only the linear dendrite case will be examined. In Chapter 3 a detailed analysis and subsequent method for approximating the hippocampal pyramidal cell geometry will be presented.

2.4 HIPPO Solves A Non-Linear, Time-Varying Electrical Network

In this modelling study the HPC is analyzed as an electrical circuit. Inputs to this circuit include stimuli provided by intracellular electrodes or by synaptic-like conductance changes, and circuit outputs include voltages at various parts of the cell, specific membrane currents, the concentration of Ca²⁺ in different compartments related to the circuit, and various state variables associated with the non-linear conductances. In a general sense, HIPPO is a program for simulating a particular class of electrical networks. HIPPO is configured to handle a limited set of topologies with a specific class of network elements, as well as linear resistors and capacitors, voltage sources, and current sources. The special class of elements are non-linear voltage-dependent and time-dependent conductances that represent the behavior of ion-specific channels in the cell membrane. The electrotonic structure of neurons (as determined by the morphometrics and linear components of the cell) is extraordinarily important to their function, and much of the effort in the development of HIPPO was in the characterization of this structure as well as that of the non-linear elements.

Figure 22 illustrates a typical network configuration for simulation. In this particular topology the network is stimulated by a current source that injects a current pulse into the soma. This source is the system input in this particular simulation. The outputs include the voltages of each of the compartments, the currents through each of the branches of the network, and the state variables that describe the behavior of the non-linear conductances.
Figure 2.2: Network schematic for typical simulation protocol, similar to that shown in Figure 2.1. Voltage for each compartment is measured relative to the outside of the cell. Determining the characteristics of the circuit elements from (a) the voltage response to current source stimulus (current clamp), (b) the current response to voltage source stimulus (voltage clamp), and (c) estimation of parameters derived from basic principles is the focus of this research.
2.5 Elements of the Model

The basic task of HIPPO is the determination of the circuit elements. Characterization of some of these components is straightforward, e.g. the membrane capacitance, while most of the others are subject to considerable speculation. Because of a lack of data, some elements cannot be determined with a high degree of certainty. For these parameters, if the behavior of the cell is strongly affected, sets of simulations were conducted over the presumed range of the parameter, resulting in a range of cell responses peculiar to changes in that parameter.

HIPPO incorporates 11 non-linear, time-varying conductances in the soma, including those that underly three putative sodium currents, ($I_{Na-trig}$, $I_{Na-tail}$, and $I_{Na-rep}$), a delayed-rectifier potassium current ($I_{DR}$), a calcium current ($I_{Ca}$), a slow calcium current ($I_{CaS}$), a calcium-mediated potassium current ($I_C$), an after-hyperpolarization potassium current ($I_{AHP}$), a muscarine-inhibited potassium current ($I_M$), a transient potassium current ($I_A$), and an anomalous rectifier potassium current ($I_Q$).

All the compartments include the leakage current ($I_L$) and the capacitance current ($I_{Cap}$) as explicit components of the network model. In addition, the soma compartment includes a non-specific shunt conductance as may be introduced by the microelectrode.

All the parameters for the model, including the kinetics of the non-linear conductances and the linear characteristics of hippocampal pyramidal cells, were derived either from the literature or from consultation with Prof. Paul Adams, Dr. Johan Storm and Prof. Christof Koch.

2.6 Reversal Potentials and Ionic Current Through Membrane Conductances

The origin of the membrane potentials will now be reviewed, as these elements are fundamental to the interpretation of the model. The reversal potentials for each conductance derive from two salient features, (1) a concentration gradient across a membrane for ionic species $X$ and, (2) selective permeability in that conductance for $X$ relative to any other ionic species in

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2Department of Neurobiology and Behavior, State University of New York at Stony Brook.
3Ibid.
4Department of Biology, California Institute of Technology.
the intra- and extra-cellular medium. The concentration gradient sets up a thermodynamic potential that drives ions of X down the gradient, and across the membrane, in order to balance the concentrations. If, however, the mobility across the membrane of any of the other species in the mediums is not the same as X, movement of X will then set up a charge imbalance across the membrane. This imbalance will create a potential difference across the membrane that will oppose movement of X down the concentration gradient. At equilibrium, there will be no net flow of X across the membrane, and the electrical potential will be equal and opposite to the thermodynamic potential caused by the concentration gradient. The relationship between concentration gradient and electrical potential is described by the Nernst equation,

\[ E_X = \frac{RT}{z_X F} \ln \left( \frac{[X]_{\text{out}}}{[X]_{\text{in}}} \right) \]

where \( E_X \) is the potential due to ionic species X (referenced to the inside of the cell), \( R \) is the gas constant, \( T \) is the temperature in degrees Kelvin, \( z_X \) is the valence of X, \([X]_{\text{out}}\) is the concentration of X outside the membrane, and \([X]_{\text{in}}\) is the concentration of X inside the membrane.

Note that if the membrane is permeable to other charge carriers in the medium, then space-charge neutrality will be maintained as counterions are dragged across the membrane with X. The concentration gradient of X will then be eliminated with no concomitant establishment of an ionic potential due to a charge imbalance from the movement of X.

The flow of ions through membrane channels has been the subject of much theoretical work, and at present there is no consensus as to the mechanisms involved (Hille, 1985). However, measurements of the intrinsic conductance of ion channels over a narrow range of membrane potentials show that to a first approximation this intrinsic conductance is linear (independent of the voltage):

\[ I_X = g_X (V_{\text{membrane}} - E_X) \]

where \( I_X \) is the ionic current, \( V_{\text{membrane}} \) is the voltage applied across the membrane, and \( g_X \) is the conductance of X through the membrane channels.

\(^5\)Typically in the physiological range of membrane potentials, and several millivolts away from the reversal potential of a given channel, where non-linearity of the intrinsic conductance is pronounced most.
An important assumption in the HIPPO model is that the flow of one ionic species across the membrane is independent of the flow of any other species; the different currents are linearly independent. This allows the different current paths to be represented as distinct independent conductances in parallel with each other, each driven by the appropriate ionic potential, as was illustrated in Figure 2.

In fact, it has been demonstrated that so-called “selective” channels are not absolutely selective for a given ion. Most channels are instead preferentially selective for one ion or another, and have a lower (perhaps much lower but non-zero) permeability for other species. The result is a reversal potential for a given channel that may be expressed by the Nernst-Goldman equation, including the appropriate ions and their relative permeabilities. For example, the reported reversal potentials for the (assumed) $K^+$ channels typically vary between -90 and -70 millivolts, whereas $E_K$, assuming standard values for the concentration of $K^+$ inside and outside the membrane, is about -98 millivolts. Likewise, data on $I_{Ca}$, which is advertised as a $Ca^{2+}$ current indicates that its reversal potential is around 0 millivolts (see Chapter 6). Finally, the resting potential in the model is assumed to be set by a non-voltage-dependent channel with a reversal potential of -70 millivolts, which implies that either there is a mixture of perfectly selective channels that contribute to give the observed “leak” channel, or there is a single channel that is permeable, to varying degrees, to more than one ion.

2.6.1 Sodium Potential - $E_{Na}$

In the HIPPO simulations, the sodium potential was not found to be a very critical parameter, probably since most of the activity of the cell occurs around potentials that are very hyperpolarized to the sodium potential. Changing this potential mainly affected the amplitude and rate of rise of the action potential. $[Na^+]_{in}$ is assumed to be 12 mM, and $[Na^+]_{out}$ is assumed to be 145 mM. At physiological temperature this corresponds to a potential of +63 mV.

2.6.2 Potassium Potential - $E_K$

The potassium potential is the most sensitive ionic potential in the model. Much of the reproduced activity takes place within 10 to 20 millivolts from rest. In addition, there is evidence that the potassium concentration adjacent to the outside membrane is substantially different than the rest of
the extracellular medium, which in turn will change $E_K$ transiently during electrical activity. Further, the intracellular potassium concentration is not measured readily. In the model presented here, however, the concentration of $K^+$ inside and outside the cell is assumed constant. $[K^+]_{in}$ is set at 155 mM, and $[K^+]_{out}$ is set at 4 mM. At 37°C, this corresponds to a potassium potential of $-85$ mV.

As shall be discussed in Chapter 7, raising the reversal potential of $I_{DR}$ to $-73$ mV was necessary, in order to obtain certain features of the voltage response as mediated by this current. Different so-called $K^+$ conductances may, in fact, have slightly different reversal potentials, reflecting, as mentioned above, a non-ideal selectivity of a given channel. For example, the higher reversal potential of $I_{DR}$ implies that this channel allows the passage of either a small proportion of $Ca^{2+}$ or $Na^+$ as well as $K^+$.

2.6.3 Calcium Potential - $E_{Ca}$

The calcium potential was calculated from the constant extracellular $Ca^{2+}$ concentration (4.0 mM) and the concentration of $Ca^{2+}$ directly underneath the membrane regions where the $Ca^{2+}$ channels are assumed to be grouped, $[Ca^{2+}]_{shell.1}$. At rest, $[Ca^{2+}]_{shell.1}$ was equal to 50 nM, resulting in a $E_{Ca}$ of 128 mV. In Chapter 6, the dynamics of the $Ca^{2+}$ system and the behavior of $E_{Ca}$ are presented in detail.
Chapter 3

HPC ELECTROTONIC STRUCTURE AND DETERMINATION OF LINEAR PARAMETERS

3.1 Introduction

This chapter describes an estimation of the electrotonic structure of the hippocampal pyramidal cell model. The parameters for this structure are derived from the literature and from theoretical considerations that are developed herein. First, the basis for this development and the role it plays in the modelling effort will be described. Next, the parameters for the electrotonic structure will be defined and described, including the membrane capacitance, the cytoplasmic resistivity, and the factors underlying the membrane resistivity. The next section will begin by describing the problem of modelling the geometry of the cell. Two methods for estimating the dimensions will be presented, the first by extrapolating data used in other modelling studies, and the second based on a histological data-based technique that I have developed.

The electrical parameters of the cell will be estimated next based on reported data. When combined with the results of the previous section, some reports may be used to derive morphometric data, but not electrical parameters, and other reports may be employed for only some electrical measurements.
In order to develop a model structure that is consistent with the available (valid) data, the next section in this chapter derives the frequency response for the general structure. Next, DTFT techniques are used with the derived frequency response to examine various model structures so that the desired linear temporal response may be obtained. Several suggestions on how some parameters may be better estimated using the phase and magnitude of the frequency response are discussed, and the accuracy of the compartmental model used in the actual simulations is verified by comparison with the previously derived response of the continuous structure. Finally, the parameters of the structure used in this study are presented, along with a discussion of some of the possible functional implications of the values for these parameters.

3.2 The Importance of the Electrotonic Structure

In order to develop descriptions of non-linear elements in the pyramidal cell using the small amount of available data, building on an accurate characterization of the electrotonic structure of the cell is necessary. The term "electrotonic" refers to the cable-like characteristics of the cell as defined by the linear properties of the cell membrane, cytoplasm, and the intricate geometry of the dendritic tree.

Starting with a valid electrotonic structure is important for a few reasons. First, in the absence of complete voltage clamp data, the estimates for many of the non-linear parameters must be evaluated by current clamp simulations. In this case, subtleties in the resulting voltage records are analyzed to determine the accuracy of a given estimation. If the linear response of the model cell is different than that of the real cell, determining whether differences between simulated and actual responses are due to errors in the estimation of the non-linear parameters or to errors in the linear parameters may be impossible.

For example, one method used to derive the $Na^+$ currents in the hippocampal pyramidal cell involves running voltage clamp simulations on the linear model (no non-linear conductances) using an actual $Na^+$-only spike record as the clamp voltage. In this protocol, as will be reviewed in Chapter 5, the clamp supplies the current necessary to cancel the linear currents (leak current, soma-dendrite current, and soma capacitance current) elicited by the spike waveform. Presumably, then, the clamp current must reflect those
currents that are mediated by Na\(^+\) channels during a Na\(^+\)-only spike. The time course of the clamp current therefore provides clues as to the non-linear processes that may underly the Na\(^+\) currents (ref. Figure 5.2). For example, does the waveform indicate that more than one HII-like conductance is operating, and what are the magnitudes of the putative components? Models with different linear response will give different clamp currents under these conditions, so it is necessary that attention is focused on a model whose linear response most closely follows a real cell.

Another motivation to carefully develop the linear structure of the model came about when various references for this structure were consulted, including reports of measurements of cells and reports of other hippocampal pyramidal simulations. As will be reviewed later, many aspects of these reports were inconsistent, and required reviewing the assumptions inherent in these analyses and integration of the valid aspects of the reported data to obtain a more consistent description of the relevant parameters.

### 3.3 Building the Linear Description

Several papers on the measurement of the linear properties of hippocampal neurons were consulted to obtain the model parameters, including other modelling studies ([48], [44]), measurements of the linear properties of hippocampal neurons ([7], [52]), and references for analytical approaches to approximations of the neuron geometry ([26]). Typically these papers derive parameters via analysis of the assumed linear response to a hyperpolarizing current step. The analysis is based often on the calculated response of the soma/short-cable structure. Several methods are available to estimate a given parameter, and more than one is often used to estimate better a given parameter (e.g. [7]).

In examining the published data, however, some problems arose when the derived parameters were checked either using the model or by running simple calculations. These inconsistencies will be addressed in this chapter.

### 3.4 HPC Linear Parameters

The linear parameters of the model include:

- Steady state input resistance as seen from the soma – \( R_{in} \) (\( \Omega \))
- Specific resistivity of the soma membrane – \( R_{m-soma} \) (K\( \Omega \) cm\(^2\))
- Specific resistivity of the dendrite membrane – \( R_{m-dend} \) (K\( \Omega \) cm\(^2\))
• Cytoplasmic resistivity – $R_i$ (KΩ cm)
• Specific membrane capacitance (assumed homogeneous) – $C_m$ ($\mu f/cm^2$)
• Radius of the soma – $a_{soma}$ (μm)
• Radius of the dendritic cable – $a$ (μm)
• Length of the dendritic cable – $l$ (μm)
• Length constant of the dendritic cable – $\lambda$ (μm)
• Electrotonic length of the dendritic cable – $L$ (dimensionless)
• Dendrite/Soma conductance ratio – $\rho$ (dimensionless)
• Terminating admittance of the dendritic cable, normalized to that of a semi-infinite cable – $B$ (dimensionless)

Some of these parameters are derived from the others, including $\lambda$ and $L$:

$$
\lambda = \sqrt{\frac{aR_{m-dend}}{2R_i}}
$$

$$
L = \frac{l}{\lambda}
$$

Other parameters that are sometimes used for convenience include:

• Cytoplasmic resistivity per unit length – $r_a$ (KΩ cm$^{-1}$)

where

$$
r_a = \frac{R_i}{\pi a^2}
$$

• (Typically dendritic) membrane time constant – $\tau_0$ or $\tau$ (milliseconds)

where

$$
\tau_0 = R_{m-dend}C_m
$$

Many investigators refer to a homogeneous membrane resistivity, $R_m$, that is constant over both the soma and dendrites. This and each of the other parameters will be discussed in this chapter. The specific membrane capacitance, the cytoplasmic resistivity, the leak conductance, the electrode shunt conductance, and the leak reversal potential will now be discussed.

### 3.4.1 Specific Membrane Capacitance

The generally accepted value for $C_m$ is 1 $\mu f/cm^2$. This value is comparable to the specific capacitance of .8 $\mu f/cm^2$ for a pure lipid bilayer ([19]). In some cells, however, a different value for $C_m$ has been reported. For example,
the apparent membrane capacity for crustacean muscle fibers is 15 to 40 $\mu F/cm^2$ ([19]). If the true capacity per unit area is 1 $\mu F/cm^2$, this indicates that the membranes of these cells is quite contorted.

The capacitance of any given compartment was then calculated based on this value multiplied by the total surface area of the compartment that faced the extracellular medium. This calculation was based on several assumptions about the structure of the cell and the structure of the membrane. For example, ideal geometries were assumed when calculating the absolute value for the capacitance for any of the compartments in the HIPPO model – a sphere for the soma compartment and right cylinders for the dendritic and axonal compartments. In fact, the cell membrane is much more convoluted than this description implies, and the net result would be an underestimation of the cell capacitance. On the other hand, the value of 1 $\mu F/cm^2$ assumes a smooth membrane, without any small-scale variations. A more realistic calculation of membrane capacitance would take into account the inhomogeneity of the membrane and the variation of the membrane thickness. These factors would tend to reduce the capacitance per unit area.

In summary, the model cell incorporates a value of 1 $\mu F/cm^2$ for $C_m$. In addition, $C_m$ is assumed to be constant over the entire cell (i.e. $C_m$ is the same for both the soma and the dendrites). Some investigators have proposed larger values for $C_m$, for example ranging from about 2 to 4 $\mu F/cm^2$ ([52]). These values were derived from estimating the membrane time constant under assumptions that are probably not valid (e.g. homogeneous time constant over the entire cell, terminating impedance of dendrites = 0). The errors incurred under the various assumptions that have been used in other studies will be examined later, particularly when the estimation of $R_m$ is discussed. These errors have likely contributed to an overestimation of $C_m$ in some of these reports.

### 3.4.2 Cytoplasmic Resistance

The resistivity of the intracellular medium, the cytoplasm, is calculated with the assumption that the interior of the cell is homogeneous. This is clearly an assumption since the cell is packed with a myriad of cytostructural elements, organelles and inclusions. To a first approximation, however, the inhomogeneity of the cytoplasm is ignored.

Shelton [44] presents the following argument as to the size of $R_i$. He proposes that the lower limit of $R_i$ is set by the conductivity of pure physiological saline solution, corresponding to a value of 50 to 60 $\Omega cm$. Measure-
ments of the resistivity of extracellular brain tissue are cited in the range of 50 - 600 Ω cm, and measurements of the resistivities of axoplasm and somatic cytoplasm in other cells are quoted as being in the range of 20 - 160 Ω cm and 70 - 390 Ω cm, respectively. Shelton proposes that the resistivity of the medium in which a microelectrode is immersed contributes to the effective electrode resistance due to the convergence resistance near the electrode tip. Since the microelectrode bridge circuit must be compensated to account for the electrode resistance, the compensation required as the electrode tip moves from outside to inside the cell will give an indication of the difference in the extra- and inter-cellular resistivities. Measurements along these lines indicate that the difference between these resistivities for the cerebellum and the Purkinje cell are less than 50 Ω cm. Assuming that the cerebellar extracellular resistivity is 200 Ω cm, Shelton then uses this result to suggest that Ri is near 250 Ω cm.

This value of Ri is significantly higher than what is used usually in the reports analyzing the linear characteristics of the pyramidal cell. Typical values in these reports are in the range of 50 - 75 Ω cm. Most studies do not indicate the rationale for these values, other than the supposed analogy to the resistivity of a Ringer's-type solution. An investigation of the significance of Ri was therefore of interest, in particular to see if large differences in this parameter could significantly affect the derivation of the other linear parameters.

The most obvious parameter that is a strong function of Ri is the dendritic length constant, λ, and thus the electrotonic length of a dendritic segment, L. λ is determined by Ri, Rm–dend, and a by the following relation:

\[
\lambda = \sqrt{\frac{R_{m-dend}a}{2R_i}}
\]

(Note that λ expresses the length over which the voltage from a constant point source attenuates by a factor of 1/e down an infinite dendritic cable.)

For a fixed value of Rm–dend and a, a four-fold increase in Ri (e.g. from 65 to 260 Ω cm) will correspond to a halving of λ. The manner in which Ri affects the input impedance of the cable is discussed later.

One of the assumptions of the compartmental model is that within each compartment the intracellular resistance can be neglected, so that the compartment is isopotential. The cytoplasmic resistivity is only considered in the electrical communication between dendritic compartments, where the
connecting resistor is calculated from the dimensions of the compartments and the cytoplasmic resistivity according to the formula –

\[ R_{coupling} = \frac{R_i \times l_{compartment}}{\pi a^2} \]

where \( l_{compartment} \) is the length of the dendrite segment.

In summary, the model incorporates an \( R_i \) of either 200 or 250 \( \Omega \) cm for most of the analyses. In some cases, \( R_i \) was set to 75 \( \Omega \) cm in order to evaluate data from other reports of intracellular measurements or modelling studies, but results presented in later chapters are obtained using the higher values of \( R_i \).

### 3.4.3 Leak Conductance, Electrode Shunt Conductance, And Leak Reversal Potential

\( R_m \), the specific membrane resistivity, is defined as a linear, time-independent conductance. The intrinsic leak conductance of the cell, \( R_{leak} \), and the electrode shunt conductance, \( R_{shunt} \), combine to form \( R_m \) when the impedance of the membrane is evaluated. \( R_{leak} \) includes the conductance of the lipid bilayer, and an ion-specific channel or channels whose conductance is or are voltage and time independent. \( R_{shunt} \) is the non-specific leak arising from the impalement of the cell with a microelectrode. Since \( R_{leak} \) is a selective conductance, it is modeled in series with a voltage source representing the leak reversal potential, \( E_{leak} \). \( R_{shunt} \), however, is non-selective, and therefore is modeled without a series voltage source.

Accurate determination of \( R_m \) is difficult, particularly because of the cable properties of the pyramidal cell and, as will be demonstrated, the non-homogeneity of \( R_m \). In this section some estimates of \( R_{shunt} \) are presented as well as a background for the measurement of the intrinsic \( R_{leak} \) and estimates of \( E_{leak} \). The estimates of \( R_m \) (actually of \( R_{m-soma} \) and \( R_{m-dend} \)) will be presented later in this chapter.

The conductance of the lipid bilayer sets an upper bound for the \( R_{leak} \) of \( 10^8 - 10^9 \) \( \Omega \) cm\(^2\) [19]. Since estimates of \( R_m \) typically are in the range of 500 to 10\(^4\) \( \Omega \) cm\(^2\), ion channels or the electrode leak appears to account for the majority of the total membrane leak.

Various estimates of the leak introduced by an electrode have been made, ranging from 50 to 200 M\( \Omega \) [44]. We can roughly estimate the magnitude of the leak introduced by the single electrode used in the single electrode clamp (SEC) protocol from the amount of constant "repair" hyperpolarizing
current that must be supplied to the soma in order to maintain a resting potential of -60 to -70 mV. Typical values for this current range from 0.5 to 1.5 nA (Storm, personal communication). If the normal resting potential is assumed to be -70 mV, and sufficient repair current is supplied to restore this membrane voltage, then the previous range of repair current magnitudes implies electrode leaks in the range of 140 to 47 MΩ, respectively.

Estimates of pyramidal cell input impedance vary over an order of magnitude. This range is more than can be explained simply by the difference in the surface area and electrotonic structure of the measured cells. The integrity of the electrode seal is variable, and could conceivably account for a large part of the input conductance.

For many cells $R_m$ is estimated by measuring the time constant of the cell in response to small steps of injected current with the cell at resting potential. In this case, either the cell membrane is assumed to be equipotential (in which case the response should consist of a single exponential and the single time constant is measured), or an infinite cable structure is assumed with a homogeneous membrane, and the largest time constant of the response is interpreted as the true membrane time constant. This formula shall be referred to later when some of the published estimates of $R_m$ are examined.

Typical values for the time constants measured under these conditions for various cells (including non-neuronal cells) range from 10 μs to 1 second. This range corresponds to $R_m$'s of 0.30 to $10^6$ Ω cm², assuming that $C_m$ can range from 1 - 30 μF/cm². Thus the number of channels that are open and contribute to the maintenance of the resting potential varies considerably between different cell types.

The stability of the resting potential may be investigated by perturbing the membrane voltage in the presence of active conductances. These simulations can test the validity of any calculated $E_{\text{rest}}$, since it is likely that the membrane voltage would be stable in the neighborhood of the actual $E_{\text{rest}}$, and that the spike threshold would be distinct (e.g. greater than 10 mV depolarized from rest). This stability of $E_{\text{rest}}$ is observed for non-spontaneously firing cells, and is advantageous since this behavior is directly related to the ability of the cell to reject noise (at a low level of perturbation) and the integrative ability of the cell. In the latter case, a firing threshold near $E_{\text{rest}}$.

1This repair current is often only transiently required, however, as if over time the leak introduced by the micro-electrode is sealed automatically (Storm, personal communication)
would cause the cell to fire for a larger set of inputs than if the threshold was more depolarized. Modulation of the firing threshold is a possible physiological mechanism for changing the computational function of a single cell. On the other hand, threshold modulation may be a factor in some pathological states, such as epilepsy where the threshold is abnormally low leading to hyperexcitability (e.g. seizures), or in states where the threshold is too high, causing hypoexcitability (e.g. paralysis at the extreme).

In most reports, $E_{\text{rest}}$ is assumed to be about -70 mV. Since the evidence for hippocampal pyramidal cells indicate that there is little current due to non-linear channels at rest (the exception being a small $I_m$, discussed in Chapter 6), I have assumed that the reversal potential for the leak conductance, $E_{\text{leak}}$, is equal to -70 mV.

### 3.5 Modelling the Cell Geometry

The shape of the hippocampal pyramidal neuron is quite complex, as Figure 3.1 illustrates.

The basic regions of the pyramidal neuron are the cell body, or soma, the basal dendrites, the apical dendrites, the axonal hillock, and the axon. Synaptic input to the cell is received at all its regions, but is primarily received on the dendritic trees. In the standard view of the HPC, the dendritic membrane is primarily linear while the somatic, axon hillock and axon membranes are active, that is contains non-linear voltage and time dependent conductances. Although recent studies show that there are non-linear conductances located on the dendrites, in the present model purely linear...
dendrites are assumed.

3.5.1 Assumption of Linear Dendrites

Defining the dendrites to be linear is an important assumption for the model. There is extensive evidence of various $Na^+$, $Ca^{2+}$, and $Cl^-$ channels in the dendrites ([53], [34], [31], [50], [5]), but the exclusion of dendritic non-linear conductances was considered reasonable as a first approximation since the present work is focused on the action of somatic currents. I assume that the behavior of the somatic non-linear conductances are relatively insensitive to regions of non-linear dendritic membrane, at least when considering cell response to somatic input. In Chapter 9, simulations of somatic response to dendritic input will be presented, in which the assumption of linear dendrites is a more restrictive one in terms of interpreting the model results.

The primary function of the dendrites is to collect and integrate synaptic input from other neurons. That input is conducted to the soma where an action potential is initiated if the soma membrane is excited above the local threshold. As far as the model is concerned, though, the contribution of the dendrites is simply that of a linear load on the soma.

3.5.2 Approaches to the Representation of HPC Structure

The possible options for representing the structure of the pyramidal cell in simulations are worthy of review. At one extreme, the entire geometry of the cell and its dendritic tree may be modeled in detail, with the dendritic tree reduced to a set of branching cylinders, perhaps including the tapering of each cylinder and the dendritic spines. The appropriate linear cable equations may then be employed to examine the steady-state input conductance of the entire tree ([52]), assuming linear dendrites. If the transient response is of interest, or if non-linear dendritic conductances are to be included, representing the cable segments with compartmental approximations and solving the network numerically is necessary ([44]).

Histological technique can supply the data necessary for this sort of representation, but the attempts to model dendritic trees at least approximate the tapering segments as right cylinders. The hippocampal pyramidal cell has been modeled in this fashion ([52]). In this study, the dendritic tree was dissected into a branching structure of right cylinders, without spines. Several cells were analyzed, with the dendritic trees modeled with 300 - 1,000 cylinders per cell. Using the equation for the input conductance of a short
cable and moving proximally from each distal termination, the steady-state input conductance of the entire tree was derived as a function of membrane resistivity and cytoplasmic resistivity. A study of a Purkinje neuron ([44]) represented the cell with 1089 coupled compartments. In this case the dynamic behavior of the linear cell was derived numerically in order to estimate its linear properties.

The next level of approximation in reducing the dendritic tree consists of collapsing branched structures into equivalent cylinders, according to the technique developed by Rall [26] (described shortly). The complexity of the resulting representation (i.e. how much will the tree be collapsed into larger cables), depends on the morphological characteristics of the dendrites and the accuracy desired by the modeller. In this model, several versions of such a geometry were used, as illustrated in Figure 3.2. For investigating somatic properties the dendritic tree was sufficiently represented as a single short cable, as shown in Figure 3.2. On the other hand, as was mentioned at the beginning of the chapter, the parameters of this approximation, the dimensions of the soma and the cable and their linear electrical properties, were critical to the response of the model, and their careful estimation is important.

At the other end of the spectrum, in representing pyramidal cell geometry, is an isopotential sphere representing the entire cell. For most modelling studies of cells with a significant dendrite tree this approach is too simplified for two reasons. First, the linear response of the sphere will consist of a simple exponential, precluding the role of the dendrites as relatively isolated stores of charge that contribute to restoring the soma voltage after short perturbations. Second, the majority of voltage-dependent ion channels are believed to be localized at the soma, and that the dendrites are either linear, or incorporate localized, lower density, non-linear conductances. Modelling the cell as an isopotential sphere prevents considering such a distribution of non-linear and linear membrane.

In summary, modelling with a detailed description of the dendritic tree is necessary if one is interested in evaluated the complex information processing that apparently occurs at the level of distinct regions of the tree. If, however, one is interested only in somatic properties, as a first approximation the tree may be collapsed so that its approximate load as that of a single short cable may be evaluated. A next step in the analysis of somatic properties may use a slightly more complicated approximation to the tree structure, as shown in Figure 3.2, and has been used by Traub and Llinas([48])(see
Figure 3.2: Different model geometries used to approximate hippocampal pyramidal cell in present study, drawn approximately to scale. The simple soma/short-cable structure on the right was used for the majority of the analyses.
also Figure 3.2). In these versions, the contribution of non-linear dendritic membrane may be considered, where the non-linear membrane is localized in some isolated section of a dendritic branch. The simulations of Traub and Llinas have provided some interesting results in this area, but their model parameters may not have been derived carefully enough to warrant any more than qualitative interpretations of the behavior of their model.

After the Rall method of reducing dendritic trees has been introduced, several methods for estimating the model geometry will be presented.

3.6 The Rall Reduction Of The Dendritic Tree To Equivalent Cylinders

Rall has shown that under certain conditions a set of dendritic branches emerging from the distal end of a dendritic segment may be collapsed into a single cable whose input impedance (as seen from the parent segment) is identical to that of the original set. The conditions for the reduction of each set of branches into a single cable are twofold: 1) the terminating impedance of each branch must be the same, and 2) the electrotonic length of each branch must be equal. The electrotonic length of the new equivalent branch is the same as the original branches, and its diameter, raised to the 3/2 power, is equal to the sum of the original diameters, each as well raised to the 3/2 power. The terminating impedance of the equivalent branch is equal to the terminating impedance of each of the original branches.

If the diameter of the equivalent branch or segment is equal to that of the more proximal parent segment, then the two cables connected in series are equivalent to a single longer cable. As long as the appropriate conditions hold, the entire dendritic tree can be represented by a single cable by applying the reduction algorithm repeatedly, starting from the distal branches and continuing proximally to the soma.

The constraints for the Rall reduction are rather severe, and several types of neurons have been analyzed to see if the above conditions are applicable. Remarkably enough, some neurons seem to follow the so-called "3/2 rule" (e.g. in lateral geniculate nucleus [44]), and the suggestion has been made that the Rall reduction is quantitatively valid for them (although it is not always clear if the authors of these studies of fully aware of the complete set of constraints in the reduction algorithm [Rall, personal communication]).

For hippocampal pyramidal cells, the reviews have been mixed, with quantitative studies based on detailed histological data suggesting that the
Rall constraints are not met at all well ([52]). Despite this, the reduction as described is still considered a good first approximation to the pyramidal trees, and some studies have suggested that in terms of the dendritic input impedance the Rall approximation is in good qualitative agreement with the actual tree structure (Brown et al). Later in this chapter the responses of a soma/single-dendritic-cable and a soma/double-dendritic-cable will be compared to show qualitatively that the Rall reduction is a useful one even when the electrotonic lengths of the daughter branches are not identical.

3.7 Approximation Of The Soma As An Isopotential Sphere

The so-called “soma” of the hippocampal pyramidal cell is not a sphere; it is more of a tapered cylinder with rounded ends. Further, the transition between soma and dendrite is not well-defined, especially for the apical processes. The soma region is assumed to be well-defined, however, in the model approximation. This region is also assumed to be isopotential. This assumption allows the use of a sphere instead of a cylinder to represent the soma, as long as the surface area of the soma is conserved. The isopotential approximation assumes that voltage gradients are minimal, despite the finite cytoplasmic resistivity. It can be shown ([26], Ch. 3) that the spread of current from a single intra-somatic point source introduces a very small voltage gradient in the soma.

The dimensions of the soma were evaluated from the model soma used in Traub and Minas’s model, and from estimating the dimensions from micrographs. The soma used in the Traub and Llinas model was a cylinder, so the surface area of this soma was used to set the radius of the spherical soma in the present model at 17.5 μm. This value is consistent with the size of the soma region seen in micrographs.

3.8 Estimating the Dimensions of the Model Dendrites

Traub and Llinas’ paper provided the default dimensions of the dendritic cable of the model as well. In their model the dendritic tree was represented by a two short cable basal dendrites and a short cable apical dendrite that terminated into two short cable apical branches (Figure 3.2). The HIPPO
model topology was initially configured the same way, using Traub and Llinas’ dimensions. In their paper, however, the effect of dendritic input and localized regions of non-linear membrane in the dendritic tree were investigated, necessitating the described geometry. Since at the present time the description of soma currents is being investigated, this tree structure was collapsed into a single cable using a variant on the Rall method.

Traub and Llinas used a homogeneous $R_m = 3.0 \, \Omega \, \text{cm}^2$, and set $R_i = 75 \, \Omega \, \text{cm}$.

3.8.1 Deriving the Dimensions of a Single Cable That is the Approximate Equivalent of Two Cables

The first step in this approximation was collapsing the basal branches and apical branches into a single basal and apical cable. This step was straightforward since both the basal branches and the apical branches were the same electrotonic length as their partners, and further that the diameter of the apical shaft satisfied the 3/2 rule with its daughter branches.

The second step was to combine the equivalent apical cable ($ac$) with the equivalent basal cable ($bc$). This was not straightforward since the equivalent apical and basal cables were not the same electrotonic length ($L_{ac} = 0.8, L_{bc} = 0.6$). The approach used was to calculate $a$ according to the 3/2 rule, and then calculate $l$ so that that the single cable would have the same steady-state input impedance as the original two cables in parallel.

First, the diameter of the single "equivalent" cable ($sc$) was derived from the 3/2 rule:

$$a_{sc} = \left( a_{ac}^{3/2} + a_{bc}^{3/2} \right)^{2/3}$$  \hspace{1cm} (3.1)

where $a_x$ is the radius of the appropriate cable, yielding $a = a_{sc} = 4.3 \mu\text{m}$. The next step was to derive the length of the single cable, starting with the formula for the parallel input impedance of the original cables:

$$Z_{sc}(s = 0) = \frac{Z_{ac}(s = 0) \cdot Z_{bc}(s = 0)}{Z_{ac}(s = 0) + Z_{bc}(s = 0)}$$  \hspace{1cm} (3.2)

From the equation for the input impedance of a short cable (Equation 3.20, derived later, with $s = 0$ since we are interested in the steady state impedance, and $G_{soma} = 0$ and $C = 0$, since we are interested in the impedance of the isolated cable), Equation 3.2 becomes
\[
\frac{1}{r_{a,sc}\lambda_{sc}} \tanh L_{sc} = \frac{1}{r_{a,ac}\lambda_{ac}} \tanh L_{ac} + \frac{1}{r_{a,bc}\lambda_{bc}} \tanh L_{bc} \quad (3.3)
\]

Now since

\[
r_{a,sc} = \frac{R_i}{\pi a^2}
\]
\[
r_{a,ac} = \frac{R_i}{\pi a_{ac}^2}
\]
\[
r_{a,bc} = \frac{R_i}{\pi a_{bc}^2}
\]

\[
\lambda_{sc} = \sqrt{\frac{a R_m}{2 R_i}}
\]
\[
\lambda_{ac} = \sqrt{\frac{a_{ac} R_m}{2 R_i}}
\]
\[
\lambda_{bc} = \sqrt{\frac{a_{bc} R_m}{2 R_i}}
\]

\[
L_{sc} = \frac{l}{\lambda_{sc}}
\]

and if \( a \) is derived from Equation 3.1, then from Equation 3.3 we obtain

\[
\tanh\left(\frac{K l}{\sqrt{a}}\right) = \frac{a_{ac}^{3/2} \tanh(L_{ac}) + a_{bc}^{3/2} \tanh(L_{bc})}{a_{ac}^{3/2} + a_{bc}^{3/2}} \quad (3.4)
\]

where

\[
K = \sqrt{\frac{2 R_i}{R_m}}
\]

By expanding the \( \tanh \) term on the left side of Equation 3.4, and by making the substitution (from Equation 3.1) of

\[
\sqrt{a} = (a_{ac}^{3/2} + a_{bc}^{3/2})^{1/3}
\]

the length, \( l \), of the single cable is found to be
\[ l = \left( \frac{a_{ac}^{3/2} + a_{bc}^{3/2}}{2K} \right)^{1/3} \ln \left( \frac{1 + \alpha_1 \tanh(L_{ac}) + \alpha_2 \tanh(L_{bc})}{1 - \alpha_1 \tanh(L_{ac}) - \alpha_2 \tanh(L_{bc})} \right) \]

where

\[ \alpha_1 = \frac{1}{1 + \left( \frac{a_{ac}}{a_{mc}} \right)^{3/2}} \]

\[ \alpha_2 = \frac{1}{1 + \left( \frac{a_{ac}}{a_{bc}} \right)^{3/2}} \]

This procedure gave \( l = 850 \mu m \), and from this \( L \) was calculated as \( L = 0.69 \). To check this reduction, the transient response to a current step of this configuration was then compared with the response of the original geometry of Traub and Llinas (Figure 3.4). The responses were nearly identical, validating the approximation between these two geometries.

Important inconsistencies arise, however, when the linear response of the Traub and Llinas model is compared with that of actual cells. These will be examined once the data derived from intracellular measurements has been presented. At this point, this model will be used only to establish a reasonable set of dimensions for the HIPPO model.

### 3.8.2 A New Method of Estimating \( l \) and \( a \) For the Equivalent Cylinder Approximation From Histological Data

In order to check the validity of the dimensions used in Traub and Llinas' model, a method was derived for estimating \( l \) and \( a \) from purely histological data, that is, without relying on estimates of electrical properties. The parameters used for this estimation include:

- Average length of the dendritic tree - \( l_{av} \) (\( \mu m \))
- Average radius of the dendrite branches - \( a_{av} \) (\( \mu m \))
- Radii of the \( i \) proximal dendrites where they attach to the soma - \( a_i \) (\( \mu m \))

The radius of the equivalent short cable of the entire tree, \( a \), is then set by the \( a_i \)'s under the assumption that the radius of each proximal segment is the same as the radius of the equivalent cylinder approximation for the portion of the tree distal to that segment. Thus –
Figure 3.3: Comparison of cell geometry approximation used by Traub and Llinas and single cable approximation used in the model. Structures are not drawn to scale.
Figure 3.4: Comparison of response to current step of geometry used by Traub and Llinas and single cable approximation used in the model.

\[
a = \left( \sum a_i^{3/2} \right)^{2/3}
\]

The length of the equivalent cable for the entire tree, \( l \), is a function of the average length of the dendritic tree, \( l_{av} \), the average diameter of the dendrite branches at about the midpoint of the tree, \( a_{av} \), and the estimated \( a \). Here an assumption is made that the tree can be represented by a number of identical cables with radius \( a_{av} \) and length \( l_{av} \). As previously mentioned, the Rall method requires that electrotonic length be conserved in the equivalent cylinder. The \( L \) for the cable representing the entire tree is therefore estimated as

\[
L = \frac{\sqrt{a_{av} R_{m-dend}}}{2R_i} \frac{l_{av}}{l_{av}}
\]

(3.5)

Note that the numerator of the right hand side of Equation 3.5 is the space constant for the "average" cable.

Since \( l \) is equal to

\[
l = \frac{\sqrt{a_{av} R_{m-dend}}}{L} \frac{2R_i}{l_{av}}
\]

(3.6)
Equations 3.5 and 3.6 can be combined to get

\[ l = l_{av} \sqrt{\frac{a}{a_{av}}} \]

This estimate for \( l \) is function only of the dimensions of the tree. The significance of this estimate is that \( l \) may be derived purely from histological measurements and does not depend on an assumed value for \( R_{m-dend} \) or \( R_i \). The estimate of \( L \), on the other hand, does depend on the estimated values of \( R_{m-dend} \) and \( R_i \). Further, \( a_{av} \) is not the same thing as the average diameter of the proximal branches. \( a_{av} \) must be used as defined since the main part of the electrotonic length of the dendritic tree is determined by the finer and more numerous distal processes. Thus the diameter of these branches must be considered in estimating \( L \) (or \( I \)).

Typical values for \( a_{av} \) for the hippocampal pyramidal cell are in neighborhood of 0.5 - 1.0 \( \mu \text{m} \). At the soma there is typically either one or two apical branches, with a diameter ranging from 3 - 10 \( \mu \text{m} \) (e.g. Johnston and Brown, 1983). There are usually several proximal basal branches, with a typical diameter of about 1 \( \mu \text{m} \). A reasonable value for \( l_{av} \) could range from 300 - 500 \( \mu \text{m} \). For example, if there are two apical dendrites originating at the soma with diameters of 3.0 \( \mu \text{m} \) and 4.0 \( \mu \text{m} \), and there are six basal branches at the soma, each with a diameter of 1.0 \( \mu \text{m} \), with the above ranges for \( a_{av} \) and \( l_{av} \), the estimated value for \( a \) is 3.6 \( \mu \text{m} \) and the estimated range for \( l \) is 570 - 1300 \( \mu \text{m} \).

As a second example, let us assume that there are two apical dendrites have diameters of 3.0 \( \mu \text{m} \) and 10.0 \( \mu \text{m} \), and the six basal branches stay the same as before with diameters of 1.0 \( \mu \text{m} \). Using the same ranges for \( a_{av} \) and \( l_{av} \), the estimated value for \( a \) now is 6.8 \( \mu \text{m} \), and the estimated range for \( l \) is 780 - 1800 \( \mu \text{m} \).

These values can be compared with the dimensions of the equivalent cylinder derived from the Traub and Llinas model. The value for \( a \) in this report was 4.3 \( \mu \text{m} \), the length of the equivalent cylinders for the basal branch and the apical branch were 555 \( \mu \text{m} \) and 820 \( \mu \text{m} \), respectively, and the length of the single equivalent cable that was derived in this paper was 850 \( \mu \text{m} \). These numbers compare well with the figures above. In fact the authors comment that their estimate for \( l \) of their model's apical cylinder was “possibly somewhat small”. How the dimensions of this model were derived is not known, but presumably an analysis similar to the one just presented was employed.
To summarize, the dimensions of the Traub and Llinas model are in good agreement with the previous estimate. These results will be used both in the next section to test the validity of another report which implies a set of dimensions, and later in this chapter when the final dimensions of the model will be determined. Another estimation of the model cell dimensions, this time based on reported parameters of CA1 cells derived from intracellular electrical measurements, will now be presented.

3.9 Evaluating Reported Linear Parameters Derived from Intracellular Measurements

The report used as a basis for this analysis is that by Brown et. al. ([7]). In this paper essentially three parameters were derived from the linear responses of hippocampal pyramidal cells. These parameters included $R_m$, which was assumed to be homogeneous over the entire cell, $L$ and $\rho$. $C_m$ was taken to be $1.0 \mu F/cm^2$, and $R_i$ was assumed to be $75 \Omega \text{cm}$. Analysis of the response of the cell to a current step applied to the soma was based on the assumption that the cell could be approximated by the soma/short-cable model with a homogeneous membrane time constant. According to Rall (,), this step response can be represented by a linear combination of exponential terms:

$$V_f - V = \sum_{i=0,\infty} C_i \exp(-t/\tau_i)$$

where $V$ is the response at the soma relative to rest, $V_f$ is the steady-state soma voltage, $\tau_0$ is the membrane time constant ($\tau_0 = R_m C_m$), and the remaining $\tau_i$'s are shorter time constants due to charge redistribution down the dendrite cable. Standard exponential peeling techniques were used to evaluate the longer $\tau_0$, whose coefficient, $C_0$ was assumed to be much larger than the remaining $C_i$'s. $R_m$ was then derived from the measured $\tau_0$. Three methods were used to derive $L$ and $\rho$, all of which were dependent on the soma/short-cable approximation and, as before, the assumption of homogeneous $R_m$. This study estimated $R_m$ as $19 K \Omega cm^2$, $\rho$ as 1.2, and $L$ as 0.95. $R_{in}$ averaged about $39 M \Omega$.

To evaluate these results, I constructed a model geometry that was consistent with the above values for $R_{in}$, $\rho$, $\tau_0$, $R_m$, $C_m$, $R_i$, and $L$. The

\[\text{Means of measurements from CA1 cells.}\]
parameters that we need to derive for the geometry are the radius of the soma, \( r_{soma} \), the radius of the dendrite, \( a \), and the length of the dendrite, \( l \).

The first step is to derive \( r_{soma} \). The conductance of the soma is calculated from \( \rho \) and \( R_{in} \). Since

\[
\rho = \frac{G_{dendrite}}{G_{soma}}
\]

and

\[
G_{dendrite} + G_{soma} = \frac{1}{R_{in}}
\]

then

\[
G_{soma} = \frac{1}{R_{in}} \left( \frac{1}{1 + \rho} \right)
\]

This gives \( G_{soma} = 11.8 \text{nS} \). The radius of the soma is then calculated from \( G_{soma} \) and \( R_{in} \):

\[
r_{soma} = \sqrt{\frac{3R_{in}G_{soma}}{4\pi}}
\]

This results in \( r_{soma} = 73 \mu m \). Now the formula for \( R_{in} \) is a function of \( l \) and \( a \), given by:

\[
R_{in} = \left( \frac{1}{r_{a} \lambda \tanh(L) + G_{soma}} \right)^{-1}
\] (3.7)

where

\[
L = l \times \sqrt{\frac{aR_{m}}{2R_{i}}}
\] (3.8)

\[
\lambda = \sqrt{\frac{R_{m} - dend a}{2R_{i}}}
\] (3.9)

\[
r_{a} = \frac{R_{i}}{\pi a^2}
\] (3.10)

Equation 3.7 is derived later (Equation 3.20, with \( s = 0 \)). Estimates for \( l \) and \( a \) were obtained by calculating \( R_{in} \), \( L \), and \( \rho \), using initial estimates for \( l \) and \( a \) with Equations 3.7-3.10, and then adjusting \( l \) and \( a \) until the desired values for \( R_{in}, L, \) and \( \rho \) were obtained. This procedure resulted in estimates for \( l = 1800 \mu m \) and \( a = 3 \mu m \).
Figure 3.5: Typical response to current step ([7]) (top) and response to current step of model based on Brown et. al. parameters (bottom), where $\rho = 1.2$, $L = 0.95$, $R_{in} = 39\,\Omega$, $a_{soma} = 73\,\mu m$, $a = 3.0\,\mu m$, and $l = 1800\,\mu m$.

The step response of the geometry just derived and a typical step response from the Brown et. al. paper is seen in Figure 3.5. These responses are in good agreement. On the other hand, note Figure 3.6, where the resulting geometry and the geometry derived in the previous section are compared. The most striking feature of the geometry derived from the Brown et. al. data is the estimated soma radius of 73 $\mu m$. This result is inconsistent with the dimensions derived earlier, where the $a_{soma}$ was estimated to be on the order of 10 to 20$\mu m$. The dendrite radius of 3.0 $\mu m$ and a dendrite length of 1800 $\mu m$ of the Brown et. al. geometry is consistent with the previously derived dimensions, but these values are in the extreme of the previously proposed ranges for $a$ and $l$. 
Figure 3.6: Comparison of soma/short-cable geometries derived from data of Brown et al. and that estimated in this chapter with camera lucida reconstruction of guinea pig hippocampal pyramidal cell ([52]).
3.10 Comparison of Linear Response of Traub and Llinas-Derived Model and Brown et. al.—Derived Model

While the geometry implied by the Brown et. al. report is incorrect based on my earlier analysis, the step response is assumed to be valid since this was measured directly from cells. On the other hand, while the geometry of the Traub and Llinas-derived model is a good approximation, as I have shown with my estimate based on purely histological data, the step response of this structure does not match that reported by Brown et. al., as shown in Figure 37. All these reports refer to pyramidal cells, though not necessarily to the same subfield (i.e. CA1, CA3).

The first difference is the $\tau_0$ for the two models; $\tau_0$ for the Traub and Llinas model is about 5 milliseconds (consistent with their value of $R_m$, $5 \, K\Omega \text{cm}^2$), and $\tau_0$ reported by Brown et. al. is about 19 milliseconds. The second difference is between the value of $\rho$ for the Traub and Llinas model (approximately 20) compared to values of $\rho$ that have been reported from intracellular measurements by Brown et. al. and others ($\rho = .5$ to 2). Comparing the directly measured value of $\rho$ from the Traub and Llinas model with the estimated $\rho$ of Brown et. al. is valid since in the latter case $\rho$ was estimated assuming models a soma/short-cable structures with homogeneous $R_m$. 
As has been mentioned earlier, these disparities were reconciled by introducing a distinct \( R_{m\text{-soma}} \) and \( R_{m\text{-dend}} \). Investigating the effect of varying \( R_i \) was also useful. Before deriving a structure which was consistent with the reported data, though, deriving the analytical response of the general soma/short-cable structure (with non-homogeneous \( R_m \)) is necessary so that the full implications of varying each free parameter may be analyzed.

### 3.11 Derivation of the Frequency Response of Soma/Short-Cable Structure with Non-homogeneous Membrane Resistivity

So far I have presented evidence that supports using a spherical isopotential soma attached to a short dendritic cable, with each section having a distinct membrane resistivity, in order to represent the hippocampal pyramidal cell. This representation, as diagrammed in Figure 3.8, is completely specified by the parameters \( R_{m\text{-soma}}, R_{m\text{-dend}}, R_i, C_m, a_{\text{soma}}, a, B, \) and \( l \).

Different investigators have considered the effect of the extreme values of \( B \): \( B = 1 \) (infinite cable termination) and \( B = 0 \) (open circuit/sealed end termination). Assuming that the distal dendrite processes end rather abruptly is common, though, and therefore the sealed end assumption is used, as is done in the present analysis.

To investigate the effect of these parameters on the linear transient and steady-state response of the cell, as measured from the soma, I derived the frequency response of this circuit as follows.

We start with the equation for the linear \( RC \) cable.

\[
\frac{\partial^2 V}{\partial X^2} = V + \frac{\partial V}{\partial T}
\]

where \( V \) = the membrane voltage at some point, \( X \); \( X \) = the distance along the cable from the soma, \( x \), normalized by \( \lambda \); \( T \) = the normalized time, \( t/\tau \); and \( \tau = R_{m\text{-dend}} C_m \).

The Laplace transform of the second-order partial differential equation is taken then to yield the second-order ordinary differential equation

\[
\frac{d^2 \hat{V}}{dX^2} = (s + 1)\hat{V}
\]

where \( \hat{V} \) = the Laplace transform of \( V \).
Figure 3.8: Circuit topology of a soma/short-cable structure. The structure is not drawn to scale.
The solution to this equation is

$$\hat{V} = \hat{A}e^{\sqrt{s+1}X} + \hat{B}e^{-\sqrt{s+1}X}$$  \hspace{2cm} (3.11)$$

where $\hat{A}$ and $\hat{B}$ are constants that depend on the boundary conditions.

Now the Laplace transform of the axial current, $\hat{I}_a$, is equal to the change in $\hat{V}$ with $X$ times $r_a$, where

$$r_a = \frac{R_i}{\pi a^2}$$

Thus

$$\hat{I}_a = \frac{-1}{r_a \lambda} \frac{d\hat{V}}{dX}$$  \hspace{2cm} (3.12)$$

Note the inclusion of $\lambda$ since $X$ is the normalized distance. Solving for $\frac{d\hat{V}}{dX}$ in Equation 3.12 (using Equation 3.11), we obtain

$$\hat{I}_a = \frac{-\sqrt{s+1}}{r_a \lambda} (\hat{A}e^{\sqrt{s+1}X} - \hat{B}e^{-\sqrt{s+1}X})$$

The boundary conditions are set at $X = 0$ (at the soma), and $X = L$ (at the end of the cable). At the soma, the axial current $I_a$ is equal to the sum of the soma currents –

$$\hat{I}_a(X = 0) = \hat{I}_{\text{stimulus}} - \hat{V}_{\text{soma}}G_{\text{soma}} - s\hat{V}_{\text{soma}}C'$$

$$= \frac{-\sqrt{s+1}}{r_a \lambda} (\hat{A} - \hat{B})$$

where $C'$ is the capacitance of the soma normalized by the dendrite time constant –

$$C' = \frac{C_m}{\tau_{dendrite} \frac{4}{3} \pi a_{\text{soma}}^2}$$  \hspace{2cm} (3.13)$$

At the end of the cable since the terminating admittance $= 0$ then $\hat{I}_a = 0$, thus

$$\hat{I}_a(X = L) = 0$$

$$= \frac{-\sqrt{s+1}}{r_a \lambda} (\hat{A}e^{\sqrt{s+1}L} - \hat{B}e^{-\sqrt{s+1}L})$$

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\[
\hat{A}e^{\sqrt{s+1}L} = \hat{B}e^{-\sqrt{s+1}L} \quad (3.14)
\]
\[
\hat{B} = \hat{A}e^{2\sqrt{s+1}L} \quad (3.15)
\]

Now since

\[
\hat{V}_{\text{soma}} = \hat{V}(X = 0) = \hat{A} + \hat{B}
\]

then

\[
\hat{V}_{\text{soma}} = \hat{A}(1 + e^{2\sqrt{s+1}L}) \quad (3.16)
\]

Solving for \(I_{\text{stimulus}}\) –

\[
I_{\text{stimulus}} = \hat{A}(1 + e^{2\sqrt{s+1}L})(G_{\text{soma}} + sC') + \hat{A} \frac{\sqrt{s + 1}}{r_a \lambda} (e^{2\sqrt{s+1}L} - 1) \quad (3.17)
\]

Now we can find \(\hat{A}\) and \(\hat{B}\) from Equations 3.15 and 3.17 –

\[
\hat{A} = \frac{I_{\text{stimulus}}}{\frac{\sqrt{s + 1}}{r_a \lambda} (e^{2\sqrt{s+1}L} - 1) + (1 + e^{2\sqrt{s+1}L})(G_{\text{soma}} + sC')} \quad (3.18)
\]

\[
\hat{B} = \frac{I_{\text{stimulus}}e^{2\sqrt{s+1}L}}{\frac{\sqrt{s + 1}}{r_a \lambda} (e^{2\sqrt{s+1}L} - 1) + (1 + e^{2\sqrt{s+1}L})(G_{\text{soma}} + sC')} \quad (3.19)
\]

And finally from Equations 3.16, 3.18, and 3.19 we obtain

\[
\hat{V}_{\text{soma}} = \frac{I_{\text{stimulus}}(1 + e^{2\sqrt{s+1}L})}{\frac{\sqrt{s + 1}}{r_a \lambda} (e^{2\sqrt{s+1}L} - 1) + (1 + e^{2\sqrt{s+1}L})(G_{\text{soma}} + sC')}
\]

which gives the expression for the input impedance as seen from the soma, \(Z_{\text{soma}}(s)\) –

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\[
Z_{\text{soma}}(s) = \frac{V_{\text{soma}}}{I_{\text{stimulus}}} = \frac{(1 + e^{2\sqrt{s+1}L})}{\sqrt{s+1} \left( e^{2\sqrt{s+1}L} - 1 \right) + (1 + e^{2\sqrt{s+1}L})(G_{\text{soma}} + sC')}
\]

In more compact form this is

\[
Z_{\text{soma}}(s) = \left( \frac{\sqrt{s} + 1}{r_a \lambda} \tanh(\sqrt{s} + 1L) + (G_{\text{soma}} + sC') \right)^{-1} (3.20)
\]

This expression for \(Z_{\text{soma}}(s)\) was not amenable to attempts to perform an inverse transformation. However, when

\[R_{\text{m-soma}} = R_{\text{m-dend}}\]

that is for the case of a homogeneous membrane time constant, the expression for \(Z_{\text{soma}}(s)\) simplifies somewhat and the inverse transform for this case has been derived. This is a rather complicated expression involving an infinite series, each term of which involves a product of exponential terms and a finite summation of the product of other exponential terms with parabolic cylinder functions ([27]).

Since an analytical expression for the inverse transform of the soma response could not be obtained, the response was analyzed in two ways – examining the frequency response directly and using DTFT techniques to estimate the temporal response (impulse response and step response). In order to evaluate the frequency response, the magnitude and phase of \(Z_{\text{soma}}(s = j\tau \omega)\) were derived (note that the factor of \(\tau\) is required because the Laplace transform was taken with respect to normalized time). So, from Equation 3.20 -

\[
Z_{\text{soma}}(j\omega) = \left[ \frac{\sqrt{j\tau \omega} + 1}{r_a \lambda} \left( \frac{1 - e^{2\sqrt{j\tau \omega}+1L}}{1 + e^{2\sqrt{j\tau \omega}+1L}} \right) + (G_{\text{soma}} + j\omega C') \right]^{-1} (3.21)
\]

The first step in this derivation was expressing the square root of \((j\tau \omega + 1)\) in rectangular form -
\[
\sqrt{j \tau \omega + 1} = \sqrt{\frac{1 + \sqrt{1 + (\tau \omega)^2}}{2}} + j \sqrt{\frac{-1 + \sqrt{1 + (\tau \omega)^2}}{2}}
\]

Letting
\[\eta = \sqrt{\frac{1 + \sqrt{1 + (\tau \omega)^2}}{2}}\]
\[\nu = \sqrt{\frac{-1 + \sqrt{1 + (\tau \omega)^2}}{2}}\]

the exponential terms may then be expanded –
\[e^{-2 \sqrt{j \tau \omega + 1}} = e^{-2L(\eta + j\nu)} = e^{-2Ln}(\cos(2Ln) - j \sin(2Ln))\]

Equation 3.21 can be rearranged to give the real and imaginary parts of the frequency response –
\[Z(j\omega) = \frac{\alpha + j\beta}{\delta + j\gamma} = \frac{\alpha\delta + \beta\gamma}{\delta^2 + \gamma^2} + j \left( \frac{-\alpha\gamma + \beta\delta}{\delta^2 + \gamma^2} \right)\]

and thus
\[|Z(j\omega)| = \sqrt{\frac{\alpha^2 + \beta^2}{\delta^2 + \gamma^2}}\]

Phase\((Z(j\omega)) = \text{atan}\left( \frac{-\alpha\gamma + \beta\delta}{\alpha\delta + \beta\gamma} \right)\]

where
\[\alpha = r_a \lambda [1 + e^{-2Ln} \cos(2Ln)]\]
\[ \beta = -r_a \lambda e^{-2L \eta \sin(2L \nu)} \]

\[ \delta = \eta + r_a \lambda G_{\text{soma}} + e^{-2L \eta \left[ -\eta \cos(2L \nu) - \nu \sin(2L \nu) + r_a \lambda G_{\text{soma}} \cos(2L \nu) + r_a \lambda \tau C \sin(2L \nu) \right]} \]

\[ \gamma = \nu + r_a \lambda \tau C + e^{-2L \eta \left[ \eta \sin(2L \nu) - \nu \cos(2L \nu) + r_a \lambda \tau C \cos(2L \nu) - r_a \lambda G_{\text{soma}} \sin(2L \nu) \right]} \]

These formulas were used to see how varying some specific parameters while keeping the remainder constant changed the frequency response. In particular, these results were used in investigating how parameters that are derived from the transient response are affected when the directly measured parameters are kept fixed and some other derived parameter is varied.

To summarize the results so far, I have proposed that the following parameters are either known with a fair degree of assurance, or may be estimated: \( C_m, R_i, a_{\text{soma}}, R_{in}, \tau_0, B \), and a limited range for \( a \) and \( l \) of the equivalent dendritic cable. On the other hand, I have shown that the reported values for \( R_m \) are inconsistent with the other data available for these cells, and in fact the soma and the dendrites may be approximated as having distinct membrane resistivities.

The problem of estimating the geometry of the model is therefore determined by the following constraints – estimate for the soma radius, estimate for the range of cable diameters, estimate for the cable length, input resistance, observed time constant, estimate of membrane capacitance, and the estimate of cytoplasmic resistivity. The free parameters then include \( R_{m-\text{soma}}, R_{m-\text{dend}}, \) and \( a \). The results of this estimation will be presented in the next section.

### 3.12 Simulating the Step Response of the Brown et. al. Geometry with Alternative Models

Once the frequency response of the general soma/short-cable model was derived, I attempted to find different values for the membrane resistivities and the cytoplasmic resistivity that would yield step responses similar to that of the model derived from the Brown et. al. parameters.

The constraints included \( a_{\text{soma}} = 17 \mu m, R_i, \) which was set at 200 \( \Omega \) cm, \( \tau_0 = 19 ms. \ R_{in} = 39 M\Omega, \) and \( C_m = 1.0 \mu F/cm^2. \ R_{m-\text{dend}} \) was then set at
either 30, 40, or 50 kΩ cm, and \(a\), was set at either 5, 6, or 7 \(\mu m\). For a given combination of \(R_{m-dend}\) and \(a\) both \(R_{m-soma}\) and \(l\) were then varied until all the above constraints were met. For this analysis the electrode shunt resistance was not specified, thus \(R_{soma}\) reflected both the leak conductance of the soma and the electrode shunt resistance.

The step response and the frequency response of the resulting structure were then compared with that derived from the Brown and Perkel model. The parameters were adjusted under these constraints to derive several structures whose time response was consistent with the data. The complete parameters for these structure are listed in Table 3.1. The responses of these structures were clustered into three groups, each group characterized by a common value for \(a\). The responses for structures B, C, and D were almost identical to each other, as were the responses of structures E and F. Therefore, the analysis suggests that the diameter of the dendrite cable was the most sensitive parameter in determining the linear response of the soma-cable structure.

For the majority of the simulations, including all those presented in this thesis, version "C" of the model structures was chosen as representative of the family of model structures. In this case the value for \(R_{m-dend}\) of 40 KΩ cm² is a similar to the value for \(R_{m-dend}\) (approximately 40 KΩ cm²) estimated by Shelton for Purkinje cells, and is much higher than the values of \(R_m\) that are quoted consistently in reports on hippocampal pyramidal cells. Also, this model has an \(R_i\) of 200 Ω cm, which is also in line with the value of \(R_i\) estimated by Shelton, as described earlier. The value of \(a\) (6.0\(\mu m\)) and \(l\) (1200\(\mu m\)) is consistent with the values estimated earlier in the chapter (Section 3.8.2).

The step responses for structures A, C, and F and that derived from the Brown et al. data are shown in Figure 3.9. An expanded view of these response is shown in Figure 3.10. In this figure the effect of the smaller soma time constant in the model structures is seen as the response of these structures initially decay much faster than the reference structure. However, as shown in Figure 3.11, all four responses eventually settle into a single exponential decay with the same time constant of 19 ms. The magnitude of the frequency responses for the same structures are shown in Figure 3.13, and the phase of the frequency responses for these structures are shown in Figure 3.12.

There are several interesting features of these simulations. The first is that the values of \(p\) and \(L\) vary greatly for the different structures – between
Table 3.1: Parameters of model structures derived to match the $\tau_0$ (19 ms) and $R_{in}$ (39 M$\Omega$) of the Brown et. al. data, with $R_i = 200 \Omega$ cm, $a_{soma} = 17 \mu$m, and $C_m = 1.0 \mu$F/cm$^2$. The values listed for structure “C” were chosen for the model.

Figure 3.9: Normalized response to injection of somatic current step for Brown et. al. structure, and representative alternative structures (A, C, and F, ref. Table 3.1) consistent with histological measurements.
Figure 3.10: Expanded view of Figure 3.9, showing difference in the initial part of the somatic current step responses.

Figure 3.11: Semi-log plot of Figure 3.9, showing the rapid approach to a single exponential decay ($\tau_0 = 19$ ms) for all the structures.
Figure 3.12: Phase of frequency response for Brown et. al. structure, and representative alternative structures (A, C, and F, ref. Table 3.1) consistent with histological measurements.
Figure 3.13: Normalized magnitude of frequency response for Brown et al. structure, and representative alternative structures (A, C, and F, ref. Table 3.1) consistent with histological measurements.
1.2 and .43 for $\rho$ and between .35 and .57 for $L$. This shows that the methods typically used for estimating $\rho$ and $L$ are not reliable unless the cell has a homogeneous membrane time constant.

The most distinctive difference in the characteristics of the structures with a non-homogeneous membrane time constant and the structure based on the Brown et. al. data is in the phase of the frequency response. For all the structures with non-homogeneous $R_m$ the phase deviates from that of the structure with homogeneous $R_m$ at a frequency of about 100Hz. This difference does not manifest itself strongly on the temporal responses, however, because of the attenuated response above 100Hz.

The characteristics of the phase response for the simulated cell structures suggest that evaluation of the linear parameters discussed in this chapter may be better served by analyzing the frequency response of the cells under protocols that ensure a linear response. Since the interesting part of the phase response occurs at frequencies where the cell impedance is relatively small, spectral estimation using averaging techniques or white-noise approaches may be applicable.

The values for $R_{soma}$ and $R_{dendrite}$ differ by about two orders of magnitude in all the derived structures. If the contribution of an electrode shunt is considered, this difference is reduced, but by only a factor of about two since the typical soma resistance (including the electrode shunt resistance) is around 70 MΩ and the electrode shunt resistance is about 100 MΩ as estimated earlier.

In summary, there are many versions of the soma/short-cable model that can give the same $\tau_0$ and $R_{in}$ with differences in the distribution of $R_m$ between soma and dendrite, and realistic variations in $a$. Examination of the frequency response indicates that this measurement may provide a way to better estimate the electrotonic parameters of these cells, particularly under the assumption of non-homogeneous membrane resistivity. While the magnitude of the frequency responses for the various structures are rather similar, the phase of the frequency responses differ markedly, and this metric may be usefully exploited in order to better estimate the linear parameters of the soma/short-cable model.
3.13 Discrete (Lumped) Approximation To Dendritic Cables and Comparison Of HIPPO Results To Analytical Solution Of Linear Cable - Dependence Of Segment Dimensions

Once the response to a current step of the soma/short-cable structure was derived from the inverse DFT of the analytical frequency response, the compartmental approximation of the cable was evaluated by comparing the model's response in current clamp simulations to the estimated response of the continuous cable. In Figure 3.14 the response of the model with different numbers of compartments is compared to the estimated response. As can be seen in the figure, the response of the model with 5 segments is in very good agreement with the estimated response.
3.14 Summary of Results from the Determination of Electronic Structure

To recapitulate, the HIPPO model electrotonic parameters are as follows:

- $a_{soma} = 17 \mu m$
- $a = 6.0 \mu m$
- $l = 1200 \mu m$
- $R_{shunt} = 100 \text{ M}\Omega$
- $R_{m-soma} = 850 \Omega \text{ cm}^2$
- $R_{m-dend} = 40 \text{ K}\Omega \text{ cm}^2$
- $R_i = 200 \Omega \text{ cm}$
- $C_m = 1.0 \mu f/\text{cm}^2$
- $B = 0$
- $\lambda = 2450 \mu m$
- $L = .49$
- $\rho = .69$
- $\tau_0 = 19 \text{ milliseconds}$
- $R_{in} = 39 \text{ M}\Omega$
- $E_{leak} = -70 \text{ millivolts}$

3.15 Is It Important to Capture Dendritic Morphometric Characteristics?

The results described here tend to confirm that the actual geometry of the dendritic tree may not in itself be critical to somatic response. For example, the Rall reduction is reasonably accurate even if the constraints specified in this algorithm are not met exactly. What is very important, however, is the various parameters that characterize the tree (or its equivalent single cable) as a whole, that is as a lumped element (cable). This result has been reported elsewhere ([51]). Specifically, the equivalent cylinder approximation works well even when the constraints on subsequent cable diameters and conservation of electrotonic length are not met exactly. The parameters characterizing that cylinder are important to the electrical load as seen by the soma, however, and can have a large effect on the processing of information that occurs there.

As shown, the assumption of a homogeneous membrane time constant allows the construction of a soma/short-cable approximation of the pyramidal cell whose linear response closely matches that of the real cell. On the
other hand, this construction is inconsistent with histological measurements, and a structure with a non-homogeneous membrane time constant can be proposed which successfully addresses these problems.

Although the two constructions yield models with distinct frequency responses, the significant differences occur at frequencies that are substantially attenuated in both structures, so that the step responses are rather similar. Why, then, is it important to revise the earlier model with the homogeneous membrane time constant? As shown, although the somatic responses of the two models are similar, the values of \( \rho \) and \( L \) are very different. This is important when considering the role of the dendritic tree in integrating synaptic input. In particular, the smaller \( L \) that has been suggested in the present study indicates that the dendritic tree is more electrically compact than previously thought. In functional terms, this means that there is less distinction, from the point of view of the soma, between distal and proximal dendritic input. This could enhance the computational flexibility of the dendritic tree since a fundamental limit such as linear attenuation of EPSPs and (possibly) IPSPs will be reduced by the smaller \( L \), and selective enabling/disabling of various sections of the tree could be accomplished more effectively by non-linear mechanisms (e.g. other synapses).

The effect of the lower \( \rho \) that is indicated in the present study is to reduce the burden on the somatic conductances imposed by the dendritic load, for example during the spike depolarization and repolarization.
Chapter 4

APPLYING THE HODGKIN-HUXLEY (HH) MODEL OF IONIC CHANNELS TO PUTATIVE HIPPOCAMPAL CURRENTS

4.1 Introduction

An extension of the Hodgkin-Huxley (HH) model of ionic channels in the squid axon ([21],[20],[22],[23]) is the foundation for the description of the hippocampal pyramidal cell ion channels that are used in the model. This comes about in two ways. First, many of the currents that have been described in the literature have been fitted to HH-like models to start with. Second, when this model has been used either to augment sparse voltage clamp data on a particular current or to propose currents whose existence is defended purely on phenomenological grounds, these currents have been constructed using HH-like mechanisms. Examining the HH model in detail is therefore important in order to establish some of the key assumptions in
the HIPPO model.

4.2 Background of the HH Model

In the early 1950’s Hodgkin and Huxley postulated that the electrical activity of the squid axon was due to two time-dependent non-linear conductances, one of which was specific to $Na^+$ ions and another which was specific to $K^+$ ions. This result was based on data obtained with the newly-developed voltage clamp method for measuring electrical properties of non-linear membranes. Using the voltage clamp protocol and various manipulations, including replacement of the $NaCl$ in the external medium with choline chloride to eliminate the $Na^+$ current, Hodgkin and Huxley measured the time-constants and the steady state values for the two conductances as a function of the membrane voltage.

Noting the sigmoidal characteristic of the activation of the $Na^+$ channel as the membrane was depolarized, and the fact that the channel inactivated a short time after it was activated, a model for the $Na^+$ channel was derived that included four "gating" particles (three so-called $m$ activation particles and one $h$ inactivation particle). These particles can be thought of as distinct regions of the channel protein, each of which can be in one of two stable conformations or states, conducting (open) or non-conducting (closed). For a given channel to conduct, all of its gating particles must be in the open state. The macroscopic conductance of the $Na^+$ channel, $g_{Na}$, was expressed as

$$ g_{Na} = m^3h\bar{g}_{Na} $$

where $0 < m, h < 1$ and $\bar{g}_{Na}$ is the maximum conductance for the ensemble of $Na^+$ channels in the membrane. Hodgkin and Huxley determined that the transition between states is governed by first order kinetics, and the rate constants for this transition are functions of voltage, as will be described later. The likelihood of whether a given particle will be open or closed is therefore also a function of voltage.

The sigmoidal activation characteristic under voltage clamp arises from the third power of the $m$ gating particle. This number was determined by Hodgkin and Huxley by fitting powers of exponential relaxations to the observed kinetics. In a similar manner, the macroscopic conductance of the $K^+$ channel in the squid axon was described as being determined by four
gating particles, $n$. The macroscopic conductance of the $K^+$ channel was expressed as

$$g_K = n^4 \bar{g}_K$$

where $\bar{g}_K$ is the absolute conductance for the ensemble of $K^+$ channels in the membrane.

The transient behavior of the $Na^+$ channel during excitation of the neuron, through its activation and subsequent inactivation, was explained by the voltage dependencies of $m$ and $h$, and the different voltage-dependent functions for the time constants of $m$ and $h$. The steady state value of $m$ is a monotonically increasing function of the membrane voltage, while the steady state value of $h$ is a monotonically decreasing function of the membrane voltage. In addition, the time constant for $m$ is smaller than the time constant for $h$ at a given voltage. The result is that on depolarization $m$ will adapt to its (more open) steady state value quickly while $h$ will lag behind in its (more open) hyperpolarized steady state. The channel will begin to conduct with the increase of $m$. In a short time, however, $h$ will relax to its (more closed) steady-state value at the new (depolarized) membrane voltage. Even though the three $m$ “particles” are in the open state, the subsequent closing of the single $h$ “particle” will shut the channel down and turn off the $Na^+$ current.

Once Hodgkin and Huxley had a description of these two non-linear conductances and the linear parameters of the cell, they were able to numerically reconstruct the action potential in the squid axon. In the model of the hippocampal pyramidal neuron, several distinct currents, mediated by different ions, are described using variants on the HH model theme.

### 4.3 Extension of the HH Description to Pyramidal Hippocampal Cells

The Hodgkin and Huxley model approach can be extended¹ to describe some of the currents found in other electrically non-linear cells. Analysis of other currents is undertaken here under the assumption that they are based on mechanisms which undergo first-order kinetic transformations between conducting states and non-conducting states. By both qualitative and quantitative analysis, plausible mechanisms underlying non-linear currents.

¹The notion that this report “extends” on the HH model is discussed in Section 4.8.
may be deduced. These descriptions are typically based initially on voltage
clamp data. As will be explained shortly, this protocol can measure the
time constants and steady state values for the kinetic events controlling the
conductances behind these currents, assuming that indeed such a kinetic
description is valid.

4.3.1 The Voltage-Dependent First-Order Kinetics of HH-
like Conductances

To recapitulate, in the HH model each current in the electrically-active cell
is assumed to correspond to a specific type of ionic channel, which in turn
is comprised of a protein conglomeration that traverses the membrane. In
each channel ions travel through a luminal trans-membrane aqueous phase,
driven by the driving potential for the channel. As reviewed in Chapter
2, this driving potential is a function of the membrane voltage and the
trans-membrane concentration gradient of the carrier for that conductance,
according to the Nernst equation or the Nernst-Goldman equation.

The transitions of the particles between states are governed by first-
order kinetics. Each state or conformation corresponds to a free-energy
well, with a single high-energy rate-determining barrier between the two
states. Movement of the gating particles between states is assumed to be
accompanied by a movement of charge, causing the state-transition kinetics
to be dependent on the membrane voltage. These gating particles are regions
of the protein that (a) can reversibly mediate the conductivity of the channel,
possibly via steric factors, and (b) have a sufficient dipole moment and
freedom of movement so that they may act as voltage-sensors, changing the
conformation of the protein or protein group as a function of the electric field
across the channel. The magnitude of the voltage dependence is derived from
the Boltzmann equation which specifies the probabilities of state occupancies
according to the free energies of the states.

In practice, voltage clamp protocols, in which the membrane relaxation
currents are measured as the cell membrane is “clamped” at different poten-
tials with a microelectrode, are used to measure the kinetics of the various
currents. This technique assumes that the kinetics of different currents can
be measured independently, either because different currents are activated
over non-overlapping membrane voltages, because the time courses are dis-
tinct, or because the currents have distinct pharmacological sensitivities.
Implicit in this approach is the assumption that different currents interact
only through the membrane voltage. In fact, in the case of currents which
are dependent on the movement of Ca\textsuperscript{++} into the cell simple voltage-clamp measurements may give misleading results. Whatever independence exists between the different currents is exploited by the electrophysiologist as he devises protocols for intracellular measurements.

The macroscopic conductance of given type of channel is determined by the proportion of channels in the open state, the conductance of a single channel, and the total number of channels of that type in the membrane. For example, if the conductance of some channel \( Y \) is controlled by a single gating particle, and the proportion of open gating particles is \( x \), then the macroscopic conductance of that channel type is expressed by

\[
g_Y = x \cdot \tilde{g}_Y
\]

where \( g_Y \) is the actual conductance for the channel current \( I_Y \), and \( \tilde{g}_Y \) is the maximum conductance for that current. The factor \( x \) is equivalent to the probability that the gating particle for a single channel will be in the open state. As will be shown, \( x \) is both a function of the membrane voltage and of time.

The macroscopic voltage- and time-dependence of the channel conductance arises from the first-order kinetics that the gating particles obey in their transition between their open and closed states.

\[
\text{closed } (1 - x) \implies \text{open } (x)
\]

Here \( x \) represents the fraction of channels in the open state, and \( 1 - x \) represents the fraction of channels in the closed state. \( \alpha \) and \( \beta \) are the forward and backward rate constants for the reaction, respectively. This relationship yields the simple differential equation relating the derivative of \( x(t) \), \( \dot{x}(t) \), with the steady state value of \( x \), \( x_\infty \), and the time constant for the reaction, \( \tau_x \).

\[
\dot{x}(t) = \frac{x_\infty - x(t)}{\tau_x}
\]

where \( x_\infty \) and \( \tau_x \) can be expressed in terms of the rate constants \( \alpha \) and \( \beta \).

\[
x_\infty = \frac{\alpha}{\alpha + \beta}
\]

\[
\tau_x = \frac{1}{\alpha + \beta}
\]
Figure 4.1: Energy diagram for gating particle states with no applied membrane voltage. The stable open and closed states correspond to the low-energy wells. The high-energy transition state is the rate-limiting step. \( \gamma \), which is the relative position of the transition state within the membrane, can be between 0 and 1.

As will be discussed later in the sections on the various non-linear currents in the model, in the literature current kinetics are occasionally determined empirically in terms of an "\( \alpha - 3 \)" type formulation. For most currents, however, the voltage dependence of \( \tau_\infty \) and \( \tau_x \) is the figure that is reported.

The energy profile for a gating particle in the single barrier model is shown in Figure 4.1.

As mentioned earlier, the rate constants for the transitions from one side of the reaction coordinate to the other is given by the Boltzmann equation, which is a function of the difference between the energy of the rate-limiting step and the initial state. The expression for the forward rate constant in the absence of an applied voltage, \( \alpha_0 \), is

\[
\alpha_0 = C e^{\frac{\Delta G}{RT}}
\]  

(4.1)

where \( \Delta G \) is the free-energy difference between the closed state and the
transition state. \( R \) is the gas constant, \( T \) is the absolute temperature, and \( C \) is a constant.

The voltage-dependence of the kinetics arises from the distortion of the above energy diagram when a voltage is applied across the membrane, as shown in Figure 4.2. The applied voltage changes the difference in free energy between the stable states and the transition state. The effect of the voltage is reflected in the expression for the rate constants as follows:

\[
\alpha = \alpha_0 e^{z\xi \Delta V} 
\]

(4.2)

\[
\beta = \beta_0 e^{-z(1-\gamma)\Delta \xi} 
\]

(4.3)

where

\[
\Delta \xi = \frac{\Delta VF}{RT} 
\]

(4.4)

\( z \) is the effective valence of the gating particle, and \( \gamma \) is the position of the transition state within the membrane, normalized to the membrane thickness. \( \Delta V \) is equal to \( V - V_1 \), where \( V \) is the membrane voltage and \( V_1 \) is
Figure 4.3: The steady-state \( x(\infty) \) curve for the hypothetical gating particle \( x \). \( z = 8 \). \( V_1 = -20 mV \).

the membrane voltage at which \( a \) equals \( a_0 \) and \( J \) equals \( J_0 \) ([26]). \( F \) is Faraday’s constant. Normally, \( a_0 \) and \( J_0 \) are taken as equal. This can be reconciled with the different energies of the stable states as shown in Figure 4.2 by adjusting \( V_1 \).

Since the backward and forward rate constants are functions of the membrane voltage, the values for the time constant and the mean steady-state (from now on referred to as the steady-state curve) are also functions of voltage. The resulting expression for steady-state curve is a sigmoidal function.

\[
x(\infty) = \frac{1}{1 + e^{-\Delta \xi}} \quad (4.5)
\]

This type of characteristic is shown in Figure 4.3.

The expression for the time constant is a skewed bell-shaped function of the voltage -

\[
\tau_x = \frac{e^{-\gamma \Delta \xi}}{\alpha_0 + J_0 e^{-\gamma \Delta \xi}} \quad (4.6)
\]
Figure 4.4: The time constant ($\tau_\text{x}$) curve for the gating particle $x$ with $\tau_0 = 0$ and 0.3 milliseconds. $z = 8$, $V_{1/2} = -20mV$, $\gamma = 0.3$.

An example of such a function for the time constant is shown in Figure 4.4. As referred to earlier, including an additional assumption of a linear rate-limiting mechanism on the gating particle transition was useful. For example, drag on the gating portion of the protein as it changes conformation will place an upper limit on the rate constants of the gating transitions. As the rate constants defined by the Boltzmann equation increase exponentially with voltage, an assumption was made that at some point other intrinsic aspects of the channel protein would prevent an arbitrarily fast transition. For the simulations this factor was, as a first approximation, taken as a specific constant minimum value for the time constant, $\tau_0$, for each of the current’s gating particles. This is illustrated in Figure 4.4.

4.3.2 Activation and Inactivation Gating Particles

There are two types of gating particles: activation gating particles (activation variable) and inactivation gating particles (inactivation variable). The steady state curve for an activation particle increases with depolarization: the steady state curve for an inactivation particle decreases with depolar-
ization. This characteristic is determined by the sign of $z$—positive for an activation particle and negative for an inactivation particle. The activation and inactivation particles therefore have opposite effects on the channel conductance with depolarization—the activation particle opens on depolarization and the inactivation particle closes on depolarization.

4.3.3 Transient and Persistent Channels

The type of gating particles in a channel determine whether it is a transient channel or a persistent channel. A persistent channel has only activation particles; this type of channel will stay open upon prolonged depolarization. A transient channel, on the other hand, is only open for a limited time upon depolarization; a typical scenario is that upon depolarization the (typically faster) activation particles relax to their open state and thus, along with the already open (because of the lower holding potential) inactivation particles, the channel conducts. After some delay the slower inactivation particles relax to their closed position at the depolarized level, and thus close the channel.

4.3.4 Activation/De-inactivation and Inactivation/Deactivation

Recall that for a given channel to conduct, all of its gating particles must be in the open position, regardless of whether they are classified as activation or inactivation particles. When describing the change of the conductance state of a channel, then, some clarification of nomenclature is useful. When a channel goes into the conducting state because of the movement of an activation particle into its open position (state), then the process is called activation. When a channel goes into the conducting state because of the movement of an inactivation particle into its open position, then the process is called $de$-inactivation. When a channel goes into the non-conducting state because of the movement of an inactivation particle into its closed position, then the process is called inactivation. And finally, when a channel goes into the non-conducting state because of the movement of an activation particle into its closed position, then the process is called $de$activation.
4.4 Fitting the HH Parameters to Putative Current Kinetics

Fitting the HH model to the behavior of a given current began under the assumption that the channel responsible for the current had only one or two types of gating particles - either there was a single activation particle or there was an activation particle with an inactivation particle. The number of any given particle in a single channel was constrained to be at the most four, but in practice the inclusion of more than four duplicate gating particles had little effect on the overall kinetics of a channel.

The first step in formulating the expression for a given current was to determine its activation/deactivation and/or inactivation/de-inactivation properties. By examining voltage clamp and/or current clamp records, the relevant questions were as follows:

1. Does the conductance in question increase on depolarization, independent of factors such as $Ca^{2+}$ entry? If so, then the conductance is likely controlled by at least one activation particle.

2. Is the conductance transient, i.e. is the conductance removed after activation without repolarization? If so, the conductance is likely mediated by at least one inactivation particle.

3. Is there any relationship between the activation of $Ca^{2+}$ and the presence of the current in question? If so, the possibility that such a relationship may mimic or mask voltage-dependent activation or inactivation must be considered.

Once the basic type of particles that govern the channel were determined, it remained to estimate the parameters for each particle. For each gating particle (for each current) the free parameters included:

- $V_1/2$ - the voltage at which $\alpha$ and $\beta$ are equal
- $\gamma$ - a measure of the symmetry of the system ($0 < \gamma < 1$)
- $z$ - the effective valence of the gating particle (typically $z$ ranged from 3 to 30)
- $\alpha_0$ - the forward rate constant when $V = V_1/2$
• $\beta_0$ - the backward rate constant when $V = V_\frac{1}{2}$

• $\tau_0$ - the minimum time constant of the gating particle (typically $\tau_0$ ranged from 0.5 milliseconds to 4.0 milliseconds)

The first step in fitting the parameters was to adjust the steady-state activation and inactivation curves according to the available data. For some currents there was more or less complete voltage clamp measurements of these curves, while for others only the steady-state conductance as a function of voltage was available (ref. Na$^+$ currents, Chapter x). Note that in the latter case, if the current in question is transient then the steady-state conductance will be a measure of the product of the some power of an activation variable and some power of an inactivation variable (the window current). As referred to earlier, $\alpha_0$ was taken as equal to $\beta_0$ in the estimations of current kinetics, with no loss of generality.

Adjusting the steady-state curve for a gating particle is straightforward. $V_\frac{1}{2}$ is simply the voltage where the steady-state curve is equal to 0.5, as implied in Equation 4.5 and shown in Figure 4.3. Once $V_\frac{1}{2}$ is estimated, $z$ is then adjusted to set the steepness of the steady-state curve as required.

Unless good measurements on the time constant for a current were available, manipulating the remaining parameters to yield different functions of the time constant was often a tricky procedure. The data for each current gave different clues as to the form of this function, and for some currents it was not possible to derive a unique function until the current was re-evaluated in light of modified description of another current. In a few cases, however, a particular function for a particular variable turned out to be not critical (e.g. the $y$ gating particle for $I_{DR}$, whose time constant only had to be greater than some value, irregardless of voltage).

### 4.4.1 Effect of Gating Particle Valence

Observing how the variation in the free parameters affects the steady-state and time constant curves is instructive since this process was integral to the development of the conductance mechanisms. Figures 4.5 and 4.6 illustrate how the different values of $z$ change the steepness of the steady-state curve and the sharpness of the time constant curve.
Figure 4.5: Effect of the valence, \( z \), of the gating particle, \( x \), on the \( x_\infty \) curve. Note that this is an activation gating particle. \( V_2 = -20mV \).
Figure 4.6: Effect of the valence, $x$, of the gating particle, $x$, on the $\tau_x$ curve. $V_{1/2} = -20mV$. The time scale is arbitrary since it is linearly scaled by $a_0$. $\tau_0$ is set to 0 and $\gamma$ is set to 0.5.
Figure 4.7: Effect of the relative position, $\gamma$, of the transition state within the membrane for the gating particle, $x$, on the $\tau_x$ curve. $z = 16$ and $V_1 = -20mV$. The time scale is arbitrary, as in Figure 4. $\tau_0$ is set to 0.

4.4.2 Effect of Gating Particle Symmetry

Figure 4.7 illustrates how the symmetry of the system, as specified by $\gamma$, affects the curve for the time constant for $z = 16$. Extreme values of $\gamma$ (i.e. close to 1 or 0) cause the time constant to change abruptly at some voltage so, to a first approximation, as a function of voltage the time constant is either large or relatively small. This sort of characteristic was used to advantage in constructing some of the current kinetics. For example, as will be outlined in Chapter 5, the inactivation time constant for one of the $Na^+$ currents, $I_{Na-v_{ref}}$, needed such a precipitous characteristic in order that it reproduce repetitive $Na^+$-only spikes.

4.4.3 Effect of the Number of Gating Particles in a Given Channel

More than one gating particle in a single channel causes a delay in the net effect of that particle type when the membrane voltage changes. This delay
increases with the number of particles in the channel. Increasing the order (the number per channel) of the particle also makes the (effective) steady-state curve steeper and more depolarized (hyperpolarized) for activation (inactivation) particles.

Another important effect of the number of gating particles is how the resulting steady-state characteristic changes. Specifically, the activation or inactivation curves measured with the voltage-clamp protocol do not indicate the voltage-dependent steady-state characteristics of each particle. Rather, the resulting curves reflect the behavior of the ensemble of particles, a point that is not often made clear in the literature. If a channel is assumed to be governed by N activation particles, for example, then the steady-state curve for a single activation particle is found by taking the Nth root of the (overall) steady-state activation characteristic.

In the following chapters the voltage-dependent steady-state curves for both the individual gating particles for each current will be illustrated. In addition, the apparent steady-state curve of the appropriate ensemble of gating particles will be illustrated (depending on the number of gating particles assigned to a given conductance), as might be measured by the voltage-clamp protocols.

4.5 Procedure for Fitting HH Parameters

The parameters governing the kinetics of each current in the model were determined according to the data for a given current. At one extreme, non-ambiguous voltage clamp data that was almost complete specified most of the relevant parameters – for example the steady-state activation curves for $I_Q$ and $I_M$. At the other extreme, for example for the putative $Na^+$ currents, only meager voltage clamp data was available, augmented by extensive, though much more ambiguous, current clamp data. In these cases the steady-state activation curve or activation and inactivation curves as appropriate, had to be estimated and then checked with steady-state voltage clamp simulations. The functions for the time constants would then be estimated, consistent with the z and $V^*_j$ parameters that had been set by the steady-state characteristics. Simulations would then be used to check the resulting kinetics and, if necessary, the functions would be modified (e.g. changing $\gamma$ or $\alpha_0$) to yield better behavior. For all the currents specific time constant data was either incomplete or non-existent. These functions were iteratively derived by running current clamp simulations of certain proto-
cols for which I had data to compare the model behavior with. Note that these parameters amount to verifiable predictions of the model, assuming that experimental protocols may be devised that record the time and voltage dependence of different currents in isolation.

In Chapters 5, 6 and 7 the parameters for the model currents will be presented, along with the resulting curves for the steady-state and time constant functions.

4.6 Temperature Dependence of the Gating Kinetics

Temperature dependence of the kinetics described here has several elements, all of which ultimately derive from the temperature term in the Boltzmann distribution (eqns. 4.1 and 4.4). However, some of these relationships are handled explicitly while others are estimated.

Consider the expression for the forward and backward rate constants, $\alpha$ and $\beta$ (ref. eqns. 4.2 and 4.3). Each expression evaluates to the maximum of two expressions, a product of two terms and (in the current approximation) a voltage-independent rate-limiting term. The product is formed by a base reaction rate term that ultimately derives from a Boltzmann distribution, although the factors in this expression are not specified. The second, voltage-dependent term in the product is also a Boltzmann distribution, however, as has been shown, each term in this distribution is specified. Therefore, the temperature dependence of the base rate is undefined while this dependence for the voltage-dependent term is explicit. Likewise, the temperature dependence (if any) of the rate-limiting term is undefined.

The base rate term and the rate-limiting term the temperature dependence was therefore assumed to be similar to that generally observed for biologic reactions, where a $Q_{10}$ of 3 is typical. This factor is used to derive a coefficient for the rate constants as follows:

$$Q_{10-factor} = \frac{T_0 - T}{Q_{10}}$$

where $T$ is the temperature and $T_0$ is the temperature at which $\alpha_{0,base}$ is determined. $Q_{10-factor}$ is then multiplied with the both the base rate

---

2This factor is dependent on different currents, as appropriate. The $Q_{10}$ for $I_M$ is set to 5, based on Halliwell and Adams, 1982 [15], and the $Q_{10}$ for the $Na^+$ currents was also set to 5 in order to improve the performance of the model.
term and the rate-limiting term as a first approximation to the effect of temperature of these terms.

Note that the temperature dependence that derives from the voltage-dependent term is (by definition) voltage-dependent. The effect of the temperature on this term disappears when the membrane voltage is equal to \( V_{1/2} \) for a given gating particle, and the effect on the voltage-dependent term increases as the membrane voltage moves away from \( V_{1/2} \). However for most gating particles of the model this effect is smaller than the \( Q_{10} \)-factor, due to the small value of \( z \).

Another temperature dependence arises from the coefficient of the exponential term of the Boltzmann expression. To a first approximation this is typically taken to be a constant (as is done in this model). However, reviewing the significance of this term is instructive. This term is the "pacemaker" for the reaction, as it denotes the effective state transition frequency, whereas the exponential term (as explained before) relates the probability of reaching a given state after a transition. According to Eyring Rate Theory ([19]) this pacemaker term is proportional to the temperature (derived from the frequency of molecular vibrations = \( kT/h \), where \( k \) and \( h \) are Boltzmann's constant and Plank's constant, respectively).

This term contributes a linear temperature dependence of the rate constants, whereas the previous temperature-related terms were exponential functions of temperature. Considering that temperature is in degrees Kelvin, the linear contribution will be negligible on the rate constants when temperature ranges over ten degrees, e.g. between 298 °K (25 °C) and 308 °K (35 °C). The present assumption of a constant coefficient for the exponential terms in eq. 4.5 and eq. 4.6 is therefore justified.

4.7 Adequacy of the HH Model for Describing the Kinetics of Putative Hippocampal Channels?

The HH model of ion channels is clearly a simple one. First, assuming that channels can be described in terms of having discrete regions that can modulate channel conductance through the steric interaction of discrete, voltage-dependent conformational states, there are likely to be more than two stable states for any such "particle" (as opposed to just the open and closed HH states). Such multi-state models and other interpretations of gating have
been considered by other investigators ([9], [4], [3], [8]). For each additional stable state there will also be an additional transition state. A different transition state could become the rate-determining step over some range of membrane voltage, resulting in a non-sigmoidal voltage dependence of the rate constants over the entire voltage range. In addition, a gating particle could possibly influence channel conductance in a more graded fashion. In this case, different conformational states would not necessarily act as binary enabling/disabling mechanisms.

In fact, experimental data for many currents indicate that the simple thermodynamic description of the HH model is not sufficient for the gating mechanisms that govern those currents. For example, some currents have shown minimal or no voltage-dependence for either their activation/inactivation time constants nor their steady state values. In many of these cases whether this reflects the true kinetic nature of the currents, whether this is artifactual from the inherent limitations of the equipment, or whether there is contamination from other currents that has not been accounted for is not clear. In some cases, different measurement protocols can shed light on these questions. In other cases, simulations can help test speculations as to the true nature of the currents. Another explanation is that there is a distinct linear rate-limiting mechanism that alters the function for the time constant as would be expected from the HH model. Such a mechanism is considered in the present simulations, as will be described later.

Another complicating factor is one that reflects actual physiological mechanisms, yet is not explicitly described in the HH model. This factor is the effect of the concentration of various ions in the vicinity of the membrane. There will be an observable effect of different concentrations of the predominant ions (Na\(^+\), K\(^+\), Ca\(^{2+}\), and Cl\(^-\)) on the reversal potential for these species, as expressed in the Nernst equation, given that a given ion undergoes large changes in its local concentration because of sequestering, saturation of buffering mechanisms, or active transport. The model described here assumes only passive transport of the charge carriers across the membrane; for example, maintenance of the Na\(^+\) and K\(^+\) concentration gradients in light of the flux of these ions during electrical activity is assumed to occur over a long time scale. In addition, there are many cases where the local concentration of some ion is a regulator of some active process - e.g. Ca\(^{2+}\) in the activation of the actin-myosin system and as a mediator in the conductance of certain channels. As will be described later, such coupling is indicated in some of the hippocampal pyramidal cell non-linear currents, the notable
example being the $Ca^{2+}$-activated $K^+$ current, $I_C$. In this case there is
evidence that the conductance underlying this current is dependent on the
concentration of $Ca^{2+}$ underneath the membrane, as may be supplied by
the $Ca^{2+}$ currents (e.g. $I_{Ca}$ and $I_{CaS}$).

On the other hand, in support of the HH approach, there is evidence that
the HH description is valid for at least some ion channels. For example, the
movement of charge that occurs when the postulated gating particles change
state (the so-called "gating current") has been detected for some channels
([19]). The primary structure of certain channels, e.g. some $Na^+$ channels
and acetylcholine receptors, have been sequenced, and speculations on the
tertiary structure have been made on the basis of this data. There are
indications in these sequences of segments with polar residues that traverse
the membrane in such a way so that they maybe able to sense the membrane
voltage, i.e. properties expected of putative "gating particles".

On a more empirical level, simulations of non-linear membrane using HH-like
descriptions for the ion channels have been successful in reproducing the
electrical activity of several electrically-active cells. In the present work, it
was remarkable how well HH models were able to reproduce the behavior of
several channels.

4.8 The Concept of an “Extension” of the HH Model

The descriptions for the HIPPO non-linear conductances are based on extensions of the HH model. This is because the HIPPO descriptions explicitly
consider the implications of the single-barrier gating model proposed by
Hodgkin and Huxley, especially with regard to the relationship between the
parameters that define this model and the resulting voltage-dependent time
constants for the gating particles. In other studies that draw on the HH
model the relation between the steady-state characteristics of the gating
particles and their temporal characteristics is purely empirical, and is not
derived from the single-barrier model.
Chapter 5

ESTIMATING $Na^+$ CURRENTS

5.1 Introduction

This chapter describes the derivation of the kinetics for three proposed $Na^+$ currents in the hippocampal pyramidal cell. I shall begin with the background for this problem, and then I shall present the data that was used to derive the model parameters. After the motivation for using three $Na^+$ currents is discussed, the strategy I used to estimate the relevant parameters will be presented.

The parameters for the $Na^+$ currents will then be presented. Some of these parameters will be compared with the analogous parameters of the squid axon $Na^+$ channel and the $I_{Na}$ of the rabbit node of Ranvier, since these latter two currents are among the few $Na^+$ channels for which the kinetics have been measured under voltage clamp.

5.2 Background for Evaluating $I_{Na}$

One of the first applications of the model has been the estimation of the $Na^+$ currents in hippocampal pyramidal cells, including those which underlie the depolarizing phase of the action potential. The fast $Na^+$ conductance necessary for the spike corresponds to the classical $Na^+$ current described by Hodgkin and Huxley. To initiate the action potential, this current rapidly turns on when the membrane voltage passes the firing threshold for the cell. Almost as rapidly, the fast $Na^+$ turns itself off as the cell depolarizes,
contributing substantially to the repolarization of the action potential.

A quantitative description of the \( Na^+ \) currents is vital because these currents are the progenitors of the action potential and therefore are some of the basic determinants of neuronal function. Also the activation/inactivation properties of the \( Na^+ \) currents set the stage for the entrance of the numerous outward currents.

There is little voltage clamp data for \( Na^+ \) currents since these currents are typically large and fast, exceeding the current sourcing ability and the temporal response of the single-electrode clamp circuit used to make the measurements. Since the data is not complete, it was necessary to look to sources of data other than that from hippocampal preparations. These included estimations of the kinetics of a fast \( Na^+ \) current in rabbit node of Ranvier ([10]) and in the bullfrog (Koch and Adams, bullfrog sympathetic ganglion simulations, personal communication. In addition parameters used in other neuron simulations were consulted ([48], hippocampal simulations).

In the HIPPO model, this problem has been approached several ways, including using the descriptions just mentioned. I also tried using \( I_{Na} \) kinetics based on measurements from rabbit node of Ranvier, with some modifications. In particular, the time constants for the \( m \) and the \( h \) variables were scaled by two, in addition to the appropriate temperature compensation \( (\tau_{10} = 3, \text{Adams, personal communication}) \). Attempts to derive the original source for the kinetics used by Traub et al, were unsuccessful. My impression is that the kinetics used in this model are simply the ones derived by Hodgkin and Huxley for squid axon, modified slightly to yield acceptable empirical results for the simulation of some protocols. Initially I tried such an approach.

Specifically, I have attempted to derive channel kinetics that are consistent with current clamp records of \( Na^+\)-only spikes (Storm, personal communication), the steady-state \( Na^+ \) dependent current-voltage characteristic ([12], Storm ibid), and current clamp records of normal action potentials obtained under various conditions, under the assumption that any channels that conduct \( Na^+ \) may be described by the HH-like kinetics described earlier, and further that each channel may have one or two types of gating particles. The task was therefore to try to fit the behavior of this class of voltage-dependent channels to the data. I began by considering the \( Na^+\)-only spike.

\[ ^1 \text{From scaling of time constants for } I_{Na} \text{ in bullfrog myelinated nerve and bullfrog sympathetic ganglion soma.} \]
In particular, it was desired to describe the fast Na$^+$ so that the cell had the capacity for a stable resting potential that in turn could be perturbed enough to result in an action potential. This implied that at the resting potential the inactivation variable ($h$) was turned on and that the activation variable ($m$) was well turned off. In addition, the time constant for the $m$ variable had to be substantially less than the time constant for the $h$ variable throughout most of the depolarized range of the membrane potential above rest. This insured that once threshold was reached, the $m$ variable would have a chance to fully activate and allow Na to enter the cell before the $h$ variable caught up with the depolarization and subsequently go into the closed state, thus shutting off the conductance.

Although a useful description was found empirically, it will be important to compare this description to actual measurements of the fast Na current kinetics whenever they become available.

5.3 Deriving Na$^+$ Conductance Kinetics

5.3.1 Implications of Na$^+$-only Spike

Current clamp records taken using hippocampal slices which had been treated with agents that blocked all potassium and calcium currents enables one to look at the behavior of the Na$^+$ currents and, presumably, the leak conductance in isolation. Such protocols assume that 1) all non-linear currents other than Na$^+$ currents are blocked, and 2) such treatment leaves the leak conductance unchanged. Figure 5.1 shows a record of a Na$^+$-only spike under such conditions.

This spike gives several clues about the Na$^+$ currents in this cell. First, the spike threshold is quite sharp. Also the subthreshold response shows very little activation of inward current. This behavior of the spike threshold implies that the activation curve for the Na$^+$ current underlying the initiation is steep, with the curve centered around -55 millivolts.

The second feature is the biphasic repolarization of the spike. The trajectory of the spike repolarization under the specified conditions is due to two factors - the inactivation of the Na$^+$ current(s) and the linear leak of the membrane. Initially, the spike repolarizes rapidly. Assuming that the major portion of the spike is due to a Na$^+$ current similar to the classical fast Na$^+$ current described in squid axon, this initial repolarization is consistent with the rapid inactivation of the channel with depolarization. At depolarized membrane potentials, the time constant for inactivation is on
Figure 5.1: $Na^+$-only Spike and Subthreshold Response - Current clamp protocol with cesium chloride electrode, TEA, 4AP, and $Mn^{++}$ added to block the calcium and potassium currents. Resting potential is -65 mv. Stimulus current is top trace. From Storm (unpublished data).
the order of a few milliseconds. However, approximately 7 milliseconds after the spike peak the repolarization slows drastically. This slow phase of the repolarization, which commences when the membrane voltage is about -20 millivolts, lasts approximately 60 milliseconds. Since this decay is too slow to be accounted for by the time constant of the cell, we propose that the long tail is due to an non-linear (Na⁺) inward current.

We can determine whether a Na⁺ tail current is likely to be present during a spike that is repolarized by outward currents. The action potential is repolarized by K⁺ currents, in addition to the leak conductance and the inactivation of the Na⁺ currents. If any Na⁺ tail current has been activated during the fast spike, then it must be canceled by a slow residual component of the outward currents, since no long lasting depolarized tail is observed. During a normal action potential there is therefore either a completely activated slow component of the fast Na⁺ current that is canceled by a slow K⁺ current(s), or there is a separate slow Na⁺ current that has not had a chance to be activated during the short spike, or there is some middle ground where an incompletely-activated inward current is canceled by a residual outward current.

The time course of the actual spike was used as the clamp voltage in a voltage clamp simulation using the linear cell in order to estimate the current during a Na⁺-only spike. As was described in Chapter 3, the resulting simulated clamp current revealed the total current that must be supplied by non-linear conductances during the spike. Incidentally, this protocol was an example of the power of the simulation technique, since controlling an actual microelectrode voltage clamp with such a fast time-varying signal is not always possible.

The result of the voltage clamp simulation is shown in Figure 5.2. The time course of the clamp current implied that the non-linear mechanisms underlying the spike had at least two distinct components, an early, large component which quickly deactivated/inactivated, and a later small component which deactivated/inactivated slowly, remaining for approximately 100 milliseconds.

The fast component was assumed analogous to the classical fast Na⁺ current of the squid axon as described by Hodgkin and Huxley.

For the repolarizing tail I considered two possible mechanisms: an abrupt slowing of inactivation of the fast Na⁺ current underlying the spike, or the action of another kind of Na⁺ channel. For the present this first possibility has been discounted for two reasons. First, I have not been able to derive a function for the voltage-dependent time constant for inactivation for the fast
Figure 5.2: Clamp current during voltage clamp simulation using time course of Na$^+$-only spike (Figure 5.1) as command voltage.
Na\(^+\) that was consistent with the single-barrier gating assumptions and that had the necessary sharp increase at the appropriate voltage. Second, in light of the present assumptions regarding the behavior of the K\(^+\) currents, it was determined that the mechanism for the slow tail would only be significantly activated during a long (e.g. non-repolarized) spike, thereby removing the requirement of an outward current that would cancel out the slow tail current after the normal spike.

In considering the possibility of a distinct tail current, the important characteristics of this current was that it had to have a high threshold and a slow onset, consistent with the lack of a long after-depolarization in normal spikes. For example, if this current had a threshold of approximately -10 millivolts with a slow activation time constant, i.e. 4 milliseconds, then during a normal spike this current will not have time to activate fully. On the other hand, during the slower repolarization that occurs without non-linear outward currents, this tail current will have time during the peak of the spike to activate more, and thereby contribute to a long repolarization. I called this current \(I_{Na\text{-tail}}\). I attempted to adapt the activation data for \(I_{NaP}\) (discussed next) to account for the action of the so-called \(I_{Na\text{-tail}}\), but this has been unsuccessful to date. This is primarily because the low threshold of the activation curve for \(I_{NaP}\) has thwarted attempts at deriving a function for the time constant of activation that is consistent with the single-barrier model and which in turn reproduces the Na\(^+\)-only spike.

### 5.3.2 Implications of Na\(^+\)-only Repetitive Firing

Repetitive firing elicited in cells in which all currents except Na\(^+\) have been blocked offer additional clues as to the nature of the Na\(^+\) currents in hippocampal pyramidal cells. Figure 5.3 illustrates such a record. The key features of these voltage traces are 1) higher threshold of spikes following initial spike (i.e. higher threshold of the secondary spikes), 2) reduced amplitude of repetitive spikes, 3) reduction of spike amplitude with increasing stimulus, 4) repetitive firing elicited only in a narrow range of membrane voltages.

### 5.3.3 Implications of Tetrodotoxin Sensitive Steady State Current-Voltage Characteristic

Figure 5.4 shows a steady-state current-voltage characteristic from hippocampal pyramidal cells that demonstrates a tetrodotoxin (TTX) sensitive
Figure 5.3: \( Na^+ \)-only Repetitive Spiking - Current clamp protocol under same conditions as Figure 5.1. Current stimuli is bottom trace. From Storm (unpublished data).
Figure 5.4: Inward Rectification by $Na^+$. Curve derived from steady-state activation of a persistent $Na^+$ current, $I_{NaP}$ ([12]).

inward-rectification ([12]). Assuming that a sensitivity to TTX means that $Na^+$ currents underlie this rectification, the characteristic can be accounted for by either the “window current” of a transient $Na^+$ current, by a persistent (non-inactivating) $Na^+$ current ($I_{NaP}$), or by some combination of these types of channels.

5.3.4 The Role of Window Currents

Window current is due to any overlap in the voltage-dependent steady state curves of the activation and inactivation variables, thereby making a normally transient current contribute a persistent component over some range of membrane voltage. Since any overlap in the activation and inactivation curves will be limited, rectification due to a window current alone would disappear at depolarized membrane voltages. The steady-state current-voltage characteristic would then continue the linear characteristic established prior to the onset of rectification. The data for this cell, however, would not necessarily demonstrate a depolarized removal of rectification since the steady-state current-voltage curve was only measured to -35 millivolts.

Important aspects of this characteristic include the lack of inward rectification around the $Na^+$-only spike threshold, which implies that the $m$ and
$h$ curves for the current activated at the threshold do not overlap at that threshold.

### 5.3.5 Adding Together All of the Evidence

Taken all together, the data presented so far implies several characteristics of any TTX-sensitive (presumably $Na^+$-carried) currents. These may be summarized as follows:

1. $Na^+$ mediated repetitive firing in cells depolarized from the resting potential implies that the inactivation curve for the current underlying the higher threshold spikes is non-zero at the depolarized level.

2. The lack of inward-rectification at the lower spike threshold contradicts the earlier conclusion that the activation curve for the fast $Na^+$ current is steep at the lower threshold.

3. A steep activation curve at the lower threshold taken with the non-zero inactivation at depolarized membrane potentials would result in an appreciable window current. This window current in turn would contribute to inward rectification starting at the lower spike threshold of -55 millivolts. This is inconsistent with the data.

To explain these phenomena, I suggest that there is an additional fast $Na^+$ channel whose threshold for firing is depolarized from that of the original fast $Na^+$ channel, and whose activation and inactivation kinetics are such that it might mediate $Na^+$-only repetitive firing. In the absence of repolarization from any non-linear outward currents, simulations indicated that there must be a finite overlap of the activation and inactivation curves of any HH-like $Na^+$ channel that can mediate repetitive firing. This overlap will result in a finite window current, and thus a steady state inward rectification. I was able to adjust this rectification to qualitatively reproduce the onset of the observed rectification discussed earlier. Because it mediates repetitive $Na^+$-only spikes, I named the high threshold current $I_{Na-trp}$. Since I deduced that the original fast $Na^+$ current had a sensitive, low threshold for initiating the action potential, I called this current $I_{Na-trig}$.

The steady-state $Na^+$ mediated rectification also constrains the behavior of the $I_{Na-tail}$. In particular, if this current contributed any window current then such a window current could only activate above -30 millivolts, in order to be consistent with the steady-state IV characteristic.
The implications of a sharp threshold for the \( \text{Na}^+ \)-only spike, and a small subthreshold response imply steep and/or activation characteristics for the current underlying the initiation of the spike. On the other hand, presumed modulation of the spike threshold by outward (\( K^+ \)) currents (see Chapter 7) which in turn do not greatly effect the slope or amplitude of the action potential implies that around threshold \( \text{Na}^+ \) activation is not instantaneous, in other words a small outward conductance would be able to counter the sub-threshold inward rectification of the \( \text{Na}^+ \) current sufficiently to raise the firing threshold. Note that the faster the \( \text{Na}^+ \) current activated around threshold, the larger the outward current would have to be to suppress the initiation of the spike. Since threshold is only about 30 millivolts above \( E_K \), the small driving force for an outward \( K^+ \) current means that a large conductance is required. However, a large \( K^+ \) conductance that is enabled immediately prior to the spike would allow a large outward current on the upstroke of the spike, due to the increasing driving force that the \( K^+ \) ions see. An alternative explanation is that the threshold-modulating \( K^+ \) current shuts off prior to or during the upstroke of the spike, and thus a \( K^+ \) conductance of sufficient size to transiently counteract a quickly activating \( \text{Na}^+ \) current would not then serve to attenuate the spike itself. A final alternative is that the size of the spike current is large enough that a sub-threshold activated outward conductance would not attenuate the spike noticeably.

5.4 Strategy for Determining \( \text{Na}^+ \) Current Kinetics

Once it was determined that three \( \text{Na}^+ \) currents might model the observed behavior, the following strategy used to derive their kinetics:

1. Estimate the absolute \( \text{Na}^+ \) conductance for the fast \( \text{Na}^+ \) currents (\( I_{\text{Na-trig}} \) and \( I_{\text{Na-rep}} \)) by running voltage clamp simulations using the \( \text{Na}^+ \)-only spike as the command voltage.

2. A reasonable set of equations governing the kinetics (backward and forward rate constants for the activation gating particle \( m \) and inactivation gating particle \( h \)) for the three putative \( \text{Na}^+ \) currents was determined. The free parameters for each function include the free energy changes between the stable states and the transition state, the
location of the transition state within the membrane, and the effective valence of the gating particle. Voltage-dependent functions of the time-constants and steady-state values of the gating particles are then derived from the appropriate rate functions.

3. Run (current clamp) simulations of the $Na^+$-only single and repetitive spike protocols.

4. Compare the simulations with the data.

5. Adjust the appropriate rate-constant functions and repeat the simulations.

6. Once a good match between the current clamp simulations and the data was reached, the steady state current-voltage characteristic of the cell with all three $Na^+$ currents activated was derived to measure the inward-rectification generated by the estimated currents.

7. This characteristic was compared with that of one from the model with the derived $Na^+$ currents replaced by the reported persistent $Na^+$ current.

8. If needed, return to step 5 in order to obtain a good fit to all the available data.

This process eventually converged to yield a model description that was in good qualitative agreement with the data pertaining to $Na^+$-only behavior. The derived $Na^+$ currents were then tested by running simulations in which various $K^+$ currents were added, once they were derived. This led to a modification of some of the parameters of the $Na^+$ currents, while preserving the $Na^+$-only behavior, which provided a rigorous set of constraints on the parameter adjustment. The entire process was and is one of adding one piece of information at a time to the model, and then running simulations to find out how the new data affects the model’s behavior.

5.5 Results

5.5.1 Simulation of $Na^+$-Mediated Inward-Rectification and Spikes

Figure 5.5 compares the steady-state current-voltage characteristic of the model with 1) the reported $I_{NaP}$, and 2) the $I_{Na-trig}$, $I_{Na-tail}$, $I_{Na-rep}$ cur-
Figure 5.5: Current-voltage characteristics of model showing inward-rectification mediated by $I_{NaP}$ and by $I_{Na-trig}$, $I_{Na-tail}$, and $I_{Na-rep}$ currents.

The model currents cause an onset of inward rectification that is in qualitative agreement with the published data. However, since this steady-state inward current is mainly due to the transient $I_{Na-rep}$ window current, the rectification only occurs over a limited range of membrane voltages. This is not necessarily inconsistent with the characteristic of $I_{NaP}$ because of the limited range over which this current was measured, as explained earlier. Possibly the so-called persistent $Na^+$ current is actually a transient current which would demonstrate removal of inward-rectification at more depolarized membrane potentials. Given more data, the derived characteristics of the so-called $I_{Na-rep}$ might be adjusted to better match the steady-state current-voltage relationship of the model.

Figure 5.6 illustrates a simulation of the $Na^+$-only single spike. The model's behavior is in good agreement with the data, in particular in regards to the sharp threshold of the spike, the time course of the depolarizing phase, the initial fast repolarization, and the slower late repolarization. Also in the figure are the three model $Na^+$ currents that underlie the $Na^+$-only spike. In this figure the initial activation of $I_{Na-trig}$, the subsequent recruitment of the higher threshold $I_{Na-rep}$, and the slow time course of $I_{Na-tail}$ after the first two currents have inactivated can be seen.
Figure 5.6: Current clamp simulation of $Na^+$-only single spike. Spike stimulus - 0.78 nA. Top - Simulation of spike compared with record taken from data. Bottom - $I_{Na-trig}$, $I_{Na-tail}$, $I_{Na-rep}$ currents during spike.
Figure 5.7 illustrates a simulation of \(Na^+\)-only repetitive firing under different constant current inputs. At the bottom of the figure are the \(Na^+\) currents underlying the marked spike train. After the first spike, the initiation of later spikes is mediated completely by \(I_{Na-\text{trig}}\).

### 5.6 Parameters of the Three Putative \(Na^+\) Conductances

The parameters for the three proposed hippocampal \(Na^+\) currents will now be presented in detail. Some of these parameters will then be compared with the analogous parameters of the squid axon \(Na^+\) channel and the \(I_{Na}\) of the rabbit node of Ranvier.

All parameters were set assuming a temperature of 24°C. It was necessary to use a high value for the \(q_{10} (= 5)\) for these currents since simulations of action potential repolarization at the higher temperature used for interpreting most of the \(K^+\) current data (32°C) indicated that significantly faster activation/inactivation was required. Figure 5.8 shows the resulting effect of different temperatures on the \(Na^+\)-only spike. The striking effect of temperature in these simulations suggest that measuring the temperature dependence of \(Na^+\)-only spikes in HPC may provide a good test for the model description of the \(Na^+\) currents.

### 5.7 Parameters of \(I_{Na-\text{trig}}\)

\(I_{Na-\text{trig}}\) is based on the classical \(I_{Na}\) of the squid axon. Important differences were required, however, so that \(I_{Na-\text{trig}}\) would have a sharp threshold with very little subthreshold activation. Also, it was necessary to adjust some parameters to obtain the desired characteristics during normal repetitive firing.

#### 5.7.1 Results

First, the valence of both the \(m\) and \(h\) particles is large \((z_m = 20, z_h = 30)\), which makes them steep functions of voltage. Likewise, the \(m_\infty\) and \(h_\infty\) curves for \(I_{Na-\text{trig}}\) do not overlap as they do in the squid axon \(I_{Na}\) (ref. Figure 5.15).
Figure 5.7: Current clamp simulation of $Na^+$-only repetitive spike protocol. Top - Spike trains in response to different stimulus strengths. Middle - $I_{Na\text{-trig}}, I_{Na\text{-tail}}, I_{Na\text{-rep}}$ currents during trace marked with the arrow. Bottom - Stimulus currents.
Figure 5.8: Current clamp simulations of $Na^+$-only single spike at different temperatures. $q_{10}$ for the three $Na^+$ current kinetics is set to 5. $q_{10}$ for the absolute conductances is set to 1.5. With increasing temperature the spike threshold drops, the depolarizing slope is steeper, and the repolarization (due to inactivation/deactivation) is faster.
The position on the voltage axis, as determined by $V_{\frac{1}{2}, m_{Na-trig}}$ and $V_{\frac{1}{2}, h_{Na-trig}}$, were set to make the firing threshold equal to about -55 millivolts. This threshold was made slightly higher than indicated by the data in order to allow subthreshold activation of $I_A$ (ref. Chapter 7).

Setting the order of the inactivation particle $h$ and the the $\tau_{h,Na-trig}$ magnitudes involved compromising between formulations that met a) the observed width (about 1.7 milliseconds at 0 millivolts) and b) the observed height (about 15 millivolts) of $Na^+$-only spike. The formula I have used includes two $h$ particles and setting $\tau_{h,Na-trig}^0 = 2.0$ milliseconds so that the current would not inactivate too quickly at the top of the spike. When a single $h$ particle was used it was necessary to adjust $\tau_{h,Na-trig}^0 = 1.5$ milliseconds to maintain the width of the spike; however, this formula made the peak amplitude too high.

The curve for $\tau_{m,Na-trig}$ was symmetrical ($\gamma_{m,Na-trig} = 0.5$), but when normal repetitive firing was simulated using the $K^+$ currents, it was necessary to make the curve for $\tau_{h,Na-trig}$ skewed to the right (depolarized) ($\gamma_{h,Na-trig} = 0.2$) so that removal of inactivation was fast enough near rest to allow for rapid firing.

The value for $g_{dens,Na-trig} (= 40 mS/cm^2$) was set in order to obtain an initial slope of the action potential of approximately 130 volts per second (measured from threshold to 0 millivolts). This value was dependent on $g_{dens,Na-rep}$ as well, since $I_{Na-rep}$ is activated within a few tenths of a millisecond after the beginning of the spike and therefore $I_{Na-rep}$ contributes substantially to the upstroke of the action potential (see Figure 5.6).

The equation for $I_{Na-trig}$ is:

$$I_{Na-trig} = g_{Na-trig} m_{Na-trig} h_{Na-trig}^2 (V - E_{Na^+})$$

where

$$g_{Na-trig} = 0.53 \mu S$$

$$g_{dens,Na-trig} = 40.0 mS/cm^2$$

Table 5.1 lists the parameters for the $I_{Na-trig}$ gating variables. These are the rate functions for the activation variable, $m$, of $I_{Na-trig}$:

$$\alpha_{m,Na-trig} = 0.3 \exp \left( \frac{(V + 47)0.5 \cdot 20 \cdot F}{RT} \right)$$

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<table>
<thead>
<tr>
<th>Gating Variable</th>
<th>z</th>
<th>γ</th>
<th>α₀</th>
<th>( V_{\frac{1}{2}} ) (mV)</th>
<th>( \tau_0 ) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( m ) (activation)</td>
<td>20</td>
<td>0.5</td>
<td>0.3</td>
<td>-47.0</td>
<td>0.5</td>
</tr>
<tr>
<td>( h ) (inactivation)</td>
<td>-30</td>
<td>0.2</td>
<td>0.003</td>
<td>-54.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table 5.1: Parameters of \( I_{Na-trig} \) Gating Variables

\[
\beta_{m,Na-trig} = 0.3 \exp\left(\frac{(-47 - V)0.5 \cdot 20 \cdot F}{RT}\right)
\]

These are the rate functions for the inactivation variable \( h \) of \( I_{Na-trig} \)

\[
\alpha_{h,Na-trig} = 0.01 \exp\left(\frac{(V + 61)0.7 \cdot -30 \cdot F}{RT}\right)
\]

\[
\beta_{h,Na-trig} = 0.01 \exp\left(\frac{(-61 - V)0.3 \cdot -30 \cdot F}{RT}\right)
\]

Figures 5.9 and 5.10 show the voltage dependence on the steady-state values and the time constants for the \( m_{Na-trig} \) and \( h_{Na-trig} \) variables.

### 5.8 Parameters of \( I_{Na-rep} \)

The kinetics of \( I_{Na-rep} \), like \( I_{Na-trig} \), is similar to the squid axon \( I_{Na} \) kinetics. In order that \( I_{Na-rep} \) be able to generate repetitive \( Na – only \) spikes,
however, it was necessary to adjust the parameters for this conductance very carefully. Experimentation revealed that a key requirement for getting high threshold \( N_a - only \) repetitive spikes was that the \( m_\infty \) and \( h_\infty \) curves for \( I_{N_a-rep} \) overlap. In addition, the curve for \( h_\infty \) had to be very steep and the curve for \( \tau_h \) had to be sharp on the hyperpolarized side. These characteristics were needed so that during the repolarization after a spike, removal of inactivation would occur while \( m_{N_a-rep} \) was large enough to allow enough current for another spike. On the other hand, \( h \) could not be so fast that there was \( N_a - only \) repetitive firing without tonic stimulation.

### 5.8.1 Results

Experimentation with the order of \( m \) and \( h \) resulted in the assignment of two \( m \) and three \( h \) particles to the \( I_{N_a-rep} \) conductance. The high order of \( h \) accentuated the steepness of the \( h_\infty \) curve so that when the cell repolarized slowly (with a tonic current stimulus) the removal of inactivation would occur abruptly enough to allow repetitive firing. A single \( m \) particle did not provide enough positive feedback on the initiation of secondary spikes to get the observed magnitudes (e.g. between -20 and 5 millivolts). Three \( m \) particles did not allow the channel to retain sufficient activation after the initial spike to initiate subsequent spikes.

The value for \( \bar{g}_{dens,N_a-rep} \) had various effects. In particular, the value for \( \bar{g}_{dens,N_a-rep} \) modulated the role of \( I_{N_a-trig} \) during the initial slope of the action potential. As introduced previously, both the value of \( \bar{g}_{dens,N_a-rep} \) and \( \bar{g}_{dens,N_a-trig} \) determined this slope.
A second consequence of $\bar{g}_{\text{dens,Na-rep}}$ was that it had to be large enough to support regenerative firing when $I_{\text{Na-trig}}$ was inactivated because of the depolarized membrane. On the other hand, $\bar{g}_{\text{dens,Na-rep}}$ could not be too large since this would give a significant depolarizing hump after the initial spike when the tonic stimulus is too small for repetitive firing - such a hump is not observed experimentally (Figure 5.3).

On a more subtle level, the relationship between stimulus magnitude and the second spike during $Na^+$-only repetitive firing is such that initially (from below threshold to just above threshold for the tonic stimulus) the greater the stimulus the sooner the second spike. However, past a certain point the greater the stimulus the later the second spike occurs, until the stimulus is too large to promote $Na^+$-only repetitive firing. During my simulations I found that this behavior was dependent on $\bar{g}_{\text{dens,Na-rep}}$ - if $\bar{g}_{\text{dens,Na-rep}}$ was too large, then there was no range of stimulus strengths in which a larger stimulus caused the second spike to occur earlier.

In practice the most critical test of $\bar{g}_{\text{dens,Na-rep}}$ was the latter relation between $\bar{g}_{\text{dens,Na-rep}}$ and the timing of the second spike during $Na^+$-only repetitive firing. Once the desired relationship was achieved the other characteristics were matched primarily by the adjustment of other relevant parameters.

The overlap for the $m_\infty$ and $h_\infty$ curves resulted in the steady state $Na^+$ mediated inward rectification discussed earlier.

In summary, the parameters for $I_{Na-rep}$ were among the most sensitive of the model, and a substantial amount of effort was needed to derive them.

The equation for $I_{Na-rep}$ is

$$ I_{Na-rep} = \bar{g}_{Na-rep} m^2_{Na-rep} h^2_{Na-rep} (V - E_{Na^+}) $$

where

$$ \bar{g}_{Na-rep} = 0.50 \mu S $$

$$ \bar{g}_{\text{dens,Na-rep}} = 35.0 \text{mS/cm}^2 $$

Table 5.2 lists the parameters for the $I_{Na-rep}$ gating variables. These are the rate functions for the activation variable, $m$, of $I_{Na-rep}$ -

$$ a_{m,Na-rep} = 0.67 \exp \left( \frac{(V + 34)0.5 - 6 - E}{RT} \right) $$

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Gating Variable | $z$ | $\gamma$ | $\alpha_0$ | $V_1$ (mV) | $\tau_0$ (ms) \\
--- | --- | --- | --- | --- | --- \\
$m$ (activation) | 6 | 0.5 | 0.67 | -34.0 | 5.0 \\
h (inactivation) | -30 | 0.17 | 0.0023 | -42.5 | 3.0 \\

Table 5.2: Parameters of $I_{Na-rep}$ Gating Variables

Figure 5.11: Steady-state curves ($m_\infty$ and $h_\infty$) for $m_{Na-rep}$ and $h_{Na-rep}$ and effective curves as would be measured by voltage-clamp experiments.

$$\beta_{m,Na-rep} = 0.67 \exp\left(\frac{(-34 - V)0.5 \cdot 6 \cdot F}{RT}\right)$$

These are the rate functions for the inactivation variable, $h$, of $I_{Na-rep}$.

$$\alpha_{h,Na-rep} = 0.0023 \exp\left(\frac{(V + 42.50.83 \cdot -30 \cdot F)}{RT}\right)$$

$$\beta_{h,Na-rep} = 0.0023 \exp\left(\frac{(-42.5 - V)0.17 \cdot 30 \cdot F}{RT}\right)$$

Figures 5.11 and 5.12 show the voltage dependence on the steady-state values and the time constants for the $m_{Na-rep}$ and $h_{Na-rep}$ variables.

### 5.9 Parameters of $I_{Na-tail}$

The key features that I defined for the proposed $I_{Na-tail}$ include significant activation only when there are prolonged spikes, e.g. when there is no
repolarization due to non-linear outward currents. Also, this current was derived to be a transient current, with no contribution to steady state inward rectification.

5.9.1 Results

The steady state curve for \( m \) was adjusted so that activation commenced only for very depolarized levels (Figure 5.13.). On the other hand, the time constant for \( m \) was derived so that once \( m \) was open it was slow to relax to the closed state as the membrane repolarized (Figure 5.14.).

Determining the parameters for \( \tau_m, \tau_Na-\text{rep} \) and \( g_{Na-\text{rep}} \) was done together, since both of these factors determined the slow repolarization inward current.

The curves for \( h \) were not so critical - the main requirement was that at rest \( h \) was fully open so that \( I_{Na-\text{tail}} \) could be turned on with the spike. However, \( h_\infty \) had to be 0 at levels depolarized from rest so that there would be no window current component from \( I_{Na-\text{tail}} \). The curve for \( \tau_h, \tau_{Na-\text{tail}} \) was set so that on one hand \( h \) did not change much during spiking, leaving the \( m \) variable in control of this current, and, on the other hand, fast enough so that \( I_{Na-\text{tail}} \) would not have an apparent persistent characteristic because of a sluggish inactivation.

There was no need for the delayed state transition characteristics of more than one \( m \) or \( h \) particle for \( I_{Na-\text{tail}} \); therefore the order of each was set to one.

Given that in general the requirements for \( I_{Na-\text{tail}} \) were not as rigid
Table 5.3: Parameters of $I_{Na-tail}$ Gating Variables

<table>
<thead>
<tr>
<th>Gating Variable</th>
<th>$z$</th>
<th>$\gamma$</th>
<th>$\alpha_0$</th>
<th>$V_\frac{1}{2}$ (mV)</th>
<th>$\tau_0$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m$ (activation)</td>
<td>8</td>
<td>0.95</td>
<td>0.025</td>
<td>-5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>$h$ (inactivation)</td>
<td>-6</td>
<td>0.2</td>
<td>0.0017</td>
<td>-47.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 5.3 lists the parameters for the $I_{Na-tail}$ gating variables. These are the rate functions for the activation variable, $m$, of $I_{Na-tail}$:

$$
\alpha_{m,Na-tail} = 0.025 \exp\left(\frac{(V + 5)0.95 \cdot 8 \cdot F}{RT}\right)
$$

$$
\beta_{m,Na-tail} = 0.025 \exp\left(\frac{(-5 - V)0.05 \cdot 8 \cdot F}{RT}\right)
$$

These are the rate functions for the inactivation variable, $h$, of $I_{Na-tail}$:

$$
\alpha_{h,Na-tail} = 0.0017 \exp\left(\frac{(V + 47)0.8 \cdot -6 \cdot F}{RT}\right)
$$

$$
\beta_{h,Na-tail} = 0.0017 \exp\left(\frac{(-47 - V)0.2 \cdot -6 \cdot F}{RT}\right)
$$

Figures 5.13 and 5.14 show the voltage dependence on the steady-state values and the time constants for the $m_{Na-tail}$ and $h_{Na-tail}$ variables.

as other currents, i.e. $I_{Na-rep}$, the derived parameters were not the only set that would demonstrate the desired behavior. For example, $h$ could be faster, as long as either $\tau_m$ was likewise decreased and/or $\bar{g}_{Na-tail}$ was increased to compensate for the resulting increase in inactivation of $I_{Na-tail}$ during the spike.

The equation for $I_{Na-tail}$ is:

$$
I_{Na-tail} = \bar{g}_{Na-tail}m_{Na-tail}h_{Na-tail}(V - E_{Na+})
$$

where

$$
\bar{g}_{Na-tail} = 0.013 \mu S
$$

$$
\bar{g}_{dens,Na-tail} = 1.0 \text{mS/cm}^2
$$
Figure 5.13: Steady-state curves ($m_\infty$ and $h_\infty$) for $m_{Na-tail}$ and $h_{Na-tail}$.

Figure 5.14: Time constant curves ($\tau_m$ and $\tau_h$) for $m_{Na-tail}$ and $h_{Na-tail}$.
5.10 Comparison of $I_{Na-trig}$ and $I_{Na-rep}$ Kinetics With Those of Squid Axon $I_{Na}$ and Rabbit Node of Ranvier $I_{Na}$

Comparing the characteristics of the squid axon $I_{Na}$ kinetics with that of $I_{Na-trig}$ and $I_{Na-rep}$ is interesting. Figures 5.15 and 5.16 illustrate the $m$ and $h$ steady-state and time constant curves for these three currents. The salient differences include the substantial overlap (giving a large window current) in the squid $m_{\infty}$ and $h_{\infty}$ curves and the much lower valence of the respective squid $I_{Na}$ gating particles implied by these curves, as compared to the HIPPO curves.

5.11 Discussion of Functional Roles of the Proposed $Na^+$ Currents

Once we have constructed the three model currents that successfully reproduce the data, it is important to ask what roles these currents might play in the pyramidal cell. Consider $I_{Na-trig}$. The characteristics of this current allow for a sharp firing threshold from resting potential. The advantage of this is that the neuron is more tuned to a specific input firing level: there is a higher noise margin in regards to the firing efficacy of a given pattern of synaptic input. In addition, the lack of a window current for $I_{Na-trig}$ means that at rest or at subthreshold membrane potentials there will be
Figure 5.16: Time constant curves ($\tau_m$ and $\tau_h$) for squid axon $I_{Na}$ and the hippocampal $I_{Na-trig}$ and $I_{Na-reg}$.

little "wasted" $Na^+$ current. This is metabolically favorable as the cell does not have to remove the buildup of $Na^+$ resulting from such a background current. Likewise, any constant inward current at rest would have to be balanced by an outward (presumably $K^+$) current in order to maintain the resting potential. Again, this loss adds to the energy requirements of the cell at "rest".

Given these characteristics of $I_{Na-trig}$, a regenerative, higher threshold $Na^+$ current is necessary in order to mediate the higher threshold spikes that are observed under various conditions, including bursting on top of a (presumably $Ca^{2+}$) depolarizing hump and repetitive $Na^+$-only firing.

What could be the advantage of this second $Na^+$ current? Such a higher threshold $Na^+$ current on top of a sharp, lower threshold $Na^+$ current could relax the requirements of the repolarization mechanism during a train of spikes in response to some tonic depolarization. An $I_{Na-reg}$-type current could mediate later action potentials without the requirement that the cell repolarize to below the threshold of an $I_{Na-trig}$-type current - all that is needed is that the cell repolarize to somewhere below the threshold of $I_{Na-reg}$. Simulation of repetitive firing (Figure 5.17) shows how $I_{Na-reg}$ could furnish the major portion of depolarizing current for spikes after the first spike of a train.

Allowing the cell to fire again from a higher threshold reduces the amount of outward current needed to sustain multiple spikes, which in turn impose less of burden on the cell’s machinery for maintaining the $K^+$ concentration gradient. In addition, the overlap of the activation and inactivation curves of
Figure 5.17: Current clamp simulation of normal repetitive firing in response to 1.0 nA tonic stimulus. Note the fast after-hyperpolarization (fAHP) after first spike, mediated by $I_C$ (Storm, ibid) (Chapter 7). Slowing of firing is due to activation of $I_{AHP}$ (Chapter 7). In lower part of figure are the $I_{Na-trig}$, $I_{Na-tail}$, $I_{Na-rep}$ currents during the train.
$I_{Na-rep}$ results in an ill-defined threshold for repetitive firing, allowing for a greater flexibility in modulating the frequency of firing by other mechanisms, e.g. distinct actions of the various $K^+$ currents.

On the other hand, when this current is blocked, there is a degenerate response to large tonic stimuli, as will be demonstrated in Chapter 9 (ref. Figure 9.9). As will be discussed later, whether this dependence of repetitive firing on $I_{Na-rep}$ is physiological or pathological is not obvious.

What about the proposed $I_{Na-tail}$? As constructed, this current contributes to a small after-depolarization during a normal spike that must be countered by an outward current. In our simulations, this is accomplished by $I_{DR}$. For now the function this slowly-inactivating $Na^+$ current might have is not clear. Perhaps this current may be inhibited in certain circumstances, allowing it to play a role in mediating repetitive firing. Such speculation awaits further evidence of such a $I_{Na-tail}$ in actual cells. An important related question is whether or not the $I_{Na-tail}$ (if it exists) is either physiologically modulated by factors that do not affect the other currents, or is its role in shaping the response of the cell a constant one?

In Chapter 9 the effect of $I_{Na-tail}$ on repetitive firing will be compared with that of other currents.
Chapter 6

ESTIMATING $Ca^{++}$ CURRENTS AND ACCUMULATION OF $Ca^{2+}$ IN THE CELL

6.1 Introduction

This chapter describes the two calcium ($Ca^{2+}$) currents that have been described for the HPC, $I_{Ca}$ and $I_{CaS}$, and possible mechanisms that establish the concentration of free $Ca^{2+}$ in various regions underneath the cell membrane.

For the current version of the model the goals set for the characterization of the $Ca^{2+}$ phenomena were quantitatively relatively modest and based partly on heuristics. In summary, the desired behavior of the system included:

- Generation of $Ca^{2+}$-only spikes that were qualitatively similar to actual $Ca^{2+}$-only spikes.

- Voltage and time-dependent changes in $[Ca^{2+}]$ underneath the membrane $-$ $[Ca^{2+}]_{shell,1}$ and $[Ca^{2+}]_{shell,2}$ so as to mediate two $K^+$ currents ($I_C$ and $I_{AHP}$).

- Response to voltage clamp protocols in qualitative agreement with the available data.
The effect of the change in $[Ca^{2+}]_{\text{shell}}$ on $E_{Ca}$ was also considered, assuming that $E_{Ca}$ is determined by the concentration gradient across the membrane in the vicinity of the $I_{Ca}$ channels.

6.2 Calcium Current - $I_{Ca}$

Many workers have reported $Ca^{2+}$ currents in HPC ([6], [13], [15], [18], [28], [33], [38], [40], [41], [53], [55]). The fast $Ca^{2+}$ current in the model, $I_{Ca}$, which underlies $Ca^{2+}$-only spikes has kinetics similar to that of $I_{Na-trig}$, except that the curves for the gating variables are less steep and the time constants are about one order of magnitude slower. These kinetics were originally based on those used by Traub and Llinas [49], [48] in their hippocampal and motorneuron models.

In deriving the kinetics of $I_{Ca}$ I attempted to reproduce current clamp records from cells in which both $Na^+$ currents and $I_{DR}$ were blocked with TTX and TEA, respectively ([41]). In these cells slow $Ca^{2+}$-mediated "spikes" were elicited by long depolarizing current steps. Spike threshold was dependent on the holding potential prior to the current stimulus. Paradoxically, the higher the holding potential the lower the threshold. At the extreme, a holding potential of -70 millivolts resulted in elimination of a regenerative response after the stimulus (though some inward current was activated during the stimulus). On the other hand, a holding potential of -40 millivolts resulted in a firing threshold for the $Ca^{2+}$ spike of about -30 millivolts. This behavior is contrary to what might be expected from a current with activation/inactivation properties similar to a fast $Na^+$ current, in which case a lower holding potential would cause the inactivation to be more completely removed, thereby lowering the firing threshold. Segal and Barker proposed that the observed behavior of the $Ca^{2+}$ spike was due to the action of the transient $K^+$ current $I_A$ (Chapter 7); when the cell was held at the lower potential, the inactivation of $I_A$ was removed so that the subsequent depolarization allowed the activation $I_A$ to counter the activation of $I_{Ca}$. Holding the cell at the higher potential inactivated $I_A$, thereby allowing the later depolarizing current pulse to elicit the $Ca^{2+}$ spike. The formulation for the kinetics of $I_{Ca}$ was therefore tied somewhat to the description of $I_A$ in the model.

Another action of $I_{Ca}$ that I attempted to reproduce was its apparent role in the slow depolarizing hump that is observed in some cells which exhibit burst firing ([48]), as I mentioned in the previous chapter in the dis-
cussion of $I_{Na-rep}$ function during repetitive and burst firing. At this point the model does not exhibit such behavior. In fact, such a hump between -60 and -40 millivolts is inconsistent with the apparent $I_{Ca}$ (slow) activation at approximately -10 millivolts. The supposed $Ca^{2+}$-mediated hump is possibly due to $I_{Ca}$ channels in the dendrites, rather than somatic $I_{Ca}$. In the dendrite current input local or distal to the site of the $I_{Ca}$ channels could activate the channels without raising the soma voltage beyond 10 millivolts or so above rest. Once activated, the dendritic $Ca^{2+}$ conductances could supply enough long-lasting inward current to cause the somatic hump in question. In future studies with HIPPO, such conductances will be placed on the dendrites to test this hypothesis (ref. Chapter 11).

Another requirement for the kinetics of $I_{Ca}$ was that this current not be significantly activated during the normal action potential. This is based on the assumption that the effect of $Ca^{2+}$ blockers on the shape of the action potential is due mainly to the subsequent inhibition of $I_C$ and $I_{AHP}$. This was accomplished by including two activation particles, $s$, in order to force a delay in activation with depolarization, and likewise adjusting the curves for $s_\infty$ and $\tau_s$ so that during the regular spike $s$ would change little, while during the sustained depolarization required to elicit the $Ca^{2+}$ spike $s$ would have enough time to move to the open position.

In addition, it was necessary to set the order of $s$ to three so that sub-threshold activation of $s$ during regular spikes did not allow significant (in terms of membrane depolarization) $I_{Ca}$.

An important characteristic of $Ca^{2+}$ spikes is the abruptly-biphasic repolarization (see [41]). The initial decay after the peak of the spike is relatively slow, presumably due to residual $I_{Ca}$, until the membrane potential reaches about -10 millivolts. The membrane then rapidly repolarizes to the resting (or holding) potential, as if $I_{Ca}$ was suddenly turned off.

Since this knee occurs well depolarized from the spike threshold (between -40 and -30 millivolts), it cannot be due to complete de-activation of the activation gating particle ($s$) that underlies the threshold.

Also, I was not able to adjust either the number of nor the kinetics of the inactivation particle ($w$) so that a delayed yet abrupt inactivation could account for the knee. However, by adjusting the steepness of the $s_\infty$ curve so that the effective steady state activation (in the hyperpolarizing direction) began to drop off around -5 millivolts, the start of de-activation as the $Ca^{2+}$-only spike repolarized to this level contributed a moderate knee in the simulated spike. With the present version of $I_{Ca}$, simulated $Ca^{2+}$ spikes (Figure 6.1 have an analogous repolarization knee, but this is not as steep
Gating

Variable $z_1$ ao 1,71 (MV)

$7$ (MS)

s (activation) 4 0.5 0.10 -24.0 2.0

w (inactivation) -12 0.2 0.001 -35.0 5.0

Table 61: Parameters of $I_{Ca}$ Gating Variables

and does not occur quite as depolarized from the spike threshold as some of the reported $Ca^{2+}$-only spikes.

In these simulations inactivation of the $w$ variables contribute to the repolarization knee. Future versions of the $I_{Ca}$ description may include either more than one inactivation or activation gating variables, or may use a gating variable with a more complicated state domain (e.g. more than two stable states). Also to be considered is the possibility that in these reports un-blocked outward currents also are involved, particularly because different data suggest that the repolarizing phase of $Ca^{2+}$-only spikes is quite long and without the described knee (Storm, personal communication).

With present description of $I_{calc}$ and $Ca^{2+}$ accumulation underneath the membrane the amount of $Ca^{2+}$ that flows across the membrane during regular action potentials changes $E_{Ca}$ by at most 20 millivolts (see Figure 6.8. The $Ca^{2+}$ influx during the pure $Ca^{2+}$ spike, however, is enough to change $E_{Ca}$ so that at the peak of the spike $E_{Ca}$ drops to about 10 millivolts (ref. Figure 6.8). The reduction of $E_{Ca}$ during $Ca^{2+}$-only spikes is a contributor to the reduction of $I_{Ca}$, and in fact is the limiting factor as to the magnitude of the $Ca^{2+}$-only spike. These results suggest that measurement of $E_{Ca}$ during $Ca^{2+}$-only spikes can help validate the description of $Ca^{2+}$-accumulation underneath the membrane described here or suggest alternative descriptions.

The equation for $I_{Ca}$ is -

$$I_{Ca} = \bar{g}_{Ca} s_{Ca}^2 w_{Ca}^4 (V - E_{Ca})$$

where

$$\bar{g}_{Ca} = .64 \mu S$$

For example by using hybrid clamp protocol in which the reversal potential for the spike current is measured at different points of a $Ca^{2+}$-only spike by switching from current clamp to voltage clamp.
Figure 6.1: Current clamp simulation of $Ca^{2+}$ spike. Non-linear currents include $I_{Ca}$, $I_{AHP}$, and $I_A$. 

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Figure 6.2: Steady-state curves ($x_\infty$ and $w_\infty$) for $s_{Ca}$ and $w_{Ca}$ and effective curves as would be measured by voltage-clamp experiments.

Table 6.1 lists the parameters for the $I_{Ca}$ gating variables. These are the rate functions for the activation variable, $s$, of $I_{Ca}$ -

$$\alpha_{s,Ca} = 0.1 \exp\left(\frac{(V + 24)0.5 \cdot 4 \cdot F}{RT}\right)$$

$$\beta_{s,Ca} = 0.1 \exp\left(\frac{(-24 - V)0.5 \cdot 4 \cdot F}{RT}\right)$$

These are the rate functions for the inactivation variable, $w$, of $I_{Ca}$ -

$$\alpha_{w,Ca} = 0.001 \exp\left(\frac{(V + 35)0.2 \cdot -12 \cdot F}{RT}\right)$$

$$\beta_{w,Ca} = 0.001 \exp\left(\frac{(-35 - V)0.8 \cdot -12 \cdot F}{RT}\right)$$

Figure 6.2 and Figure 6.3 show the voltage dependence on the steady-state values and the time constants for the $x_{CA}$ and $y_{CA}$ variables.

### 6.3 Slow Calcium Current - $I_{CaS}$

$I_{CaS}$ is a slow, non-inactivating current (e.g. [28]). While it has been reported that this current is a true $Ca^{2+}$ current, careful examination of the data for $I_{CaS}$ suggests that the reversal potential for this current is around 0 millivolts, implying that $I_{CaS}$ is a mixed carrier current.
Figure 6.3: Time constant curves (τ_1 and τ_2) for s_{Ca} and w_{Ca}.

<table>
<thead>
<tr>
<th>Gating Variable</th>
<th>z</th>
<th>γ</th>
<th>α_0</th>
<th>V_{1/2} (mV)</th>
<th>τ_0 (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>x (activation)</td>
<td>25</td>
<td>0.5</td>
<td>-4.0</td>
<td>-30.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 6.2: Parameters of $I_{CaS}$ Gating Variables

The small conductance of this current (0.08 μS), combined with the slow onset of its activation variable x (τ_x is reported to range from 50 to 100 milliseconds) suggest that $I_{CaS}$ has only a small functional role during repetitive firing. At this stage of the model, such a role has not been demonstrated.

The equation for $I_{CaS}$ is

$$I_{CaS} = \bar{g}_{CaS} x_{CaS}(V - E_{CaS})$$

where

$$E_{CaS} = 0$$ millivolts

$$\bar{g}_{CaS} = 0.08 \mu S$$

Table 6.2 lists the parameters for the $I_{CaS}$ gating variables. These are the rate functions for the activation variable, x, of $I_{CaS}$:

$$\alpha_{x,CaS} = 4.0 \exp \left( \frac{(V + 30)0.5 \cdot 25 \cdot F}{RT} \right)$$

$$\beta_{x,CaS} = 4.0 \exp \left( \frac{(-30 - V)0.5 \cdot 25 \cdot F}{RT} \right)$$
Figure 6.4: Steady-state curve ($x_\infty$ for $x_{CaS}$).

Figure 6.4 show the voltage dependence on the steady-state value for the $x_{CaS}$ variable.

6.4 Mechanisms Regulating $[Ca^{2+}]_{shell.1}$ and $[Ca^{2+}]_{shell.2}$

To recapitulate, there were three reasons to consider the accumulation of $Ca^{2+}$ underneath the membrane as a result of the influx of $Ca^{2+}$ currents:

1. Activation of $I_{AHP}$ is presumed to be dependent on the influx of $I_{Ca}$.

2. Activation of $I_C$ is presumed to be dependent on the influx of $I_{Ca}$.

3. The very low resting value of $[Ca^{2+}]_{in}$ (typically assumed to be about 50nM) and the low resting value of $[Ca^{2+}]_{out}$ (on the order of a few mM) implies that the influx of $Ca^{2+}$ from $I_{Ca}$ can significantly change the ratio of the extra-cellular and intra-cellular $[Ca^{2+}]$, changing $E_{Ca}$, resulting in negative feedback via reduction of the driving force for the $Ca^{2+}$ currents.

For the activation of $I_{AHP}$ and $I_C$, the observed $Ca^{2+}$ dependence is assumed to involve some mechanism between free intracellular $Ca^{2+}$ and the individual channels. The simple relationship that is used in the present model assumes that activation of both $I_{AHP}$ and $I_C$ is (partially) dependent on $Ca^{2+}$-binding gating particles in these two types of channels. The

\[ \text{Many versions of this mechanism have been proposed ([19]). In this study a fairly simple mechanism is employed.} \]
binding of \( \text{Ca}^{2+} \) to the gating particles is reversible and the behavior of the particles obey first order kinetics (Chapter 7).

The time course of \( I_C \) and \( I_{AHP} \) set some constraints on the kinetics of \( \text{Ca}^{2+} \) accumulation underneath the soma membrane. As shall be discussed in detail in Chapter 7, \( \text{Ca}^{2+} \)-mediated activation and inactivation of \( I_C \) must be sudden and complete, in accordance with the sudden onset of \( I_C \) and the apparent removal of \( I_C \) prior to subsequent spikes in a spike train. Given the sigmoidal relationship between the \( \text{Ca}^{2+} \)-dependent gating particles and the log of the concentration of \( \text{Ca}^{2+} \) (ref. Chapter 7, Figure X), this means that the \([\text{Ca}^{2+}]\) that mediates \( I_C \) must rise and then fall quickly with every spike. On the other hand, \( \text{Ca}^{2+} \)-mediated activation of \( I_{AHP} \) is gradual, getting stronger with each spike in a train, and then gradually decaying over one second or longer.

In order to accommodate these two patterns of \( \text{Ca}^{2+} \)-mediated behavior, a two-region shell, single core model was developed. In this model both \( I_{Ca} \) and \( I_C \) channels communicate with a distinct part of a shell underneath the soma surface, shell.1. \( I_{AHP} \) channels, on the other hand, communicate directly with the remainder of the soma shell, shell.2. \( \text{Ca}^{2+} \) flows between the two shell regions and between each shell region and the soma core by simple diffusion.

The physical relationship between the different soma shell regions, the relevant channels, and the soma core is illustrated in Figure 6.5. Figure 6.6 shows a view of the soma membrane surface illustrating the proposed segregation of \( \text{Ca}^{2+} \) channels and \( I_C \) and \( I_{AHP} \) channels. Figure 6.7 shows the compartmental model based on this arrangement which is used to determine the concentration of \( \text{Ca}^{2+} \) in the shell regions.

The model therefore includes a shell of thickness \( d_{shell} \) on the intracellular face of the membrane. A portion of this shell is assigned to shell.1 and the remainder is assigned to shell.2. The concentration of free \( \text{Ca}^{2+} \) in shell.1, \([\text{Ca}^{2+}]_{shell.1}\), is a function of the two \( \text{Ca}^{2+} \) currents, \( I_{Ca} \) and \( I_{CaS} \) and movement of \( \text{Ca}^{2+} \) between shell.1 and shell.2 and between shell.1 and the core. Likewise, the concentration of free \( \text{Ca}^{2+} \) in shell.2 is determined by the flow of \( \text{Ca}^{2+} \) between shell.1 and shell.2 and between shell.2 and the core. The concentration of \( \text{Ca}^{2+} \) in the core is assumed to be a constant since the volume of the core is much larger than the volume of the two shells.

The movement of \( \text{Ca}^{2+} \) between the three compartments can be described as follows. Let \( X_1, X_2, \) and \( X_3 \) equal the amount of \( \text{Ca}^{2+} \) (nanomoles) in shell.1 (compartment 1), shell.2 (compartment 2), and the core (compartment...
Figure 6.5: Diagram of localization of $I_{C_3}$, $I_{C_{AS}}$, $I_C$, and $I_{AHP}$ channels in distinct regions of the soma membrane, as postulated by the model. This scheme assumes that the $I_{C_3}$, $I_{C_{AS}}$, and $I_C$ channels are all in close proximity (i.e. shell 1), such that the immediate change in $[Ca^{2+}]$ in the vicinity of the $Ca^{2+}$ current channels when these channels conduct is sensed by the $I_C$ channels. Likewise, the $I_{AHP}$ channels are assumed to reside in a relatively distant area of the soma membrane, such that the rise in local $[Ca^{2+}]$ around these channels is delayed from the onset of the $Ca^{2+}$ currents.
Figure 6.6: Proposed segregation of $I_{C_n}$, $I_{C_nS}$, $I_C$, and $I_{AH}$ channels as seen looking onto the surface of the soma. The effective area for diffusion between the two shell regions, $A_{12}$, is determined by the total length of the dotted line in the figure as well as the depth, $d_{shell}$, of the shell. In the model $A_{12}$ was lumped with $D_{12}$ to yield an effective diffusion constant for the entire flow between the regions (see text). The empirical adjustment of this metric to give the desired kinetics is then equivalent to adjusting this length (i.e. the amount of communicating surface area). Also, the dotted line does not represent a distinct physical barrier but rather a boundary for approximating the continuous diffusion case with compartments.
Figure 6.7: 3-compartment model of $Ca^{2+}$ influx and accumulation, based on structure suggested in Figures 6.5 and 6.6. Parameters of this model are given in the text.
ment 3), respectively. In the same manner let $V_1, V_2,$ and $V_3$ be the volumes (ml) and $C_1, C_2,$ and $C_3$ be the concentrations of $Ca^{2+}$ (mM) in the three compartments. Let $J_{12}, J_{13}$ and $J_{23}$ be the flux of $Ca^{2+}$ (nanomoles per second per square cm) between shell.1 and shell.2, shell.1 and the core, and shell.2 and the core, respectively, and let $D_{ij}$ be the diffusion constant (cm per second) for the flux $J_{ij}$. The area for $Ca^{2+}$ diffusion between any two compartments $i$ and $j$ is given by $A_{ij}$ (square cm).

The change in the amount of $Ca^{2+}$ in each of the compartments is as follows:

\[
\dot{X}_1 = -J_{12}A_{12} - J_{13}A_{13} - \frac{IC_a + I_{CaS}}{2 \times 10^3 F} \\
\dot{X}_2 = J_{12}A_{12} - J_{23}A_{23} \\
\dot{X}_3 = J_{13}A_{13} + J_{23}A_{23}
\]

where $F$ is Faraday's constant and the currents are in nano-amps. The two $Ca^{2+}$ currents contribute only to the change in the amount of $Ca^{2+}$ in shell.1. There is a factor of 2 in the $Ca^{2+}$ current term since each $Ca^{2+}$ ion carries two charges, and there is a minus sign preceding this term, since the inward currents are defined as negative.

The flux of $Ca^{2+}$ from compartment $i$ to compartment $j$ is given by Fick's law, as follows:

\[
J_{ij} = D_{ij}(C_i - C_j)
\]

Since the concentration in compartment $i$, $C_i$, is given by $X_i/V_i$, then, incorporating Fick's law, the time derivative of the concentration of each compartment is as follows:

\[
\dot{C}_1 = \frac{\dot{X}_1}{V_1} = \frac{1}{V_1} \left(-A_{12}D_{12}(C_1 - C_2) - A_{13}D_{13}(C_1 - C_3) - \frac{IC_a + I_{CaS}}{2 \times 10^3 F}\right) \\
\dot{C}_2 = \frac{\dot{X}_2}{V_2} = \frac{1}{V_2} \left(A_{12}D_{12}(C_1 - C_2) - A_{23}D_{23}(C_2 - C_3)\right) \\
\dot{C}_3 = \frac{\dot{X}_3}{V_3}
\]
\[
= \frac{1}{V_3} \left( A_{13} D_{13} (C_1 - C_3) + A_{23} D_{23} (C_2 - C_3) \right)
\]

The volume of the shell is determined by \( d_{\text{shell}} \) and the surface area of the soma. \( \text{shell.1} \) is set to cover 0.1% of the soma surface, with \( \text{shell.2} \) comprising the remainder of the surface. If \( A \) equals the surface area of the soma (square cm), the areas for \( Ca^{2+} \) flow between each shell region and the core are given by:

\[
A_{13} = 0.001 A \\
A_{23} = 0.999 A
\]

The volume of each shell region is given by:

\[
V_1 = A_{13} d_{\text{shell}} \\
V_2 = A_{23} d_{\text{shell}}
\]

The volume of the core is set equal to the soma volume, since \( d_{\text{shell}} \) is much smaller than the soma radius. 

\( D_{13} \) and \( D_{23} \) are equal, since each shell region is assumed have the same proximity to the core. Let

\[
D_{13} = D_{23} = D_{\text{sh-cr}}
\]

\( D_{12} \) can be considered as equal to the previous two diffusion constants without any loss of generality since the value for \( A_{12} \) may be adjusted to allow the shells to equilibrate much faster with each other than with the (low concentration) of the core. This area is the effective diffusion area for \( Ca^{2+} \) between the (intertwined) regions of the shell. For convenience, let us define

\[
D'_{\text{sh-sh}} = A_{12} D_{12}
\]

The previous expressions can now be used to give the following equations for \( \dot{C}_1, \dot{C}_2, \) and \( \dot{C}_3 \):

\[
\dot{C}_1 = \frac{1}{d_{\text{shell}}} \left[ -\frac{D'_{\text{sh-sh}}}{0.001 A} (C_1 - C_2) - D_{\text{sh-cr}} (C_1 - C_3) + \frac{I_{Ca} + I_{CaS}}{0.001 A \times 2 \times 10^3 F} \right]
\]

\[
\dot{C}_2 = \frac{1}{d_{\text{shell}}} \left[ \frac{D'_{\text{sh-sh}}}{0.999 A} (C_1 - C_2) - D_{\text{sh-cr}} (C_2 - C_3) \right]
\]

\[
\dot{C}_3 = \frac{D_{\text{sh-cr}}}{V_3} \left[ A_{13} (C_1 - C_2) + A_{23} (C_2 - C_3) \right]
\]
Now we assume that
\[
\frac{V_3}{AD_{sh-cr}} >> 1 \text{ second}
\]
so
\[
\dot{C}_3 \approx 0
\]
and \( C_3 \) is set to a constant 50 nM. At each time step \([Ca^{2+}]_{shell,1}\) and \([Ca^{2+}]_{shell,2}\) are calculated by integrating the above differential equations.

The relevant parameters were adjusted so that, given the previously estimated kinetics for \( I_{Ca} \), during single and repetitive firing the concentrations of \( Ca^{2+} \) in the two sub-membrane compartments had the time courses and relative magnitudes discussed earlier in this section. An additional constraint was that \([Ca^{2+}]_{shell,1}\) could not change so much during either normal action potentials or, especially, \( Ca^{2+}\)-only spikes so that \( E_{Ca} \) would be reduced too quickly, wiping out the \( Ca^{2+}\) driving force before the spike was complete.

The following parameters satisfied the reported constraints:

\[
d_{shell} = 0.25\mu m
\]
\[
D'_{sh-sh} = 2.0 \times 10^{-11}(\text{cm}^3/\text{millisecond})
\]
\[
D_{sh-cr} = 4.0 \times 10^{-7}(\text{cm}/\text{millisecond})
\]

The remaining parameters needed to calculate the concentration of intracellular \( Ca^{2+} \) derive directly from the previously presented soma dimensions and the \( Ca^{2+} \) current kinetics.

This description is somewhat similar to that used in other modelling studies ([48], [2]). in particular the idea that local accumulation of \( Ca^{2+} \) in a limited space underneath the membrane can mediate other processes, and that the kinetics of the \( Ca^{2+} \) in this region is governed by first-order mechanisms.

Figures 6.8 shows how the concentration of \( Ca^{2+} \) changes in the two shell regions during a single action potential. Figures 9.19, 9.23, and 9.24 show how the concentration of \( Ca^{2+} \) changes in the two shell regions during a train of action potentials. Again in Chapter 7 the relationship between these concentrations and the activation of \( I_C \) and \( I_{AHP} \) will be defined in more detail.
6.5 Calculation of $E_{Ca}$

As mentioned earlier, $E_{Ca}$ was calculated at each time step from the Nernst equation, using the current $[Ca^{2+}]_{shell,1}$ and the fixed $[Ca^{2+}]_{out}$ as the relevant concentrations for the $E_{Ca}$ equation. The change in $[Ca^{2+}]_{shell,1}$ and $E_{Ca}$ during a single action potential is illustrated in Figure 6.8. $[Ca^{2+}]_{shell,1}$ and $E_{Ca}$ during a $Ca^{2+}$-only spike is shown in Figure 6.9. During the $Ca^{2+}$-only spike the subsequent fall of $E_{Ca}$ contributes to the reduction of $I_{Ca}$.
Figure 6.9: Top - Simulation of $Ca^{2+}$-only spike. Top Middle - $I_{Ca}$ during spike. Bottom Middle - $[Ca^{2+}]_{shell1}$ during spike. Bottom - $E_{Ca}$ during spike.
6.6 Discussion

The $Ca^{2+}$ system parameters described here are highly speculative but are based on valid physical mechanisms. The net result is that the model successfully reproduces a wide variety of $Ca^{2+}$-related behavior. Many of the parameters were developed in parallel with the development other parameters (e.g. $K^+$ current parameters, in particular those defining $I_C$ and $I_{AHP}$), and this interdependence constrains the overall problem.

For example, including the two shell regions may appear somewhat artificial; yet given the nature of $I_{Ca}$\(^3\) (as determined by $Ca^{2+}$-only spikes and other relatively independent evidence) the characteristics of these compartments are constrained by (a) the dimensions of the soma; (b) the amount of $I_{Ca}$ entering the cell during $Ca^{2+}$-only spikes, which in turn effects $E_{Ca}$, providing negative feedback; (c) the amount of $I_{Ca}$ entering the cell during regular action potentials; and (d) the a priori $Ca^{2+}$-mediated characteristics of $I_C$ and $I_{AHP}$.

In sum, modification of any one parameter typically resulted in a widespread effect due to the numerous feedback loops in the system, and these loops helped to constrain the overall modelling problem. Clearly alternative mechanisms may be suggested for the model features described here (e.g. more complicated kinetics for the $Ca^{2+}$-mediated gating particles of $I_C$ or $I_{AHP}$), but at the very least such alternatives would have to be as physically plausible as those suggested here and would also be subject to the same constraints, since these constraints are inherent in the system being modelled.

\(^3\)In the results presented here the contribution of $I_{Ca}$ to model behavior is minimal.
Chapter 7

ESTIMATING $K^+$ CURRENTS

7.1 Introduction

This chapter presents the six $K^+$ currents in the model - $I_{DR}$, $I_A$, $I_C$, $I_{AHP}$, $I_M$, and $I_Q$. We begin by reviewing the strategy for evaluating the $K^+$ currents data, and the guidelines that constrain the development of the model descriptions. Next, the classical "Delayed Rectifier" $K^+$ current, $I_{DR}$, and the so-called "A" $K^+$ current, $I_A$, are described. Following this, a brief description of the $Ca^{2+}$-mediated $w$ gating particles incorporated in the model description of $I_C$ and $I_{AHP}$ is presented, followed by the discussion of these two $Ca^{2+}$-mediated $K^+$ currents. The chapter closes with descriptions of two more $K^+$ currents, $I_M$ and $I_Q$. In this chapter the action of each of the $K^+$ currents on specific features of the single spike and/or repetitive spikes will be demonstrated, primarily with comparisons between simulations and data.

7.2 Review of Strategy for Evaluating $K^+$ Currents

As described in Chapter 2, forming a plan for building the model was not trivial, given that the quality of data for the currents varied greatly and that the action of some currents was mainly seen in concert with other currents, thereby complicating the parameter estimation for a (presumably) unique...
conductance.

The data for $K^+$ currents ranges from complete to marginal, in terms of the voltage-dependence of each current's kinetics, the absolute magnitude of each conductance, and the relationship of a given current with other factors (in particular intracellular $Ca^{2+}$). In addition, for some currents (e.g. $I_A$ and $I_C$), although a plethora of data may be available much of it is inconsistent with each other. It was very difficult to sort through this body of information and decide what data could be applied, which should be discounted, and what assumptions should be used to fill in the gaps. Often consultation with Drs. Adams and Storm provided some insight for this problem.

In order to make progress a set of references had to be chosen as a "gold standard", particularly when data from different reports were inconsistent. The primary standard that I used was the data from Storm, 1986. Using this data as a first reference had the advantage that I could both examine the original data of Dr. Storm's and, when necessary, obtain insights from him as to the implications of the data. In this chapter and others many of the comparisons between simulation and experimental data are done using data from this report.

In summary, the data for $I_{DR}$, $I_A$, $I_M$, and $I_Q$ is more complete than that for $I_C$ and $I_{AHP}$. For $I_{DR}$ and $I_A$, estimations of steady state activation/inactivation parameters from voltage clamp are available, although the associated time constant data is not as complete. Also, there is strong evidence as to these currents' specific roles from various current clamp protocols. On the other hand, much of the data used to evaluate these currents are taken under conditions in which several other currents are simultaneously active, making it difficult to separate each contribution. For $I_M$ and $I_Q$ the situation is similar in that there is good data on steady state activation (the evidence shows that these currents do not inactivate) from voltage clamp studies, with sparse estimates on the time constant parameters. However, evaluating the behavior of $I_M$ and $I_Q$ is somewhat easier than doing so for $I_{DR}$ and $I_A$ since these currents are activated in relative isolation with respect to the other currents.

In the case of $I_C$ and $I_{AHP}$, little voltage clamp data is available for either their steady state or temporal properties of any presumed activation/inactivation parameters. In addition, describing these currents is complicated by the fact that they are presumably mediated by intracellular $Ca^{2+}$. Little quantitative data is available on this interaction for either current, and there is at present no consensus among workers in this field as to
the mechanisms involved. As introduced in the previous chapter and which shall be expanded upon later, I have made the simple assumption (like that used by other workers, e.g. [48]) that $I_C$ and $I_{AHP}$ are dependent on a power of the concentration of $Ca^{2+}$ either directly beneath the membrane or in a secondary "compartment". This is a highly speculative model, as discussed in the previous chapter. The parameters of this description are based primarily on heuristics, specifically the simulation of the sAHP and the AHP that is observed in HPC. Making the situation more difficult is the fact that there are no protocols to date in which $I_C$ or $I_{AHP}$ are activated without the concomitant presence of other currents, thereby inextricably tying the behavior of any set of estimated parameters for these currents to those of other currents.

In light of the above situation, I developed the present description of the $K^+$ currents in the following way:\footnote{For each $K^+$ current, as with the $Na^+$ and $Ca^{2+}$ currents, building the description of the current began with estimating the number and type of activation and/or inactivation and/or $Ca^{2+}$-mediated activation variables governing the conductance.}

1. Begin with the data on $I_M$ and $I_Q$, with estimates on the time constants derived from the data and the HH single barrier model. For $I_Q$, its parameters did not affect the later development since this current is only activated at potentials lower than that generally considered in the simulations.

2. Develop an estimation of $I_{DR}$ based on the available voltage clamp data and the simulation of data on action potentials in which $I_{DR}$ is presumably the only repolarizing current.

3. Develop an estimation of $I_A$ based on the available voltage clamp data and simulation of action potentials in which presumably the only $K^+$ currents are $I_{DR}$ and $I_A$.

4. Re-evaluate the description of $I_M$ with simulations that reflect the contribution of $I_M$ to the action of $I_{DR}$ and $I_A$.

5. To a first approximation, the actions of $I_C$ and $I_{AHP}$ are independent of one another. $I_C$ is transient over a time span of a few milliseconds during the spike, and the evidence indicates that this a large current. On the other hand, $I_{AHP}$ activates more slowly, is small, and may last from 0.5 to several seconds. However, since both these currents are
dependent on $Ca^{2+}$ entry, their estimation was tied to the description of $I_{Ca}$ and the mechanisms regulating $[Ca^{2+}]_{\text{shell,1}}$ and $[Ca^{2+}]_{\text{shell,2}}$. Therefore, while the behavior of the $I_C$ or $I_{AHP}$ descriptions could be evaluated independently, whenever the $Ca^{2+}$ mechanisms were modified to alter one of the current's action, the effect of the modification on the other current had to be checked.

6. As the descriptions for $I_C$ and $I_{AHP}$ evolved, the impact of a given version on the behavior of the other currents had to be continually re-evaluated. At times, this feedback resulted in modifications of one of the other currents. In these cases modifications were made which stayed within the envelope of parameters that had been already established. For example, modification of some aspect of $I_C$ might indicate that the parameters of $I_{Na-trig}$ had to be changed. However, this change could not alter the aspects of $I_{Na-trig}$ that had been fixed by earlier simulations (e.g. the threshold of $I_{Na-trig}$).

As described in Chapter 5, the estimation of the $K^+$ currents involved many iterations, many of which caused re-evaluation of either the $Na^+$ currents' or $Ca^{2+}$ system parameters. The linear parameters of the model, however, were kept constant, since these parameters were established based on data from cells in which all non-linear currents had been inhibited.

As mentioned earlier, certain agents are assumed to mediate selective blocking of specific currents, in accordance with the generally accepted conclusions in the literature. These agents and their actions are summarized in Table 7.1. Any blocking agent used experimentally probably does not act with perfect selectivity, particularly given the wide variety of mechanisms that have proposed for their action (e.g. receptors-site mediated, blockage of the channel lumen, secondary block of $Ca^{2+}$-dependent $K^+$ channels via block of $Ca^{2+}$ channels). However, as a first approximation, perfect selectivity is often assumed when evaluating the data (for example application of 4-AP blocks only $I_A$, leaving the remaining currents untouched).

### 7.3 Delayed Rectifier Potassium Current - $I_{DR}$

The delayed-rectifier potassium current is similar to the classical delayed rectifier for the squid axon as described by Hodgkin and Huxley. The parameters for this current were initially taken from [12], who identified $I_{DR}$ in voltage clamp studies as a large, slowly-activating ($\sim 100$ milliseconds),
Table 7.1: Typical chemical agents used to block specific currents, as reported by different investigators. (+) indicates reduction, (++) indicates blocking, (-) indicates no effect. NA = Norepinephrine, TEA = Tetra-ethyl ammonium, 4-AP = 4-Aminopyridine, Ach = Acetylcholine, Ba = Barium, Musc = Muscarine, $Ca^{2+}$-blk = $Ca^{2+}$-blockers (e.g. Cadmium, EGTA). (1) - [16]. (2) - [39]. (4) - [30]. (3) - [43]

very-slowly inactivating ($\sim$ 3 seconds), TEA-sensitive $K^+$ current. However, the voltage clamp was only taken to -35 millivolts, so it is possible that only the beginning of the $I_{DR}$ characteristics were measured. In particular, I propose that the time constant for activation, $\tau_a$, drops to about 1-2 milliseconds at membrane potentials greater than -20 millivolts.

My description of this current is based on the data of [42], specifically the reported steady-state activation/inactivation curves. In the model $I_{DR}$ is constructed so that it may function as a major repolarizing component during the action potential. Such a role is indicated by current clamp experiments in which the spike is quickly repolarized by a TEA-sensitive component in the presence of $Ca^{2+}$ blockers. These blockers, which disable the $Ca^{2+}$ currents, presumably also disable any $Ca^{2+}$-mediated $K^+$ currents, in particular $I_C$. In summary, the main actions that I determined $I_{DR}$ served included:

- Repolarize the action potential fully when all other $K^+$ currents have been blocked
- Reduce in the presence of other repolarizing currents so that no extra hyperpolarization is observed
• Mediate the medium after-hyperpolarization (mAHP), independent of any other $K^+$ currents

• Repolarize the cell sufficiently during tonic stimulation so that repetitive firing at the threshold of $I_{Na-trig}$ could occur

• Activate independently of the width of spike since the mAHP is unaffected by the slower repolarization with 4-AP or $Ca^{2+}$ blockers

As will be discussed shortly, there is evidence that $I_C$ plays a major role in spike repolarization under certain conditions, and in fact it has been suggested that this current is the major repolarizing current in bullfrog sympathetic neurons. Since action potentials are quickly repolarized in hippocampal pyramidal neurons under conditions that would eliminate $I_C$, however, it was thought that the characteristics of $I_{DR}$ would allow it to reprise its classical role when $I_C$ has been disabled.

7.3.1 Results

This effort was successful in simulating the TEA-sensitive repolarization of the action potential, as shown in Figure 7.1. In addition, this formulation of $I_{DR}$ kinetics was able to simulate the voltage clamp results as reported by [42].

Three activation particles ($x$) were used in the formula for the $I_{DR}$ conductance so that activation of this current would be delayed after the initial rise of the action potential. A single inactivation particle ($y$) was used since it has been reported that this current does indeed inactivate ([42]). However, the time constant for $y$ is quite slow over most of the physiological range of membrane voltages (ref. Figure 7.3, so that during the action potential and afterwards, the demise of $I_{DR}$ is primarily due to removal of activation rather than inactivation. Removal of $I_{DR}$ by inactivation after the spike is consistent with the mechanism of $I_{DR}$ in the squid axon as described in [21], [20], [22], [23].

The valences and the $V_{\frac{1}{2},x,DR}$ and $V_{\frac{1}{4},y,DR}$ for $x$ and $y$ was determined by the $x_\infty$ and $y_\infty$ curves reported by [42]. In the case of the $x$ particle the third power of $x_{in,fitg}$ was matched to the [42] data.

The curve for $\tau_{x,DR}$ was skewed to the left ($\tau_{x,DR} = 0.9$) so that $I_{DR}$ would remain activated after the spike long enough to cause the mAHP, and so that $\tau_{x,DR}$ was consistent with the reported values of approximately 180 milliseconds, $V < -30$ millivolts, approximately 6 milliseconds otherwise.
The curve for $\tau_{y,DR}$ was skewed to the left ($\gamma_{y,DR} = 0.2$) in order to approximate the reported approximate value of 4 seconds for $y$ (between -50 and -30 millivolts, [42]).

On the other hand, in order that activation be independent of the width of the spike, as described above, it was necessary to set the base rate for $\tau_{x,DR}$ to 0.5 milliseconds. Later in this chapter and Chapter 10 the role of $I_{DR}$ in concert with $I_A$ and $I_C$ will be demonstrated, including examination of $I_{DR}$'s role in mediating the mAHp.

Another parameter that was important to set in regards to $I_{DR}$ was its reversal potential. The standard value of -85 mV for $E_K$ caused $I_{DR}$ to be too strong near threshold, specifically, on repolarization of the spike the $I_{DR}$ wiped out the ADP seen in the data. To reconcile this problem without significantly altering the time course and strength of $I_{DR}$ during the initial stage of the spike repolarization and the later mAHp, it was necessary to set a reversal potential for this current distinct from the general $E_K$. $E_{DR}$ was set to -73 millivolts, which proved successful in obtaining the desired behavior. This was felt to be a reasonable adjustment, since (as mentioned in Chapter 2) a given channel is not necessarily perfectly selective for one species of ion – an $E_{DR}$ of -73 mV implies that $I_{DR}$ is slightly contaminated with an occasional Na$^+$ or Ca$^{2+}$ ion hitching along with the predominantly K$^+$ flow.

All $I_{DR}$ parameters were determined at 30$^\circ$C.

The equation for $I_{DR}$ is:

$$I_{DR} = \bar{g}_{DR}\tau_{3,DR}y_{DR}(V - E_{DR})$$

where

$$\bar{g}_{DR} = 0.7 \mu S$$

$$E_{DR} = -73 mV$$
Figure 7.1: A. Action potential with Ca$^{2+}$ blockers and 4-AP in external medium. B. Current clamp simulation of (A.). C. Main currents in simulation, including $I_{DR}$, $I_{Na-trig}$, $I_{Na-rep}$, and $I_{Na-tail}$.
Figure 7.2: Steady-state curves \((x_\infty, y_\infty)\) for \(x_{DR}\) and \(y_{DR}\) and effective curves as would be measured by voltage-clamp experiments.

Table 7.2 lists the parameters for the \(I_{DR}\) gating variables. These are the rate functions for the activation variable, \(x\), of \(I_{DR}\):

\[
\begin{align*}
\alpha_{x,DR} &= 0.008 \exp \left( \frac{(V + 28) 0.95 \cdot 12 \cdot F}{RT} \right) \\
\beta_{x,DR} &= 0.008 \exp \left( \frac{(-28 - V) 0.05 \cdot 12 \cdot F}{RT} \right)
\end{align*}
\]

These are the rate functions for the inactivation variable, \(y\), of \(I_{DR}\):

\[
\begin{align*}
\alpha_{y,DR} &= 0.0004 \exp \left( \frac{(V + 45) 0.8 \cdot -9 \cdot F}{RT} \right) \\
\beta_{y,DR} &= 0.0004 \exp \left( \frac{(-45 - V) 0.2 \cdot -9 \cdot F}{RT} \right)
\end{align*}
\]

Figure 7.2 and Figure 7.3 show the voltage dependence on the steady-state values and the time constants for the \(x_{DR}\) and \(y_{DR}\) variables.

7.4 A-Current Potassium Current - \(I_A\)

\(I_A\) is a transient \(K^+\) current whose classical role, first defined for molluscan neurons, is to modulate excitability. In particular, this current is selectively blocked by 4-AP, and the convulsant action of this drug is attributed to its inhibition of \(I_A\).
Several workers have reported an $I_A$ in HPC. However, the data obtained by voltage clamp differs somewhat in different reports, and the functional effect of $I_A$ (inferred from current clamp stimulation with and without 4-AP or other $I_A$-agonists) varies considerably. In general, $I_A$ has been reported to modulate the width of the action potential and influences the excitability of the cell. References which report voltage-clamp measurements of this current include Segal and Barker, 1984 [42], Halliwell et al., 1986 [17], Zbicz and Weight, 1985 [54], Gustafsson et al., 1982 [14], and Segal et al., 1984 [43]. In addition, the action of $I_A$ on spike repolarization is reported in Storm, 1986b [47]. Some of these reports will now be summarized.

Segal et al. measured $I_A$ in cultured rat hippocampal cells (subfield not specified). Making their measurements at 21-24°C, they report that $I_A$ is half-inactivated at rest (-70 mV), has a $V_{1/2}$ for activation at about -20 to -30 mV, and (apparently) is described by $b a^4$ kinetics, where $b$ is inactivation and $a$ is activation. The maximum conductance for $I_A$ was estimated to be greater than .5 μS. The time constant of decay at (24°C) is about 24 ms, independent of voltage. The time constant to peak was within 10 ms. Application of 4-AP lowered spike threshold from -44 to -50 mV, but this procedure did not broaden the spike. ²

Interestingly, the current clamp record shown in this report demonstrated spikes with a) a high threshold (-50 to -44 millivolts, as compared to typical thresholds of about -55 millivolts) and b) small amplitudes, peaking at about +5 millivolts, as compared to typical action potential peaks of

²This is contrary to the data of [47] although it is possible that in the [43] report they did not look at the spike carefully enough.
approximately +20 millivolts. There are several implications of this data. First, the lowering in threshold with 4-AP implies that for a spike-producing stimulus that is not too large, over a voltage range of about 5 millivolts and for almost 10 ms there is little inactivation of the threshold $Na^+$ current. If this “trigger” current is the spike initiation current here, then this means that at either threshold the steady state inactivation is practically complete. For no inactivation to take place during the approach to the higher threshold spike, this means that the time constant for inactivation of the $Na^+$ current in this range must be greater than 20 ms. Likewise, the fact that 4-AP does not change the amplitude of the spike, but (probably) changes (slightly) the width of the spike implies that either a) in the control $I_A$ transiently activates and is gone during the upstroke of the spike, only to reactivate during repolarization in order to contribute to the repolarization, or b) $I_A$ is present during the entire spike, but the slower onset to the threshold as mediated by $I_A$ allows stronger activation of the $Na^+$ current, which in turn cancels out the effect of $I_A$ during the upstroke and peak of the spike. The first possibility is not likely because removal of inactivation for $I_A$ cannot take place during repolarization since steady state inactivation is complete at -50mv.

Halliwell et al. investigated CA1 cells in slices of rat and guinea pig hippocampus, measuring, at 28°C, the effects of dendrotoxin (DTX) and 4-AP. They report an $I_A$ which is sensitive to both these agents, has a very fast onset and an activation curve that starts near -60mV. The DTX-sensitive component was 0.5nA at a -40mV clamp voltage (v-holding = -76mV). Inactivation starts at about -60 mV, and was linear to -100 mV. The time constant for decay of the DTX-sensitive component was 20 ms at -40 mV, and seemed to slow at lower potentials; a faster decaying outward component which was resistant to 4AP or DTX (perhaps $I_C$) decays within about 10 ms.

Gustafsson et al measured guinea pig CA3 pyramidal cells from slice, this time at 33°C or 26°C. This report shows activation and inactivation characteristics similar to that reported for the cultured cells in Segal et al, 1984, with a peak current at -30 mV of 5 nA. A faster decaying outward component of similar size remained after application of 4AP, and this component may in fact have two components; two time constants of the faster component were measured — about 10ms and about 1sec (26°C). This might partially reflect contribution of $I_C$.

Zbicx and Weight also measured guinea pig CA3 pyramidal cells from slice, this time at either 32°C or 33°C. These workers report a decay time
constant = 200 - 400 mS. The activation to peak was within 10 mS, independent of voltage. Peak current at -35 mV was 4 nA. Threshold for activation of \( I_A \) was -55 to -50 mV. It appeared that above about -40 mV inactivation had two components, a fast one with a time constant of about 100 mS and (after about 100 mS) a slow one of about 380 mS. Lack of 4-AP-sensitive tail current below -54 mV suggests that this current deactivates very rapidly upon hyperpolarization.

Finally, Storm reports that \( I_A \) mediates a rapid onset, pre-spike transient (several hundred milliseconds) outward rectification that delays onset of repetitive firing for a narrow range of tonic stimulus strengths. This \( I_A \) does not, however, alter the frequency of firing once the spike train starts. This data implies that under the reported protocol \( I_A \) inactivates during the IR (initial ramp). These experiments were done with Mn, which presumably will block the \( Ca^{2+} \) currents or the \( Ca^{2+} \)-mediated currents. Also, [47], reports that 4-AP broadens the repolarization of single spikes, but does not effect the fAHP or the mAHP. Under some protocols addition of 4-AP (or Cd) caused a second (almost twice as broad) spike to be fired spontaneously within 10 milliseconds of the first spike. The second spike was also about 5-10 millivolts smaller and lacked a fAHP under either 4-AP or Cd. Pre-hyperpolarizations (-80mV for 900ms) enhanced the effect of 4-AP on spike repolarization; pre-depolarizations (-58mV for 900 ms) reduced effect by about half that of the hyperpolarizing protocol, implying that inactivation is not complete at -58mV. In the current study the records from this report [47], are the primary ones used to compare the simulations with actual data.

A related report describes the putative role of \( I_A \) at the post-synaptic terminal. Application of 4-AP has been described as enhancing synaptic transmission [45]. Irregular firing subsequent to the IR reported by [46] may therefore be partially due to enhancement of spontaneous EPSPs from inhibition of synaptic \( I_A \).

To summarize the so-called \( I_A \) has been reported by different investigators to:

1. Delay onset of spike
2. Raise spike threshold
3. Mediate transient "initial ramp" (strong outward rectification) prior to initial spike in response to tonic stimulus without strong role during later spikes (particularly frequency of later spikes)
4. Selectively modulate repolarization of single spike without effecting mAHP or sAHP and have a minimal effect on spike amplitude

The data includes fairly complete measurement of the steady state activation and inactivation curves, but there is not complete data on the voltage dependence of the appropriate time constants. Current clamp data showing the previously mentioned effects of $I_A$ are available, however. Therefore in order to simulate this current I began with the reported steady-state curves and then derived functions for the time constants that were consistent with the voltage clamp data and that reproduced the current clamp results.

One of the key features of this current that had to be matched in the simulations was the fact that during the spike the appearance of the $I_A$ was exquisitely timed to influence just the main part of the repolarizing phase. As previously mentioned, experiments in which spikes were elicited with and without 4-AP showed that blockage of $I_A$ did not influence the ADP or mAHP ([47]), thus indicating that the $I_A$ was fully deactivated/inactivated within a few milliseconds of its onset.

7.4.1 Results

The results for the derived kinetics are shown in Figure 7.9, which includes the reported steady state curves for the activation variable $x$ and the inactivation variable $y$.

The channel was configured with three activation gating particles ($x$) to obtain a delay in activation with depolarization. The effect of $I_A$ is seen only 1 to 2 milliseconds after the peak of the spike. Raising the power of $x$ was necessary to obtain the required delay consistent with the position of $x_\infty$ curve on the voltage axis, as reported by [42].

On the other hand, given the $y_\infty$ curve in the same report, no delay was necessary for the inactivation of $I_A$, and only one $y$ variable was used in the channel formulation.

Figure 7.4 illustrates the contribution of $I_A$ on the repolarization of the single action potential in the presence of Ca$^{2+}$ blockers (which will inhibit the contribution of $I_C$ on the repolarization) and without these blockers. The experimental data was taken by measuring the response with and without 4-AP.

Figures 7.5, 7.6, and 7.7 illustrate the data from [46] and simulations of this data which demonstrate the role of $I_A$ in mediating the IR prior to repetitive firing. In the simulations the IR is very sensitive to stimulus
strength, and that beyond a narrow range this response is quite diminished. This characteristic is consistent with data taken under similar conditions (Storm, personal communication).

The reported action of $I_A$ related to the increased excitability of the cell with the addition of 4-AP is shown in Figure 7.8. In this figure recordings from Segal et al are compared with simulations of similar protocols. The delay in firing in the cell without 4-AP is similar to that demonstrated earlier with the simulations of Storm’s data.

All $I_A$ parameters were determined at 30°C.

The equation for $I_A$ is:

$$I_A = 0.5 x_A^3 y_A (V - E_K)$$

where

$$\bar{g}_A = 0.5 \mu S$$

Table 7.3 lists the parameters for the $I_A$ gating variables. These are the rate functions for the activation variable, $x$, of $I_A$ -

$$\alpha_{x,A} = 0.2 \exp \left( \frac{(V + 52)0.8 \cdot 3.5 \cdot F}{RT} \right)$$

$$\beta_{x,A} = 0.2 \exp \left( \frac{(-52 - V)0.2 \cdot 3.5 \cdot F}{RT} \right)$$

These are the rate functions for the inactivation variable, $y$, of $I_A$ -

$$\alpha_{y,A} = 0.0015 \exp \left( \frac{(V + 72)0.6 \cdot -7 \cdot F}{RT} \right)$$

$$\beta_{y,A} = 0.0015 \exp \left( \frac{(-72 - V)0.4 \cdot -7 \cdot F}{RT} \right)$$

Figure 7.9 and Figure 7.10 show the voltage dependence on the steady-state values and the time constants for the $x_A$ and $y_A$ variables.
Figure 7.4: Current clamp data of action potentials which demonstrate the role of $I_A$ during repolarization. A. Action potential with and without 4-AP. B. Current clamp simulation of (A.). Non-linear currents here include $I_A$, $I_{DR}$, $I_C$, $I_{Ca}$, $I_{Na-trig}$, $I_{Na-rep}$, and $I_{Na-tail}$. C. Action potential with and without 4-AP ($Ca^{2+}$ blockers added). D. Current clamp simulation of (C.). Non-linear currents here include $I_A$, $I_{DR}$, $I_{Na-trig}$, $I_{Na-rep}$, and $I_{Na-tail}$.
Figure 7.5: Current clamp records (Storm, 1986a) of repetitive firing in response to tonic, small amplitude current stimulus, with and without application of 4-AP. Mn added. With 4-AP on the left; control on the right. Each stimulus began with a long hyperpolarizing prepulse, which presumably removed most of the resting inactivation of $I_A$. 
Figure 7.6: Current clamp simulation of repetitive firing in response to tonic, small amplitude current stimulus, with and without $I_A$. No $Ca^{2+}$ currents. Simulations with $I_A$ are on the left. Without $I_A$ on the right. Each stimulus begins with a 20 ms -0.5 nA pulse (hyperpolarizing) in order to remove most of the resting inactivation of $I_A$. These simulations follow from the records shown in Figure 7.5.
Figure 7.7: Record of $I_A$ during response to 0.33 nA stimulus, as shown in previous figure. The pre-threshold activation of $I_A$ serves to delay the initial spike.
Figure 7.8: Current clamp data of action potentials which demonstrate the role of $I_A$ during strong tonic stimulus. Left - Record of successive spikes in response to tonic stimulus before and after application of 4-AP ([43]). Note the advance of spike and slight lowering of threshold with application of 4-AP. Right - Current clamp simulation of record on left. Stimulus is 2 nA.

Figure 7.9: Steady-state curves ($x_\infty$ and $y_\infty$) for $x_A$ and $y_A$ and effective curves as would be measured by voltage-clamp experiments.
Figure 7.10: Time constant curves ($\tau_x$ and $\tau_y$) for $x_A$ and $y_A$.

7.5 $Ca^{2+}$-Mediation of $K^+$ Currents by $Ca^{2+}$-binding Gating Particle $w$

In order to cause $I_C$ and $I_{AHP}$ to be mediated by intracellular $Ca^{2+}$, I incorporated a $Ca^{2+}$-binding gating particle in the expressions for both of these currents. Several workers have postulated mechanisms for such an interaction between intracellular $Ca^{2+}$ and different ion channels, ranging from complex multi-state kinetic models based on experimental data to very simple descriptions for modelling studies ([48]).

In light of the paucity of quantitative data on such mechanisms in HPC, my goals for the description of a putative, generic $Ca^{2+}$-binding gating particle were as follows:

- Relationship between $Ca^{2+}$ concentration and particle activation allowing for non-degenerate kinetics considering the range of $Ca^{2+}$ concentrations during various cell responses.
- Binding kinetics based on a simple but reasonable model.
- Kinetic description that could be easily modified to yield significantly different behavior, that is a description that could be modified to suit a wide range of desired behaviors.

To this end the following description for a $Ca^{2+}$-binding gating particle, $w$, was used. Each $w$ particle can be in one of two states, open or closed, just as the case for the Hodgkin-Huxley-like voltage-dependent activation...
and inactivation gating particles. Each $w$ particle is assumed to have $n$ $\Ca^{2+}$ binding sites, all of which must be bound in order for the particle to be in the open state. Binding is cooperative in a sense that reflects the two states available to a given particle, i.e. either a particle has no $\Ca^{2+}$ ions bound to it, and therefore it is in the closed state, or all $n$ binding sites are filled, and the particle is in the open state. The state diagram for this reaction is as follows:

$$w_{\text{closed}} + n \Ca^{2+}_{\text{in}} \overset{\alpha}{\underset{\beta}{\rightleftharpoons}} w_{\text{open}}^{*}$$

where the $*$ notation means that the particle is bound to all $n$ (intracellular) $\Ca^{2+}$ ions. $\alpha$ and $\beta$ are the forward and backward rate constants, respectively.

This scheme results in the following differential equation for $w$, where now $w$ is the fraction of particles in the open state, assuming that the concentration of $\Ca^{2+}$ is large enough that the reaction does not significantly change the store of intracellular $\Ca^{2+}$:

$$\frac{dw}{dt} = \alpha (1 - w)[\Ca^{2+}]_{\text{in}}^{n} - \beta w$$

The steady state value for $w$ (the fraction of particles in the open state) as a function of the intracellular $\Ca^{2+}$ concentration is then:

$$w_{\infty} = \frac{\alpha[\Ca^{2+}]_{\text{in}}^{n}}{\alpha[\Ca^{2+}]_{\text{in}}^{n} + \beta}$$

The time constant for the differential equation is:

$$\tau_{w} = (\alpha[\Ca^{2+}]_{\text{in}}^{n} + \beta)^{-1}$$

The order of the binding reaction, $n$, that is the number of $\Ca^{2+}$ binding sites per $w$ particle, determines the steepness of the previous two expressions, as a function of $[\Ca^{2+}]_{\text{in}}$. Given the constraints on the range for $[\Ca^{2+}]_{\text{shell,1}}$ and $[\Ca^{2+}]_{\text{shell,2}}$ during single and repetitive firing, $n$ was set to three for both the $I_C$ $w$ particle and the $I_{AHP}$ $w$ particle. On the other hand, as shall be presented shortly, the range of $\Ca^{2+}$ concentrations for which the $I_{AHP}$ $w$ particle is activated is set to about one order of magnitude lower than that for the $I_C$ $w$ particle, since $I_C$ was exposed to the larger $[\Ca^{2+}]_{\text{shell,1}}$.
7.6 C-Current Potassium Current - $I_C$

$I_C$ is a $Ca^{2+}$-dependent $K^+$ current that plays a large role during an single, isolated action potential. It has been proposed that this current, which is apparently inhibited when $Ca^{2+}$ blockers are added, is the underlying current of the fast-afterhyperpolarization (fAHP) which is observed in single spikes and (sometimes) to a lesser degree after spikes of repetitive trains. Studies of bullfrog sympathetic ganglion neurons suggest that $I_C$ is a major repolarizing current during the spike in these cells (Adams et al.

Limited voltage clamp data was available for this current (Segal and Barker, Madison et al), and in many of the reports measurements of a reputed $I_C$ was likely corrupted by $I_{AHP}$, since both are identified by, among other methods, sensitivity to $Ca^{2+}$ blockers.

On the other hand, [47] has demonstrated well the role of $I_C$ during the fast repolarization of the action potential, distinct from the much slower role of $I_{AHP}$ as a hyperpolarizing current. In addition, $I_C$ is selectively blocked with TEA at concentrations much lower than that required to block $I_{DR}$. Storm has tentively isolated the role of $I_C$ in current clamp protocols, and this data was the primary standard I used in the estimation of the $I_C$ parameters.

In my simulations of the role of $I_C$ the challenge can be summarized as follows:

- Formulate the kinetics of $I_C$ so that the fAHP is reproduced
- Devise a $Ca^{2+}$ and voltage dependence for $I_C$ such that $I_C$ is activated significantly only during spike repolarization.
- Adjust $I_{DR}$ parameters so that activation of $I_C$ does not inhibit activation of $I_{DR}$, otherwise the presumably fast inactivation of $I_C$ would allow the residual inward currents to immediately depolarize the cell following the fAHP. Also the mAHP, which is mediated by $I_{DR}$, is insensitive to $Ca^{2+}$-blockers, further indicating that activation of $I_{DR}$ is not affected by the faster spike repolarization mediated by $I_C$.

Although the estimation of the $I_C$ necessitated the re-evaluation of every other current to a greater or lesser degree, not only was the estimation of $I_C$ dependent on the characteristics of $I_{DR}$ and vica versa, but also the dependence of $I_C$ on $Ca^{2+}$ meant that estimation of the $I_C$ and $[Ca^{2+}]_{shell.1}$-system parameters took into account the behavior of $I_C$. 

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The first step in analyzing $I_C$ was estimating with simulations the current that is necessary to generate the observed fAHP. The results of these simulations indicating that $I_C$ had to have two salient characteristics - very fast activation/inactivation and large maximum conductance (on par with $I_{DR}$). In fact, the time course of the fAHP-producing current was a sharp and large spike reminiscent of the $Na^+$ currents that initiated the action potential.

The characteristics that I have derived for $I_C$ are different from those proposed in the literature, in particular the kinetics described here are somewhat faster than those reported elsewhere. However, as mentioned earlier, the interpretations of the voltage clamp data for $I_C$ is possibly complicated by the activation of $I_{AHP}$, which is also $Ca^{2+}$-dependent. In fact, the simulations described here indicate that if $I_C$ is the current responsible for the fAHP, then $I_C$ must have the fast activation/inactivation/deactivation kinetics proposed here.

7.6.1 Results

The $Ca^{2+}$-dependence of $I_C$ was constructed so that after only a small delay the influx of $Ca^{2+}$ into shell.1 would activate $I_C$. The conductance of the $I_C$ channel was therefore mediated in part by a single $w$ particle, implying that each $I_C$ channel has three independent $Ca^{2+}$-binding sites on a single gating particle, each of which, in turn, must be bound to $Ca^{2+}$ in order for the channel to conduct.

The very fast turn off of $I_C$ necessary to obtain a significant ADP after the fAHP was accomplished by incorporating four $x$ particles, by making the steady state curve for activation steep and centered only a few millivolts above the resting potential, and by making the time constant for $x$ very fast, especially when the $x_\infty$ curve goes to zero. As the spike is repolarized past about -60 millivolts the $x$ particles quickly relax to their closed state, shutting off $I_C$ leaving a minimal tail that, if larger, could otherwise wipe out the ADP.

A voltage-dependent inactivation particle, $y$, was included since the available voltage clamp data indicate that $I_C$ is a transient current at depolarized potentials, with a time constant on the order of greater than several milliseconds. Simulations indicate, however, that during normal activity removal of $I_C$ is accomplished by de-activation of either the $x$ or the $w$ particles.

In summary, the turning on of $I_C$ is mediated by influx of $Ca^{2+}$; removal
of $I_C$ is mediated by the repolarization of the spike. During the spike, the $x$ particles turn on first with the depolarization of the beginning of the spike. As the $I_{Ca}$ channels open (slower than the $I_{Na-trig}$ and $I_{Na-rep}$ channels), the subsequent influx of $Ca^{2+}$ into shell.1 raises $[Ca^{2+}]_{shell.1}$ to turn on the $w$, turning on $I_C$. As the cell repolarizes, the four $x$ particles close quickly, shutting off $I_C$ abruptly enough to allow the observed ADP. Soon after the spike (within 30 ms) $[Ca^{2+}]_{shell.1}$ drops as $Ca^{2+}$ flows into shell.2 and the core, thereby shutting off $w$ so that activation of $x$ on the upstroke of a subsequent spike does not turn on $I_C$ too soon (see Figure 9.27).

Figure 7.11 illustrates the contribution of the fully activated $I_C$ to the repolarization of the action potential and how the fAHP is eliminated when $I_C$ is blocked. In the next section an expanded view of this simulation will be presented.
Figure 7.12: Left – Expanded view of the action potential with and without $Ca^{2+}$ blockers (Storm), showing spike broadening with $Ca^{2+}$ blockers. Right – Simulation of protocol.
Table 7.4: Parameters of $I_C$ Gating Variables. * = ($mS^{-1}mM^{-3}$), ** = ($mS^{-1}$)

\begin{center}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Gating Variable & $z$ & $\gamma$ & $\alpha_0$ & $V_{1/2}$ (mV) & $\tau_0$ (ms) & $\alpha_{C_a}$ & $\beta_{C_a}$ \\
\hline
$x$ (activation) & 25 & 0.2 & 0.007 & -65.0 & 0.25 & - & - \\
$y$ (inactivation) & -20 & 0.2 & 0.003 & -60.0 & 15 & - & - \\
w ($Ca^{2+}$-activation) & - & - & - & - & 1000 & 0.125 & - \\
\hline
\end{tabular}
\end{center}

The equation for $I_C$ is:

$$I_C = \bar{g}_C \cdot x_C^4 \cdot y_C \cdot w_C \cdot (V - E_K)$$

where

$$\bar{g}_C = 0.4 \mu S$$

Table 7.4 lists the parameters for the $I_C$ gating variables. These are the rate functions for the activation variable, $x$, of $I_C$:

$$\alpha_{x,C} = 0.007 \exp \left( \frac{(V + 65)0.2 \cdot 25 \cdot F}{RT} \right)$$

$$\beta_{x,C} = 0.007 \exp \left( \frac{(-65 - V)0.8 \cdot 25 \cdot F}{RT} \right)$$

These are the rate functions for the activation variable, $y$, of $I_C$:

$$\alpha_{y,C} = 0.003 \exp \left( \frac{(V + 60)0.2 \cdot 20 \cdot F}{RT} \right)$$

$$\beta_{y,C} = 0.003 \exp \left( \frac{(-60 - V)0.8 \cdot 20 \cdot F}{RT} \right)$$

Figure 7.13 and Figure 7.14 show the voltage dependence on the steady-state values and the time constants for the $x_C$ and $y_C$ variables.

As mentioned above, each $w$ particle was assumed to have three non-competitive $Ca^{2+}$ binding sites, all of which were either empty (corresponding to the closed state) or filled (corresponding to the open state). Figure 7.15 shows the dependence of the steady-state value of the $w_C$ variable on $\left[Ca^{2+}\right]_{shell}$. Figure 7.16 shows the dependence of the time constant for the $w_C$ variable on $\left[Ca^{2+}\right]_{shell}$. 

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Figure 7.13: Steady-state curves ($x_\infty$ and $y_\infty$) for $x_C$ and $y_C$ and effective curves as would be measured by voltage-clamp experiments.

Figure 7.14: Time constant curves ($\tau_x$ and $\tau_y$) for $x_C$ and $y_C$.

Figure 7.15: Relation between $w_\infty$ and $[Ca^{2+}]_{shell}$ for $w_C$. 

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Figure 7.16: Relation between $\tau_W$ and $[Ca^{2+}]_{shell}$ for $w_C$.

7.7 AHP Potassium Current - $I_{AHP}$

$I_{AHP}$ is a slow, $Ca^{2+}$-mediated $K^+$ current that underlies the long after-hyperpolarization (AHP). Typically the AHP is about 1 to 2 millivolts and lasts from 0.5 - 3 seconds after a single spike. Adding $Ca^{2+}$ blockers or noradrenaline to the extracellular medium eliminates the AHP, and likewise markedly reduces the cell’s accommodation to tonic stimulus.

Since most of the data on the proposed $I_{AHP}$ is derived from various current clamp protocols, the model description of this current is based on that used in other models (Koch and Adams, 1986) and from heuristics derived from the properties of other currents, in particular $I_C$, and $I_{DR}$. The important relationship between the $I_{AHP}$ and $I_{DR}$ parameters arose when I attempted to simulate both the mAHP (mediated by $I_{DR}$) and the AHP according to data from Storm (1). In addition, since $I_{AHP}$ is dependent on $Ca^{2+}$ entry, the derivation of this current and the dynamics of $[Ca]_{shell.1}$ and $[Ca]_{shell.2}$ was done simultaneously. In fact, it was determined that in order for the activation of $I_{AHP}$ to be delayed from the onset of the spike, it was necessary to introduce the second intracellular space (shell) that was described in Chapter 6. Such a relationship between $Ca^{2+}$ influx and the subsequent delayed activation of $I_{AHP}$ has been suggested in the literature ([30]).

7.7.1 Results

I propose that the conductance underlying $I_{AHP}$ is dependent both on $Ca^{2+}$ and voltage. The $Ca^{2+}$ dependence of this current is clearly demonstrated
since the AHP is removed when $Ca^{2+}$ blockers are added, and construction of a reasonable model of $Ca^{2+}$ dynamics such that $I_{AHP}$ may be dependent on this is possible.

The mechanism that I use for $Ca^{2+}$-mediation of $I_{AHP}$ is similar to that for $I_C$, that is the $I_{AHP}$ channel includes a single $Ca^{2+}$-binding $w$ particle, with the same binding reaction as shown in Equation x.

Voltage-clamp studies ([30]) indicate that there is no voltage-dependent activation of $I_{AHP}$, however. This puts a greater constraint on the $Ca^{2+}$-mediated mechanism for this current since the activation necessary to underly the long, small hyperpolarization after a single spike is significantly less than that required to squelch rapid spikes after some delay in response to tonic stimulus. In particular, these requirements provided rather restricted constraints on the buildup of $Ca^{2+}$ during each spike in region of the $I_{AHP}$ channels, shell.2, and likewise the dependence of the $I_{AHP}$ $w$ particle on this localized concentration of $Ca^{2+}$.

On the other hand I have included two inactivation gating particles, $y$ and $z$. The rationale for the $y$ particle is based on two pieces of evidence. First, it has been reported that $Ca^{2+}$ spikes are insensitive to noradrenaline in protocols where $I_{DR}$ and $I_A$ have been blocked by TEA and 4-AP, respectively (Segal and Barker). The fact that these spikes are unchanged with the addition of noradrenaline implies that under this protocol $I_{AHP}$ is inactivated by some other mechanism, since presumably $I_{AHP}$ has not been disabled. Since the protocol involves a long (approximately 30 milliseconds) depolarization of the cell before the $Ca^{2+}$ spike, it was possible to include an inactivation particle for $I_{AHP}$ that was (a) fast enough to disable $I_{AHP}$ under these conditions, but (b) was slow enough so that normal spiking did not cause the $y$ particle to change states.

A second indication for the voltage-dependent inactivation particle $y$ is consistent with the previous evidence, that is the amplitude and rate of rise of action potentials singly or in trains appears independent of the presence $I_{AHP}$. In particular, the size of the $I_{AHP}$ conductance necessary to repress repetitive firing is large enough to significantly effect the spike once threshold is achieved if this conductance remained during the spike. Such a role for $I_{AHP}$ has not been demonstrated. $y$ therefore causes $I_{AHP}$ to shut off during an action potential so that this current does not reduce the amplitude of the spike.

The second inactivation particle, $z$, was included to account for the delayed peak seen in the large afterhyperpolarization that occurs after a long (greater than 100 ms) stimulus (Madison and Nicoll, 1982 and others). At
rest, $z$ is partially closed. With a large, lengthy hyperpolarization the $z$ particle becomes more open, thereby slowly increasing $I_{AHP}$ and the magnitude of the sAHP, until the $Ca^{2+}$ in shell.2 eventually drains down to its resting level and subsequently shutting off $w$. The time constant for $z$ was set very slow above rest so that it did not change appreciably during firing. Below about -75 mV, however, the time constant approaches 120 milliseconds so that the desired role of $z$ during the sAHP is obtained.

No voltage-dependence for $I_{AHP}$ has been noted in the literature. However, the dependence of $I_{AHP}$ on $Ca^{2+}$ influx may have precluded voltage-clamp experiments which might verify the voltage-dependencies indicated by the simulations.

With the present formulation for $I_{AHP}$, this current plays an important role during repetitive firing by shutting off the spike train after several hundred milliseconds. This occurs primarily through the dependence of $I_{AHP}$ on $[Ca]_{shell.2}$, which slowly increases during repetitive firing. Eventually the rise of $[Ca]_{shell.2}$ causes $I_{AHP}$ to provide sufficient outward rectification for counter-acting the stimulus current and thus stop the cell from firing (Figure 7.19). The fact that $I_{AHP}$ is strongly activated by this protocol is indicated by the long hyperpolarization at the end of the stimulus (Madison and Nicoll, 1982, and see simulation of their results in Figure 7.19). Madison and Nicoll, 1982 [32] report that noradrenaline blocks accommodation by selectively blocking $I_{AHP}$.

The characteristics demonstrated by the model $I_{AHP}$ are in qualitative agreement with many of the characteristics reported in the literature (e.g. [30], [11]), including the increased activation of $I_{AHP}$ with increasing numbers of spikes in a single train, delayed activation from onset of $Ca^{2+}$ influx, the role of $I_{AHP}$ in modulating repetitive firing, time constant for inactivation/deactivation of greater than one second, the apparent voltage insensitivity (the transition of $y$ and $z$ with sub-threshold depolarization is slow, and once $x$ is activated deactivation takes several seconds.

The action of $I_{AHP}$ resulting in the sAHP is illustrated in Figure 7.17. Expanded view of this figure (same simulation as Figure 7.11) is shown in Figure 7.18.

The equation for $I_{AHP}$ is

$$I_{AHP} = g_{AHP}^2 z_{AHP} w_{shp} (V - E_K)$$

where
Figure 7.17: Top - Repolarization of the action potential with and without $Ca^{2+}$ blockers (Storm). Note absence of sAHP when $Ca^{2+}$ blockers are added. Bottom - Simulation of protocol.
Figure 7.18: A. Simulation of Figure 7.11 showing entire action potential, with and without \( Ca^{2+} \) blockers. B. \( I_C \), \( I_{DR} \) and \( I_A \) when \( Ca^{2+} \) blockers absent. C. \( I_{DR} \) and \( I_A \) when \( Ca^{2+} \) blockers present. D. \( I_{AHP} \) and \( I_{DR} \) with and without \( Ca^{2+} \) blockers. \( I_C \) and \( I_{DR} \) are the principle repolarizing currents when there are no \( Ca^{2+} \) blockers, and \( I_{DR} \) increases when \( I_C \) is disabled. Also the fast time course of \( I_C \) allows it to produce the sharp \( fAHP \).
Figure 7.19: Influence of $I_{AHP}$ on accommodation. Top - Repetitive firing in response to tonic depolarizing stimulus with and without noradrenaline [32]. Middle - Simulation of above responses. Bottom - $I_{AHP}$ during simulations. When $I_{AHP}$ is enabled there is a gradual rise in this conductance with each spike until subsequent spikes are blocked.
Table 7.5: Parameters of $I_{AHP}$ Gating Variables. $\; * = (mS^{-1} M^{-3}), \; ** = (mS^{-1})$

<table>
<thead>
<tr>
<th>Gating Variable</th>
<th>$z$</th>
<th>$\gamma$</th>
<th>$\alpha_0$</th>
<th>$V_{1/2}$ (mV)</th>
<th>$\tau_0$ (ms)</th>
<th>$\alpha_{Ca}^*$</th>
<th>$\beta_{Ca}^{**}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$y$ (inactivation)</td>
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<td>0.8</td>
<td>0.015</td>
<td>-50.0</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$z$ (inactivation)</td>
<td>-12</td>
<td>0</td>
<td>0.0002</td>
<td>-72.0</td>
<td>120.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$w$ ($Ca^{2+}$-activation)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$10^5$</td>
<td>0.005</td>
</tr>
</tbody>
</table>

$g_{AHP} = 0.35 \mu S$

Table 7.5 lists the parameters for the $I_{AHP}$ gating variables. These are the rate functions for the activation variable, $x$, of $I_{AHP}$:

$$
\alpha_{y,AHP} = 0.015 \exp \left( \frac{(V + 50)0.8 \cdot -15 \cdot F}{RT} \right)
$$

$$
\beta_{y,AHP} = 0.015 \exp \left( \frac{(-50 - V)0.2 \cdot -15 \cdot F}{RT} \right)
$$

These are the rate functions for the activation variable, $y$, of $I_{AHP}$:

$$
\alpha_{z,AHP} = 0 (\gamma = 0)
$$

$$
\beta_{z,AHP} = 0.0002 \exp \left( \frac{(-72 - V) \cdot -12 \cdot F}{RT} \right)
$$

Figure 7.20 and Figure 7.21 show the voltage dependence on the steady-state values and the time constants for the $x_{AHP}$ and $y_{AHP}$ variables.

Again, each $w$ particle was assumed to have three non-competitive $Ca^{2+}$ binding sites, all of which were either empty (corresponding to the closed state) or filled (corresponding to the open state). Figure 7.22 shows the dependence of the steady-state value of the $w_{AHP}$ variable on $[Ca^{2+}]_{shell,2}$. Figure 7.23 shows the dependence of the time constant for the $w_{AHP}$ variable on $[Ca^{2+}]_{shell,2}$.

### 7.8 M-Current Potassium Current - $I_M$

$I_M$ is a small persistent $K^+$ current that is activated near rest and that is selectively inhibited by muscarinic agonists ([16]). This current has been
Figure 7.20: Steady-state curves \( (x_\infty, y_\infty) \) for \( x_{AHP} \) and \( y_{AHP} \) and effective curves as would be measured by voltage-clamp experiments.

Figure 7.21: Time constant curve \( (\tau_x, \tau_y) \) for \( x_{AHP} \) and \( y_{AHP} \).

Figure 7.22: Relation between \( \omega_x \) and \( [Ca^{2+}]_{shell.2} \) for \( w_{AHP} \).
reported to contribute to cell excitability and to the mediation of repetitive firing in different species [1].

There is evidence for massive cholinergic projection from the medial septum to the hippocampus ([16]. Kuhar, in [24], [25]) so the mediation of HPC behavior by cholinergic agonists via specific currents is potentially a very important mechanism for modulation of either single HPCs or local populations of HPCs.

### 7.8.1 Results

For the model the steady state parameters of the activation variable of \( I_M \), \( x \), were inferred from [16]. Data on the temporal properties of this current is sparse. The time constant for activation for \( I_M \) has been estimated at being between 50 and 300 milliseconds within 20 millivolts of rest. The \( Q_{10} \) for \( I_M \) has been estimated at 5 ([16]). This means that the \( I_M \) is much faster at physiological temperature than would be indicated by the reported data, which was measured at 23°C. Since the activation is slow and no clear recordings of the time course of activation are available, I included a single activation particle, \( x \), in the formula for the \( I_M \) conductance.

As mentioned in Chapter 3, originally I assumed that at the resting potential the only conductances that were open were linear, and therefore \( E_{\text{leak}} \) was set equal to \( E_{\text{rest}} \) (= -70mV). However, the data suggests that at rest a small amount of \( I_M \) is activated. In the model, then, inclusion of \( I_M \) shifted \( E_{\text{rest}} \) slightly from -70.0 mV to -72.3 mV.

Current clamp simulations suggest that \( I_M \) has two roles: 1) changing

---

Figure 7.23: Relation between \( \tau_w \) and \([Ca^{2+}]_{shell.2}\) for \( w_{AHP} \).
### Gating Variable $z$ (activation)

<table>
<thead>
<tr>
<th>Gating Variable</th>
<th>$z$</th>
<th>$\gamma$</th>
<th>$\alpha_0$</th>
<th>$V_{1/2}$ (mV)</th>
<th>$\tau_0$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x$</td>
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<td>0.5</td>
<td>0.0015</td>
<td>-45.0</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 7.6: Parameters of $I_M$ Gating Variable

The current stimulus threshold for $I_{Na-trig}$ mediated spikes, and 2) modulating repetitive firing in response to tonic stimulus. The first characteristic comes about since $I_M$ is partially activated at the resting potential, and therefore decreases the input impedance of the cell. Figure 7.24 illustrates that blocking $I_M$ increases the firing frequency of the cell in response to tonic stimulus. However, this increase is much less than that usually reported for cholinergic modification of HPC firing. This result implies that the major effector of the cholinergic response is $I_{AHP}$, as has been demonstrated earlier.

The equation for $I_M$ is:

$$I_M = \bar{g}_M \cdot x_M (V - E_K)$$

Table 7.6 lists the parameters for the $I_M$ gating variable.

These are the rate functions for $I_M$:

$$\alpha_{x,M} = 0.0015 \exp\left(\frac{(V + 45)0.5 \cdot 5 \cdot F}{RT}\right)$$

$$\beta_{x,M} = 0.0015 \exp\left(\frac{(-45 - V)0.5 \cdot 5 \cdot F}{RT}\right)$$

Figure 7.25 and Figure 7.26 show the voltage dependence on the steady-state values and the time constants for the $x_M$ and $y_M$ variables.

### 7.9 Q-Current Potassium Current - $I_Q$

$I_Q$ is a small current that is activated when the cell is hyperpolarized with respect to resting potential. The reversal potential for the $I_Q$ has been estimated at approximately -80 millivolts. Since $E_K$ is about -90 millivolts, this current might be due to a mixed conductance.

At the present time the functional characteristics of $I_Q$ have not been investigated.
Figure 7.24: Influence of removal of $I_M$ on accommodation. $I_{AHP}$ blocked to allow immediate repetitive firing. Stimulus 1.0 nA for 300 milliseconds. Top - $I_M$ enabled. Bottom - $I_M$ disabled. Disabling $I_M$ increases the firing rate by about 7% in this protocol.
Figure 7.25: Steady-state curve ($x_\infty$) for $x_M$.

Figure 7.26: Time constant curve ($\tau_x$) for $x_M$. 

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Gating Variable | \( z \) | \( \gamma \) | \( \alpha_0 \) | \( V_1 \) (mV) | \( \tau_0 \) (ms) \\
---|---|---|---|---|---
\( x \) (activation) | 15 | 0.98 | 0.0003 | -45.0 | 6.0 \\

Table 7.7: Parameters of \( I_Q \) Gating Variable

7.9.1 Results

The current description for \( I_Q \) is based solely on the data from [16].

The equation for \( I_Q \) is:

\[
I_Q = \bar{g}_Q x_Q (V - E_K)
\]

where

\[
\bar{g}_Q = 0.002 \mu S
\]

Table 7.7 lists the parameters for the \( I_Q \) gating variable.

These are the rate functions for the activation variable, \( x \), of \( I_Q \):

\[
\alpha_{x,Q} = 0.0003 \exp \left( \frac{(V + 45)0.98 \cdot 15 \cdot F}{RT} \right)
\]

\[
\beta_{x,Q} = 0.0003 \exp \left( \frac{(-45 - V)0.02 \cdot 15 \cdot F}{RT} \right)
\]

Figure 7.27 and Figure 7.28 show the voltage dependence on the steady-state values and the time constants for the \( x_Q \) and \( y_Q \) variables.

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Figure 7.28: Time constant curve ($\tau_x$) for $x_Q$. 

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Chapter 8

VOLTAGE CLAMP SIMULATIONS

8.1 Introduction

Simulating voltage clamp data was an important verification of the parameters derived for both currents and the linear structure of the model. In particular, these simulations estimated how much the current flow due to the unclamped dendrites contributed to errors in parameters derived with voltage clamp protocols.

8.2 Non-Ideal Space Clamp

The non-zero $R_i$ means that a voltage clamp applied at the soma will not clamp the dendrites ideally. This distortion of the clamp signal is shown in Figure 8.1, where the soma has been clamped to -50 mV from a resting potential of -70 mV for 50 milliseconds. The distortion of the clamp voltage has two components. First, the rise time of the clamp signal gets progressively longer further down the dendrite. Second, the final voltage reached is lower the further down the dendrite.

If we assume that the non-linear conductances are perfectly segregated in the soma, with the dendrite being linear, then this situation is not intractable. In this case the protocol will perform the correct voltage clamp on the non-linear conductances, and the current that passes through them will be a function of only the time, the holding potential, and the clamp potential. There will be a component of the clamp current due to the non-
Figure 8.1: Voltage clamp simulation with clamp applied to the soma. The
voltage step seen by the different parts of the dendrite membrane is distorted.

ideal clamping of the dendrite, but this current may be compensated for by
estimating the linear properties of the dendrite.

On the other hand, no clear cut distribution of non-linear conductances
is more likely; there may be significant non-linear membrane in dendrite
that is at a significant electrotonic distance from the soma. Referring to
Figure 8.1, if there is any non-linear conductance in the proximal dendrite
(in this simulation this refers to the proximal 240 \( \mu \)m of dendrite), then
the steady state voltage caused by the clamp is not very different than the
soma voltage (-50.5 mV and -50.0 mV, respectively). However, during the
initial 10 milliseconds of the clamp the voltage in the proximal dendrite is
significantly different, and therefore any non-linear membrane in this region
will be poorly clamped. This will be a problem if the conductances are
fast in this region, e.g. activation or inactivation on the order of several
milliseconds. Although the results of the analysis presented in Chapter
3 indicates that the dendrite are electrically compact, the high value for
\( R_s \) that has been proposed causes the dendrite voltage to lag significantly
behind the soma voltage.
8.3 Contamination of \( Na^+ \) Parameters Derived by Voltage Clamp

The problem of unclamped dendrites is most severe for the faster currents. This can be demonstrated by examining the putative \( Na^+ \) currents with voltage clamp simulations.

The simulated voltage clamp protocol in which all currents except for \( Na^+ \) currents have been blocked is shown in Figure 8.2.

Ideally, the soma-dendrite current may be measured in isolation by running the voltage clamp on a cell where all the non-linear currents have been blocked. This current may then be subtracted from the clamp current when the all none-\( Na^+ \) components are blocked or disabled in order to estimate the \( Na^+ \) currents.

Figure 8.3 illustrates the various components of the response of a 70 to 0 mV voltage clamp of just the \( Na^+ \) currents. The soma-dendrite current contributes substantially to the clamp current. If this current is not taken into account then the estimated \( Na^+ \) component will be significantly smaller and faster than the actual \( Na^+ \) component.
Figure 8.2: Voltage clamp simulations in which all currents have been blocked except for the Na⁺ currents.
Figure 8.3: Voltage clamp simulation under same conditions of Figure 8.2 illustrating different components of the clamp current. A considerable portion of the clamp current is due to delayed charging of the dendrite's distributed capacitance. Clamp step is from -70 mV to 0 mV for 50 milliseconds.
Chapter 9

CURRENT CLAMP SIMULATIONS

9.1 Introduction

This chapter presents some illustrative simulations of current clamp protocols that demonstrate the overall behavior of the model. The behavior of the model under various protocols is examined, assuming that the current descriptions based on simulation of actual data, as demonstrated in Chapters 5, 6, and 7, sets a realistic stage for more speculative simulations.

Finally, a typical simulation will be presented along with the records of the major currents and the time course of their gating variables in order to demonstrate the full output of HIPPO.

9.2 Regulation of Repetitive Firing – Effect of Blockade of Specific Currents

Consider Figure 9.1. In this simulation the response to long tonic stimuli of different strengths is demonstrate with all the HIPPO currents present. For most of the stimuli the cell responds with an initial burst of action potentials followed by a slow train of spikes.

As we have seen in the previous chapters the major mechanisms mediating these responses is the buildup of intracellular $Ca^{2+}$, the subsequent activation of $I_{AHP}$ and the high, broad threshold of $I_{Na-trig}$. The burst phase is mediated by $I_{Na-trig}$, but once $I_{AHP}$ becomes large enough,
another $I_{Na\text{-}trig}$-mediated spike is delayed by the outward rectification of $I_{AHP}$.

Investigating what happens under the same stimulus protocols when specific currents are blocked illustrates some of the predictions of the model. First, note Figures 9.2, 9.3, and 9.4, which show spike trains in which $I_A$, $I_M$, and $I_{Na\text{-}tail}$ have been blocked, respectively. The model results suggest that although $I_A$ can have a significant role in delaying the onset of firing and in modulating the width of the spike (ref. Chapter 7), this current does not alter repetitive firing once it has been initiated. $I_M$ and $I_{Na\text{-}tail}$, on the other hand, appear to have little functional role under any of the protocols presented. If these currents ($I_M$ and $I_{Na\text{-}tail}$) are assumed to be in the HPC for a reason, then this result suggests that either the model description for them is incomplete or that their site of action is primarily non-somatic (see Section 10.2.4).

In Figures 9.5, 9.6, and 9.7, the response of the cell to tonic stimulus is shown where the $Ca^{2+}$ currents, $I_C$, and $I_{AHP}$ have been blocked, respectively. Here some marked departures from the response of Figure 9.1 can be seen, in particular the change in accommodation. When all $Ca^{2+}$ activity is blocked, as in Figure 9.5, the frequency of repetitive firing is constant, that is the cell reaches a steady-state condition immediately with the first action potential.

Figures 9.6 and 9.7 show how $I_C$ and $I_{AHP}$ both contribute to the accommodation response. When $I_C$ is blocked the initial accommodation is quite similar to the normal response. However (especially for the stronger stimuli), later in the spike train the frequency of firing begins to increase slightly, as if $I_{AHP}$ was partially wearing out in its role as headmaster. When $I_{AHP}$ is selectively blocked, on the other hand, accommodation is immediately compromised and the burst phase lasts for many spikes. Eventually a reduced accommodation starts, though, slowly putting on the brakes to prevent excessive spiking.

This accommodation is due to $I_C$, as can be seen in Figure 9.8. In this figure the response to a 2.2 nA tonic stimulus as was shown in the previous figure is reproduced along with the time course of the intracellular $Ca^{2+}$ concentrations and $I_C$. Here it can be seen that at the beginning of the train $I_C$ fulfills its normal role as a transient repolarizing agent, active only during the spike. When the subsequent spikes come too fast, however, the concentration of $Ca^{2+}$ in shell.2 has a chance to build up, thereby raising the basal level of $[Ca^{2+}]_{\text{shell.1}}$ between spikes. This rise is enough to activate $I_C$
Figure 9.1: Simulations of response to tonic somatic input. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.
Figure 9.2: Simulations of response to tonic somatic input with $I_A$ disabled. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.
Figure 9.3: Simulations of response to tonic somatic input with $I_M$ disabled. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.
Figure 9.4: Simulations of response to tonic somatic input with $I_{Na-tail}$ disabled. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.

Response of cell to tonic stimulus with $I_{Na-tail}$ blocked.

Time scale in seconds. Voltage scale in millivolts.
interictally so that this current provides a suppressing influence to the latter part of the train. The simulations suggest, among other things, that $I_C$ may have a dual role – under “normal” conditions $I_C$ just modulates the width of the individual spike, and under conditions when $I_{AHP}$ is blocked (which easily could be physiological considering $I_{AHP}$ is inhibited by cholinergic agonists) $I_C$ steps in to provide a controlling influence suppressing strong repetitive firing.

Finally, Figure 9.9 shows the response of the cell with just $I_{Na-rep}$ blocked. Here a fairly bizarre response is seen, since it seems that this current would only contribute to the strength of individual spikes and the extension of the effective range for firing threshold. However, in these simulations removal of $I_{Na-rep}$ has an additional (possibly pathologic) effect. At low stimuli, the standard burst/accommodation response is seen, but as the stimulus intensity is increased the cell response degenerates into a series of low amplitude $Ca^{2+}$ spikes followed by a cessation of activity – the cell effectively becomes mute.

In Figures 9.10 through 9.16, this response is examined more closely and compared with the response of the normal cell to the same stimulus. In Figure 9.10 the two responses and their current records are compared over the entire 2 seconds. At this level the most striking difference is the large $I_{DR}$ and $I_{Ca}$ (also $[Ca^{2+}]_{shell,1}$ and $[Ca^{2+}]_{shell,2}$) in the latter portion of the $I_{Na-rep}$-blocked response. Examining the first part of the response in detail (Figures 9.12 and 9.13), the differences are not as obvious. However, even though $I_{Na-trig}$ is about the same for the two protocols, the blocking of $I_{Na-rep}$ causes a significant reduction in the spike amplitude. The result is that $I_{DR}$ is not activated as strongly as in the normal case, thereby reducing the interictal hyperpolarization and increasing the frequency of firing. This is shown more clearly in Figures 9.14 and 9.15, where the initial spikes for both responses are shown. Other than these changes, however, it appears that nothing degenerate is occurring.

The situation changes, though, as accommodation (mediated by $I_{AHP}$) sets in, as shown in Figure 9.16, where the activated $I_{AHP}$ reduces the amplitude of the later spikes even further, which in turn prevents the full turning on of $I_{DR}$. The net result is that the cell becomes more depolarized on the average, allowing $I_{Ca}$ to fully activate. This inward current, while now superseding $I_{Na-trig}$ as the “spike” current, cannot depolarize the cell enough to activate $I_{DR}$ fully, which could repolarize the cell back to $E_{rest}$ and reset the firing cycle. Eventually, then, after a few oscillatory $Ca^{2+}$-spikes,
Figure 9.5: Simulations of response to tonic somatic input with $I_{Ca}$ and $I_{CaS}$ disabled. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.
Figure 9.6: Simulations of response to tonic somatic input with $I_C$ disabled. Stimulus strengths include 0.6 nA. 0.8 nA, 1.0 nA. 1.2 nA. 1.4 nA. 1.6 nA, 1.8 nA. 2.0 nA. and 2.2 nA.
Figure 9.7: Simulations of response to tonic somatic input with $I_{AHP}$ disabled. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.
Figure 9.8: Role of $I_C$ during spike train in response to 2.2 nA stimulus with $I_{AHP}$ blocked. Top – Soma response. Middle – $I_C$ during train. Bottom – $[Ca^{2+}]_{shell.1}$ and $[Ca^{2+}]_{shell.2}$ during train. The buildup of $[Ca^{2+}]_{shell.2}$ as a result of the sustained high rate of repetitive firing, causes a rise in $[Ca^{2+}]_{shell.1}$ between spikes and subsequent persistent activation of $I_C$. 

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Figure 9.9: Simulations of response to tonic somatic input with $I_{Na-rep}$ disabled. Stimulus strengths include 0.6 nA, 0.8 nA, 1.0 nA, 1.2 nA, 1.4 nA, 1.6 nA, 1.8 nA, 2.0 nA, and 2.2 nA.
Figure 9.10: Comparison of spike train with and without $I_{Na-rep}$ - Soma response and $Na^+$ and $K^+$ currents.
Figure 9.11: Comparison of a spike train with and without $I_{Na-rep} - I_{Ca}$ and intracellular $Ca^{2+}$ concentrations.
Figure 9.12: Comparison of beginning of spike train with and without $I_{Na-rep}$ – Soma response and $Na^+$ and $K^+$ currents.
Figure 9.13: Comparison of beginning of spike train with and without $I_{N_{a-rho}} - I_{C_{a}}$ and intracellular $Ca^{2+}$ concentrations.
Figure 9.14: Comparison of initial spikes of spike train with and without $I_{N_a - r_p}$ – Soma response and $Na^+$ and $K^+$ currents.
Figure 9.15: Comparison of initial spikes of spike train with and without $I_{Na-p} - I_{Ca}$ and intracellular $Ca^{2+}$ concentrations.
the cell reaches a stable, depolarized level until the stimulus is removed.

9.3 Conduction of Dendritic Input to Soma

Figure 9.17 illustrates a current clamp simulation in which a series of four 1.3 nA, 3 millisecond current pulses was injected into the distal dendrite. These pulses approximate excitatory synaptic input, assuming that an excitatory synapse consists of a selective conductance with a reversal potential around -25 mV, a total conductance on the order of 60 nS, and an activation period of 3 milliseconds. As seen in the figure, these events propagate down the dendrite and sum at the soma until spike threshold is reached.

An interesting detail from this simulation is the shape of the repolarization of this spike. Recall that single spikes evoked by somatic stimuli display a distinct fAHP (ref. Figure 7.18). In Figure 9.17 the bottom of the fAHP is elevated so that there no longer is a short depolarizing phase prior to the ADP. This is caused by the increased soma-dendrite gradient, which in turn results from the fact that the original depolarization is due to the dendrites rather than from soma input.

As mentioned in Chapter 5 a characteristic of $I_{Na-trig}$ is its sharp threshold. This characteristic is demonstrated in Figure 9.18. Here simulations with two inputs are illustrated. One input consists of the previous pulse train. The second input is identical except that the interval between pulses has been increased by 1 millisecond. This input evokes essentially a linear response (compare with the step responses in Chapter 3), demonstrating the fine tuning of $I_{Na-trig}$.

9.4 Demonstration of the Full Output of the HIPPO Simulations

I shall now present a typical simulation protocol in order to show the collection of variables that underly the behavior of the model. Figure 9.19 shows the overall response of the model to the soma stimulus shown in the lower part of the figure. An initial hyperpolarizing current step is applied

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1In the earlier simulation of the single action potential the repolarization of the spike also caused the dendrite to momentarily be at a higher potential than the soma due to the charge stored in the dendritic capacitance, which in turn contributed to the ADP, but here this potential difference is greater as explained above.
Figure 9.16: Degeneration of spike train without $I_{Na, rep}$ - Soma response. $Na^+$ currents, $K^+$ currents, $I_{Ca}$ and intracellular $Ca^{2+}$ concentrations. Note the eventual strong activation of $I_{Ca}$ preceding stable depolarization.
Figure 9.17: Propagation of spike-producing dendritic input down cable to soma. Current pulse train injected into distal dendritic segment (ref. Figure 9.18 Stimulus 1 (top)).
Figure 9.18: Superimposed response to the stimulus used in the previous figure (Stimulus 1, Response 1) and a subthreshold stimulus (Stimulus 2, Response 2). Note the near linear response of the subthreshold stimulus. Both voltage traces are the soma response (bottom). Current pulse trains injected into the distal dendritic segment (top).
to the soma, bringing the soma voltage down from its resting potential of about -72 mV to about -83 mV. Next, a 220 millisecond 1.8mA depolarizing current step is applied, resulting in the characteristic burst of action potentials, whose frequency just begins to reduce as the action of $I_{AHP}$ starts. After the stimulus, the beginning of the long-lasting after-hyperpolarization is seen.

In Figures 9.20, 9.21, 9.22 the $Na^+$ currents and their associated gating variables during the response of Figure 9.19 are illustrated (note change of time scale).

In Figures 9.23, and 9.24 $I_{Ca}$ its gating variables and the time course of the intracellular $Ca^{2+}$ concentrations are shown during the response of Figure 9.19 are illustrated (note change of time scale).

In Figures 9.25, 9.26, 9.27, 9.28, and 9.29 the $K^+$ currents and their associated gating variables during the response of Figure 9.19 are illustrated (note change of time scale). The relationship between the activation of the $Ca^{2+}$-mediated gating variables ($w$) for $I_C$ and $I_{AHP}$ and the time courses for $[Ca^{2+}]_{shell,1}$ and $[Ca^{2+}]_{shell,2}$ shown in Figure 9.24 is clear. The conductance underlying $I_M$ remains relatively constant (the time course of $I_M$ closely matches the time course of the voltage), and therefore while this current is almost as large as $I_{AHP}$, it has the relatively uncolorful role of mediating repetitive firing only slightly by changing the effective (linear) impedance of the cell.

Finally, in Figures 9.30 and 9.31 the linear components of the somatic response are shown, i.e. the capacitive and leak soma currents and the dendritic voltages, respectively.
Figure 9.19: Typical simulated response of the cell (top) to short hyperpolarizing current stimulus followed by longer depolarizing step (bottom).
Figure 9.20: $I_{Na-trig}$ and its gating variables during response shown in Figure 9.19.
Figure 9.21: $I_{\text{Na-rep}}$ and its gating variables during response shown in Figure 9.19.

Figure 9.22: $I_{\text{Na-tail}}$ and its gating variables during response shown in Figure 9.19.
Figure 9.23: $I_{Ca}$ and its gating variables during response shown in Figure 9.19.
Figure 9.24: $[Ca^{2+}]_{shell.1}$ and $[Ca^{2+}]_{shell.2}$ during response shown in Figure 9.19.
Figure 9.25: $I_{DR}$ and its gating variables during response shown in Figure 9.19.

Figure 9.26: $I_A$ and its gating variables during response shown in Figure 9.19.
Figure 9.27: $I_C$ and its gating variables during response shown in Figure 9.19.

Figure 9.28: $I_{AHP}$ and its gating variables during response shown in Figure 9.19.
Figure 9.29: $I_M$ during response shown in Figure 9.19.

Figure 9.30: The soma capacitive and leak currents during response shown in Figure 9.19.
Figure 9.31: The dendritic voltages during response shown in Figure 9.19.
Chapter 10

DISCUSSION

10.1 Introduction

This chapter will address some of the more general implications and conclusions derived from the model, in particular those issues not covered in earlier chapters. The overall question remains that if neural nets are realizable with elements that just exhibit integrative all-or-nothing responses that are connected with regenerative conductors, then why are all the channels needed? The results of the model suggest some rationale as well as some specific questions addressed at the apparent role of many of the currents described.

10.2 Physiological Roles of Specific Currents in Information Processing

How can the different currents described here contribute to the information processing capability of the pyramidal cell? The first step in answering this question is primarily mechanical, that is we need to show how a given current shapes the response to a repertoire of inputs. At this stage, the repertoire considered has been very basic – short depolarizing current steps that evoke single spikes, long lasting depolarizing current steps that evoke spike trains, and (to a lesser degree) simple dendritic input consisting of depolarizing current steps applied to the distal portion of the dendritic cable. By examining the response to these inputs the functional roles of the model currents can be grouped into three (non-exclusive) categories:
Table 10.1: Functional roles of hippocampal somatic currents. Entries in parentheses indicate secondary role, e.g. $Ca^{2+}$ activation of $K^+$ current. "?" means that the role is unknown.

1. Modulation of shape of single action potential (Spike Shape).

2. Modulation of firing threshold, both for single and repetitive spikes (Threshold).

3. Modulation of repetitive firing, specifically the relationship between strength of tonic input and frequency of initial burst and later “steady state” spike train (Freq-Inten).

Table 10.1 summarizes the main roles for each of the described currents as indicated by the simulations.

### 10.2.1 Possible Roles for the Modulation of the FI Characteristic

Traditionally neural information is assumed to be encoded by frequency modulation (specifically PCM), that is the number of spikes per second encompasses the message of a neuron. For example, the strength of contraction for a muscle fiber is, over some range, a linear function of the spike frequency of its efferent neuron. If action potential propagation is assumed to be a stereotyped phenomena, then clearly the only way to modulate neuronal output is by changing the spike frequency. If the inhibition of a
specific current changes the FI characteristic, this allows the modulation of that neuron's information processing by various agents.

10.2.2 Possible Roles for the Modulation of the Threshold of the Somatic Action Potential

The setting of the somatic threshold will determine the minimal input for eliciting a spike, and in effect change the sensitivity of a cell. For example, if $I_{Na-trig}$ was blocked by some endogenous agent, then the firing threshold for that cell will be raised by about 10 millivolts. This would cause the cell to ignore a wide variety of input patterns that would otherwise generate soma spikes. Even subtle changes in soma threshold, as might for example be mediated by selective inhibition of $I_M$, could significantly alter the overall transfer function of a local population of neurons, assuming that the cholinergic input is spread out over that population and not just directed at a single cell ([24], [25], [35], [36]).

There are actually two aspects of the "threshold" for a cell - static and dynamic. In other words the rate at which the soma membrane approaches threshold is as important as the absolute level of that threshold. In general the threshold rises with a slower approach because there is a small range for which sub-threshold activation of $I_{Na-trig}$ is possible. The most striking evidence for this was demonstrated in Chapter 7, where the role of $I_A$ in delaying spike initiation by (effectively) slow stimulus was shown. $I_A$ therefore may help to distinguish tonic dendritic (particularly distal) input versus tonic somatic input. For input that eventually will supply the same depolarizing current at the soma. dendritic input will have a slower onset due to the cable properties. This slow onset could allow $I_A$ to transiently delay the onset of the spike or spikes, as was shown. A similar depolarizing current of somatic origin (e.g. somatic synapses) would have a faster onset such that $I_A$ would not be activated in time on the depolarizing phase to delay the spike. Extending this possibility further, blocking $I_A$ could have the physiological or pathological result of reducing the ability of the soma to discriminate proximal versus distal inputs.

10.2.3 Possible Roles for the Modulation of the Shape of the Somatic Action Potential

How important is the shape of an individual spike at the soma? In general this question has not been addressed in the literature, but we can speculate
on the possibilities. First, we can assume that spike shape, in particular spike width, is unimportant to a first degree at the soma – once the soma fires, it fires. However, the role of the spike beyond the soma may or may not depend on the spike shape, and this possibility is dependent on to what extent spike propagation is a linear or non-linear phenomena.

This in turn will determine the degree to which an axonal termination “see’s” the actual time course of the somatic event. At one extreme, the proximal axon could transmit the spike a purely non-linear fashion – once threshold was reached, the classic “all-or-nothing” response would transmit a stereotyped action potential down the axon whose shaped would be completely independent of the (immediate) post-threshold behavior at the soma. At the other extreme, i.e. if the axonal membrane were purely linear, the propagation of the somatic event at any point down the axon would be a convolution of the entire somatic signal, rather than just a function of when the soma potential passed some threshold.

The situation in the brain probably lies somewhere between these limits, that is electrical activity at the axon terminal is somewhat dependent on the shape of the somatic spike. The extent to which this is true will in turn be dependent on the wavelength of the propagated spike. For example, consider a typical un-myelinated axon of an HPC with a diameter of 1 micron and a conduction velocity on the order of 10 meters/second. For this axon a 1 millisecond action potential will have a wavelength on the order of 10 millimeters. Since the distance between the soma and an axon terminal may fall in this range, the post-threshold waveform at the soma may influence the presynaptic waveform, despite the non-linearity of the axon.

Consider what happens if the axon is myelinated. Myelination means that its $C_m$ will be much less and its $R_m$ will be much greater. This results in (a) the conduction velocity increasing (which increases the wavelength proportionally) and (b) a reduction of the attenuation of the somatic signal as it travels down the axon, in particular the high-frequency components of the signal. In sum, if the HPC axon is myelinated, the electrical activity at its terminals will even more likely depend on the time course of the somatic waveform, despite the excitable membrane at (in particular) the axon’s nodes of Ranvier.

So, given the possibility that the shape of the somatic action potential may modulate the signal at the pre-synaptic terminal, what role could this serve? There are at least two possibilities. First, it has been demonstrated that the release of transmitter at the pre-synaptic terminal is not an all-or-nothing event, that is the amount of transmitter released is a function of the
time course of the terminal spike ( ). For example, modulation of the somatic
spike width may in turn determine how much transmitter is released down
the line, thereby allowing a mechanism for changing the effective strength
of the spike as seen by the distal neuron. Second, pyramidal cell axons often
project collaterals back to the originating cell, forming axo-somatic synapses,
resulting in a feedback loop. In this case, modulation of the somatic spike
could affect this feedback in complicated ways, particularly since the length
of the collaterals is not large.

There may also be a role for the somatic spike shape during the transmis-
sion of an action potential at axonal branch points. For example, consider
a axonal branch point with an impedance mismatch and where there is one
thin and one thick proximal branch. In this case an orthodromic spike that
is too narrow may not be able to depolarize the thick branch sufficiently for
transmission of the spike down that branch, and as a result the spike would
propagate only down the thin branch. If this is possible, then modulation
of the somatic spike shape could be used to direct the cell’s output in a
time-varying way, i.e. some times allowing blanket transmission to all the
cell axon’s destinations, and at other times allowing reception of that output
by only a limited set of the proximal neurons.

To summarize, encoding information as spike frequency is clearly part
of the story, but it may not be the whole story. Modulation of somatic
spike width could be equivalent to a modulation of the “loudness” of a given
neuron’s message. As mentioned previously, considering that some of the
currents may be modulated by non-cell-specific factors (e.g. local, non-
synaptic release of cholinergic agonists), the “message” being turned up or
down may be one being broadcast from a local population of cells, not just
a single cell.

In order to further examine the above scenarios, it will be necessary to
investigate the relationship between somatic spike shape and pre-synaptic
potential, in particular the effect of axon length, diameter, etc. We have to
answer the question of whether the pre-synaptic membrane (and, more im-
portantly, the post-synaptic membrane via modulation of transmitter release
or gap-junction interactions) see what is happening at the soma? We also
have to analyze at what point does axonal transmission reduce to a stere-
typed all-or-nothing action potential such that the pre-synaptic response is
independent of the soma potential beyond threshold.
10.2.4 Other Implications of Somatic Currents

In this thesis the somatic response of the HPC has been modelled, under the assumption that the dendrites present a linear load to the soma, and that the data on HPC currents reflect the activity of channels localized at the soma. The assumption of a linear dendritic tree has already been discussed (Chapter 2). However, the idea that currents measured at the soma reflect channels whose functional role is defined at the soma may be questioned as follows. Specifically, all channel proteins, regardless of their final (functional) destination are manufactured at the soma. Some of the so-called somatic channels may actually be vestiges of channels intended for axonal and/or pre-synaptic membrane. Some percentage of the channels which are manufactured at the soma for eventual export may be expressed in somatic membrane either on their way to final destination or when they are transported back to the soma for recycling. For example, it has been demonstrated that application of 4-AP modulates post-synaptic events (enhancement of EPSPs []). Does this mean that $I_A$, which has been tacitly assigned a primarily somatic role in this report, actually does most of its work at synaptic membrane sites on the dendrites? This question should be addressed in order to fully establish the functional role of the currents in the HPC.

However, if the spike-shaping channels are intended for pre-synaptic membrane, then modulation by endogenous factors (e.g. ACH) obviously takes place at target neuron. Now this is disadvantageous if we want factor to act selectively on some afferent tract. On the other hand, perhaps in a given dendritic field only some afferents have certain channels, so there still could be some selectivity.

10.3 Why Do the HPC Currents Span Such a Broad Kinetic Spectrum?

A related question is what could be the usefulness of several types of currents with a range of activation/inactivation characteristics for information processing function at the single cell level. Again, these currents primarily define somatic integration; the role of the dendritic tree will further complicate matters.

For example, do current kinetics serve to stabilize the cell, that is is the cell response relatively sensitive or insensitive to variations in a) chan-
nel configurations or b) channel kinetics/voltage-dependencies? The model suggests that many of the parameters have a strong effect on cell behavior. Now, the question remains as to what is the functionally important aspects of HPC response. For example, does a delay to onset of repetitive firing due to tonic dendritic input as opposed to somatic input (ref. $I_A$) have any functional aspect? Considering that this delay can be on the order of several hundred milliseconds, then the delay may have a very important functional role.

A crude analogy to a computer may be instructive (adapted from [37]). Cognitive processes execute on the order of hundreds of milliseconds, thus a delay of this magnitude, as demonstrated by the action of, for example, $I_{AHP}$, could correspond to an "instruction cycle" delay mechanism. Likewise, some currents seen to function as delay mechanisms on the order of a "machine cycle" (about tens of milliseconds), for example $I_C$. Along these lines, a tentative categorization of the described currents is as follows:

- $I_A$ - can differentiate tonic dendritic input from somatic input
- $I_{AHP}$ - can terminate initial train of repetitive firing
- $I_C$ - just modulates spike width
- $I_M$ - helps set threshold in general, may effect F-I
- $I_{DR}$ - basal repolarizer
- $I_{Na-tail}$ - modulates repetitive firing
- $I_{Na-rep}$ - allows repetitive firing with lower metabolic cost
- $I_{Na-trig}$ - basal spike current
- $I_Q$ - ?

### 10.4 Pathological Roles of Specific Currents

Are specific currents mediated in isolation under certain pathologic conditions? The selective action of neurotransmitters on some of the currents, e.g. muscarine on $I_M$, noradrenaline on $I_{AHP}$, supports this possibility. Other examples include reports of various endogenous substances found in vitro that selectively affect distinct currents, e.g. the role of ethyl alcohol on mediation of $I_A$ in *Aplysia* (Biophysics Abstracts, 1987).
As shown in Chapter 9, blocking the putative \( I_{Na-c} \) has the surprising effect of causing the cell to "latch-up" in response to certain strengths of tonic stimulus that would otherwise elicit well-bounded stable spike trains. Although the existence of this current is problematical, the possibility of selective blocking for it raises the possibility of an intriguing pathology, in which neurons stimulated over a certain threshold will simply give up and remain silent until the stimulus stops. On the other hand, it just as likely that this would be a physiological response, that is under some conditions putting an upper bound, not just a lower one, on the intensity of a cell's input may be advantageous.

The relationship between intracellular \( Ca^{2+} \) and \( I_C \) and \( I_{AHP} \) can also indicate possible pathologic mechanisms. One role for these \( Ca^{2+} \)-mediated outward currents that may be important is that they limit \( Ca^{2+} \) influx by repolarizing the cell when \( Ca^{2+} \) currents are turned on. Intracellular \( Ca^{2+} \) is an important messenger for several mechanism, for example muscular contraction, but excessive \([Ca^{2+}]_{in}\) is a noxious agent. There are thus at least three negative feedback mechanisms for limiting the flow of \( Ca^{2+} \) - first, voltage-dependent inactivation (e.g. the \( w \) particle of \( I_{Ca} \)) of \( Ca^{2+} \) currents; second, reduction of \( E_Ca \) with \( Ca^{2+} \) influx; and finally, the just mentioned \( Ca^{2+} \)-mediation of repolarizing currents. These mechanisms suggest possible pathologic roles for some of the mechanisms. For example, as shown in Chapter 9 blocking of \( I_{AHP} \) causes \( I_C \) to step in and eventually limit further repetitive firing. On the other hand, if both these currents are blocked repetitive firing may go unchecked, with a subsequent larger buildup of \([Ca^{2+}]_{in}\) to, perhaps, pathological levels.

### 10.5 Why Model?

Why a model provides more information than that which is put into it, particularly when the model attempts to describe a fairly complicated system, is not always obvious. However, there are some compelling reasons to employ this approach, including the following:

- Modelling helps answer the question as to whether or not the collection of currents described experimentally for this cell is sufficient to account for the observed behavior.

- Limited data for a non-linear system cannot uniquely specify the system. Modelling is a way to generate plausible mechanisms that can
then be tested as more data becomes available.

- Modelling provides the experimentalist with a way to examine high-
  uncertainty data and can stimulate alternative explanations when ex-
  perimental results are inconsistent with the current body of knowledge,
  as is embodied in the model.

- More specific to the results discussed here, if modelling indicates that
  some currents only affect spike shape then this is evidence for some
  interesting role for spike shape modulation. This in turn can give
  suggest new ideas as to how information is encoded in CNS.

10.6 Questions Posed by the Model in Regard to
Current Mechanisms and Kinetics

Does it really matter what the time constant for decay is at potentials greater
than about -10 mV, as long as it is much greater than the time constant for
activation, considering that the spike will be repolarized before inactivation
can take place? Also, what is the usefulness of inactivation mechanisms for
some currents, in particular for the $K^+$ currents? As demonstrated
by the model, during normal activity these currents are removed primarily by the
removal of activation. So far, a clear role for inactivation mechanisms has
not been established, but finding such a role is tempting, if one assumes that
these mechanisms do not exist solely for the complication of voltage-clamp
protocols.

Since we do not see all aspects of current-specific behavior in all HPC
(e.g. do all HPC exhibit $Ca^{2+}$-dependent fAHP?) the question remains as
to why some cells have certain characteristics while others don’t.

10.7 Interpreting the Model Behavior

Given the speculative nature of many of the currents that I have presented
in the model, any results that reflect the interaction of many of the model
elements must be regarded as preliminary. None the less, there are a few
interpretations that we can draw that may reflect mechanisms in actual cells.

A key question to be answered for any of the currents is whether or
not a given current is modulated \textit{in vivo}, either physiologically or patho-
physiologically. From an evolutionary standpoint, for a current to have a
physiological role via selective control of that current, clearly the controlling factor must be present under physiological conditions. On the other hand, in certain pathophysiological states a specific current may be modulated in order to compensate for the problem. One would suspect that if a current has evolved (that is survived) there must be a motivation for its presence that is manifested in either physiologic conditions (e.g. as a computational mechanism) or pathologic conditions (e.g. as a compensatory or protective mechanism), or as well a computational mechanism.

For several of the currents described here such endogenous factors have been identified. For example, $I_M$ is inhibited by muscarinic (physiologically, cholergic) agonists. $I_A$ has been reported to be inhibited by acetylcholine (Nakajima et al, 1986), and $I_{AHP}$ is inhibited by muscarinic agonists (Madison et al, 1987) and noradrenaline (Madison and Nicoll, 1986). Speculation as to whether there are as yet undiscovered mechanisms in vivo for modulating some of the other currents, for example the three proposed $Na^+$ currents, is interesting.

10.8 The Effect of Populations of Neurons as Distinct from Single Cells, and the Implications for Graded Inhibition of HPC Currents

We have considered the all-or-nothing contribution of the various currents, i.e. either a given current is present at its normal strength or it is blocked completely. This description may be oversimplified in two ways. First, the mechanism that blocks a given current may have a graded effect with respect to a single neuron. For example, cholergic input may be diffuse over the soma, and at a given time only a portion of these afferents may be activated and, subsequently, only a portion of the $I_M$ channel or $I_{AHP}$ channel population inhibited. Second, inhibition of a given current must be thought of not only in terms of a single cell but of a local population of cells, the size of the population depending on the neuro-architecture of a given region and the efferents of interest. Activation of a cholergic tract which terminates in a localized area in CA3 may impinge on thousands of HPCs. Assuming that (worst case) the $I_M$ of a given HPC in the area is then either turned on or off completely, the behavior of the population is such that there will be a graded response. This graded response will in turn depend on the strength of the cholergic tract activity.

The key point here is that thinking about the information processing
properties of single neurons only in isolation deals with just part of the problem. Rather, considering how a population of neurons behaves is imperative. No single cell is an island, and removal of a single pyramidal cell from the hippocampus will probably have zero functional effect.

On the other hand, understanding the spectrum of behavior inherent in the individual functional unit (in this case the single neuron\(^1\) is vital to deriving the behavior of the group, particularly when the size of that group varies depending on the system being considered.

### 10.9 Other Issues Suggested by the Modelling Approach

One interesting possibility posed by the model is that \(Ca^{2+}\)-mediated currents might be used as a fast-response transducer for monitoring intracellular \(Ca^{2+}\). Previously, this problem has been addressed by different methods, including via measurement with microelectrodes [29], with questionable results.

In order to use \(Ca^{2+}\)-mediated currents as a transducer, it will be required to verify the relationships between activation of these currents and \(Ca^{2+}\) concentration appropriate for these currents, for example by using patch clamp protocols. Modelling can then be used to extract estimates of the time course of \(Ca^{2+}\) concentration given limited data, since the simulation of current clamp protocols establish useful constraints between the relevant parameters. In the results presented here, the time course of intracellular \(Ca^{2+}\) was tightly linked to both the membrane voltage and the different currents.

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\(^1\)Of course the definition of what constitutes the "individual functional unit" is not fixed - this may range from single channels to specific areas of a dendritic tree to the single cell to subfields to fields on up through the main systems in the CNS.
Chapter 11

FUTURE DIRECTIONS

11.1 Introduction

The model presented here is a preliminary one; at this point there are only a few conclusions that may be drawn from it with confidence regarding the functional aspects of the entire cell. The data base, at present, is sparse, and it was necessary to augment the available information with reasonable speculations on unknown mechanisms. In some respects this effort has been successful in reproducing the qualitative aspects of HPC response. Other aspects have not been simulated well, and it remains to obtain additional data from cells in order to fill in the gaps.

11.2 Some Experiments for the Future

Some experiments that are suggested by the model results include the following:

- Validate assumptions regarding electrotonic structure using frequency domain techniques.

- Evaluate the method for estimating the electrotonic parameters of the dendritic tree from histological data that was presented in Section 3.8.2.

- Investigate contribution of apparent soma leak by microelectrode. If contribution is significant during electrophysiological measurements, then use model to determine behavior of undamaged cell.
• Validate presence of proposed Na⁺ channels.
• Validate voltage-dependence of \( I_C \) and \( I_{AHP} \).
• Determine Ca²⁺-dependence of \( I_C \) and \( I_{AHP} \).
• Develop versions of model for different hippocampal sub-fields or different species.
• Further investigation of the relationship between various parameters and functional sensitivity, e.g. does changing \( I_{Na-rep} \) parameters affect firing patterns.
• In general, devise voltage-clamp protocols to validate assumptions for current parameters.
• Test description of \( Ca^{2+} \) system.
• Investigate more quantitively the temperature-dependence on HPC parameters.
• Run experiments to check the model predictions, as possible, for the various patterns of repetitive firing as shown in Chapter 9.

11.3 Testing the "Super" Cell Assumption

During the analysis of the HPC literature it became apparent that developing an experimental protocol in which evaluation of several currents and the linear response for a single preparation would be very valuable. A significant handicap in the building of HIPPO was that the available data was derived from a vast variety of cells. On the other hand, the HIPPO description tacitly assumes that all the currents/characteristics reviewed could be expressed in a single cell, and in fact this (probably fictional) "super" HPC is the system being modelled. Indeed, one of the more remarkable aspects of the model is that it was possible to derive a single system description that simulated such a wide range of responses.

On the other hand, a single real cell may not embody every detailed response presented here, and a given cell probably expresses only some limited subset of the reported behavior. Running future experiments with this in mind, and to design a suitable protocol that would shed light on the complete behavior of a given preparation in order to test the conclusions of the model will be useful.
Appendix A

A SAMPLE SIMULATION SESSION

In this appendix a typical simulation session will be demonstrated. The first step in running HIPPO is configuring the LISP environment with the proper window frame. This is done by calling the function STARTUP. Next, the function CLAMP is called. The first task of CLAMP is to present the user with a series of menus that set the parameters for the current simulation. These menus will be illustrated below.

The first menu to appear is:

<table>
<thead>
<tr>
<th>Choose Variable Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>First time program is being run?: Yes No</td>
</tr>
<tr>
<td>Current or voltage clamp: Current clamp Voltage clamp</td>
</tr>
<tr>
<td>Modify soma parameters: Yes No</td>
</tr>
<tr>
<td>Change the plotted dendrite voltages?: Yes No</td>
</tr>
<tr>
<td>Modify dendrite parameters: Yes No</td>
</tr>
<tr>
<td>Update all the current kinetics: Yes No</td>
</tr>
<tr>
<td>Modify overall simulation parameters: Yes No</td>
</tr>
<tr>
<td>Exit 3</td>
</tr>
</tbody>
</table>

In this simulation all the options will be selected. The next menu to appear asks which soma parameters will be modified:

<table>
<thead>
<tr>
<th>Choose Variable Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modify the soma currents: Yes No</td>
</tr>
<tr>
<td>Modify soma geometry and passive components: Yes No</td>
</tr>
<tr>
<td>Modify the soma stimulus: Yes No</td>
</tr>
<tr>
<td>Modify the soma synapse: Yes No</td>
</tr>
<tr>
<td>Exit 3</td>
</tr>
</tbody>
</table>

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In this case $I_{Ca}$ and $I_{CaS}$ will be killed (as if $Ca^{2+}$ blockers had been added to the cell medium) and the parameters for $I_{DR}$ will be modified.

The next menu changes the parameters for $I_{DR}$ -

<table>
<thead>
<tr>
<th>Passive components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soma sphere radius (micrometers)</td>
</tr>
<tr>
<td>Leakage battery [mV]</td>
</tr>
<tr>
<td>Na reversal potential [mV]</td>
</tr>
<tr>
<td>K reversal potential [mV]</td>
</tr>
<tr>
<td>Ca reversal potential [nV]</td>
</tr>
<tr>
<td>Calculate C-mem from geometry (yes) or use input capacitance (no): Yes No</td>
</tr>
<tr>
<td>Membrane capacitance [microfarads-cm]</td>
</tr>
<tr>
<td>Input capacity [nF]</td>
</tr>
<tr>
<td>Calculate *RS-MEM from geometry (yes) or use input impedance (no): Yes No</td>
</tr>
<tr>
<td>Membrane resistance [ohms-cm-cm]</td>
</tr>
<tr>
<td>Input impedance [MOhm] (used to substitute for soma and dendrite Rin only)</td>
</tr>
<tr>
<td>Temperature of experiment [Celsius]: 30</td>
</tr>
<tr>
<td>Q-10 [Rate constant coefficient per 10 degrees]</td>
</tr>
<tr>
<td>D-10 [Ionic conductance coefficient per 10 degrees]</td>
</tr>
<tr>
<td>Include electrode shunt conductance (if no the g-shunt will be ignored)?: Yes No</td>
</tr>
<tr>
<td>Electrode shunt [Mohms]</td>
</tr>
<tr>
<td>Constant current injected [nA]: -0.25</td>
</tr>
</tbody>
</table>
In this case the temperature of the simulation has been set to 30°C.
Now the menu for the soma current stimulus comes up. This is set to inject 1nA into the soma for 5 milliseconds at the beginning of the simulation run.

### Setting Up Current Clamp

- Do you want current injected into the soma?: Yes No
- Current clamp by : Command array

**Entered steps**

- Enter name of current command array : NIL
- Step 1 amplitude [na]: 0  For how long [ns]: 60
- Step 2 amplitude [na]: 0  For how long [ns]: 0
- Step 3 amplitude [na]: 0.0  For how long [ns]: 0.0
- Step 4 amplitude [na]: 0.0  For how long [ns]: 0.0
- Step 5 amplitude [na]: 0.0

For how long (this will change the duration of the simulation) [ns]: 60

### Exit

Now the dendrite will be set up -

### Setting Up The Dendrites

#### Dendrite Structure

- How many apical dendrite shaft segments? : 5
- Include apical dendrite shaft: Yes No
- Modify it?: Yes No
- How many apical dendrite left branch segments? : 0
- Include apical dendrite left branch: Yes No
- Modify it?: Yes No
- How many apical dendrite right branch segments? : 0
- Include apical dendrite right branch: Yes No
- Modify it?: Yes No
- How many basal dendrite segments? : 0
- Include basal dendrite: Yes No
- Modify it?: Yes No

#### Dendrite Characteristics

- Modify dendrite passive components: Yes No
- Modify the dendrite current stimulus: Yes No
- Modify the dendrite synapse: Yes No
- Modify the currents of the modified dendrites: Yes No

### Exit

Choose Variable Values

- Do all the 5 apical shaft segments have the same geometry?: Yes No

### Exit

Choose Variable Values

- Length of segment [micrometers]: 240
- Diameter of segment [micrometers]: 12.0

### Exit

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The passive characteristics of the dendrite segments will now be set -

<table>
<thead>
<tr>
<th>Passive Properties of dendrite Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>axon membrane capacitance [µF/cm²]</td>
</tr>
<tr>
<td>axon membrane resistance [Ω·cm]</td>
</tr>
<tr>
<td>axon axoplasm resistance [Ω·cm]</td>
</tr>
<tr>
<td>dendrite membrane capacitance [µF/cm²]</td>
</tr>
<tr>
<td>dendrite membrane resistance [Ω·cm]</td>
</tr>
<tr>
<td>dendrite axoplasm resistance [Ω·cm]</td>
</tr>
<tr>
<td>dendritic leak potential [mV]</td>
</tr>
</tbody>
</table>

Plot all the voltages in solid lines: Yes | No

And current - 2na from 25 milliseconds to 30 milliseconds into the simulation - will be injected into the distal dendritic segment -

<table>
<thead>
<tr>
<th>Choose Variable Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you want current injected into the apical dendrite shaft?: Yes</td>
</tr>
<tr>
<td>Segment to inject current into - : 5</td>
</tr>
<tr>
<td>Step 1 amplitude [na]: 0.0</td>
</tr>
<tr>
<td>For how long [ms]: 25</td>
</tr>
<tr>
<td>Step 2 amplitude [na]: 2</td>
</tr>
<tr>
<td>For how long [ms]: 50</td>
</tr>
<tr>
<td>Step 3 amplitude [na]: 0.0</td>
</tr>
<tr>
<td>For how long [ms]: 0.0</td>
</tr>
<tr>
<td>Step 4 amplitude [na]: 0.0</td>
</tr>
<tr>
<td>For how long [ms]: 0.0</td>
</tr>
<tr>
<td>Step 5 amplitude [na]: 0.0</td>
</tr>
<tr>
<td>For how long [ms]: 0.0</td>
</tr>
</tbody>
</table>

HIPPO now begins calculating the network response. While the simulation is running, the elapsed time is displayed -

Length of simulation + time for steady state - 76.07ms Current time - 12.2ms

HIPPOCAMPAL PYRAMIDAL CELL SIMULATION

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When the simulation is complete, the relevant voltages and currents are plotted, along with a printout of the parameters. The output of the simulation run is shown.

Various characteristics of the simulation can be examined more closely as desired. For example, suppose the response to the dendritic stimulus is of interest. The relevant portions of the plots can be readily zoomed as shown.
Appendix B

HIPPO ALGORITHM

In this model a spherical-soma/dendritic-cable approximation of the pyramidal cell is reduced to an electrical network. HIPPO calculates the response of the network using a modified predictor-corrector scheme, based on that used by Cooley and Dodge. [11]. At any given time step this algorithm finds the set of solutions by a iteration from the previous set. The inputs to the network include:

- intrinsic non-linear conductances and their equilibrium potentials
- current injected into one or more compartments
- controlled voltage source placed in parallel in the soma
- synaptic conductances

The outputs of the network include:

- voltage and the derivative of the voltage
- state variable values and their derivatives
- individual branch currents

These values are found for every compartment in the network.

The program first calculates the steady state of the network (if one exists) for the current set of simulation conditions. If a steady state does not exist (e.g, the cell fires spontaneously) a quasi-steady-state solution is used as the initial values for the simulation. The algorithm then proceeds as follows for each time increment:
1. Estimate the voltage of each compartment by open integration using the value at the last time step, the value of the derivative at the last time step, and the time step. If this is the first time step, then the previous voltage is the steady-state voltage.

\[ V'(n\Delta t) = V([n-1]\Delta t) + (\Delta t \times \dot{V}([n-1]\Delta t)) \]

where \( V'(n\Delta t) \) is the estimate of the voltage of a given compartment, \( V([n-1]\Delta t) \) is the voltage at the previous time step, \( \Delta t \) is the size of the time increment, and \( \dot{V}([n-1]\Delta t) \) is the time derivative of the voltage at the last time step.

2. Estimate the steady state values of the state variables and their time constants at the current time using the voltage estimates. For example, the steady state value of the \( I_{Na-trig} m \) variable is estimated as:

\[ m'_{Na-trig,\infty}(n\Delta t) = f(V'(n\Delta t)) \]

Likewise the time constant for the \( I_{Na-trig} m \) is estimated:

\[ \tau'_{m,Na-trig}(n\Delta t) = g(V'(n\Delta t)) \]

where \( f() \) gives the steady state value \( (m_{Na-trig,\infty}) \) of \( m_{Na-trig} \) at a given voltage, and \( g() \) gives the time constant \( (\tau_{m,Na-trig}) \) at a given voltage. Similar equations are used for the activation and inactivation variables for all the currents that are included in any given compartment. Note that functions like \( f() \) and \( g() \) are among the key results either measurements of cell parameters or the estimates derived with the model.

3. Estimate the present value for the state variables by trapezoidal approximation, using the old values for the state variables and their derivatives, the estimates for their current steady state value, and the estimates for their time constants. For example,

\[ m'_{Na-trig}(n\Delta t) = \frac{m_{Na-trig}([n-1]\Delta t) + \frac{\Delta t}{2} (\dot{m}_{Na-trig}([n-1]\Delta t) + m'_{Na-trig,\infty}(n\Delta t))}{1 - \frac{\Delta t}{\tau'_{m,Na-trig}(n\Delta t)}} \]

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4. The conductances are estimated from the state variable estimates. For example, for the $I_{Na-trig}$ conductance the estimates for $m_{Na-trig}$ and $h_{Na-trig}$ are used as follows:

$$g'_{Na-trig}(n\Delta t) = m'_{Na-trig}(n\Delta t)h'_{Na-trig}^2(n\Delta t)\bar{g}_{Na-trig}$$

where $g'_{Na-trig}(n\Delta t)$ is the current estimate for the $I_{Na-trig}$ conductance, and $\bar{g}_{Na-trig}$ is the total conductance for the $I_{Na-trig}$ current. The $Ca^{2+}$-dependent $K^+$ conductances are estimated using the values of $[Ca^{2+}]_{shell,1}$ and $[Ca^{2+}]_{shell,2}$ calculated at the previous time step.

5. Conservation of currents at circuit nodes (KCL) and the appropriate branch equations are used to calculate the estimated capacitive current for each compartment at the current time. This current is then used with the value of the capacitance of the compartment to calculate the derivative of the compartment voltage, given the estimates for the conductances, the estimates for the voltages in adjacent compartments, and the value of any injected current into the compartment. For the circuit topology most often used in the simulations (see Figure 1.1) the expression of KCL for the estimated soma currents is:

$$I'_{stimulus} + I'_{capacity} + I'_{Na-trig} + I'_{Na-rerp} + I'_{Na-tail} + I'_{A} + I'_{DR} + I'_{C} + I'_{M} + I'_{AHP} + I'_{Q} + I'_{C-a} + I'_{C-s} + I'_{L} + I'_{dendrite-soma} = 0$$

The relevant branch equations are

$$I'_{capacity} = C_{soma} \dot{V}'_{soma}(n\Delta t)$$

$$I'_{Na-trig} = g'_{Na-trig}(n\Delta t) \times (E_{Na} - V'_{soma}(n\Delta t))$$

$$I'_{Na-rerp} = g'_{Na-rerp}(n\Delta t) \times (E_{Na} - V'_{soma}(n\Delta t))$$

$$I'_{Na-tail} = g'_{Na-tail}(n\Delta t) \times (E_{Na} - V'_{soma}(n\Delta t))$$

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\[ I'_A = g'_A(n\Delta t) \times (E_K - V'_{soma}(n\Delta t)) \]

\[ I'_{AHP} = g'_{AHP}(n\Delta t) \times (E_K - V'_{soma}(n\Delta t)) \]

\[ I'_D = g'_D(n\Delta t) \times (E_K - V'_{soma}(n\Delta t)) \]

\[ I'_C = g'_C(n\Delta t) \times (E_K - V'_{soma}(n\Delta t)) \]

\[ I'_M = g'_M(n\Delta t) \times (E_K - V'_{soma}(n\Delta t)) \]

\[ I'_Q = g'_Q(n\Delta t) \times (E_K - V'_{soma}(n\Delta t)) \]

\[ I'_{Ca} = g'_{Ca}(n\Delta t) \times (E_{Ca} - V'_{soma}(n\Delta t)) \]

\[ I'_{CaS} = g'_{CaS}(n\Delta t) \times (E_{Ca} - V'_{soma}(n\Delta t)) \]

\[ I'_L = g_L \times (E_{L钙} - V'_{soma}(n\Delta t)) \]

\[ I'_{Shunt} = g_{Shunt} \times V'_{soma}(n\Delta t) \]

\[ I'_{dendrite-soma} = g_{dendrite-soma} \times (V'_{dendrite-segment}(n\Delta t) - V'_{soma}(n\Delta t)) \]

Rearranging to get an expression for \( V'_{soma}(n\Delta t) \).

\[ V'_{soma}(n\Delta t) = \frac{1}{C_{membrane}} \times \left( (g'_{Na-trig}(n\Delta t) + g'_{Na-rep}(n\Delta t) + g'_{Na-trig}(n\Delta t)) \times (E_{Na} - V'_{soma}(n\Delta t)) \right) \]
\[ + (g'_A(n\Delta t) + g'_{AHP}(n\Delta t) + g'_{DR}(n\Delta t)) \\
+ g'_C(n\Delta t) + g'_M(n\Delta t) + g'_Q(n\Delta t)) \times (E_K - V'_{\text{soma}}(n\Delta t)) \\
+ (g'_{C-a}(n\Delta t) + g'_{C-S}(n\Delta t)) \times (I_{C-a} - V'_{\text{soma}}(n\Delta t)) \\
+ g_L \times (E_{\text{Leak}} - V'_{\text{soma}}(n\Delta t)) + g_{\text{shunt}} \times -V'_{\text{soma}}(n\Delta t) \\
+ g_{\text{dendrite-soma}} \times (V'_{\text{dendrite-segment}}(n\Delta t) - V'_{\text{soma}}(n\Delta t)) \]

Similar equations are derived for all the other compartment voltage derivatives.

6. A second estimate of the compartment voltages is made with trapezoidal approximation using the previous values for the voltages and their derivatives and the estimate for the present derivative. For example, the second estimate of the soma voltage is derived as follows:

\[ V''(n\Delta t) = V([n-1]\Delta t) + \frac{1}{2}(V([n-1]\Delta t) + \dot{V}'(n\Delta t)) \]

where \( V''(n\Delta t) \) is the second estimate for the compartment voltage. Recall that both the voltage, \( V([n-1]\Delta t) \), and its derivative, \( \dot{V}'([n-1]\Delta t) \), were stored as results from the previous time step.

7. The new voltage estimates are compared with the previous voltage estimates. If any of these estimates is not within some convergence criteria \( c \), then the algorithm goes back to step 2 using the mean of the previous and present voltage estimates.

8. If all the voltage estimates are within the convergence criteria then these estimates are taken as the present values for the voltages. A final estimate of the state variables and the derivatives of the voltages are then calculated, once again using steps 2 through 6. The derivatives of the state variables are also calculated using the appropriate differential equations (ref eq. 1.). These values are also stored as the state of the network at the present time.

9. \([Ca^{2+}]_{\text{shell,1}}\) and \([Ca^{2+}]_{\text{shell,2}}\) for the current time step is calculated using the current value of \( I_{C-a} \) and \( I_{C-S} \) and the appropriate differential equations (see Chapter 6).

10. Increment the time and continue simulation.
Note that $[Ca^{2+}]_{shell.1}$ and $[Ca^{2+}]_{shell.2}$, and thus the interaction between these concentrations and $I_C$ and $I_{AHP}$, are calculated out of the predictor-corrector loop in order to speed up execution time. This is reasonable since the time constants for the influx of $Ca^{2+}$ and the change in the compartment concentrations are much slower than the typical time step used in the simulations (0.05 milliseconds).

The stability of the algorithm was primarily a function of the time step and the state variables with the fastest kinetics. Runs for a given simulation were done with the largest time step that resulted in a convergent solution. Typically simulations were run with a time step of 0.05 milliseconds, and an $\epsilon$ of 0.1 millivolts. The accuracy of key simulations was checked by re-running the simulation with a small time step and a small epsilon (typically 0.01 milliseconds and 0.01 millivolts, respectively). Running time for simulations with a 0.05 millisecond time step and $\epsilon = 0.1$ millivolts was between 0.5 and 1 second (real time) per millisecond of simulation.
Appendix C

OVERVIEW OF THE HIPPO CODE

The HIPPO program is written in ZetaLisp, a dialect of Lisp that is implemented on the Symbolics 3600-type computer. Although this code will not run under Common Lisp, converting it should not be very difficult.

The output of HIPPO assumes that a plotting package written by Patrick O'Donnell has been loaded into the machine. Again, this part of the program could be readily modified to run on another system.

Some of the features of this code include the evaluation of the voltage-dependent gating variable functions and storage of the results in arrays before simulation runs so as to speed run times. In addition, it is relatively straightforward to add new conductances to the model due to the modularity of the program.

Copies of this code are available on cartridge tape from the author.
Appendix D

HIPPO LISTING
All dimensions are as follows -
- Time (milliseconds) except for *time* output array where the units are seconds.
- Distance (micrometers)
- Surface area (square cm)
- Volume (cubic micrometers)
- Voltage (millivolts)
- Current (nano-amps)
- Specific membrane capacitance (microfarads per square cm)
- Specific membrane resistivity (ohms cm cm)
- Capacitance (nano-farads)
- Resistance (mega-ohms)
- Conductance (microsiemens)
- Conductance density (millisiemens per square cm)

Define all the global variables and arrays

The naming convention for the variables is as follows -
- variable-name = local variable
- *variable-name = global variable
- VARIABLE-NAME$ = global array
- variable-name$ = slot location in array
- *variable-name* = global (output) list

These arrays hold all the state variables for each compartment. DENDRITE is a two dimensional array to include all the dendritic segments.

```
(defun BASAL-DENDRITE (make-array '(50 200) :initial-value 1.0))
(defun APICAL-1-DENDRITE (make-array '(50 200) :initial-value 1.0))
(defun APICAL-2-DENDRITE (make-array '(50 200) :initial-value 1.0))
(defun APICAL-SHAFT-DENDRITE (make-array '(50 200) :initial-value 1.0))
(defun TOTAL-SEGMENTS 10)
(defun SOMA (make-array 200 :initial-value 0.0))
```

(defvars-w-value (*dendrite-synapse-step 0)(*soma-synapse-step 0)
  (*start-dendrite-synapse 10.0)(*start-soma-synapse 10.0))

```
(defun m-nal-inf-array (make-array 1700 :initial-value 1.0))
(defun h-nal-inf-array (make-array 1700 :initial-value 1.0))
(defun t-m-nal-array (make-array 1700 :initial-value 1.0))
(defun t-h-nal-array (make-array 1700 :initial-value 1.0))
(defun m-na2-inf-array (make-array 1700 :initial-value 1.0))
(defun h-na2-inf-array (make-array 1700 :initial-value 1.0))
(defun t-m-na2-array (make-array 1700 :initial-value 1.0))
(defun t-h-na2-array (make-array 1700 :initial-value 1.0))
(defun m-na3-inf-array (make-array 1700 :initial-value 1.0))
(defun h-na3-inf-array (make-array 1700 :initial-value 1.0))
(defun t-m-na3-array (make-array 1700 :initial-value 1.0))
(defun t-h-na3-array (make-array 1700 :initial-value 1.0))
```

(defvar x-nal-inf-array (make-array 1700 :initial-value 1.0))
```
(defun s-ca-inf-array (make-array 1700 :initial-value 1.0))
(defun t-s-ca-array (make-array 1700 :initial-value 1.0))
(defun t-w-ca-array (make-array 1700 :initial-value 1.0))
(defun x-cas-inf-array (make-array 1700 :initial-value 1.0))
(defun t-x-cas-array (make-array 1700 :initial-value 1.0))
```

(defvar x-a-inf-array (make-array 1700 :initial-value 1.0))
```
(defun x-c-inf-array (make-array 1700 :initial-value 1.0))
(defun y-c-inf-array (make-array 1700 :initial-value 1.0))
(defun t-x-c-array (make-array 1700 :initial-value 1.0))
(defun t-y-c-array (make-array 1700 :initial-value 1.0))
```
(defvar x-dr-inf-array (make-array 1700 :initial-value 1.0))
(defvar t-x-dr-array (make-array 1700 :initial-value 1.0))
(defvar t-y-dr-array (make-array 1700 :initial-value 1.0))
(defvar x-q-inf-array (make-array 1700 :initial-value 1.0))
(defvar t-x-q-array (make-array 1700 :initial-value 1.0))
(defvar voltage-array (make-array 1700 :initial-value 1.0))

(defun set-up-labels()
  (defvars-w-value)

(defun set-last-constant-values()
  (defvars-voltage)

(defun passive-parameters()
  (defvars-capacitance)

(defun set-last-variable-values()
  (defvars-voltage)

(defun absolute-conductances()
  (defvars-conductances)

(defun flags-for-dendrite-currents()
  (defvars-flags)

(defun steady-state-values()
  (defvars-steady-state-values)

(defun time-constants()
  (defvars-time-constants)

(defun use-this-array-for-plotting-variables()
  (defvars-array)

(defun set-up-labels()
  (defvars-w-value)

(defun set-last-constant-values()
  (defvars-voltage)

(defun passive-parameters()
  (defvars-capacitance)

(defun set-last-variable-values()
  (defvars-voltage)

(defun absolute-conductances()
  (defvars-conductances)

(defun flags-for-dendrite-currents()
  (defvars-flags)

(defun steady-state-values()
  (defvars-steady-state-values)

(defun time-constants()
  (defvars-time-constants)

(defun use-this-array-for-plotting-variables()
  (defvars-array)
Use the arrays which hold the soma and dendrite synaptic conductances [micro-S]

(defvar SOMA-SYNAPSE (make-array 10000))
(defvar DENDRITE-SYNAPSE (make-array 10000))

Various global variables

(defvars *gs-nal-est *gs-na2-est *gs-na3-est
*gs-nap-est *gs-ca-est *gs-a-est *gs-c-est *gs-dr-est *gs-cas-est *gs-ahp-est
*gs-q-est *gs-leak *gs-synapse *gs-coupling *time *clamp-voltage *vstep *time-for-steady-state
DENDRITE-ARRAY *g-electrode)

(defvars *a-m-nal *b-m-nal *a-h-nal *b-h-nal)
(defvars *a-m-na2 *b-m-na2 *a-h-na2 *b-h-na2)
(defvars *a-m-na3 *b-m-na3 *a-h-na3 *b-h-na3)
(defvar vclamp-command-flag 1)
(defvar *voltage-command* nil)
(defvar *iclamp-command-flag 1)
(defvar *current-command* il)
(defvar *stim-seg 4)
(defvars *lot-listl label-listl *plot-list2 *abel-list2 *plot-list3 *abel-list3 *plot-list4 *label-list4
*plot-list5 *label-lists)

(defvars-w-value (*i-stim-1 0.0)(*i-stim-2 0.0)(*i-stim-3 '0)(*i-stim-4 0.0)(*i-stim-5 0.0)
(*t-stim-1 0.0)(*t-stim-2 0.0)(*t-stim-3 0.0)(*t-stim-4 0.0)(*t-stim-5 0.0)
(*i-den-stim-1 0.0)(*i-den-stim-2 0.0)(*i-den-stim-3 0.0)(*i-den-stim-4 0.0)
(*i-den-stim-5 0.0)
(*i-den-stim-6 0.0)(*i-den-stim-7 0.0)(*i-den-stim-8 0.0)(*i-den-stim-9 0.0)(*i-den-stim-10 0.0)
(*t-den-stim-1 0.0)(*t-den-stim-2 0.0)(*t-den-stim-3 0.0)(*t-den-stim-4 0.0)
(*t-den-stim-5 0.0)
(*t-den-stim-6 0.0)(*t-den-stim-7 0.0)(*t-den-stim-8 0.0)(*t-den-stim-9 0.0)(*t-den-stim-10 0.0)
(*current-stimulus-segment 5)(*i-den-stim 0.0)(*i-den-stim 0.0)
(*time-step 0)(*duration 50)(Onclude-s'na-current t)(*include-dendrite-current nil)

(defvar *qten 30)

391 :Temperature dependence of rate constants. The rate constants
392 are multiplied by Q(T/25) raised to
393 0.289
394 0.289
395 where T is the
396 0.289
397 temperature of the simulation, and Tbas is the temperature of
398 0.289
399 the experiment that measured the rate constants.

(defvars-w-value (*qten-factor-at-25 1.0)(*qten-factor-at-32 1.0)(*qten-factor-at-24 1.0)
(*qten-factor-at-22 1.0)(*qten-factor-at-37 1.0)
(*qten-factor-at-14 1.0)(*qten-factor-at-25-m 1.0))

(defvars-w-value (*soma-synapse-tau 1.0)(*soma-synapse-amplitude 1.0)(*e-synapse 25.0)
(*dendrite-synapse-tau 1.0) (*dendrite-synapse-amplitude 1.0) (*synapse-segment )
(*total-apical-l-segments 0) (*total-apical-2-segments 0) (*total-apical-shaft-segments 5)
(*total-basal-segments 0)
(*i-constant-inJection 0.0))

(defvars-w-value (*axonal-cap-mem M*axonal-r-mem 50000.0)(*axonal 'r-int 5.0))

Miscellaneous flags

(defvars-w-value (#modify-soma-passive-components t)(#modify-soma-stimulus t)(#modify-soma-synapse nil)
(#modify-soma-currents t)(#modify-dendrite t)
(#segments-all-the-same t)(#simulation-flag t)(#include-soma-synapse nil)
(#include-dendrite-synapse nil)
(#modify-dendrite-synapse nil)(#modify-dendrite-stimulus NIL)(#include-dendrite t)
(#modify-dendrite-geometry NIL)(#modify-dendrite-passive-components NIL)
(#modify-dendrite-currents NIL)(#plot-voltages-solid t)(#overlay-simulations nil)
(#change-plot-dendrite NIL)
(#update-apical-1 nil)
(#update-apical-2 nil)
(#update-apical-shaft NIL)
(#update-basal nil)
(#include-apical-1 nil)
(#include-apical-2 nil)
(#include-apical-shaft t)
(#include-basal nil)
(#modify-dendrite-currents nil)
(#plot-results t)
(#update-all-kinetics nil)))

(defvars-w-value (#plot-as1 nil) (#plot-as3 nil) (#plot-as5 nil) (#plot-as10 nil)
(#plot-all nil) (#plot-all2 nil) (#plot-all4 nil)
(#plot-b1 nil) (#plot-b4 nil))

Flags for the currents

(defvars-w-value (#include-na1 T)
(#include-na2 T)
(#include-na3 T)
(#include-asp nil)(#include-ahp nil)(#include-cas nil)
(setf *dt* .01)

epsilon is the convergence criteria for the compartment voltages; *dot-epsilon is the convergence criteria for the derivative of the compartment voltages when trying to calculate the steady state.

(setf *epsilon* .01)
(setf *dot-epsilon* .01)

(setf *plot-step* 1)
(setf *point-index* 1)
(setf *plot-points* 300)
(setf *vclamp-run* nil)
(setf *iclamp-run* nil)
(setf *clamp-type* nil)

(setf *plot-points* 300)

(setf *i-stim* (make-array *plot-points* :initial-value 0.0)
*ca-conc-shell* (make-array *plot-points* :initial-value 0.0)
*ca-conc-sheII2* (make-array *plot-points* :initial-value 0.0)
*e-ca* (make-array *plot-points* :initial-value 0.0)
*I-current* (make-array *plot-points* :initial-value 0.0)
*caps-current* (make-array *plot-points* :initial-value 0.0)
*current* (make-array *plot-points* :initial-value 0.0) *time* (make-array *plot-points* :initial-value 0.0)
*voltage* (make-array *plot-points* :initial-value 0.0) *e-eff* (make-array *plot-points* :initial-value 0.0)
*shunt-current* (make-array *plot-points* :initial-value 0.0)
*coupling-current* (make-array *plot-points* :initial-value 0.0)
*stim-current* (make-array *plot-points* :initial-value 0.0)
*aslvoltage* (make-array *plot-points* :initial-value 0.0)
*as3voltage* (make-array *plot-points* :initial-value 0.0)
*as5voltage* (make-array *plot-points* :initial-value 0.0)
*aslOvoltage* (make-array *plot-points* :initial-value 0.0)
*x-nal* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0)
*h-na2* (make-array *plot-points* :initial-value 0.0)
*g-na2* (make-array *plot-points* :initial-value 0.0)
*m-na2* (make-array *plot-points* :initial-value 0.0)
*h-na3* (make-array *plot-points* :initial-value 0.0)
*g-na3* (make-array *plot-points* :initial-value 0.0)
*m-na3* (make-array *plot-points* :initial-value 0.0)
*h-na4* (make-array *plot-points* :initial-value 0.0)
*g-na4* (make-array *plot-points* :initial-value 0.0)
*m-na4* (make-array *plot-points* :initial-value 0.0)
*h-nal* (make-array *plot-points* :initial-value 0.0)
*g-nal* (make-array *plot-points* :initial-value 0.0)
*m-nal* (make-array *plot-points* :initial-value 0.0))

(setf *include-nal* (setf *nal-current* (make-array *plot-points* :initial-value 0.0)))
(setf *include-na2* (setf *na2-current* (make-array *plot-points* :initial-value 0.0)))
(setf *include-na3* (setf *na3-current* (make-array *plot-points* :initial-value 0.0)))
(setf *include-dr* (setf *dr-current* (make-array *plot-points* :initial-value 0.0)))
(setf *include-a* (setf *a-current* (make-array *plot-points* :initial-value 0.0)))
(setf *include-q* (setf *q-current* (make-array *plot-points* :initial-value 0.0)))
(setf *include-ca* (setf *ca-current* (make-array *plot-points* :initial-value 0.0)))

(setf *include-kinetics* nil)
(setf *include-dr* nil)
(setf *include-k* nil)
(setf *include-m* nil)
(setf *include-ca* nil)
(setf *include-qn* nil)
(setf *include-shunt* nil)
(setf *include-v* nil)
(setf *include-ca* nil)
(setf *include-qn* nil)
(setf *include-shunt* nil)
*w-ca* (make-array plotted-points :initial-value 0.0)
*g-ca* (make-array plotted-points :initial-value 0.0))

*include-dr (setq *x-dr* (make-array plotted-points :initial-value 0.0)
*Y-dr* (make-array plotted-points :initial-value 0.0)
*fits :initial-value 0.0)
*g-dr* (make-array plotted-points :initial-value 0.0))

*include-a (setq *x-a* (make-array plotted-points :initial-value 0.0)
*Y-a* (make-array plotted-points :initial-value 0.0)
*g-a* (make-array plotted-points :initial-value 0.0)))

*include-m (setq *x-m* (make-array plotted-points :initial-value 0.0)))

(*include-ahp (setq *x-ahp* (make-array plotted-points :initial-value 0.0)
*Y-ahp* (make-array plotted-points :initial-value 0.0)
*w-ahp* (make-array plotted-points :initial-value 0.0)
*g-ahp* (make-array plotted-points :initial-value 0.0)))

(*include-c (setq *x-c* (make-array plotted-points :initial-value 0.0)
*Y-c* (make-array plotted-points :initial-value 0.0)
*w-c* (make-array plotted-points :initial-value 0.0)
*g-c* (make-array plotted-points :initial-value 0.0)
*g-c-conc* (make-array plotted-points :initial-value 0.0))))

(defvar plot-pane-1 plot-pane-2 plot-pane-3 plot-pane-4 plot-pane-5 plot-pane-6)

;;; SETUP-MENU4 Sets up all the parameters for the current run.
(defun setup-menu4 ()
  (tv:choose-variable-values
   '((first-run "First time program is being run?" :boolean)
     (clamp-type "Current or voltage clamp" :choose "Current clamp" "Voltage clamp")
     (modify-soma "Modify soma parameters" :boolean)
     (change-plot-dendrite "Change the plotted dendrite voltages" :boolean)
     (modify-dendrite "Modify dendrite parameters" :boolean)
     (update-all-kinetics "Update all the current kinetics" :boolean)
     (simulation-flag "Modify overall simulation parameters" :boolean))
  (if *first-run (initialize-dendrites))
  (if (equal *clamp-type "Current clamp")
    (setq *iclamp-run t *vclamp-run nil)
    (setq *iclamp-run nil vclamp-run 0)
  (cond-every (*simulation-flag (menu-for-simulation))
    (*modify-soma (menu-for-soma))
    (*modify-dendrite (menu-for-dendrite))
    (*change-plot-dendrite (menu-for-dendrite-plotting))
    (*change-plot-points (set-up-output-arrays *plot-points*)
     (format t "Made new output arrays")
     (update-all-kinetics (variable-array-setup))))

(defun menu-for-dendrite-plotting ()
  (tv:choose-variable-values
   '((plot-as1 "Plot shaft segment 1" :boolean)
     (plot-as2 "Plot shaft segment 2" :boolean)
     (plot-as3 "Plot shaft segment 3" :boolean)
     (plot-as4 "Plot shaft segment 4" :boolean)
     (plot-as5 "Plot shaft segment 5" :boolean)
     (plot-as6 "Plot shaft segment 6" :boolean)
     (plot-as7 "Plot left segment 1" :boolean)
     (plot-as8 "Plot left segment 2" :boolean)
     (plot-as9 "Plot left segment 3" :boolean)
     (plot-as10 "Plot left segment 4" :boolean)
     (plot-ar1 "Plot right segment 1" :boolean)
     (plot-ar2 "Plot right segment 2" :boolean)
     (plot-ar3 "Plot right segment 3" :boolean)
     (plot-ar4 "Plot right segment 4" :boolean)
     (plot-b1 "Plot basal segment 1" :boolean)
     (plot-b2 "Plot basal segment 2" :boolean)
     (plot-b3 "Plot basal segment 3" :boolean)
     (plot-b4 "Plot basal segment 4" :boolean)
     (label "Choose Plotted Segments")
     (assert (if *plot-as1 t nil) APICAL-SHAFT-DENDRITE 0 plot-mes)
     (assert (if *plot-as2 t nil) APICAL-SHAFT-DENDRITE 2 plot-mes)
     (assert (if *plot-as3 t nil) APICAL-SHAFT-DENDRITE 4 plot-mes)
     (assert (if *plot-as4 t nil) APICAL-SHAFT-DENDRITE 6 plot-mes)
     (assert (if *plot-as5 t nil) APICAL-1-DENDRITE 0 plot-mes)
     (assert (if *plot-as6 t nil) APICAL-1-DENDRITE 2 plot-mes)
     (assert (if *plot-as7 t nil) APICAL-1-DENDRITE 4 plot-mes)
     (assert (if *plot-as8 t nil) APICAL-1-DENDRITE 6 plot-mes)
     (assert (if *plot-as9 t nil) APICAL-2-DENDRITE 0 plot-mes)
     (assert (if *plot-as10 t nil) APICAL-2-DENDRITE 2 plot-mes)
     (assert (if *plot-as11 t nil) APICAL-2-DENDRITE 4 plot-mes)
     (assert (if *plot-as12 t nil) APICAL-2-DENDRITE 6 plot-mes)
     (assert (if *plot-b1 t nil) BASAL-DENDRITE 0 plot-mes)
     (assert (if *plot-b2 t nil) BASAL-DENDRITE 2 plot-mes)
     (assert (if *plot-b3 t nil) BASAL-DENDRITE 4 plot-mes)
     (assert (if *plot-b4 t nil) BASAL-DENDRITE 6 plot-mes))

;;; MENU-FOR-SOMA Sets up all the parameters for the current run.
(defun menu-for-soma ()
  (tv:choose-variable-values
   '((modify-soma-currents "Modify the soma currents" :boolean)
     (modify-soma-passive-components "Modify soma geometry and passive components" :boolean)
     (modify-soma-stimulus "Modify the soma stimulus" :boolean)
     (modify-soma-currents :boolean)
     (modify-soma-passive-components :boolean)
     (modify-soma-stimulus :boolean)
     (assert (if *plot-as1 t nil) APICAL-SHAFT-DENDRITE 0 plot-mes)
     (assert (if *plot-as2 t nil) APICAL-SHAFT-DENDRITE 2 plot-mes)
     (assert (if *plot-as3 t nil) APICAL-SHAFT-DENDRITE 4 plot-mes)
     (assert (if *plot-as4 t nil) APICAL-SHAFT-DENDRITE 6 plot-mes)
     (assert (if *plot-as5 t nil) APICAL-1-DENDRITE 0 plot-mes)
     (assert (if *plot-as6 t nil) APICAL-1-DENDRITE 2 plot-mes)
     (assert (if *plot-as7 t nil) APICAL-1-DENDRITE 4 plot-mes)
     (assert (if *plot-as8 t nil) APICAL-1-DENDRITE 6 plot-mes)
     (assert (if *plot-as9 t nil) APICAL-2-DENDRITE 0 plot-mes)
     (assert (if *plot-as10 t nil) APICAL-2-DENDRITE 2 plot-mes)
     (assert (if *plot-as11 t nil) APICAL-2-DENDRITE 4 plot-mes)
     (assert (if *plot-as12 t nil) APICAL-2-DENDRITE 6 plot-mes)
     (assert (if *plot-b1 t nil) BASAL-DENDRITE 0 plot-mes)
     (assert (if *plot-b2 t nil) BASAL-DENDRITE 2 plot-mes)
     (assert (if *plot-b3 t nil) BASAL-DENDRITE 4 plot-mes)
     (assert (if *plot-b4 t nil) BASAL-DENDRITE 6 plot-mes)))

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(modify-soma-synapse "Modify the soma synapse" :boolean))
(cond-every (modify-soma-currents (menu-for-soma-currents))
  (modify-soma-passive-components (menu-for-soma-geometry-and-passive-components))
((and *iclamp-run* modify-soma-stimulation) (menu-for-soma-current-stimulation))
((and *iclamp-run* modify-soma-stimulation) (menu-for-soma-voltage-stimulation))
(modify-soma-synapse (menu-for-soma-synapse)))

;;; MENU-FOR-DENDRITE Sets up all the parameters for the current run.
(defun menu-for-dendrite ()
  (tv:choose-variable-values
   '(*
     "--- DENDRITE STRUCTURE ---"
     (total-apical-shaft-segments "How many apical dendrite shaft segments?" :number)
     (include-apical-shaft "Include apical dendrite shaft" :boolean)
     (update-apical-shaft "Modify it?" :boolean)
     (total-apical-1-segments "How many apical dendrite left branch segments?" :number)
     (include-apical-1 "Include apical dendrite left branch" :boolean)
     (update-apical-1 "Modify it?" :boolean)
     (total-apical-2-segments "How many apical dendrite right branch segments?" :number)
     (include-apical-2 "Include apical dendrite right branch" :boolean)
     (update-apical-2 "Modify it?" :boolean)
     (total-basal-segments "How many basal dendrite segments?" :number)
     (include-basal "Include basal dendrite" :boolean)
     (update-basal "Modify it?" :boolean)
   )
   "--- DENDRITE CHARACTERISTICS ---"
   (modify-dendrite-passive-components "Modify dendrite passive components" :boolean)
   (modify-dendrite-stimulation "Modify the dendrite current stimulus" :boolean)
   (modify-dendrite-synapse "Modify the dendrite synapse" :boolean)
   (modify-dendrite-currents "Modify the currents of the modified dendrites" :boolean)
)

'(**
 'label " *** SETTING UP THE DENDRITES *** "
(set-dendrite-segments-and-flags)
  (cond-every
    (update-apical-1 (aset *total-apical-1-segments APICAL-1-DENDRITE 0 total-segments$)
      (menu-for-dendrite-geometry APICAL-1-DENDRITE)
      (if modify-dendrite-currents
        (menu-for-dendrite-currents APICAL-1-DENDRITE))
    (update-apical-2 (aset *total-apical-2-segments APICAL-2-DENDRITE 0 total-segments$)
      (menu-for-dendrite-geometry APICAL-2-DENDRITE)
      (if modify-dendrite-currents
        (menu-for-dendrite-currents APICAL-2-DENDRITE))
    (update-apical-shaft (aset *total-apical-shaft-segments APICAL-SHAFT-DENDRITE 0 total-segments$)
      (menu-for-dendrite-geometry APICAL-SHAFT-DENDRITE)
      (if modify-dendrite-currents
        (menu-for-dendrite-currents APICAL-SHAFT-DENDRITE))
    (update-basal (aset *total-basal-segments BASAL-DENDRITE 0 total-segments$)
      (menu-for-dendrite-geometry BASAL-DENDRITE)
      (if modify-dendrite-currents
        (menu-for-dendrite-currents BASAL-DENDRITE))
      (modify-dendrite-passive-components (menu-for-dendrite-passive-components))
      (modify-dendrite-stimulation (menu-for-dendrite-stimulation))
      (modify-dendrite-synapse (menu-for-dendrite-synapse))))

;;; SET-DENDRITE-SEGMENTS-AND-FLAGS
(defun set-dendrite-segments-and-flags ()
  (aset *total-apical-1-segments APICAL-1-DENDRITE 0 total-segments$)
  (aset *total-apical-2-segments APICAL-2-DENDRITE 0 total-segments$)
  (aset *total-apical-shaft-segments APICAL-SHAFT-DENDRITE 0 total-segments$)
  (aset *total-basal-segments BASAL-DENDRITE 0 total-segments$)
  (if *include-apical-shaft*
    (aset *APICAL-SHAFT-DENDRITE 0 include-m$)
    (if *include-apical-1*
      (aset *APICAL-1-DENDRITE 0 include-me$)
      (if *include-apical-2*
        (aset *APICAL-2-DENDRITE 0 include-m$)
        (if *include-basal*
          (aset *BASAL-DENDRITE 0 include-m$)
          (aset *BASAL-DENDRITE 0 include-m$))))

;;; INITIALIZE-DENDRITES Initializes the length and diameter of the dendrite segments, and sets the Na and Ca currents to NIL.
(defun initialize-dendrites ()
  (aset "left apical branch" APICAL-1-DENDRITE 0 label$)
  (aset "right apical branch" APICAL-2-DENDRITE 0 label$)
  (aset "apical shaft" APICAL-SHAFT-DENDRITE 0 label$)
  (aset "basal branch" BASAL-DENDRITE 0 label$)
  (aset 10 APICAL-1-DENDRITE 0 total-segments$)
  (aset 0 APICAL-2-DENDRITE 0 total-segments$)
  (aset 5 APICAL-SHAFT-DENDRITE 0 total-segments$) ; Default - just 5 apical segments.
  (aset 10 BASAL-DENDRITE 0 total-segments$)
(tv:choose-variable-values
  ((axon-cap-mem "axon membrane capacitance [microfarads/sq-cm"] :number)
   (axon-r-mem "axon membrane resistance [ohm-cm]" :number)
   (axon-r-int "axon axoplasm resistance [ohm-cm]" :number)
   (capd-mem "dendrite membrane capacitance [microfarads/sq-cm]" :number)
   (rd-mem "dendrite membrane resistance [ohm-cm]" :number)
   (rd-int "dendrite axoplasm resistance [ohm-cm]" :number)
   (edl "dendritic leak potential [mv]" :number)
   (plot-voltages-solid "Plot all the voltages in solid lines" :boolean))
  :label "Passive Properties of dendrite Segments")

(let (DENDRITE-ARRAY (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
  (do ((segment 0 (incf segment)))
      (;* total-segments)
    (update-dendrite DENDRITE-ARRAY))))

(defun update-dendrite (DENDRITE-ARRAY)
  (let ((total-segments (aref DENDRITE-ARRAY total-segments$))
        (rdmem (if (eq DENDRITE-ARRAY "BASEL-DENDRITE") *rd-mem *rd-mem))
        (rdint (if (eq DENDRITE-ARRAY "BASEL-DENDRITE") *rd-int *rd-int))
        (capdmem (if (eq DENDRITE-ARRAY "BASEL-DENDRITE") *axon-cap-mem *capd-mem)))
    (do ((segment 0 (incf segment)))
        (;* total-segments)
      (aset ((#* (aref DENDRITE-ARRAY segment length$) 3.14159
                (aref DENDRITE-ARRAY segment diameter$) 1.0e-3)
            (aref DENDRITE-ARRAY segment g-leak$) rdmem)
            (aref DENDRITE-ARRAY segment length$) 3.14159
            (aref DENDRITE-ARRAY segment diameter$) capdmem 1.0e-5)
        (DENDRITE-ARRAY segment capacitances)
      (aset (aref DENDRITE-ARRAY segment length$) 3.14159
            (aref DENDRITE-ARRAY segment diameter$) 0.5
dendrite array segment g-axial$)))))

(defun menu-for-dendrite-currents (DENDRITE-ARRAY)
  (let ((total-segments (aref DENDRITE-ARRAY total-segments$)))
    (do ((segment 0 (incf segment)))
        (;* total-segments)
      (let (list (list (list Na Na "Na current in this segment" (list (list :include (aref DENDRITE-ARRAY segment include-na$) :modify)))
                  (list Ca "Ca current in this segment" (list (list :include (aref DENDRITE-ARRAY segment include-ca$) :modify))))
          (let ((result (tv:multiple-chosen (format nil "Currents in -A dendrite segment-2d" (aref DENDRITE-ARRAY 0 label$)
                                              (+ 1 segment))
                  (list (list (list Na Na "Na current in this segment" (list (list :include (aref DENDRITE-ARRAY segment include-na$) :modify)))
                          (list Ca "Ca current in this segment" (list (list :include (aref DENDRITE-ARRAY segment include-ca$) :modify))))
                (if (memq :modify item)
                    (selectq (car item)
                        (Na (aset nil DENDRITE-ARRAY segment include-na$))
                        (Ca (aset nil DENDRITE-ARRAY segment include-ca$)))
                    (if (memq :include item)
                        (selectq (car item)
                            (Na (aset t DENDRITE-ARRAY segment include-na$))
                            (Ca (aset t DENDRITE-ARRAY segment include-ca$)))))
          )))

(defun menu-for-soma-currents ()
  (let (list (list 'Na1 "Na1 (trigger mutha) current" (list (list :include (aref DENDRITE-ARRAY 0 include-na$) :modify))
                  (list 'Na2 "Na2 (slow tail) current" (list (list :include (aref DENDRITE-ARRAY 0 include-na2) :modify))
                  (list 'Na3 "Na3 (repetitive) current" (list (list :include (aref DENDRITE-ARRAY 0 include-na3) :modify))
                  (list 'nap "Nap current" (list (list :include (aref DENDRITE-ARRAY 0 include-nap) :modify))))
        (loop for item in result
              do (progn (if (not (memq :include item))
                             (selectq (car item)
                               (Na (aset nil DENDRITE-ARRAY segment include-na$))
                               (Ca (aset nil DENDRITE-ARRAY segment include-ca$)))
                             (memq :modify item)
                              (selectq (car item)
                                (Na (menu-for-Nad-current DENDRITE-ARRAY segment)
                                (Ca (menu-for-Cad-current DENDRITE-ARRAY segment)))
                              (memq :include item)
                              (selectq (car item)
                                (Na (aset t DENDRITE-ARRAY segment include-na$))
                                (Ca (aset t DENDRITE-ARRAY segment include-ca$)))))
          )))
(let ((result (tv:multiple-choose "Pyramidal Currents" list))
  ((include-nil nil) nil) (:modify))
(loop for item in result
  do (progn
    (if (not (memq :include item))
      (selectq (car item)
        (Na1 (setq *include-na1 nil))
        (Na2 (setq *include-na2 nil))
        (Na3 (setq *include-na3 nil))
        (NaP (setq *include-nap nil))
        (Ca (setq *include-Ca nil))
        (Cas (setq *include-Cas nil))
        (K (setq *include-K nil))
        (DR (setq *include-DR nil))
        (C (setq *include-C nil))
        (AHP (setq *include-AHP nil))
        (M (setq *include-M nil))
        (Q (setq *include-Q nil))
        (A (setq *include-A nil))))
    (if (memq :modify item)
      (selectq (car item)
        (Na1 (and (setq flag t *n'al-mod t)(menu-for-Na-curren'))
        (Na2 (and (setq flag t *na2-mod t)(menu-for-Na-current)))
        (Na3 (and (setq flag t *na3-mod t)(menu-for-Na-current)))
        (NaP (and (setq flag t *nap-mod t)(menu-for-Na-current)))
        (Ca (and (setq flag t *ca-mod t)(menu-for-Ca-current)))
        (Cas (and (setq flag t *cas-mod t)(menu-for-Cas-current)))
        (K (and (setq flag t *k-mod t)(menu-for-K-current)))
        (DR (and (setq flag t *dr-mod t)(menu-for-DR-current)))
        (C (and (setq flag t *c-mod t)(menu-for-C-current)))
        (AHP (and (setq flag t *ahp-mod t)(menu-for-AHP-current)))
        (M (and (setq flag t *m-mod t)(menu-for-M-current)))
        (Q (and (setq flag t *q-mod t)(menu-for-Q-current)))
        (A (and (setq flag t *a-mod t)(menu-for-A-current))))
      (cond (flag (variable-array-setup)(print "Updated current kinetics"))
        (update-gbars)))
      (setq v)
      (defvar v))
(--- VARIABLE-ARRAY-SETUP Before the clump run this fills (or updates) the state variable arrays for the currents that are currently enabled.
(defun variable-array-setup ()
  (do ((voltage -100.0 (+ voltage 0.1))
        (i 0 (+ i 1)))
      ((> i 1500) 1)
    (setq v)
    (aset voltage voltage-array i))
    (defun update-gbars ()
      (aset (gbar-na 1 (surf-area 'soma-radius)) SOMA gbar-na1$)
      (aset (gbar-na 2 (surf-area 'soma-radius)) SOMA gbar-na2$)
      (aset (gbar-na 3 (surf-area 'soma-radius)) SOMA gbar-na3$)
      (aset (gbar-ca (surf-area 'soma-radius)) SOMA gbar-ca$)
      (aset (gbar-cas SOMA gbar-cas$)
        (gbar-ca (surf-area 'soma-radius)) SOMA gbar-ca$)
      (aset (gbar-ahp SOMA gbar-ahp$)
        (gbar-ahp SOMA gbar-ahp$)
      (aset (gbar-q SOMA gbar-q$)
        (gbar-q SOMA gbar-q$))
    (defvar v)
(cond-every ((or *update-all-kinetics* *na1-mod*)
  (setq *a-m-na1* (a-m-na 1 voltage) *b-m-na1* (b-m-na 1 voltage))
  (*a-h-na1* (a-h-na 1 voltage) *b-h-na1* (b-h-na 1 voltage))
  (aset (m-na-inf 1) m-na-inf-array i)
  (aset (h-na-inf 1) h-na-inf-array i)
  (aset (t-m-na 1) t-m-na-array i)
  (aset (t-h-na 1) t-h-na-array i))
((or *update-all-kinetics* *na2-mod*)
  (setq *a-m-na2* (a-m-na 2 voltage) *b-m-na2* (b-m-na 2 voltage))
  (*a-h-na2* (a-h-na 2 voltage) *b-h-na2* (b-h-na 2 voltage))
  (aset (m-na-inf 2) m-na-inf-array i)
  (aset (h-na-inf 2) h-na-inf-array i)
  (aset (t-m-na 2) t-m-na-array i)
  (aset (t-h-na 2) t-h-na-array i))
((or *update-all-kinetics* *na3-mod*)
  (setq *a-m-na3* (a-m-na 3 voltage) *b-m-na3* (b-m-na 3 voltage))
  (*a-h-na3* (a-h-na 3 voltage) *b-h-na3* (b-h-na 3 voltage))
  (aset (m-na-inf 3) m-na-inf-array i)
  (aset (h-na-inf 3) h-na-inf-array i)
  (aset (t-m-na 3) t-m-na-array i)
  (aset (t-h-na 3) t-h-na-array i))
((or *update-all-kinetics* *nap-mod*)
  (setq *a-M-W* (a-m-na 2 voltage) *b-n-W* (b-m-na 2 voltage))
  (*a-h-W* (a-h-na 2 voltage) *b-h-W* (b-h-na 2 voltage))
  (aset (m-na-inf 2) m-na2-inf-array i)
  (aset (h-na-inf 2) h-W-inf-array i)
  (aset (t-m-na 2) t-m-W-array i)
  (aset (t-h-na 2) t-h-W-array i))
((or *update-all-kinetics* *ca-mod*)
  (setq *a-m- WC* (a-m-na 3 voltage) *b-m- WC* (b-m-na 3 voltage))
  (*a-h- WC* (a-h-na 3 voltage) *b-h- WC* (b-h-na 3 voltage))
  (aset (m-na-inf 3) m-na-inf-array i)
  (aset (h-na-inf 3) h-na3-inf-array i)
  (aset (t-m-na 3) t-m-W-array i)
  (aset (t-h-na 3) t-h-W-array i))
((or *update-all-kinetics* *cas-mod*)
  (setq *a-m- CAS* (a-m-na 3 voltage) *b-m- CAS* (b-m-na 3 voltage))
  (*a-h- CAS* (a-h-na 3 voltage) *b-h- CAS* (b-h-na 3 voltage))
  (aset (m-na-inf 3) m-na-inf-array i)
  (aset (h-na-inf 3) h-na3-inf-array i)
  (aset (t-m-na 3) t-m-CAS-array i)
  (aset (t-h-na 3) t-h-CAS-array i))
((or *update-all-kinetics* *ahp-mod*)
  (setq *x-ahp-inf* voltage) *x-ahp-inf-array i)
  (aset (t-x-ahp voltage) t-x-ahp-array i))
((or *update-all-kinetics* *c-mod*)
  (setq *x-c-inf* voltage) *x-c-inf-array i)
  (aset (t-x-c voltage) t-x-c-array i))
((or *update-all-kinetics* *dr-mod*)
  (setq *x-dr-inf* voltage) *x-dr-inf-array i)
  (aset (t-x-dr voltage) t-x-dr-array i))
((or *update-all-kinetics* *q-mod*)
  (setq *x-q-inf* voltage) *x-q-inf-array i)
  (aset (t-x-q voltage) t-x-q-array i))
((or *update-all-kinetics* *ahp-mod*)
  (setq *x-ahp-inf* voltage) *x-ahp-inf-array i)
  (aset (t-x-ahp voltage) t-x-ahp-array i))
((or *update-all-kinetics* *c-mod*)
  (setq *x-c-inf* voltage) *x-c-inf-array i)
  (aset (t-x-c voltage) t-x-c-array i))
((or *update-all-kinetics* *dr-mod*)
  (setq *x-dr-inf* voltage) *x-dr-inf-array i)
  (aset (t-x-dr voltage) t-x-dr-array i))
((or *update-all-kinetics* *q-mod*)
  (setq *x-q-inf* voltage) *x-q-inf-array i)
  (aset (t-x-q voltage) t-x-q-array i)))
(setq *vclamp-command-flag* (if (equal command "Command array") 2 1))
(+ 1000 (fixr (* 10 voltage)))))

(defun menu-for-soma-voltage-stimulus ()
  (setq command (if (+ 1 *vclamp-command-flag*) "Command array" "Entered steps"))
  (by:choose-variable-values "((command "Voltage clamp by" :choose ("Command array" "Entered steps"))
  (x:voltage-commands "Enter name of voltage command array " :eval-form)
  (x:v1 "Step 1 amplitude [mv]" :number)
  (x:v2 "Step 2 amplitude [mv]" :number)
  (x:v3 "Step 3 amplitude [mv]" :number)
  (x:v4 "Step 4 amplitude [mv]" :number)
  (x:v5 "Step 5 amplitude [mv]" :number)
  (x:duration "For how long (this will change the duration of the simulation) [ms]" :number))
  (label "Setting Up Voltage Clamp")
  (setq *vclamp-command-flag* (if (equal command "Command array") 1 2)))

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MEW-FOR-SOAM-CURRM-MMMM Sets the current, stimulus to the soma.

(defun menu-for-soma-current-stimulus ()
  (setq command (if (= 1 *iclamp-command-flag) "Command array" "Entered steps"))
  (tv:choose-variable-values
   '((*include-soma-current "Do you want current injected into the soma?" :boolean)
     (command "Current clamp by " :choose ("Command array" "Entered steps"))
     (xstim-1 "Step 1 amplitude [na]" :number)
     (xstim-2 "Step 2 amplitude [na]" :number)
     (xstim-3 "Step 3 amplitude [na]" :number)
     (xstim-4 "Step 4 amplitude [na]" :number)
     (xstim-5 "Step 5 amplitude [na]" :number)
     (duration "For how long (this will change the duration of the simulation) [ms]" :number)
   )
  )
(setq *iclamp-command-flag (if (equal command "Command array") 2)

SET-SOMA-VOLTAGE-STIMULUS Set up the voltage clamp.

(defun set-soma-voltage-stimulus (time-step)
  (setq *clamp-voltage (if (= 1 *iclamp-command-flag) (aref *voltage-command* time-step)
    (cond ((= time-step 0) *v1)
      ((= time-step (fixr time-step 1)) *v2)
      ((= time-step (fixr time-step 2)) *v3)
      ((= time-step (fixr time-step 3)) *v4)
      (T *clamp-voltage))))

MENU-FOR-DENDRITE-STIMULUS Sets the current stimulus to the dendrite and the segment that is to be injected.

(defun menu-for-dendrite-stimulus ()
  (tv:choose-variable-values
   '((*include-dendrite-current "Do you want current injected into the apical dendrite shaft?" :boolean)
     (stim-seg "Segment to inject current into - " :number)
     (xden-stim-1 "Step 1 amplitude [na]" :number)
     (xden-stim-2 "Step 2 amplitude [na]" :number)
     (xden-stim-3 "Step 3 amplitude [na]" :number)
     (xden-stim-4 "Step 4 amplitude [na]" :number)
     (xden-stim-5 "Step 5 amplitude [na]" :number)
     (xden-stim-6 "Step 6 amplitude [na]" :number)
     (xden-stim-7 "Step 7 amplitude [na]" :number)
     (xden-stim-8 "Step 8 amplitude [na]" :number)
     (xden-stim-9 "Step 9 amplitude [na]" :number)
     (xden-stim-10 "Step 10 amplitude [na]" :number)
     (duration "For how long (this will change the duration of the simulation) [ms]" :number)
   )
  )
(setq *current-stimulus-segment (- *stim-seg 1))

MENU-FOR-DENDRITE-SYNAPSE Sets the alpha function for the dendrite synapse.

(defun menu-for-dendrite-synapse ()
  (tv:choose-variable-values
   '((*include-dendrite-synapse "Do you want a synapse on the left apical dendrite branch?" :boolean)
     (dendrite-synapse-tau "Dendrite alpha synapse time constant [ms]" :number)
     (dendrite-synapse-amplitude "Dendrite synapse amplitude [micro-S]" :number)
     (syn-seg "Segment with synapse " :number)
     (start-dendrite-synapse "Start the synapse conductance [ms]" :number)
   )
  )
(set-up-synapse DENDRITE-SYNAPSE *dendrite-synapse-tau *dendrite-synapse-amplitude)

MENU-FOR-SOMA-SYNAPSE Sets the alpha function for the soma synapse.

(defun menu-for-soma-synapse ()
  (tv:choose-variable-values
   '((*include-soma-synapse "Do you want a soma synapse?" :boolean)
     (soma-synapse-tau "Soma alpha synapse time constant [ms]" :number)
     (soma-synapse-amplitude "Soma synapse amplitude [micro-S]" :number)
     (start-soma-synapse "Start the synapse conductance [ms]" :number)
   )
  )
(set-up-synapse SOMA-SYNAPSE *soma-synapse-tau *soma-synapse-amplitude)
;;; SET-SOMA-CURRENT-STIMULUS Set up the injected current to the soma, if any.
(defun set-soma-current-stimulus ()
  (let ((time (*time-for-steady-state))
    (let ((time (- time 0.0)))
      (if include-soma-current
        (setq *i-stim (*random* 1) (*time* time)
          (cond (time *t-stim-1) *i-stim-1)
            (time *t-stim-2) *i-stim-2)
              (time *t-stim-3) *i-stim-3)
                (time *t-stim-4) *i-stim-4)
                  (t *i-stim-5))))
  (setq *i-stim 0.0)))

;;; SET-DENDRITE-CURRENT-STIMULUS Set up the injected current to the dendrite, if any.
(defun set-dendrite-current-stimulus ()
  (let ((time (*time-for-steady-state))
    (if include-dendrite-current
      (setq *i-den-stim (*random* 1) *i-den-stim)
      (time *t-den-stim-1) *i-den-stim-1)
        (time *t-den-stim-2) *i-den-stim-2)
          (time *t-den-stim-3) *i-den-stim-3)
            (time *t-den-stim-4) *i-den-stim-4)
              (time *t-den-stim-5) *i-den-stim-5)
                (time *t-den-stim-6) *i-den-stim-6)
                  (time *t-den-stim-7) *i-den-stim-7)
                    (time *t-den-stim-8) *i-den-stim-8)
                      (time *t-den-stim-9) *i-den-stim-9)
                        (t *i-den-stim-10)))))

;;; SET-UP-SYNAPSE Fills the array argument with an alpha function that is set by the time-constant and amplitude.
;;; arguments. The array is 10000 dt's long.
(defun set-up-synapse (array tau amplitude)
  (dotimes (i 10000)
    (if (time (* i (1/dt))) -10.0) (aset 0.0 array)
      (aset (* i dt amplitude (exp (/ time (* i (1/dt))))) array)))

;;; INITIALIZE-SOMA-VOLTAGE Sets the initial soma voltage to the holding voltage.
(defun initialize-soma-voltage ()
  (aset *e-holding SOMA voltage$)
  (aset *e-holding SOMA voltage-est1$)
  (aset *e-holding SOMA voltage-est2$))

;;; INITIALIZE-SOMA STATES sets all the state variables under the assumption that the system is at steady state,!
;;; with the membrane voltage at the holding voltage (now this is "e-holding"). For example, the activation and
;;; inactivation variables are set to their "inf" values for the holding potential, and the derivatives are set
;;; to 0. Once the state variables are set, the derivative of the membrane voltage is calculated using the
;;; circuit equation.
(defun initialize-soma-states ()
  (let* ((g-na1) (g-na2) (g-na3)
    (g-cl) (g-total) (e-eff) (left-voltage) (right-voltage-1) (right-voltage-2)
      (this-voltage) (g-shunt)
        (g-coupling-left) (g-coupling-right-1) (g-coupling-right-2)
          (voltage (aref SOMA voltage-index) voltage-index (+ 1000 (* time (10 10 voltage)))))))
  (setq *soma-synapse-step 0)
  (aset *ca-c6hc-shell1-rest SOMA ca-c6hc-shell1$)
  (aset *ca-c6hc-shell12-rest SOMA ca-c6hc-shell12$)
  (aset .0 SOMA ca-c6hc-shell-dot$)
  (aset *ca-c6hc-shell12-rest SOMA ca-c6hc-shell12$)
  (aset .0 SOMA ca-c6hc-shell-dot$)
  (aset (aref m-na1-inf-array voltage-index) SOMA m-na1$)
  (aset (aref h-na1-inf-array voltage-index) SOMA h-na1$)
  (aset .0 SOMA m-na2-dot$)
  (aset (aref m-na2-inf-array voltage-index) SOMA m-na2$)
  (aset (aref h-na2-inf-array voltage-index) SOMA h-na2$)
  (aset .0 SOMA h-na2-dot$)
  (aset *Fast Na 1 current (Trig) (aref x-dr-inf-array voltage-index) SOMA x-dr$)
  (aset *Fast Na 2 current (Tail) (aref x-dr-inf-array voltage-index) SOMA x-dr$)
  (aset .0 SOMA h-na3-dot$)
  (aset (aref m-na3-inf-array voltage-index) SOMA m-na3$)
  (aset (aref h-na3-inf-array voltage-index) SOMA h-na3$)
  (aset .0 SOMA m-na3-dot$)
  (aset .0 SOMA h-na3-dot$)
  (aset *Fast Na 3 current (Rep) (aref x-dr-inf-array voltage-index) SOMA x-dr$)
  (aset (aref y-a-inf-array voltage-index) SOMA y-a$)
  (aset (aref y-a-inf-array voltage-index) SOMA y-a$)
  (aset .0 SOMA x-a-dot$)
  (aset .0 SOMA y-a-dot$)
  (aset *A current (aref x-dr-inf-array voltage-index) SOMA x-dr$)
  (aset (aref y-dr-inf-array voltage-index) SOMA y-dr$)
  (aset (aref y-dr-inf-array voltage-index) SOMA y-dr$)
  (aset .0 SOMA x-dr-dot$)
(seto 0.0 SOMA y-dr-dot$) ; DR current
(seto 0.0 SOMA x-m-dot$) ; M current
(seto (aref y-ahp-inf-array voltage-index) SOMA y-ahp$)
(seto 0.0 SOMA y-ahp-dot$)
(seto (w-ahp-inf (aref SOMA ca-conc-shell$)) SOMA w-ahp$)
(seto (w-c-inf (aref SOMA ca-conc-shell$)) SOMA w-c$)
(seto 0.0 SOMA w-c-dot$)
(seto (aref z-ahp-inf-array voltage-index) SOMA z-ahp$)
(seto 0.0 SOMA z-ahp-dot$)
(seto (aref x-n-inf-array voltage-index) SOMA x-n$)
(seto 0.0 SOMA x-n-dot$)
(seto (aref x-c-inf-array voltage-index) SOMA x-c$)
(seto 0.0 SOMA x-c-dot$)
(seto (aref y-c-inf-array voltage-index) SOMA x-c$)
(seto 0.0 SOMA y-c-dot$)
(seto (aref y-ahp-inf-array voltage-index) SOMA y-ahp$)
(seto 0.0 SOMA y-ahp-dot$)
(seto (aref x-cas-inf-array voltage-index) SOMA x-cas$)
(seto 0.0 SOMA x-cas-dot$)
(seto (aref s-ca-inf-array voltage-index) SOMA s-ca$)
(seto 0.0 SOMA s-ca-dot$)
(seto (aref w-ca-inf-array voltage-index) SOMA w-ca$)
(seto 0.0 SOMA w-ca-dot$)
(seto 0.0 SOMA w-ca-dot$)
(seto (aref x-nap-inf-array voltage-index) SOMA x-nap$)
(seto 0.0 SOMA x-nap-dot$)
(seto (aref x-nap-inf-array voltage-index) SOMA x-nap$)
(seto 0.0 SOMA x-nap-dot$)
(seto (aref s-ca-inf-array voltage-index) SOMA s-ca$)
(seto 0.0 SOMA s-ca-dot$)
(seto 0.0 SOMA w-ca-dot$)
(seto ncap SOMA capacitances$)
(seto 0.0 SOMA g-synapses$)
;; Now calculate the conductances based on the state variable values. If a given current has been disabled,;
;; then the appropriate conductance is set to 0.
(setq g-nal1 (if *include-nal (g-nal (aref SOMA gbar-nal$)(aref SOMA m-nal$)(aref SOMA h-nal$)) 0.0)
g-na2 (if *include-na2 (g-na2 (aref SOMA gbar-na2$)(aref SOMA m-na2$)(aref SOMA h-na2$)) 0.0)
g-na3 (if *include-na3 (g-na3 (aref SOMA gbar-na3$)(aref SOMA m-na3$)(aref SOMA h-na3$)) 0.0)
g-c (if *include-c (g-c (aref SOMA gbar-c$) (aref SOMA h-c$)) (aref SOMA v-c$) (aref SOMA w-c$)) 0.0)
g-m (if *include-m (g-m (aref SOMA gbar-m$) (aref SOMA h-m$)) (aref SOMA v-m$) (aref SOMA w-m$) 0.0)
g-a (if *include-a (g-a (aref SOMA gbar-a$) (aref SOMA h-a$)) (aref SOMA v-a$) (aref SOMA w-a$) 0.0)
g-dr (if *include-dr (g-dr (aref SOMA gbar-dr$) (aref SOMA h-dr$)) (aref SOMA v-dr$) (aref SOMA w-dr$) 0.0)
g-cas (if *include-cas (g-cas (aref SOMA gbar-cas$) (aref SOMA h-cas$)) (aref SOMA v-cas$) (aref SOMA w-cas$) 0.0)
g-ca (if *include-ca (g-ca (aref SOMA gbar-ca$) (aref SOMA h-ca$)) (aref SOMA v-ca$) (aref SOMA w-ca$) 0.0)
g-nap (if *include-nap (g-nap (aref SOMA gbar-nap$) (aref SOMA h-nap$)) (aref SOMA v-nap$) (aref SOMA w-nap$) 0.0)
g-leak (if *include-leak (g-leak) (aref SOMA h-leak) (aref SOMA v-leak) (aref SOMA w-leak) 0.0)
g-shunt (if *include-shunt (g-shunt) (aref SOMA h-shunt) (aref SOMA v-shunt) (aref SOMA w-shunt) 0.0)
(eff (g-eff (aref SOMA h-eff) (aref SOMA v-eff) (aref SOMA w-eff) 0.0)
(set (g-total) (g-total))
;; Now calculate the derivative of the voltage based on the steady-state values for the state variables at
;; the holding potential.
(left-voltage (if *is-constant-injection (g-parallel (aref BASAL-DENDRITE 1 voltage$) (aref BASAL-DENDRITE 0 voltage$) (aref BASAL-DENDRITE 1 voltage$) (aref SOMA voltage$)) 0.0)
g-coupling-left (if *is-constant-injection (g-parallel (aref BASAL-DENDRITE 1 voltage$) (aref BASAL-DENDRITE 0 voltage$) (aref BASAL-DENDRITE 1 voltage$) (aref SOMA voltage$)) 0.0)
(right-voltage-1 (if *is-constant-injection (g-parallel (aref APICAL-SHAFT-DENDRITE 1 voltage$) (aref APICAL-SHAFT-DENDRITE 0 voltage$) (aref APICAL-SHAFT-DENDRITE 1 voltage$) (aref SOMA voltage$)) 0.0)
g-coupling-right-1 (if *is-constant-injection (g-parallel (aref APICAL-SHAFT-DENDRITE 1 voltage$) (aref APICAL-SHAFT-DENDRITE 0 voltage$) (aref APICAL-SHAFT-DENDRITE 1 voltage$) (aref SOMA voltage$)) 0.0)
(right-voltage-2 (if *is-constant-injection (g-parallel (aref APICAL-SHAFT-DENDRITE 2 voltage$) (aref APICAL-SHAFT-DENDRITE 1 voltage$) (aref APICAL-SHAFT-DENDRITE 2 voltage$) (aref APICAL-SHAFT-DENDRITE 1 voltage$)) 0.0))
;; "V-DOT" gets the derivative of the voltage. Then store it as the last permanent value.
(setv v-dot g-coupling-left g-coupling-right-1 g-coupling-right-1 g-total e-eff left-voltage right-voltage-1 right-voltage-2 *caps (+ *i-constant-injection *i-stim))
SOMA voltage-dot$)

---

**INITIALIZE-DENDRITE-VOLTAGES** Sets the initial dendrite segment voltages to the dendrite leak potential.

(defun initialize-dendrite-voltages ()
  (do ((DENDRITE-ARRAY (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
       (segment 0 (incf segment)))
    (do ((segment (aref DENDRITE-ARRAY total-segments) 0 total-segments))
        (aset ed-1 DENDRITE-ARRAY segment voltage-est1$)$)

**INITIALIZE-DENDRITE-STATES** sets all the state variables under the assumption that the system is at steady state, with the membrane voltages at the holding voltage (now this is 7 text). For example, the activation and inactivation variables are set to their "inf" values for the holding potential, and the derivatives are set to 0. Once the state variables are set, the derivatives of the membrane voltages are calculated using the circuit equation.

(defun initialize-dendrite-states ()
  (do ((DENDRITE-ARRAY (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
        (segment 0 (incf segment)))
    (do ((segment (incf segment))
         (a segment total-segments))
        (do ((voltage (aref DENDRITE-ARRAY segment voltage-est1$)$) (voltage-index 1000 (fixr (+ 10 voltage))))
            (aset ed-1 DENDRITE-ARRAY segment voltage-est1$)$)

**DENDRITE-DERIVATIVE** This function finds the derivative of the dendrite segment voltage given the current estimated state.

(defun dendrite-derivative (DENDRITE-ARRAY total-segments segment i-stim e-eff)
  (let ((this-voltage (aref DENDRITE-ARRAY segment voltage-est1$)$)
             (voltage-index (+ 1000 (fixr (+ 10 voltage))))
             (include-na (aref DENDRITE-ARRAY segment include-na$))
             (include-ca (aref DENDRITE-ARRAY segment include-ca$))
             (g-coupling-left (g-parallel (aref DENDRITE-ARRAY segment g-axial$) (aref DENDRITE-ARRAY 0 g-axial$)))
             (g-coupling-right-1 (g-parallel (aref DENDRITE-ARRAY 0 g-axial$) (aref DENDRITE-ARRAY g-coupling-right-2)))
             (g-coupling-right-2 (g-parallel (aref DENDRITE-ARRAY 0 g-axial$) g-coupling-right-1))
             (g-coupling-left (g-parallel g-coupling-right-1 g-coupling-right-2)))
    (let ((voltage (aref DENDRITE-ARRAY segment voltage-est1$)$))
        (do ((segment total-segments) 0 total-segments))
            (aset ed-1 DENDRITE-ARRAY segment voltage-est1$)$)

---

DFNDRM-DJW4MT 7X* AnctiOn TAds the derivative of the dendrite moment voteap shen the current estimated state.
(setq right-voltage-1 (aref DENDRITE-ARRAY segment voltage-estis) g-coupling-right-1 0.0))
(if (and (EQ DENDRITE-ARRAY APICAL-SHAFT-DENDRITE) *include-apical-2)
  ; left branch with r branch gets r-v-2 as r
  (setq right-voltage-2 (aref APICAL-2-DENDRITE 0 voltage-estis) g-coupling-right-2 (g-parallel (aref APICAL-2-DENDRITE 0 g-axial$) (aref DENDRITE-ARRAY segment g-axial$)))
  ; (iff no segments distal
  (setq right-voltage-2 (aref DENDRITE-ARRAY segment voltage-estis) g-coupling-right-2 0.0))
)((= total-segments (+ 1 segment)) ; At the distal segment of this part of the tree, and there is more
  ; than one segment, so I will be seg proximal in same part of tree
  (setq left-voltage (aref DENDRITE-ARRAY (_ segment 1) voltage-estis) g-coupling-left (g-parallel (aref DENDRITE-ARRAY segment g-axial$) (aref DENDRITE-ARRAY segment g-axial$)))
  ; (iff no segments distal
  (setq left-voltage (aref DENDRITE-ARRAY segment voltage-estis) g-coupling-left 0.0))
  (if (and (EQ DENDRITE-ARRAY APICAL-1-DENDRITE) *include-apical-1)
    ; if shaft w/0 branch then r->v-1 will be proximal seg off
    (setq right-voltage-1 (aref APICAL-1-DENDRITE 0 voltage-estis) g-coupling-right-1 (g-parallel (aref APICAL-1-DENDRITE 0 g-axial$) (aref DENDRITE-ARRAY segment g-axial$))
      ; (iff no segments distal
      (setq right-voltage-1 (aref DENDRITE-ARRAY segment voltage-estis) g-coupling-right-1 0.0))
    (if (or (EQ DENDRITE-ARRAY MAL-1-DENDRITE) (EQ DENDRITE-ARRAY APICAL-2-DENDRITE))
      ; prox seg of either l or r branch will get distal shaft as l-v
      (setq left-voltage (aref APICAL-SHAFT-DENDRITE (- *total-apical-shaft-segments 1) voltage-estis) g-coupling-left (g-parallel (aref APICAL-SHAFT-DENDRITE (- *total-apical-shaft-segments 1) g-axial$) (aref DENDRITE-ARRAY segment g-axial$))
        ; prox seg of apical or basal shaft will get soma as l-v
        (setq left-voltage (aref SOMA voltage-estis) g-coupling-left (g-parallel (aref SOMA g-axial$) (aref DENDRITE-ARRAY segment g-axial$)))
        ; prox seg of all parts of tree w/o at least 2 segs will get seg 2 from same
        ; part as r-v-1, no r-v-2
        (setq left-voltage (aref DENDRITE-ARRAY (+ 1 segment) voltage-estis) right-voltage-2 (aref DENDRITE-ARRAY segment voltage-estis))
        ; (iff no segments distal
        (setq left-voltage (aref DENDRITE-ARRAY segment voltage-estis) right-voltage-2 (aref DENDRITE-ARRAY segment voltage-estis) g-coupling-left 0.0))
      (if (or (EQ DENDRITE-ARRAY MAL-1-DENDRITE) (EQ DENDRITE-ARRAY APICAL-2-DENDRITE))
        ; prox seg of either l or r branch will get distal shaft as l-v
        (setq right-voltage-1 (aref APICAL-1-DENDRITE 0 voltage-estis) g-coupling-right-1 (g-parallel (aref APICAL-1-DENDRITE 0 g-axial$) (aref DENDRITE-ARRAY segment g-axial$)))
        ; prox seg of all parts of tree w/o at least 2 segs will get seg 2 from same
        ; part as r-v-1, no r-v-2
        (setq right-voltage-1 (aref DENDRITE-ARRAY (+ 1 segment) voltage-estis) right-voltage-2 (aref DENDRITE-ARRAY segment voltage-estis))
        ; (iff no segments distal
        (setq right-voltage-1 (aref DENDRITE-ARRAY segment voltage-estis) right-voltage-2 (aref DENDRITE-ARRAY segment voltage-estis) g-coupling-right-1 0.0))
      (if (or (EQ DENDRITE-ARRAY MAL-1-DENDRITE) (EQ DENDRITE-ARRAY APICAL-2-DENDRITE))
        ; prox seg of either l or r branch will get distal shaft as l-v
        (setq left-voltage (aref APICAL-1-DENDRITE 0 voltage-estis) g-coupling-left (g-parallel (aref APICAL-1-DENDRITE 0 g-axial$) (aref DENDRITE-ARRAY segment g-axial$)))
        ; prox seg of all parts of tree w/o at least 2 segs will get seg 2 from same
        ; part as r-v-1, no r-v-2
        (setq left-voltage (aref DENDRITE-ARRAY (+ 1 segment) voltage-estis))
        ; (iff no segments distal
        (setq left-voltage (aref DENDRITE-ARRAY segment voltage-estis))
      )
    ; "V-DOT" gets the derivative of the segment voltage. Then store it as the last permanent value.
    (v-dot g-coupling-left g-coupling-right-1 g-coupling-right-2 g-total e-eff left-voltage this-voltage right-voltage-1 right-voltage-2 (aref DENDRITE-ARRAY segment capacitances) i-stim))
)

; ; LOAD-FIRST-ESTIMATES starts the estimation loop with an initial "latest" estimate (est2) of the voltages.
; ; "prevvoltage" is calculated from the previous voltage, the previous derivative of the voltage, and the time step.
; ; The initial "est2" is calculated using an open integration formula.
; (defun load-first-estimates ()
; ; First get all the dendrite segments.
; (dolist (DENDRITE-ARRAY (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
; (if (aref DENDRITE-ARRAY 0 include-mes)
;   (do (segment 0 (incf segment))
;     (aset (+ (aref DENDRITE-ARRAY segment voltages) ; Estimated voltage = Previous vol. +
;       (+ (aref DENDRITE-ARRAY segment voltage-dot$))
;       (= dvt (aref DENDRITE-ARRAY segment voltage-dot$))))
;   DENDRITE-ARRAY segment voltage-est$)
; ))
; 254 255
Now for the soma.

(cond (or *steady-state-run* *iclamp-run*)
  (setq (+ (aref SOMA voltage-est2$) (* dt (aref SOMA voltage-dot$))) SOMA voltage-est2$)
  ;; For the voltage clamp the soma voltage is always the current clamp voltage.
  (vclamp-run)
  (setq (if (+ 1 *iclamp-command-flag*) (aref *voltage-command* *time-step*) *clamp-voltage*)
    SOMA voltage-est2$)
  (aset (if (+ 1 *iclamp-command-flag*) (aref *voltage-command* *time-step*) *clamp-voltage*)
    SOMA voltage-est2$)))

(defvar flag t)

;;; TEST-ESTIMATES - IF ANY of the estimated voltages are not within the convergence criterium, then immediately
;;; exit with "nil", otherwise return "t".
(defun test-estimates ()
  (setq flag t)
  (and (test (aref SOMA voltage-est1$)
              (aref SOMA voltage-est2$))
       (dolist (DENDRITE-ARRAY
                (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
           (if (equal DENDRITE-ARRAY "end")
               (return T))
           (if (not (if (aref DENDRITE-ARRAY 0 INCLUDE-MES)
                        (do ((segment (incf segment)))
                          (* segment (aref DENDRITE-ARRAY 0 total-segments$))
                            (if (not (test (aref DENDRITE-ARRAY segment voltage-est1$)
                                          (aref DENDRITE-ARRAY segment voltage-est2$)))
                              (return nil)))))
       (return nil))))

;;; TEST-FOR-RESTING-STATE Checks to see if the compartment voltages have settled down to a quasi-resting state by
;;; testing all the stored derivatives of the compartment voltages. If the magnitude of ALL the derivatives are
;;; less than *dot-epsilon, then return "t". The system is then assumed to be at steady state.
(defun test-for-resting-state ()
  (setq flag t)
  (and (< (abs (aref SOMA voltage-dot$)) *dot-epsilon)
       (or (dolist (DENDRITE-ARRAY
                    (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
             (if (aref DENDRITE-ARRAY 0 INCLUDE-MES)
                 (do ((segment (incf segment)))
                   (* segment (aref DENDRITE-ARRAY 0 total-segments$))
                     (if (not (< (abs (aref DENDRITE-ARRAY segment voltage-dot$)) *dot-epsilon))
                         (setq flag nil))))))

;;; G-PARALLEL
(defun g-parallel (g1 g2)
  (if (> g1 g2 4.0)
      (+ (* 2.0 g1)(* 2.0 g2)))

;;; STORE-NEW-SOMA-ESTIMATE Make the old soma voltage estimate (est1) equal to the new voltage estimate (est2).
(defun store-new-soma-estimate ()
  (aset (= 0.5 (+ (aref SOMA voltage-est1$)(aref SOMA voltage-est2$))) SOMA voltage-est1$))

;;; STORE-NEW-DENDRITE-ESTIMATES Make the old dendrite voltage estimate (est1) equal to the new voltage estimate
;;; (est2).
(defun store-new-dendrite-estimates ()
  (dolist (DENDRITE-ARRAY
           (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
       (if (aref DENDRITE-ARRAY 0 INCLUDE-MES)
           (do ((segment (incf segment)))
             (* segment (aref DENDRITE-ARRAY 0 total-segments$))
               (aset (= 0.5 (+ (aref DENDRITE-ARRAY segment voltage-est1$)
                                (aref DENDRITE-ARRAY segment voltage-est2$)))
                 (DENDRITE-ARRAY segment voltage-est1$)))))

;;; STORE-NEW-SOMA-VOLTAGE Make the old soma voltage equal to the new voltage estimate (est2).
(defun store-new-soma-voltage ()
  (aset (aref SOMA voltage-est2$) SOMA voltage$))

;;; STORE-NEW-DENDRITE-VOLTAGES Make the old dendrite voltage equal to the new voltage estimate (est2).
(defun store-new-dendrite-voltages ()
  (dolist (DENDRITE-ARRAY
           (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
       (if (aref DENDRITE-ARRAY 0 INCLUDE-MES)
           (do ((segment (incf segment)))
             (* segment (aref DENDRITE-ARRAY 0 total-segments$))
               (aset (aref DENDRITE-ARRAY segment voltage-est2$) DENDRITE-ARRAY segment voltages$))))
::: SET-DENDRITE-STATES-AND-V-DOTS Calculates the conductances based on the current voltage estimate (estv).

::: Based on these values the derivative of the voltage (est-v-dot) is calculated according to KCL. If the

::: loop-done flag is set, then the derivative of the voltage, the state variables and their derivatives are

::: stored as the final estimates (voltage-dot, m-na, m-na-dot, etc.).

(defun set-dendrite-states-and-v-dots (loop-done)
  (do ((DENDRITE-ARRAY (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE)))
      (if (aref DENDRITE-ARRAY 0 INCLUDE-NESS)
        (let ((total-segments (aref DENDRITE-ARRAY 0 total-segments)))
          (do ((segment 0 (incf segment))
               ((segment total-segments)

            (let ((v-est (aref DENDRITE-ARRAY segment voltage-est))
                  (voltage-index (+ 1000 (* 10 v-est))))
                (include-na (aref DENDRITE-ARRAY segment include-na)))
              (include-c (aref DENDRITE-ARRAY segment include-c))
              (m-na-est) (h-na-est)
              (s-ca-est) (w-ca-est)
              (e-eff) (g-na-est) (g-synapse) (i-stim)
              (g-leak) (g-total-est))
            (if include-na
                (setq m-na-est (trap-approx (aref DENDRITE-ARRAY segment m-na)
                                            (aref m-na-inf-array voltage-index)
                                            (aref t-m-na-array voltage-index))
                (setq h-na-est (trap-approx (aref DENDRITE-ARRAY segment h-na)
                                             (aref h-na-inf-array voltage-index)
                                             (aref t-h-na-array voltage-index)))
                (setq g-na-est (= (aref DENDRITE-ARRAY segment gbar-na) m-na-est m-na-est h-na-est))
            )
            (if include-c
                (setq s-ca-est (trap-approx (aref DENDRITE-ARRAY segment s-ca)
                                             (aref s-ca-inf-array voltage-index)
                                             (aref t-s-ca-array voltage-index))
                (setq w-ca-est (trap-approx (aref DENDRITE-ARRAY segment w-ca)
                                             (aref w-ca-inf-array voltage-index)
                                             (aref t-w-ca-array voltage-index)))
            )

            g-ca-est (g-ca (aref DENDRITE-ARRAY segment gbar-ca) s-ca-est w-ca-est)
            (setq g-ca-est 0.0)
            )
            (if (and include-synapse (= segment *synapse-segment)
                    (= *time *start-dendrite-synapse)
                    (= *dendrite-synapse-step 10000))
                (setq g-synapse (aref DENDRITE-ARRAY segment *dendrite-synapse-step)
                  (setq g-synapse (* g-synapse (aref dendrite-synapse-step (+ *dendrite-synapse-step step)))))
          )

          (setq i-stim (if (and (EQ DENDRITE-ARRAY APICAL-SHAFT-DENDRITE)
                                (aref i-stim-segment *current-stimulus-segment))
              (include current injection
              (= i-stim 0.0)
              g-leak (aref DENDRITE-ARRAY segment g-leak)
              g-total-est (+ g-na-est g-ca-est g-leak g-synapse)
              e-eff (/ (+ (+ (= g-na-est me-na) (= g-ca-est me-ca) (= g-leak me-leak) (= g-synapse me-synapse))
                  g-total-est))

              (:If still in the loop, then voltage derivative is just an estimate, otherwise it is stored.
              (cond ((not loop-done)
                        (aset (dendrite-derivative DENDRITE-ARRAY total-segments segment i-stim g-total-est e-eff)
                              DENDRITE-ARRAY total-segments segment i-stim g-total-est e-eff)
                  t)
              )
              )
          )
          )
        )
      )
    )
)

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SET-SOMA-STATES-AND-V-DOT-FOR-CURRENT-CLAMP Calculates the conductances based on the current voltage estimate.

Based on these values the derivative of the voltage (..est-dot) is calculated according to KCL. If the loop-done flag is set, then the derivative of the voltage, the state variables and their derivatives are stored as the final estimates (voltage-dot, m-nal, m-na2-dot, etc.).

(defun set-soma-states-and-v-dot-for-current-clamp (loop-done)
  (let* ((v (aref SOMA voltage-est)) ;'V' is the current voltage estimate
    (m-na1-est) (h-na1-est) (g-na1-est) (m-na2-est) (h-na2-est) (g-na2-est) (m-na3-est) (h-na3-est) (g-na3-est) (x-est) (g-est) (w-est) (z-est) (y-est) (w-ahp-est) (g-ahp-est) (voltage-index (+ 1000 (fixr (* 1 OM))))
      (cond-every
        (*include-nal (setq m-nal-est (trap-approx (aref SOMA m-nal$) (aref SOMA m-nal-dot$)
          (aref m-nal-inf-array voltage-index) (aref t-m-nal-array voltage-index)
          (aref t-h-na1-array voltage-index)
          (aref t-m-na1-array voltage-index)
          (aref t-h-na1-array voltage-index)))
      (not *include-nal) (setq g-nal-est 0.0))
        (*include-na2 (setq m-na2-est (trap-approx (aref SOMA m-na2$) (aref SOMA m-na2-dot$)
          (aref m-na2-inf-array voltage-index) (aref t-m-na2-array voltage-index)
          (aref t-h-na2-array voltage-index) (aref t-m-na2-array voltage-index)
          (aref t-h-na2-array voltage-index)))
      (not *include-W) (setq g-W-est 0.0))
        (*include-nap (setq x-nap-est (trap-approx (aref SOMA x-nap$) (aref SOMA x-nap-dot$)
          (aref x-nap-inf-array voltage-index) (aref t-x-nap-array voltage-index)))
      (not *include-nap) (setq g-nap-est 0.0))
        (*include-cas (setq x-cas-est (trap-approx (aref SOMA x-cas$) (aref SOMA x-cas-dot$)
          (aref x-cas-inf-array voltage-index) (aref t-x-cas-array voltage-index)))
      (not *include-cas) (setq g-ca-est 0.0))
        (*include-a (setq x-a-est (trap-approx (aref SOMA x-a$) (aref SOMA x-a-dot$) (aref x-a-inf-array voltage-index)))
      (not *include-a) (setq g-a-est 0.0))
        (*include-c (setq x-c-est (trap-approx (aref SOMA x-c$) (aref SOMA x-c-dot$) (aref x-c-inf-array voltage-index)))
      (not *include-c) (setq g-ca-est 0.0))
        (*include-b (setq x-b-est (trap-approx (aref SOMA x-b$) (aref SOMA x-b-dot$) (aref x-b-inf-array voltage-index)))
      (not *include-b) (setq g-b-est 0.0))
        (*include-coupling (setq x-coupling-est (trap-approx (aref SOMA x-coupling$) (aref SOMA x-coupling-dot$) (aref x-coupling-inf-array voltage-index) (aref t-x-coupling-array voltage-index)))
      (not *include-coupling) (setq g-coupling-est 0.0))
        (*include-decoupling (setq x-decoupling-est (trap-approx (aref SOMA x-decoupling$) (aref SOMA x-decoupling-dot$) (aref x-decoupling-inf-array voltage-index) (aref t-x-decoupling-array voltage-index)))
      (not *include-decoupling) (setq g-decoupling-est 0.0))
        (*include-synapse (setq x-synapse-est (trap-approx (aref SOMA x-synapse$) (aref SOMA x-synapse-dot$) (aref x-synapse-inf-array voltage-index) (aref t-x-synapse-array voltage-index)))
      (not *include-synapse) (setq g-synapse-est 0.0))))

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(setq 9-est 0.0)
(*include-ahp (setq z-ahp-est (trap-approx (aref SOMA z-ahp$) (aref SOMA z-ahp-dot$) (aref z-ahp-inf-array voltage-index) y-ahp-est (trap-approx (aref SOMA y-ahp$) (aref SOMA y-ahp-dot$) (aref y-ahp-inf-array voltage-index) w-ahp-est (g-ahp *gbar-ahp x-c-est y-c-est w-ahp-est)))
((not *include-ahp) (setq g-ahp-est 0.0))
(*include-m (setq x-m-est (trap-approx (aref SOMA x*$) (aref SMA x-m-dot$) (aref x-m-inf-array voltage-index)
(aref t-x-m-array voltage-index)) g-s-est (* (aref SOMA gbar-m$) x-m-est)))
((not *include-m) (setq g-m-est 0.0))
(*include-dr (setq x-dr-est (trap-approx (aref SOMA x-dr$) (aref SOMA x-dr-dot$) (aref x-dr-inf-array voltage-index) (aref t-x-dr-array voltage-index)
(y-dr-est (trap-approx (aref SOMA y-dr$) (aref SOMA y-dr-dot$) (aref y-dr-inf-array voltage-index) (aref t-y-dr-array voltage-index) g-dr-est (g-dr (aref SOMA gbar-dr$) x-dr-est y-dr-est)))
((not *include-dr) (setq g-dr-est 0.0))
(*include-q (setq x-q-est (trap-approx (aref SOMA x-q$) (aref SOMA x-q-dot$) (aref x-q-inf-array voltage-index)
(aref t-x-q-array voltage-index))
(g-q-est (* (aref SOMA gbar-q$) x-q-est)))
((not *include-q) (setq g-q-est 0.0)))

(setq g-leak (aref SOMA g-leak$) g-shunt (if *include-shunt *g-electrode 0.0)
(g-total-est (+ g-na1-est g-na2-est g-na3-est g-ca-est g-nap-est g-ae-est g-c-est g-ahp-est g-dr-est g-m-est g-q-est g-leak g-synapse g-shunt)
(e-eff (/ (+ (* g-na1-est g-na2-est g-na3-est g-nap-est) *e-na) (* g-ae-est g-c-est g-m-est g-q-est g-ahp-est) *e-k)
(* g-ca-est *e-ca)
(* g-leak *e-leak)
(* g-dr-est *e-dr)
(* g-synapse *e-synapse)
(g-total-est)
left-voltage (if (aref BASAL-DENDRITE 0 include-me$)
(aref BASAL-DENDRITE 0 voltage-est$) (aref SOMA voltage-est$)
(g-coupling-left (if (aref BASAL-DENDRITE 0 include-me$)
(g-parallel (aref BASAL-DENDRITE 0 g-axial$) (aref SOMA g-axial$))
0.0)
this-voltage (aref SOMA voltage-est$)
right-voltage-1 (if (aref APICAL-SHAFT-DENDRITE 0 include-me$)
(aref APICAL-SHAFT-DENDRITE 0 voltage-est$) (aref SOMA voltage-est$)
(g-coupling-right-1 (if (aref APICAL-SHAFT-DENDRITE 0 include-me$)
(g-parallel (aref APICAL-SHAFT-DENDRITE 0 g-axial$) (aref SOMA g-axial$))
0.0)
right-voltage-2 (aref SOMA voltage-est$) ; Soma never has a second righthand connection.
g-coupling-right-2 0.0)

:""V-DOT" gets the derivative of the voltage. Then store it as the last permanent value.
(cond
(if still-in-the-loop then voltage-derivative is just an estimate
(not loop-done)
(aset (+ v-dot g-coupling-left g-coupling-right-1 g-coupling-right-2 g-total-est e-eff left-voltage this-voltage right-voltage-1 right-voltage-2 $)
(caps (+ x1-constant-injection xi-stim))
SOMA voltage-est-1$)
;"Otherwise, calculated derivative becomes the stored derivative.
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Likewise, all the state variables and their derivatives are calculated according to the current voltage estimate, and stored.

\begin{verbatim}
(setq new-ca-conc-shell (+ (# xdt (aref SOKA ca-conc-shell-dots$))(aref SOKA ca-conc-shell$)))
(if (> new-ca-conc-shell @core-conc) (setq new-ca-conc-shell @core-conc))
(setq new-ca-conc-shell12 (+ (# xdt (aref SOKA ca-conc-shell12-dots$))(aref SOKA ca-conc-shell12$)))
(if (> new-ca-conc-shell12 @core-conc) (setq new-ca-conc-shell12 @core-conc))

(set new-ca-conc-shell SOKA ca-conc-shell$)
(set new-ca-conc-shell2 SOKA ca-conc-shell2$)

(set (ca-conc-shell-dot
  (+ (@ca-est (@v e-ca)))
  (((@ca-est (- @v x-ca)))
    new-ca-conc-shell new-ca-conc-shell2)
  SOKA ca-conc-shell-dots$))

(*include-nal
  (set (dxdt-eq m-nal-est (aref m-nal-inf-array voltage-index) (aref t-m-nal-array voltage-index))
  SOKA m-nal-dot$)

(*include-na2
  (set (dxdt-eq h-na2-est (aref h-na2-inf-array voltage-index) (aref t-h-na2-array voltage-index))
  SOKA h-na2-dot$)

(*include-na3
  (set (dxdt-eq x-a-est (aref x-a-inf-array voltage-index) (aref t-x-a-array voltage-index))
  SOKA x-a-dot$)

(*include-c
  (set (dxdt-eq x-c-est (aref x-c-inf-array voltage-index) (aref t-x-c-array voltage-index))
  SOKA x-c-dot$)

(*include-ahp
  (set (dxdt-eq y-ahp-est (aref y-ahp-inf-array voltage-index) (aref t-y-ahp-array voltage-index))
  SOKA y-ahp-dot$)

(*include-m
  (set (dxdt-eq x-m-est (aref x-m-inf-array voltage-index) (aref t-x-m-array voltage-index))
  SOKA x-m-dot$))

(*include-q
  (set (dxdt-eq x-q-est (aref x-q-inf-array voltage-index) (aref t-x-q-array voltage-index))
  SOKA x-q-dot$))

(*include-dr
  (set (dxdt-eq x-dr-est (aref x-dr-inf-array voltage-index) (aref t-x-dr-array voltage-index))
  SOKA x-dr-dot$))

(*include-dr
  (set (dxdt-eq x-dr-est (aref x-dr-inf-array voltage-index) (aref t-x-dr-array voltage-index))
  SOKA x-dr-dot$))
\end{verbatim}

(set (dxdt-eq x-dr-est (aref x-dr-inf-array voltage-index) (aref t-x-dr-array voltage-index))
  SOMA x-dr-dot$)
(set (y-dr-est SOMA y-dr$)
(aset (dxdt-eq y-dr-est (aref y-dr-inf-array voltage-index) (aref t-y-dr-array voltage-index))
  SOMA y-dr-dot$))
(*include-ca
  (aset s-ca-est SOMA x-ca$)
  (aset (dxdt-eq s-ca-est (aref s-ca-inf-array voltage-index) (aref t-s-ca-array voltage-index))
    SOMA s-ca-dot$)
  (aset w-ca-est SOMA w-ca$)
  (aset (dxdt-eq w-ca-est (aref w-ca-inf-array voltage-index) (aref t-w-ca-array voltage-index))
    SOMA w-ca-dot$))
(*include-nap
  (aset x-nap-est SOMA x-nap$)
  (aset (dxdt-eq x-nap-est (aref x-nap-inf-array voltage-index) (aref t-x-nap-array voltage-index))
    SOMA x-nap-dot$)))))

::: SET-SOMA-STATES-AND-V-DOT-FOR-VOLTAGE-CLAMP
(defun set-soma-states-and-v-dot-for-voltage-clamp ()
  (let ((new-ca-conc-shell)(new-ca-conc-shell2)
        (s-ca)(w-ca)(x-cas)
        (voltage-index (1000 (fixr (* 10.0 *clamp-voltage)))))
    (cond ((or *vstep (a *vcIamp-command-flag))
      (cond-every
        (*include-ahp (setq *zahpinf (aref z-ahp-inf-array voltage-index) *tzahp (aref t-z-ahp-array voltage-index) *yahpinf (aref y-ahp-inf-array voltage-index) *tyahp (aref t-y-ahp-array voltage-index)
          *wahpinf (aref w-ahp-inf (aref SOMA ca-conc-shell2$)) *twahp (t-w-ahp (aref SOMA ca-conc-shell2$)))
        (*include-c (setq *xci'f (aref x-c-inf-array voltage-index) *txc (aref t-x-c-array voltage-index) *ycinf (aref y-c-inf-array voltage-index) *tyc (aref t-y-c-array voltage-index) *wcinf (w-c-inf (aref SOMA ca-conc-shell$)) *twc (t-w-c (aref SOMA ca-conc-shell$)))
        (*include-q (setq *xqinf (aref x-q-inf-array voltage-index) *tq (aref t-x-q-array voltage-index)))
        (*include-m (setq xinf (aref x-m-inf-array voltage-index) *to (aref t-x-m-array voltage-index)))
        (*include-nal (setq *mnalinf (aref a-nal-inf-array voltage-index) *nonal (aref t-m-nal-array voltage-index) *hnalinf (aref h-nal-inf-array voltage-index) *thnal (aref t-h-nal-array voltage-index))
        (*include-na2 (setq *mna2inf (aref m-na2-inf-array voltage-index) *tmna2 (aref t-m-na2-array voltage-index)))
        (*include-na3 (setq *mna3inf (aref m-na3-inf-array voltage-index) *tmna3 (aref t-m-na3-array voltage-index)))
        (*include-ca (setq *cainf (aref s-ca-inf-array voltage-index) *tca (aref t-s-ca-array voltage-index) *hcainf (aref w-ca-inf-array voltage-index) *thca (aref t-w-ca-array voltage-index))
        (*include-nap (setq *xnapinf (aref x-nap-inf-array voltage-index) *txnap (aref t-x-nap-array voltage-index)))
        (*include-cas (setq *casinf (aref x-cas-inf-array voltage-index) *txcas (aref t-x-cas-array voltage-index)))
        (*include-dr (setq *drinf (aref x-dr-inf-array voltage-index) *txdr (aref t-x-dr-array voltage-index) *hca (w-ca (aref SOMA ca-conc-shell$)) *tca (t-w-ca (aref SOMA ca-conc-shell$)))
        (set (dxdt-eq x-dr-est (aref x-dr-inf-array voltage-index) (aref t-x-dr-array voltage-index))
          SOMA x-dr-dot$))
      (aset *clamp-voltage (aref SOMA voltage$) *dt) SOMA voltage-dot$)
      (T (aset 0.0 SOMA voltage-dot$))
    (cond-every
      (*include-cas (setq x-cas (vclamp-new-x *dt (aref SOMA x-cas$) xcasinf *txcas))
        (aset x-cas SOMA x-cas$))
      (not (*include-ca (setq x-cas 0)))
      (*include-ca (setq s-ca (vclamp-new-x *dt (aref SOMA s-ca$) *macainf *tmaca) *w-ca (vclamp-new-x *dt (aref SOMA w-ca$) *hcainf *thca))
        (aset s-ca SOMA s-ca$) (aset w-ca SOMA w-ca$))
      (not (*include-ca (setq s-ca 0 w-ca 0)))
      (T (setq new-ca-conc-shell (+ (* (fixr (* 10.0 *clamp-voltage))) (aref SOMA ca-conc-shell$)))))

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(setq new-ca-conc-shell (som-a-ca-conc-shell-dot$))
(aset new-ca-conc-shell (som-a-ca-conc-shell-dot$))
(aset new-ca-conc-shell (som-a-ca-conc-shell-dot$))
(aset new-ca-conc-shell (som-a-ca-conc-shell-dot$))

(*include-ahp (aset (vclamp-new-x dt (aref soma z-ahp$) zahpinf zahp) soma z-ahp$)
(aset (vclamp-new-x dt (aref soma y-ahp$) yahpinf yahp) soma y-ahp$)
(aset (vclamp-new-x dt (aref soma w-ahp$) wahpinf wahp) soma w-ahp$))
(*include-c (aset (vclamp-new-x dt (aref soma x-cs) xcsinf xcs) soma x-cs)
(aset (vclamp-new-x dt (aref soma y-cs) ycsinf ycs) soma y-cs)
(aset (vclamp-new-x dt (aref soma w-cs) wcisinf wcis) soma w-cs))
(*include-q (aset (vclamp-new-x dt (aref soma x-qs) xqisinf xqis) soma x-qs)
(aset (vclamp-new-x dt (aref soma y-qs) yqisinf yqis) soma y-qs)
(aset (vclamp-new-x dt (aref soma w-qs) wqisinf wqis) soma w-qs))
(*include-m (aset (vclamp-new-x dt (aref soma x-m$) xmminf xmm) soma x-m$)
(aset (vclamp-new-x dt (aref soma y-m$) ymminf ymm) soma y-m$)
(aset (vclamp-new-x dt (aref soma w-m$) wmminf wmm) soma w-m$))
(*include-nap (aset (vclamp-new-x dt (aref soma x-nap$) xnapinf xnap) soma x-nap$)
(aset (vclamp-new-x dt (aref soma y-nap$) ynapinf ynap) soma y-nap$)
(aset (vclamp-new-x dt (aref soma w-nap$) wnapinf wnap) soma w-nap$))
(*include-dr (aset (vclamp-new-x dt (aref soma x-dr$) xdrinf xdr) soma x-dr$)
(aset (vclamp-new-x dt (aref soma y-dr$) ydrinf ydr) soma y-dr$))
(*include-a (aset (vclamp-new-x dt (aref soma x-as) xasinf xas) soma x-as)
(aset (vclamp-new-x dt (aref soma y-as) yasinf yas) soma y-as)
(aset (vclamp-new-x dt (aref soma x-es) xesinf xes) soma x-es)
(aset (vclamp-new-x dt (aref soma y-es) yesinf yes) soma y-es))
(*include-na1 (aset (vclamp-new-x dt (aref soma m-na1$) mna1inf mna1) soma m-na1$)
(aset (vclamp-new-x dt (aref soma h-na1$) hna1inf hna1) soma h-na1$)
(aset (vclamp-new-x dt (aref soma n-na1$) nna1inf nna1) soma n-na1$))
(*include-na2 (aset (vclamp-new-x dt (aref soma m-na2$) mna2inf mna2) soma m-na2$)
(aset (vclamp-new-x dt (aref soma h-na2$) hna2inf hna2) soma h-na2$)
(aset (vclamp-new-x dt (aref soma n-na2$) nna2inf nna2) soma n-na2$))
(*include-na3 (aset (vclamp-new-x dt (aref soma m-na3$) mna3inf mna3) soma m-na3$)
(aset (vclamp-new-x dt (aref soma h-na3$) hna3inf hna3) soma h-na3$)
(aset (vclamp-new-x dt (aref soma n-na3$) nna3inf nna3) soma n-na3$))

(*include-dendrite-synapse (update-dendrite-synapse-list soma-voltage)
(aset (vclamp-new-x dt (aref soma synapse-dot$) synapseinf synapse) soma synapse)
(aset (vclamp-new-x dt (aref soma synapse-estl-dot$) synapseestlinf synapseestl) soma synapseestl))

(*include-dendrite-synapse-current-list)
(aset (vclamp-new-x dt (aref soma synapse-current-dot$) synapsecurrentinf synapsecurrent) soma synapsecurrent)
(aset (vclamp-new-x dt (aref soma synapse-current-estl-dot$) synapsecurrentestlinf synapsecurrentestl) soma synapsecurrentestl))

(t (setq new-ca-conc-shell (som-a-ca-conc-shell-dot$))
(aset new-ca-conc-shell (som-a-ca-conc-shell-dot$))

--- ESTIMATE-SOMA-VOLTAGE Gets and stores new estimate (...) of soma voltage using the previous voltage
-voltage, the previous derivative (voltage-dot$), and the current estimate of the derivative
- (...esti-dot$). The function "APPROX-X" is used for the trapezoidal approximation. Note that this function is
-only required by the current clamp protocol.
---
(defun estimate-soma-voltage ()
(aset approx-x (aref soma voltage$) (aref soma voltage-dot$)
(aref soma voltage-estl-dot$)) soma voltage-est2$))

--- ESTIMATE-DENDRITE-VOLTAGES Gets and stores new estimate (...) of dendrite voltages using the previous
-voltage (voltage$), the previous derivative (voltage-dot$), and the current estimate of the derivative
- (...esti-dot$). The function "APPROX-X" is used for the trapezoidal approximation.
(defun estimate-dendrite-voltages ()
(dolist (dendrite-array (list basal-dendrite apical-shaft-dendrite apical-1-dendrite apical-2-dendrite))
(if (aref dendrite-array 0 include-me$)
(do ((segment 0 (inf segment)))
(*segment (aref dendrite-array 0 total-segments$))
(aset (approx-x (aref dendrite-array segment voltage$)
(aref dendrite-array segment voltage-dot$)
(aref dendrite-array segment voltage-estl-dot$)) dendrite-array segment voltage-est2$))))

--- UPDATE-OUTPUT-LISTS Stores the latest values in the enabled lists.
(defun update-output-lists ()
(let ((soma-voltage (aref soma voltage$)))
(update-soma-lists soma-voltage)
(update-dendrite-lists soma-voltage)
(if (vclamp-run (update-vclamp-list soma-voltage))))

--- UPDATE-DENDRITE-LISTS
(defun update-dendrite-lists (soma-voltage)
(update-coupling-current-list soma-voltage)
(aset xi-den-stim dendrite-stim-current* point-index)
(cond-every
(include-dendrite-synapse (update-dendrite-synapse-current-list))
(aref apical-shaft-dendrite 0 include-me$)
(cond-every
((aref apical-shaft-dendrite 0 plot-me$)
(aset (aref apical-shaft-dendrite 0 voltage$) aslvoltage* point-index))
)
((and (aref APICAL-SHAFT-DENDRITE 2 plot-me$) (> (aref APICAL-SHAFT-DENDRITE 0 total-segments$) 3))
(aset (aref APICAL-SHAFT-DENDRITE 2 voltages$) *as3voltage* *point-index$))
)((and (aref APICAL-SHAFT-DENDRITE 4 plot-me$) (> (aref APICAL-SHAFT-DENDRITE 0 total-segments$) 5))
(aset (aref APICAL-SHAFT-DENDRITE 4 voltages$) *as5voltage* *point-index$))
((and (aref APICAL-SHAFT-DENDRITE 9 plot-me$) (> (aref APICAL-SHAFT-DENDRITE 0 total-segments$) 10))
(aset (aref APICAL-SHAFT-DENDRITE 9 voltages$) *as10voltage* *point-index$)))

((aref APICAL-1-DENDRITE 0 include-me$)
(cond-every
((aref APICAL-1-DENDRITE 0 plot-me$)
(aset (aref APICAL-1-DENDRITE 0 voltages$) *allvoltage* *point-index$))
((and (aref APICAL-1-DENDRITE 1 plot-me$) (> (aref APICAL-1-DENDRITE 0 total-segments$) 4))
(aset (aref APICAL-1-DENDRITE 3 voltages$) *allvoltage* *point-index$))))

((aref APICAL-SHAFT-DEWRIYE 0 include-me$)
(cond-every
((aref APICAL-SHAPT-DENDRITE 0 plot-me$)
(aset (aref APICAL-SHAFT-DENDRIT 0 voltages$) *allvoltage* *point-index$))
((and (aref APICAL-1-DEWTORITE 3 plot-me$) (> (aref APICAL-1-DENDRITE 0 total-segments$) 5))
(aset (aref APICAL-1-DENDRITE 3 voltages$) *allvoltage* *point-index$))))

((aref BASAL-DENDRITE 0 include-me$)
(cond-every
((aref BASAL-DENDRORITE 0 plot-me$)
(aset (aref BASAL-DENDRITE 0 voltages$) *allvoltage* *point-index$))
((and (aref BASAL-DENDRITE 3 plot-me$) (> (aref BASAL-DENDRITE 0 total-segments$) 4))
(aset (aref BASAL-DENDRITE 3 voltages$) *allvoltage* *point-index$))))

(aset (nal-current (gbar-nad (* (aref APICAL-SHAFT-DENDRITE 0,'Iength$)
3.1419e-8 (aref APICAL-SHAFT-DENDRIT 0 diameter$)))
*nadl-current* *point-index$))
(aset (ca-current (gbar-cad (* (aref APICAL-SHAPT-DENDRITE 2 length$)
3.1415e-8 (aref APICAL-SHAFT-DENDRIT 2 diameter$)))
*cadl-current* *point-index$))

(defun update-coupling-current-list (soma-voltage)
(aset (+ (* (if (aref BASAL-DENDRITE 0 include-me$)
(g-parallel (aref BASAL-DENDRITE 0 g-axial$)
(aref SOMA g-axial$))
0.0)
(- soma-voltage (aref BASAL-DENDRITE 0 voltages$)))
(* (if (aref APICAL-SHAFT-DENDRITE 0 include-me$)
(g-parallel (aref APICAL-SHAFT-DENDRIT 0 g-axial$)
(aref SOMA g-axial$))
0.0)
(- soma-voltage (aref APICAL-SHAFT-DENDRITE 0 voltages$))))
*xcoupling-current* *point-index$))

(defun update-dendrite-synapse-current-list ()
(aset (+ (aref APICAL-1-DEWTORITE synapse-segment g-synapse$)
(- (aref APICAL-1-DENDRITE synapse-segment voltages$)
*esynapse$))
*dendrite-synapse-current* *point-index$))

(defun update-vclamp-list (soma-voltage)
(aset (+ (if *include-dr (dr-current (aref SOMA x-dr$)(aref SOMA y-dr$) soma-voltage)
0)
(if *include-c (c-current (aref SOMA x-c$)(aref SOMA y-c$)(aref SOMA w-c$)
soma-voltage) 0)
(if *include-ahp (ahp-current (aref SOMA x-ah$p)(aref SOMA y-ah$)(aref SOMA w-ahp$)
soma-voltage) 0)
(if *include-q (* (aref SOMA gbar-q$)(aref SOMA x-q$)
(- soma-voltage xe-k)) 0.0)
(if *include-nal (nal-current (aref SOMA gbar-na1$
(aref SOMA h-na1$) soma-voltage) 0)
(if *include-na2 (na2-current (aref SOMA gbar-na2$
(aref SOMA h-na2$) soma-voltage) 0)
(if *include-na3 (na3-current (aref SOMA gbar-na3$
...
(if *include-nap (nap-current (aref SOMA gbar-nap$) (aref SOMA x-napS) soma-voltage) 0)
(if *include-cas (cas-current (aref SOMA x-cas$) soma-voltage) 0)
(if *include-ca (ca-current (aref SOMA gbar-caS) (aref SOMA s-caS) (aref SOMA w-cas$) soma-voltage) 0.0)
(+ (* (if (aref BASAL-DENDRITE 0 include-me$) (= 2.0 (aref BASAL-DENDRITE 0 g-axial$)) 0.0)
    (if soma-voltage (aref BASAL-DENDRITE 0 voltage$))
    (* (if (aref APICAL-SHAFT-DENDRITE 0 include-me$) (= 2.0 (aref APICAL-SHAFT-DENDRITE 0 g-axial$)) 0.0)
        (if soma-voltage (aref APICAL-SHAFT-DENDRITE 0 voltage$)))
    (- current soma-voltage)
    (if *include-shunt (= *g-electrode soma-voltage) 0)
    (* *caps (aref SOMA voltage-dot$)))
  (*current* *point-index))

(defun update-soma-lists (soma-voltage)
  (cond-every
    (*include-kinetics
      (cond-every
        (include-nal
          (aset (aref SOMA m-na$) m-na$ =point-index) (aset (aref SOMA h-na$)(aref SOMA h-na$) =point-index)
          (aset (aref SOMA h-na$) (aref SOMA h-na$) =point-index)
        (include-na2
          (aset (aref SOMA m-na2$) m-na2$ =point-index) (aset (aref SOMA h-na2$)(aref SOMA h-na2$) =point-index)
          (aset (aref SOMA h-na2$) (aref SOMA h-na2$) =point-index)
        (include-na3
          (aset (aref SOMA m-na3$) m-na3$ =point-index) (aset (aref SOMA h-na3$)(aref SOMA h-na3$) =point-index)
          (aset (aref SOMA h-na3$) (aref SOMA h-na3$) =point-index)
        (include-ca
          (aset (aref SOMA m-ca$) m-ca$ =point-index) (aset (aref SOMA h-ca$)(aref SOMA h-ca$) =point-index)
          (aset (aref SOMA h-ca$) (aref SOMA h-ca$) =point-index)
        (include-dr
          (aset (aref SOMA x-dr$) x-dr$ =point-index) (aset (aref SOMA y-dr$)(aref SOMA y-dr$) =point-index)
          (aset (aref SOMA y-dr$) (aref SOMA y-dr$) =point-index)
        (include-a
          (aset (aref SOMA x-a$) x-a$ =point-index) (aset (aref SOMA y-a$)(aref SOMA y-a$) =point-index)
          (aset (aref SOMA y-a$) (aref SOMA y-a$) =point-index)
        (include-ahp
          (aset (aref SOMA z-ahp$) z-ahp$ =point-index) (aset (aref SOMA y-ahp$)(aref SOMA y-ahp$) =point-index)
          (aset (aref SOMA y-ahp$) (aref SOMA y-ahp$) =point-index)
        (include-c
          (aset (aref SOMA x-c$) x-c$ =point-index) (aset (aref SOMA y-c$)(aref SOMA y-c$) =point-index)
          (aset (aref SOMA y-c$) (aref SOMA y-c$) =point-index)
        (t
          (aset (= 1.0e-3 *time) *time* =point-index) (aset soma-voltage =voltage* =point-index)
          (aset (* *caps (aref SOMA voltage-dot$)) *caps-current =point-index)
          (aset (aref SOMA voltage-dot$) =stim-current =point-index)
          (aset *i-constant-injection =i-stim) =stim-current =point-index)
          (aset (aref SOMA ca-conc-shell2$) *ca-conc-shell2) =point-index)
          (include-shunt
            (aset (* *g-electrode soma-voltage) =shunt-current =point-index)
          (include-nal
            (aset (aref SOMA gbar-na$) (aref SOMA w-cas$) (aref SOMA w-cas$) =point-index)
            (include-na2
              (aset (aref SOMA gbar-na2$) (aref SOMA m-na2$) (aref SOMA m-na2$) =point-index)
            (include-na3
              (aset (aref SOMA gbar-na3$) (aref SOMA m-na3$) (aref SOMA m-na3$) =point-index)
            (include-ca
              (aset (aref SOMA gbar-ca$)(aref SOMA s-ca$) (aref SOMA s-ca$) =point-index)
              (include-nap
                (aset (aref SOMA gbar-nap$) (aref SOMA x-napS) (aref SOMA x-napS) =point-index)
                (include-cas
                  (aset (aref SOMA x-cas$) (aref SOMA x-cas$) =point-index)
                  (include-c
                    (aset (aref SOMA x-c$)(aref SOMA y-c$)(aref SOMA w-c$) =point-index)
                    264
\( \text{\textbf{V-DOT}:} \text{Gives the derivative of the membrane voltage given the current conductances, the membrane capacitance, the adjacent voltages, the local voltage, and any injected current.} \)

\[
\text{\textbf{VCLAMP-NEW-X}}(x, x_{\text{inf}}, \text{tau}_x)
\]

\[
\text{\textbf{APPROX-X}:} \text{Calculates the trapezoidal approximation of a state variable that is described by first order kinetics given the initial value of the variable, the old value of its derivative, the new value of its steady state, and the new value of its time constant.} \]

\[
\text{\textbf{DXDT-EQ}:} \text{Calculates the derivative of the state variable \((x)\) according to original differential equation characterizing the gating variables.} \]

\[
\text{\textbf{TEST}}(x, y)
\]

\[
\text{\textbf{PRINT-PARAMETERS}:} \text{Print all the parameters for the current run in the interaction pane.} \]

\[
\text{\textbf{TRAP-APPROX}:} \text{Computes the trapezoidal approximation of a state variable that is described by first order kinetics given the initial value of the variable, the old value of its derivative, the new value of its steady state, and the new value of its time constant.} \]

\[
\text{\textbf{V-DOT}:} \text{Gives the derivative of the membrane voltage given the current conductances, the membrane capacitance, the adjacent voltages, the local voltage, and any injected current.} \]

\[
\text{\textbf{VCLAMP-NEW-X}}(x, x_{\text{inf}}, \text{tau}_x)
\]

\[
\text{\textbf{APPROX-X}:} \text{Calculates the trapezoidal approximation of a state variable that is described by first order kinetics given the initial value of the variable, the old value of its derivative, the new value of its steady state, and the new value of its time constant.} \]

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\text{\textbf{DXDT-EQ}:} \text{Calculates the derivative of the state variable \((x)\) according to original differential equation characterizing the gating variables.} \]

\[
\text{\textbf{TEST}}(x, y)
\]

\[
\text{\textbf{PRINT-PARAMETERS}:} \text{Print all the parameters for the current run in the interaction pane.} \]

\[
\text{\textbf{TRAP-APPROX}:} \text{Computes the trapezoidal approximation of a state variable that is described by first order kinetics given the initial value of the variable, the old value of its derivative, the new value of its steady state, and the new value of its time constant.} \]
(if *include-na2 (format t "gNa2 [microS] ~4f, (aref SOMA gbar-na2$) (format t "Na2 poisoned, ")")
(if *include-na3 (format t "gNa3 [microS] ~4f, (aref SOMA gbar-na3$) (format t "Na3 poisoned, ")
(if *include-ca (format t "gCa [microS] ~4f-x" (aref SOMA gbar-ca$) (format t "Ca poisoned-x")
(if *include-nap (format t "gNaP [microS] ~4f, (aref SOMA gbar-nap$) (format t "NaP poisoned, ")
(if *include-cas (format t "gCaS [microS] ~4f-x" (aref SOMA gbar-cas$) (format t "CaS poisoned-x")
(if *include-c (format t "gC [microS] ~4f,* (aref SOMA gbar-c$)) (format t *X-C poisoned ")
(if *include-ahp (format t "gAHP [microS] ~4f-w (aref SOMA gbar-ahp$) (format t "AHP poisoned-w")
(if *include-dr (format t "gDR [microS] ~4f (aref SOMA gbar-dr$)) (format t "DR poisoned")
(if (and *include-dr W*dr-block 1.0)) (format t *OR block a -01 *dr-bldck)
(if *include-a (format t "gA [microS] ~4f-%-%' (aref SOMA gbar-at$) (format t 1-A poisoned-%-%O))
(cond-every
((aref APICAL-SHAFT-DENDRITE 0 include-me$)
(let* ((lambda (~ (/ (* r*d-mm (/ (aref APICAL-SHAFT-DENDRITE 0 diameter$) 2.0) 10000.0) (+ 2.0 *rd-int)) 0.5))
(aref APICAL-SHAFT-DENDRITE 0 0 total-segments$) (aref APICAL-SHAFT-DENDRITE 0 0 length$) lambda))
(format t "Apical shaft dendrite with -2d segments. Length = -4f microns.-x" (aref APICAL-SHAFT-DENDRITE 0 0 total-segments$) (aref APICAL-SHAFT-DENDRITE 0 0 length$))
(format t "Apical shaft dendrite 0 length$) lambda)
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\[
\lambda = \text{format t } \times \lambda \text{(per segment)} = -4f
\]
\[
\times 100.0 \text{ / (aref BASAL-DENDRITE length\$) \lambda(m\$))}
\]
\[
\text{(format t } -\times \text{time required to reach steady-state -4f msec } \times \text{time-for-steady-state})
\]

::: MAKE-\text{LIST1}
(defn make-list1 ()
(setq plot-list1 nil
(label-list1 nil)
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Soma\$"))))
(cond-every
((aref APICAL-SHAFT-DENDRITE 0 include-me$)
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Shaft Seg 1\$"))))
((and (aref APICAL-SHAFT-DENDRITE 0 plot-me$) (aref APICAL-SHAFT-DENDRITE total-segments$ 3))
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Shaft Seg 3\$"))))
((and (aref APICAL-SHAFT-DENDRITE 4 plot-me$) (aref APICAL-SHAFT-DENDRITE total-segments$ 5))
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Shaft Seg 5\$"))))
((and (aref APICAL-SHAFT-DENDRITE 9 plot-me$) (aref APICAL-SHAFT-DENDRITE total-segments$ 10))
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Shaft Seg 10\$"))))
((aref APICAL-1-DENDRITE 0 include-me$)
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Left Seg 1\$"))))
((and (aref APICAL-1-DENDRITE 3 plot-me$) (aref APICAL-1-DENDRITE total-segments$ 4))
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Left Seg 4\$"))))
((aref APICAL-2-DENDRITE 0 include-me$)
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Right Seg 1\$"))))
((and (aref APICAL-2-DENDRITE 3 plot-me$) (aref APICAL-2-DENDRITE total-segments$ 4))
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Right Seg 4\$"))))
((aref BASAL-DENDRITE 0 include-me$)
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Basal Seg 1\$"))))
((and (aref BASAL-DENDRITE 3 plot-me$) (aref BASAL-DENDRITE total-segments$ 4))
(setq plot-list1 (nconc plot-list1 (list ("\text{voltage}\ . \times\text{time}\$))
(label-list1 (nconc label-list1 (list (format nil "Basal Seg 4\$"))))

::: MAKE-\text{LIST3}
(defn make-list3 ()
(setq plot-list3 nil
(label-list3 nil)
(if include-dr
(setq plot-list3 (nconc plot-list3 (list ("dr-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "DR Current\$"))))
(if include-a
(setq plot-list3 (nconc plot-list3 (list ("a-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "A Current\$"))))
(if include-m
(setq plot-list3 (nconc plot-list3 (list ("m-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "M Current\$"))))
(if include-c
(setq plot-list3 (nconc plot-list3 (list ("c-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "C Current\$"))))
(if include-ahp
(setq plot-list3 (nconc plot-list3 (list ("ahp-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "AHP Current\$"))))
(if include-q
(setq plot-list3 (nconc plot-list3 (list ("q-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "Q Current\$"))))
(if include-dendrite
(setq plot-list3 (nconc plot-list3 (list ("coupling-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "Soma-dendrite current\$"))))
(setq plot-list3 (nconc plot-list3 (list ("l-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "L Current\$"))))
(if include-shunt
(setq plot-list3 (nconc plot-list3 (list ("shunt-current\ . \times\text{time}\$))
(label-list3 (nconc label-list3 (list (format nil "Shunt current\$"))))

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\begin{verbatim}
;;; MAKE-LIST2
(defun make-list2 ()
  (setq *plot-list2 nil
        *label-list2 nil)
  (cond (include-nal
          (setq *plot-list2 (nconc *plot-list2 (list "(*nal-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Na\_LJM Current")))))
       (include-na2
        (setq *plot-list2 (nconc *plot-list2 (list "(*na2-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Na\_2 Current")))))
       (include-na3
        (setq *plot-list2 (nconc *plot-list2 (list "(*na3-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Na\_3 Current")))))
       (include-nap
        (setq *plot-list2 (nconc *plot-list2 (list "(*nap-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Na\_P Current"))))
       (include-cas
        (setq *plot-list2 (nconc *plot-list2 (list "(*cas-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Ca\_S Current"))))
       (include-ca
        (setq *plot-list2 (nconc *plot-list2 (list "(*ca-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Ca\_A Current"))))
       (include-ca-
        (setq *plot-list2 (nconc *plot-list2 (list "(*caps-current* . *time*)"))
                *label-list2 (nconc *label-list2 (list (format nil "Ca\_P Current"))))

;;; MAKE-LIST4
(defun make-list4 ()
  (setq *plot-list4 nil
        *label-list4 nil)
  (if include-dendrite-synapse
      (setq *plot-list4 (nconc *plot-list4 (list "(*dendrite-synapse-current* . *time*)"))
            *label-list4 (nconc *label-list4 (list (format nil "Dendrite Synapse")))))
  (if include-soma-synapse
      (setq *plot-list4 (nconc *plot-list4 (list "(*soma-synapse-current* . *time*)"))
            *label-list4 (nconc *label-list4 (list (format nil "Soma Synapse")))))

;;; MAKE-LISTS
(defun make-list5 ()
  (setq *plot-list5 nil
        *label-list5 nil)
  (setq *plot-list5 (nconc *plot-list5 (list "(*ca-conc-shell* . *time*)"))
            *label-list5 (nconc *label-list5 (list (format nil "Shell Ca Concentration"))))
  (setq *plot-list5 (nconc *plot-list5 (list "(*ca-conc-shell2* . *time*)"))
            *label-list5 (nconc *label-list5 (list (format nil "Shell2 Ca Concentration"))))

;;; PLOT-RESULTS Plot all the output lists automatically.
(defun plot-results ()
  (cond (iclamp-run (plot-current-clamp))
        (vclamp-run (plot-voltage-clamp))))

;;; PLOT-CURRENT-CLAMP
(defun plot-current-clamp ()
  (make-list1) (make-list2) (make-list3) (make-list4) (make-list5)
  (send *plot-pane-1 :plot "Soma And Dendritic Potentials [mV]" *plot-list1
        *label-list1
        :all-solid-lines *plot-voltages-solid
        :y-min -90
        :y-max 40
        :y-interval 10
        :overlay *overlay-simulations
        :leave-window *overlay-simulations)
  (send *plot-pane-2 :plot "Inward Soma Currents [na]" *plot-list2
        *label-list2
        :y-min -10
        :y-max 8
        :y-interval 2
        :overlay *overlay-simulations
        :leave-window *overlay-simulations)
  (send *plot-pane-3 :plot "Outward Soma Currents [na]" *plot-list3
        *label-list3
        :y-min -4
        :y-max 10)
\end{verbatim}
; overlay *overlay-simulations
; leave-window *overlay-simulations
) ;

; (if (or (arf APICAL-SHAFT-DENDRITE 3 include-nas) (arf APICAL-SHAFT-DENDRITE 3 include-cas))
; (send *plot-pane-5 :plot "Dendrite Currents [na]"
; *plot-list5
; *label-list5
; :y-min -10
; :y-max 10
; :y-interval 2
; :overlay *overlay-simulations
; :leave-window *overlay-simulations)
; nil)

(defvar plot-frame
()
(tv:bordered-constraint-frame)
:settable-instance-variables
(:default-init-plist
 :activate-p t
 :expose-p t
 :save-bits t))

;;; PLOT-VOLTAGE-CLAMP
(defun plot-voltage-clamp ()
(make-list1) (make-list2) (make-list3))

(defun startup ()
(tv:make-window
'Plot-frame
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X
Y)

(defvar tv:plotter-pane () (g:plot-hack tv:pane-mixin))

;;; STARTUP Setup up the simulation frame with 6 plot panes for the relevant output lists and one lisp listener
;;; pane for input and parameter printing.
(defvar tv:plotter-pane () (g:plot-hack tv:pane-mixin))
(defun startup ()
(tv:make-window
'plot-frame
269
O:panes '(*plot-pane-1 tv:plotter-pane
 :label "Voltages n Soma And dendrites")
(*plot-pane-2 tv:plotter-pane
 :label "Outward Currents In Soma")
(*plot-pane-3 tv:plotter-pane
 :label "Inward Currents In Soma")
(*plot-pane-4 tv:plotter-pane
 :label "Stimulus and Synapse Conductance Currents [na]")
(*plot-pane-5 tv:plotter-pane
 :label "Calcium Concentrations")
(interaction-pane tv:lisp-listener
 :label "HIPPOCAMPAL PYRAMIDAL CELL SIMULATION")
:'configurations '((cl
 (layout
 (cl :column r1 r2 *plot-pane-1)
 (r1 :row interaction-pane c2)
 (r2 :row *plot-pane-2 *plot-pane-3)
 (c2 :column *plot-pane-5 *plot-pane-4))
 (:sizes
 (cl (*plot-pane-1 200)
 :then (r2 200)
 :then (r1 :even))
 (r1 (interaction-pane .500)
 :then (c2 :even))
 (r2 (*plot-pane-2 .50)
 :then (*plot-pane-3 :even))
 (c2 (*plot-pane-5 .5)
 :then (*plot-pane-4 :even))))
:'expose-p t)
 (name-plot-panes)
 (variable-array-setup))

::: NAME- PLOT- PANCES Name the plot windows. They must be already in place
::: But first go to the corresponding Lisp window
defvar interaction-pane
(defun name-plot-panes ()
 (loop for pane in (send (send tv:selected-window :superior) :inferiors)
 with count a 1
 when (typep pane 'tv:plotter-pane)
 do (set (intern (format nil **PLOT-PANE--Dw count)) pane)
 (incf count))))

::: SETUP-STIMULUS Updates the stimulus current to the soma and the dendrites for current clamp, or the clamp
::: voltage for voltage clamp.
(defun setup-stimulus ()
 (cond (*iclamp-run (set-soma-current-stimulus)
 :Set up the stimulus current to the soma.
 (set-dendrite-current-stimulus))
 (setvclamp-run (set-soma-voltage-stimulus *time-step))))

::: CLAMP
(defun clamp ()
 (setup-menu)
 (without-floating-underflow-traps
 (if *calculate-steady-state
 
 (initialize-w-new-steady-state)
 (initialize-w-old-steady-state))
 (setq *time 0.0)
 ; (cl:time (run-clamp))
 (run-clamp)
 (beep)
 (reverse-lists)
 (if *plot-results (plot-results))
 (print-parameters))
 (beep)
 (setq *first-run nil))

(defun autoclamp ()
 (setup-menu)
 (autoclamp (list *voltage2-norm2* *voltage3-norm2* *voltage4-norm2*))
 (setq *include-a nil))

::: CLAMP
'defun clamp ()
(setup-menu)
(without-floating-underflow-traps
 (if *calculate-steady-state
 
 (initialize-w-new-steady-state)
 (initialize-w-old-steady-state))
 (setq *time 0.0)
 ; (cl:time (run-clamp))
 (run-clamp)
 (beep)
 (reverse-lists)
 (if *plot-results (plot-results))
 (print-parameters))
 (beep)
 (setq *first-run nil))

(defun autoclamp ()
 (setup-menu)
 (autoclamp (list *voltage2-norm2* *voltage3-norm2* *voltage4-norm2*))
 (setq *include-a nil))

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(defun autoclamp2 (second-vlist)
  (do ((stimulus-list (0.33 0.35 0.37) (cdr stimulus-list))
        (voltage-list second-vlist (cdr voltage-list))
        (voltage-array) ((null voltage-list))
    (setq voltage-array (car voltage-list)
          *i-stim-1 0.5
          *t-stim-1 20.0
          *t-stim-2 1000.0
          *i-stim-2 (car stimulus-list))
    (without-floating-underflow-traps
      (if *calculate-steady-state
          (initialize-w-new-steady-state)
          (initialize-w-old-steady-state))
      (setq *time 0.0)
      (run-clamp)
      (fillarray voltage-array *voltage*)

    (defun initialize-w-old-steady-state
      (clear-lists)
      (setq *time 0.0
            *point-index
            (if *first-run
                (and (initialize-soma-voltage)
                     (initialize-dendrite-voltages)))
                (initialze-soma-voltage)
                     (initialize-dendrite-voltages)))
      (initialze-soma-states)
      (initialize-dendrite-states)
      (update-output-lists)
      (setq *time 0.0))

    (defun initialize-w-new-steady-state
      (setq *i-stim 0.0
            *i-den-stim 0.0
            tsteady-state-run t)
      (initialize-w-old-steady-state)
      (and (aset *e-holding SOMA voltage$)
            (aset *holding SOMA voltage-est1$)
            (aset *holding SOMA voltage-est2$))
      (do ((time 0 (+ time *dt))
           (time-step 0 (+ time-step 1)))
        (test-for- resting-state)
        (test-for-steady-state time time-step time-step *time)
        (:before the evaluation loop, evaluate the first approximations to the voltages using previous values and their derivatives. Also load in dummy values for next estimates in order to force initial integration.
        (load-first-estimates)
        (:this evaluation loop performs successive approximations to the model voltages at the present time step
           until the all the estimates satisfy the convergence criterion.
           (do ()
             (:test-estimates))
             (:true if all estimates are within epsilon (e-st1's & e-st2's)
          (store-new-soma-estimate)
          (if *include-dendrite (store-new-dendrite-estimates))
          (:estimate (trap approximations) state variables (m-na-est, etc.) based on voltage estimates (e-st1) and
          previous estimates (m-na-dot, m-na-dot, etc.), and then estimate w-dot (e-st1-dot) w/ state estimates
          (:e.g. m-na-est) & current voltage estimates (e-st1) using KCL.

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(set-soma-states-and-v-dot-for-current-clamp nil)
  (if *include-dendrite (set-dendrite-states-and-v-dots nil))
    ;; Estimate (approx. approx.) voltage (v-rest) \(\frac{\partial}{\partial t}\) new v-rest-dot, previous voltage (voltage) and the
    ;; previous derivative (voltage-dot).
    (estimate-soma-voltage)
    (if *include-dendrite (estimate-dendrite-voltages)))
  ;; Set new voltage (voltage) to last estimate (voltage-est2). Also set v-rest to v-rest2 for final
  ;; "SET-SOMA-STATES-AND-V-DOTS" and "SET-DENDRITE-STATES-AND-V-DOTS".
  (store-new-soma-voltage)
  (store-new-soma-estimate)
  (cond (*include-dendrite (store-new-dendrite-voltages) (store-new-dendrite-estimates)))
    ;; Calculate (approx. approx.) final estimates of state variables (m-na, etc.) based on stored voltage value
    ;; (v-rest) and previous states (m-na, m-na-dot, etc.). Calculate state variable derivatives (e.g. m-na-dot)
    ;; \(\frac{\partial}{\partial t}\) diff. eqn., the final state estimates (e.g. m-na) and final voltage estimate (voltage). Update
    ;; (replace) the stored values for the state variables and their derivatives. Calculate v-dot (voltage-dot)
    ;; \(\frac{\partial}{\partial t}\) states (e.g. m-na) & current voltages (voltage and voltage-dot) using circuit equation (KCL), and store
    ;; the values.
    (set-soma-states-and-v-dots-for-current-clamp nil)
    (if *include-dendrite (set-dendrite-states-and-v-dots nil))
  ;; Print simulation time and concatenate the just calculated variables to the appropriate output lists.
  (cond ((zerop (*time-step *plot-step))
    ;; UPDATE-OUTPUT-LISTS))
    (update-output-lists))) ; Store the steady state values for repeat runs.
  (setq steady-state-run nil)
  (time-step 0)

; STORE-STEADY-STATE
(defun store-steady-state ()
  (aset (aref SOKA voltage) SOMA e-rest$)
  (dolist (DENDRITE-ARRAY (list BASAL-DENDRITE APICAL-SHAFT-DENDRITE APICAL-1-DENDRITE APICAL-2-DENDRITE))
    (if (aref DENDRITE-ARRAY 0 INCLUDE-ME$)
      (do ((segment 0 (incf segment)))
        (aset (aref DENDRITE-ARRAY segment voltage) ENDRITE-ARRAY segment e-rest$))))

; RUN-CLAMP
(defun run-clamp ()
  ;; This is the main loop which generates the state variables and voltages for each time increment.
  (do ((i 0 (incf i)))
    ((and (i *time-step-estimates)))
    ;; This evaluation loop performs successive approximations to the model voltages at the present time step
    ;; until all the estimates satisfy the convergence criterion.
    (do (((1 (incf i)))
      (and (< 1 (test-estimates)))))
      ;; True if ALL estimates are within epsilon (v-est1's & v-est2's)
      (setq v-est1's= v-est2's to prepare for generating new estimate (est2)).
      (if *clamp-run (store-new-soma-estimate)
        (if *include-dendrite (store-new-dendrite-estimates))
          ;; Estimate (approx. approx.) state variables (m-na, etc.) based on voltage estimates (v-est1) an
          ;; previous (m-na, m-na-dot, etc.), and then estimate v-dot (v-est1-dot) \(\frac{\partial}{\partial t}\) state
          ;; estimate \(\frac{\partial}{\partial t}\) states (e.g. m-na) & current voltage estimates (v-est1) using KCL.
          (if *clamp-run (set-soma-states-and-v-dots-for-current-clamp nil))
            (if *include-dendrite (set-dendrite-states-and-v-dots nil))
              ;; Estimate (approx. approx.) voltage (v-est2) \(\frac{\partial}{\partial t}\) new v-est1-dot, previous voltage (voltage) and the
              ;; previous derivative (voltage-dot).
              (if *clamp-run (estimate-soma-voltage)
                (if *include-dendrite (estimate-dendrite-voltages)))
                  ;; Set new voltage (voltage) to last estimate (voltage-est2). Also set v-rest to v-rest2 for final
                  ;; "SET-SOMA-STATES-AND-V-DOTS" and "SET-DENDRITE-STATES-AND-V-DOTS".
                  (store-new-soma-voltage)
                    (if *clamp-run (store-new-soma-estimate))))
                      272
(cond (*include-dendrite (store-new-dendrite-voltages) (store-new-dendrite-estimates)))
  ;; Calculate trap. qprom. ftnd esum ates of state arIqUes (M -na,'etc.) based on store d voltag VUe (v-estl) andprevious states -na, m-na-dot, etc.). Cdculati state variaNe derivatives (e.g. m-na-dot)
  ;; diff. eq., the ftnd state estim ates ire. g. M -net) andflnd voltage estim ate age). Update
  ;; the values.
  (if (*include-dendrite (set-dendrite-states-and-v-dots T))
    (if (iclamp-run (set-soma-states-and-v-dot-for-current-clamp T))
      (cond ((ze'rop *time-step *plot-'step))
        (send terminal-io :home-down)(send terminal-io :clear-rest-of-line)
        (format t "Length of simulation + time for steady state -4fms Current time -4fasm + time-for-steady-state *duration) *time)
        (update-output-lists)
        (setq *point-index (+ 1 *point-index))))
    (defvars *v-start *v-final *voltage-normal*)
    ;; NORMALIZE
    (defun normalize (v-start v-final)
      (setq *v-start v-start
        *v-final v-final
        *voltage-normal* mapcar #'normalize-op *voltage*))
    ;; NORMALIZE-OP
    (defun normalize-op (voltage)
      (voltage v-final)
        *v-start *v-final))
    ;; Soma geometry **************
    ;; Assume soma is a sphere
    (defvar *soma-radius 17.5) ; micrometers
    (defun surf-area (radius)
      (* 4.0 .9 (3.1416 #+float (* radius radius)) 1.0e-6))
    ;; ************** PASSIVE COMPONENTS
    (defvar *temperature 27.0) ; mV
    (defvar *e-na 50.0) ; mV
    (defvar *e-ca 110.0) ; mV
    (defvar *e-k -85.0) ; mV
    (defvar *e-holding -70) ; mV
    (defvar *e-l 70.0)
    (defvar *ed-l 70.0)
    (defvar *faraday 9.64B44) ; Coulombs/mole
    (defvar R 8.314) ; Gas constant — (Volts*Coulombs)/(DegreesKelvin*mole)
    (defvar *ca-conc-extra 1.8) ; Extra-cellular Ca++ concentration [mM]
    (defvar L 1.5 mM Ca out, <10-7 mM in.
    (defvar *segal-and-barker, 1986 use 4.0 mM Ca out
    (defvar *madison-and-nicoll, 1983 use 2.5 mM Ca out
    (defvar *blaxter et al, 1986 use ACSF with 3.25 mM Ca
    (defvar *wong-and-prince, 1981 use 2.0 mM Ca
    ;; Electrode shunt resistance (Mohm)
    (defvar *r-electrode 1000000.0)
    ;; Soma input resistance (Mohm)
    (defvar *r-in 35.0)
    ;; Soma membrane resistance (ohm-cm-cm)
    (defvar *r-mem 950.0)
    ;; Dendrite membrane resistance (ohm-cm-cm)
    (defvar *r-d-mem 4000.0)
    ;; Dendrite axoplasmic resistance (ohm-cm)
    (defvar *r-d-int 200.0)
... Dendritemembraw cqw1tawe (lcrofkrad4jq-=)

i'd"efvar *capd-mm 1.0)

Input capacitaweofsoma (nfl
(defvar *caps-in 0.150)
Soma membraw ctowitawe (jcrof4radAls4j-m)
(defvar *caps-mm 1.0)

ll#....
Mal capacityof soma Jq

(defvar *caps)

(defvar *soma-area)
(defvar *gs-1)

,Soma surfxe Wea

***** sq. Micron$

MENU-POR-SOMA-GBOAfMY-AArD-PA$$"-COAM"Jft
defvar *calc
TY
(defvar *r-calc T)
(defvar *qten-ionic 1.5)
(defun menu-for soma-geometry-and-passive-components
(tv:choose-va;iable-values
'((*soma-radius
*Soma sphere radius tmicrometers]
:number)
(*e-I
*Leakage battery oV]
:number)
(*e-na
Na reversal ptential CAVY *':number)
(*e-k
OK reversal potential mV]
:number)
(*e-ca
"Ca reversal potential a]
:number)
(*c-calc 'Cakulate"C-Nem from geometry yes) or use input capacitance 004 :boolean)
(*caps-mm
"Membrane capAditance toicrofarads/sq-cm]
:number)
(*caps-in Input capacity EnF3
:number)
(*r-calc wCalculate *RS-MEM'from ge6metr
oo ean)

(yes) or use input impedance (no)" b
(*rs-mm "Membrane resistance ohm-co-cal
:number)
(*a-I
Winput impedance Nohml'(usedto sbstitute for soma and dendrite Rin only)
:number)
(*temperature mTemperature of experiment [CelsiusIO'inumber)
(*qten OQ-10 [Rate constant coefficient per 10 degrees]* :number)
(*qten-ionic NQ-10 iolnid'teionducti6ce oefficient per 10 degrees]* :number)
(*include-shuht "Include ele6trodejhqnt conductance (if no the g-shunt will be ignored)?' :boolean)
(*r-electrode NElectrdde Auk M6hms1O':num0ir)
(*i-constant-inJection"'Consitant c6rreint'injeic'teld [nA]* :number))
:label
'Passive components")
(setq *soma-area (* 1.0e8 (surf-area *soma-radius))
*gs-1 (if *r-calc (//'(surf-area *soma-radius) (* *rs-mem 1.0e-6))
U/ 1.0 *a-l )
*g-electrode (// 1.0 *r-electrode)
*caps (if *c-calc (* (surf-area *soma-radius) *caps-mem 1.0e3) *caps-in))
(aset *gs-1 SOKA g-leak$)
(aset 100.0 SOMA g-axial$)
Atwme th $a haamnitaffy zero auxom IC awtvity.
(update-qtens)
(update-gbars))

(defun update-qtens ()
(setq *qten-factor-at-25 (ten-tau-factor 25.0 *temperature *ten)
*qten-factor-at-25-a (te'-tau.'fact6r'25.'O *temperature *ten-n)
*qten-factor-at-32 (qten- tau- fictor`31. 0
eratujrie *ten)
ahwliw
*qten-factor-at-30 ('qten-ta6-factor"30''.0'
rature *qt6n)
-Dgmid A kinetics
*qten-factor at-27 (qten-tA6-fa'ct6r!'2y,.'O'*
ea re *qten
*qten-factor-at--2 (qten-tau. factor 2t.'O
ratui *Oten)
*qten-factor-at-24 Wen-tau-f"
`24'
atutii 5.0)
I-Na Idnetid.
, ptqr , .q
er
I .. .11
*qten-g-24 qten-rati-fact6i A"A i t em"'
*4t6h-;'ioMc)
en f
currents.
'p
re,
-orlonk conc*ctance of Na
*qten-g-30 (qten'-rat46-fa'c`ti'j4.b it
e:;r iue: *qtehl' ionic)
;Von for onic conductame of DR'and
X

*qten-g-32 (qten-rat6-factor 32.0 *temoe t6rl *Oelh-ionic)
*qten-factor-at-37 (ten-tau-factor 37''O'
ratue'*qten)
*qten-factor-at-14
city r e *qten)))
qten-.tau- actor 14
...QTEN-TAU-F4C7VR Ms cdculates the 4yzen factor for
(defun qten-tau-fiict;6'r'('refe'ren'ce-'temp temp, qt6n)
qten
reference.temptim'p ) 10.0)))

-Oonfor lonk conductance of Ca currents.

temperaturegoes up, tau goes down).

;,-,-QTBN-R.4TE-FAC7VR 7M cdculates the ten ftor for roe consrants(as temperwuregoes p, so does rate).
(defu 'n qten-rate-factor (reference-temp temp'qten)
qten
temp, reference-tOmp, ) 10.0)))
(defvars-w-value (*qten-9-2 10)(*qten-factor-at-27 1.0))
(defvars-w-value (*qten-g-30 1.0)(*qten-factor-at-30 1.0))
(defvars-w-value (*qten-g-32 1.0)(*qten-h-t6r-at-32 10))

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L-CURRENT
The leakage current.
(defun l-current (v)
  (* g-leakage (- v v-leakage)))

AURA and BB7.4 set functions for the voltage and forward rate constants for the single barrier model, where alpha is the forward rate constant and beta is the backward rate constant. "v-half" is the voltage at which the forward and backward rate constants are equal. Note that there are two aspects of the temperature dependence of these rate constants. The first derives from the voltage-dependent Boltzmann distribution, which is explicitly calculated in these functions. The second arises in a bumped "Qten" factor that is strictly a coefficient for the "base-rate", that is the rate derived from the original free-energy changes of the gating particle. Since this factor depends on each current, the Qten factor is not included here but in the time constants functions for each gating variable.

(defun alpha (voltage v-half base-rate valence gamma)
  (let ((exponent (/ (- voltage v-half) 1.0e-3 valence faraday gamma) (= R (+ temperature 273.0)))))
    (setq exponent (cond (0 exponent 20.0) 20.0) (( exponent -10.0) -10.0)
      (t exponent))
    (* base-rate (exp exponent))))

(defun beta (voltage v-half base-rate valence gamma)
  (let ((exponent (/ (- voltage v-half) 1.0e-3 valence faraday (- 1.0 gamma)) (= R (+ temperature 273.0)))))
    (setq exponent (cond (0 exponent 20.0) 20.0) (( exponent -10.0) -10.0)
      (t exponent))
    (* base-rate (exp exponent))))

C-CURRENT
*************

Ca dependent K-current

For now make it analogous to the A current, except that the C current is faster and is dependent on the concentration of Ca++. The conductance in micro-siemens

(defvar *gbar-c 0.40)
(deffvars-w-value (*v-half-cx 65.0) (*alpha-base-rate-cx 0.007) (*valence-cx 5.0) (*gamma-cx 0.20)
  (*v-half-cy 60.0) (*alpha-base-rate-cy 0.003) (*valence-cy 2.0) (*gamma-cy 0.2)
  (*base-tcx 0.25)(*base-tcy 15))
(deffvars-w-value (*alpha-c 1.0) (*beta-c 1.0))
(deffvars-w-value (*tau-alpha-c 0.001) (*tau-beta-c 8.0))

W-C-INF w-c is calcium-dependent gating variable for C-current

(defvar w-c-inf (calc-conc-shell)
  (((= *calc-conc-shell calc-conc-shell calc-conc-shell calc-conc-shell) (+ *beta-c (*calc-conc-shell calc-conc-shell)))))

T-W-C

(defvar t-w-c (calc-conc-shell)
  (let ((tau (if < tau 0.2 0.2)
      (* qten-factor-at-27 (if (< tau 0.2) 0.20
        tau)))))

A-X-C

(defvar a-x-c-inf-midpoint 0.0)
(defun a-x-c-inf (voltage)
  (alpha voltage v-half-cx *valence-cx *gamma-cx))

B-X-C
(defun b-x-c-inf (voltage)
  (beta voltage v-half-cx *valence-cx *gamma-cx))

A-Y-C
(defun a-y-c-inf (voltage)
  (alpha voltage v-half-cy *valence-cy *gamma-cy))

B-Y-C
(defun b-y-c-inf (voltage)
  (alpha voltage v-half-cy *valence-cy *gamma-cy))

X-C-INF
x-inf is activation variable for C-current
(defvar x-c-inf-midpoint 0.0)
(defun x-c-inf (voltage)
  (if (x-x-c-inf (voltage)
      (+ (x-x-c-inf (voltage)) (b-x-c-inf (voltage))))
    (1)))

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Y-C-INF
---
y-inf is inactivation variable for c-current
(defvar my-c-inf-nilpoint 5.0)
defun y-c-inf (voltage)
  ;; (a-y-c voltage) (+ (a-y-c voltage) (b-y-c voltage)))
  (let ((steepness 2.0)) ;Segal and Barker; Segal, Rogowski, and Barker
    (/ 1.0 (exp ((- voltage my-c-inf-nilpoint) steepness)))))

T-X-C
---
tau-c-current(activation) = msec (estimate)
(defvar tb-x-c 0.5)
defun t-x-c (optional voltage)
  (let ((tx (/* 1.0 (+ (a-x-c voltage) (b-x-c voltage)))))
    ;(defun t-x-c (voltage) ;tau tail current (Brown and Griffith) (msec)
      (cond ((< voltage -30.0) (* 20.0 (exp ((+ voltage 40.0) 18.0))))
            (t (* 20.0 (exp ((- 40.0 (+ voltage 60.0)) 18.0)))))))

T-Y-C
---
tau-c-current(inactivation) = msec
(defvar ty-c 1.0)
defun t-y-c (optional voltage)
  (let ((ty (/* 1.0 (+ (a-y-c voltage) (b-y-c voltage))))
    (* *qten-factor-at-27 (if (< ty *base-tcy) *base-tcy ty))))

MENU-FOR-C-CURRENT
---
defvar x-shift 0.0
(defun menu-for-c-current ()
  (tv:choose-variable-values
   "((gbar-c "C-current conductance [micro-S]\n  :number)
   "x Variable Kinetics 
   "(x-half-cx "V/12 for x":number)
   "(alpha-base-rate-cx "Alpha-base value for x at V1/2":number
    :documentation "Increase makes it faster")
   (valence-cx "Valence for x":number)
   (gamma-cx "Gamma for x":number)
   "Y Variable Kinetics 
   "(x-half-cy "V/12 for y":number)
   "(alpha-base-rate-cy "Alpha-base value for y at V1/2":number
    :documentation "Increase makes it faster")
   (valence-cy "Valence for y":number)
   (gamma-cy "Gamma for Na 1 y":number)
   "Minimum value for time constant [ms]":number)
   "W Variable Kinetics 
   "(tau-alpha-c "Forward time constant for Ca++-binding to W particle":number)
   (tau-beta-c "Backward time constant for Ca++-binding to W particle":number)
   )))
  (setq alpha-c 1.0 *tau-alpha-c)
  (setq beta-c 1.0 *tau-beta-c))

C-CURRENT Function to calculate the C current.
(defun c-current (x-c y-c w-c v)
  (* g-c *gbar-c x-c y-c w-c (- v *g-k)))

G-C
---
defun g-c (gbar-c x-c y-c w-c)
  (if (< x-c 0.01) (setq x-c 0.0))
  (* gbar-c x-c x-c x-c x-c y-c w-c))

X-C-EFF, Y-C-EFF
---
defun x-c-eff (x-c)
  (if (< x-c 0.01) 0.0
    (* x-c 4.0))
(defun y-c-eff (y-c)
  (* y-c 1.0))

C-Plot
---
defvars xx-c-inf xx-c-inf xx-c-effs xx-c-effs st-x-ce st-y-ce sg-c-inf
(defun c-plot ()
  (cplot xx-c-inf st-x-ce st-y-ce sg-c-inf))
(defun c-plot ()
  (cplot xx-c-inf st-x-ce st-y-ce sg-c-inf))
(menu-for-c-current)
(setq *volts* nil *y-c-inf* nil *x-c-inf* nil *y-c-eff* nil *x-c-eff* nil
*xt-x-c* nil *st-y-c* nil *g-c-inf* nil)
(do ((v -100.0 (+ v 0.5))) ((> v 50))
  (setq *y-c-inf* (nconc *y-c-inf* (list (y-c-inf v))))
  (setq *x-c-inf* (nconc *x-c-inf* (list (x-c-inf v))))
  (setq *y-c-eff* (nconc *y-c-eff* (list (y-c-eff (x-c-inf v))))
  (setq *x-c-eff* (nconc *x-c-eff* (list (x-c-eff (x-c-inf v))))
  (setq *t-x-c* (nconc *t-x-c* (list (t-x-c v)))
  (setq *t-y-c* (nconc *t-y-c* (list (t-y-c v)))
  *volts* (nconc *volts* (list v))
  *g-c-inf* (nconc *g-c-inf* (list (g-c 1.0 (x-c-inf v)))))

;; W-C- PLOT
(defun w-c-plot ()
  (menu-for-c-current)
  (setq *w-c-inf* nil *calconc* nil *t-w-c* nil)
  (do ((Ca .0e-6 (* a 12)) ((> Ca TO .0))
  (setq *w-c-inf* (nconc *w-c-inf* (list (w-c-inf a)))
  *t-w-c* (nconc *t-w-c* (list (t-w-c a)))
  *calconc* (nconc *calconc* (list Ca)))

;; I-M current **************
;;
;; The muscarinle-sensitive K current of Paul Adams

;; M-CURRENT
(defun m-current (x-m v)
  (* gbar-m x-m (- v *e-k)))

;; I-M conductance - Only activate between -70 mv and -30mv (micro-siemans)
(defun wbar-m .005)

;; I-M time constant - from two values given by Paul (msec)
;; Constant says ~125 ms @ -40 mv (olfactory cortical cells)

;; T-X-M
(defun t-x-m (voltage)
  (let ((b (beta voltage *v-half-mx *base-rate-mx *valence-mx *gamma-mx)))
    (a (alpha voltage *v-half-ax *base-rate-ax *valence-ax *gamma-m)))
  (tx (* qten-factor-at-25 (+ a b)))
  (/ (* t-x-m (qten-factor-at-25)) (* qten-factor-at-25 *base-tmx)))

;; X-M-INF x-inf is activation variable for M-current
(defun x-m-inf (voltage)
  (let ((b (beta voltage *v-half-mx *base-rate-mx *valence-mx *gamma-mx)))
    (a (alpha voltage *v-half-ax *base-rate-ax *valence-ax *gamma-m)))
  (a (+ a b)))

;; MENU-FOR-M-CURRENT
(defun menu-for-m-current ()
  (tv:choose-variable-values
   '((symbol-name "M-current absolute conductance [micro-S]" :number)
     (symbol-name "Block some fraction of absolute conductance [0-1]" :number)
     (symbol-name "X Variable Kinetics" :number)
     (symbol-name "V/12 for M x" :number)
     (symbol-name "Alpha-base value for M x at V/2" :number)
     (symbol-name "Valence for M x" :number)
     (symbol-name "Gamma for M x" :number)
     (symbol-name "Minimum value for time constant [mss]" :number)
     (symbol-name "M Potassium Current" :number)))

;; M-PLOT
(defun m-plot ()
  (menu-for-m-current)
  (setq x-m-inf nil *volts* nil *x-m-inf* nil)
  (do ((v -100.0 (+ v 0.5))) ((> v 50.0))
    (setq &x-m-inf (nconc &x-m-inf (list (x-m-inf v))))
\[ t-x-q = (\text{con} t-x-q (\text{list} t-x-q v)) \]
\[ v\text{olts} = (\text{con} v\text{olts} (\text{list} v)) \]

\[ \text{I-Q current} \]

\[ \text{This is the outward "abnormal rectifier current" that is activated by hyperpolarizing the cell.} \]
\[ \text{Ref. - Segal and Barker, Halliwell and Adams} \]

\[ \text{E-Q Q current may be a mixed conductance.} \]
\[ (\text{defvar e-q -65.0}) \]

\[ \text{I-Q conductance (microsiemens)} \]
\[ (\text{defvar} \text{gbar-q} .002) \]

\[ \text{Q-CURRENT} \]
\[ (\text{defun q-current (v-x-q v)}) \]
\[ (* \text{gbar-q} x-q (- v e-q)) \]

\[ \text{X-Q-INF} \]
\[ (\text{defun} x-q-inf (v)) \]
\[ ((/ 1 (+ 1 (exp (// (+ v 84.0) 4.0)))))) \]

\[ \text{T-X-Q} \]
\[ (\text{defun} t-x-q (v)) \]
\[ (\text{Paul reports Q-10 for both M and Q currents to be ~5.}) \]

\[ \text{MENU-FOR-Q-CURRENT} \]
\[ (\text{defun menu-for-q-current} () \]
\[ (\text{tv:choose-variable-values}) \]
\[ '((\text{gbar-q} "Q current conductance [micro-S]" :number)) \]
\[ ((e-q "Q current reversal potential [mv]" :number))) \]

\[ \text{Q-PLOT} \]
\[ (\text{defvars xx-q-inf xx-x-q}) \]
\[ (\text{defun q-plot}()) \]
\[ (\text{setq xx-q-inf nil volts nil xx-x-q nil}) \]
\[ (\text{do ((v -100.0 (+ v 0.5)))}) \]
\[ (\text{setq xx-x-q-inf (nconc xx-x-q-inf (list (x-q-inf M))}) \]
\[ (\text{vols} = (\text{nconc volts (list v)})) \]

\[ \text{DR-current} \]

\[ (\text{defvars-w-value}) \]
\[ (\text{#dr-block 1.0}) \]
\[ (\text{#base-txdr 0.50)} \]
\[ (\text{#valence-drx 12)} \]
\[ (\text{#gamma-drx 95)} \]
\[ (\text{#gamma-dry 0.2)} \]
\[ (\text{#valence-dry 9)} \]
\[ (\text{#base-tydr 60)} \]
\[ (\text{defvar e-dr 73.50)} \]

\[ \text{DR conductance (microsiemens)} \]
\[ (\text{defvar} \text{gbar-dr} .07) \]

\[ \text{Y-DR-INF} \]
\[ (\text{y-inf is inactivation variable for DR-current}) \]
\[ (\text{Segal and Barker}) \]
\[ (\text{defun} y-dr-inf (voltage)) \]
\[ (\text{let ((b (alpha voltage sv-half-dry \text{base-rate-dry \text{valence-dry} \text{gamma-dry}}))}) \]
\[ (a (beta voltage sv-half-dry \text{base-rate-dry \text{valence-dry} \text{gamma-dry}}))) \]
\[ (a (+ a b))) \]

\[ \text{T-Y-DR} \]
\[ (\text{tau-DR-current (inactivation)}) \]
\[ (\text{Segal and Barker 40 msec}) \]
\[ (\text{defun t-y-dr (voltage)) \]
\[ (\text{let ((b (alpha voltage sv-half-dry \text{base-rate-dry \text{valence-dry} \text{gamma-dry}})))}) \]
\[ (a (beta voltage sv-half-dry \text{base-rate-dry \text{valence-dry} \text{gamma-dry}}))) \]
\[ (a (+ a b))) \]

\[ \text{X-DR-INF} \]
\[ (\text{x-inf is activation variable for DR-current}) \]
\[ (\text{Segal and Barker}) \]
\[ (\text{defun} x-dr-inf (voltage)) \]
\[ (\text{let ((a (alpha voltage sv-half-dry \text{base-rate-dry \text{valence-dry} \text{gamma-dry}})))}) \]
\[ (b (beta voltage sv-half-dry \text{base-rate-dry \text{valence-dry} \text{gamma-dry}}))) \]
\[ (a (+ a b))) \]

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::: T-X-DR
::: tau-DR-current(activation) - msec
::: Segal and Barker 180 ms < -30mV, 8 ms else

(defun t-x-dr (voltage)
  (let* ((a (alpha voltage sv-half-dr x base-rate-dr x valence-dr x gamma-dr x))
           (b (beta voltage sv-half-dr x base-rate-dr x valence-dr x gamma-dr x))
           (tx (max (* qtten-factor-at-30 (+ a b)))
                (if (< tx (* qtten-factor-at-30 base-txdr)) (* qtten-factor-at-30 base-txdr) tx)))

::: MENU-FOR-DR-CURRENT
(defun menu-for-dr-current ()
  (tv:choose-variable-values
   ('(*gbar-dr "Dr-current absolute conductance [micro-SIO]" :number)
    (gdr-block "Block some fraction of absolute conductance [0-1]\n    "
    (sv-half-dr "V/2 for Dr x" :number)
    (base-rate-dr "Alpha-base value for Dr x at V1/2" :number)
    (valence-dr "Valence for Dr x" :number)
    (gamma-dr "Gamma for Dr x" :number)
    (base-txdr "Minimum value for time constant [ms]\n    "
    (sv-half-dry "V/2 for Dr y" :number)
    (base-rate-dry "Alpha-base value for Dr y at V1/2" :number)
    (valence-dry "Valence for Dr y" :number)
    (gamma-dry "Gamma for Dr y" :number)
    (base-tydr "Minimum value for time constant [ms]\n    "
    :label "Delayed-Rectifier Potassium Current")

::: DR-CURRENT
(defun dr-current (x-dr y-dr)
  (* (g-dr (aref SOMA gbar-dr$) x-dr y-dr) v *e-dr)))

::: G-DR
(defun g-dr (gbar-dr x-dr y-dr)
  (* gbar-dr *dr-block
     x-dr x-dr y-dr y-dr))

::: X-DR-EFF, Y-DR-EFF
(defun x-dr-eff (x-dr)
  (x-dr-eff 30))
(defun y-dr-eff (y-dr)
  (y-dr-eff 1.0))

::: DR-PLOT
(defun dr-plot ()
  (menu-for-dr-current)
  (setq *volts* nil
        *y-dr-inf* nil
        *x-dr-inf* nil
        *t-x-dr* nil
        *t-y-dr* nil
        *g-dr-inf* nil)
  (do ((v -100.0 (v 0.5))
       ((v 50))
    (setq
      *dr-inf* (nconc *dr-inf* (list (y-dr-inf v)))
      *x-dr-inf* (nconc *x-dr-inf* (list (y-dr-inf v)))
      *y-dr-inf* (nconc *y-dr-inf* (list (y-dr-inf v)))
      *x-dr-eff* (nconc *x-dr-eff* (list (y-dr-eff v)))
      *y-dr-eff* (nconc *y-dr-eff* (list (y-dr-eff v)))
      *x-y-dr* (nconc *x-y-dr* (list (y-dr-inf v)))
      *y-y-dr* (nconc *y-y-dr* (list (y-dr-inf v)))
      *g-dr-inf* (nconc *g-dr-inf* (list (g-dr 1.0 (x-dr-inf v) (y-dr-inf v))))))

::: AHP-current  ***************
::: Iahp will have two voltage-dependent inactivation particles, y and z, and
::: a calcium-dependent gating particle, w.
::: AHP-CURRENT
(defun ahp-current (z-ahp y-ahp w-ahp v)


(* (g-ahp *gbar-ahp z-ahp y-ahp w-ahp) 
   (- v xe-k))

::: AHP conductance (micro-Siemens)
(defvar *gbar-ahp 0.35)

::: G-AMP - new version
(defun g-ahp (gbar-ahp z-ahp y-ahp w-ahp) 
  (* gbar-ahp 1.0 y-ahp y-ahp w-ahp z-ahp))

(defun y-ahp-eff (y-ahp) 
  (* y-ahp 2.0))

(defvars alpha-ahp beta-ahp)
(defvars w-value (*tau-alpha-ahp 1.0e-5) (*tau-beta-ahp 200.0))
(defvars w-value (*v-half-ahpz 72.0) (*alpha-base-rate-ahpz 2.0e-4) 
  (*valence-ahpz 12.0) (*gamma-ahpz 0) 
  (*alpha-base-rate-ahpy 0.015) (*valence-ahpy 15.0) (*gamma-ahpy 0.8) 
  (*base-tahpz 120.0) (*base-tahpy 2.5))

::: W-AMP-INF w-ahp is calcium-dependent gating variable for AHP-current
(defun w-ahp-inf (calc-conc-shell) 
  (/ (* alpha-ahp calc-conc-shell calc-conc-shell calc-conc-shell) 
     (+ beta-ahp (* alpha-ahp calc-conc-shell calc-conc-shell calc-conc-shell))))

::: T-W-AMP
(defun t-w-ahp (calc-conc-shell) 
  (/ tau ((+ (* beta-ahp (* alpha-ahp calc-conc-shell calc-conc-shell calc-conc-shell)) 
     (* qten-factor-at-27 (if (< tau 0.002) 0.0020 tau)))))

::: V-AHP-INF y-inf is inactivation variable for AHP-current
(defun y-ahp-inf (voltage) 
  (let ((b (alpha voltage *v-half-ahpy *alpha-base-rate-ahpy *valence-ahpy *gamma-ahpy)) 
     (a (beta voltage *v-half-ahpy *alpha-base-rate-ahpy *valence-ahpy *gamma-ahpy))) 
    (if (< ty *base-tahpy) *base-tahpy ty)))

::: T-Y-AMP tau-AHP-current(inactivation) - msec
(defun t-y-ahp (voltage) 
  (let ((b (alpha voltage *v-half-ahpy *alpha-base-rate-ahpy *valence-ahpy *gamma-ahpy)) 
     (a (beta voltage *v-half-ahpy *alpha-base-rate-ahpy *valence-ahpy *gamma-ahpy)) 
     (ty (/ 1.0 (+ a b)))) 
    (if (< ty *base-tahpy) *base-tahpy ty)))

::: Z-AHP-INF
::: z-inf is activation variable for AHP-current
(defun z-ahp-inf (voltage) 
  (let ((b (alpha voltage *v-half-ahpz *alpha-base-rate-ahpz *valence-ahpz *gamma-ahpz)) 
     (a (beta voltage *v-half-ahpz *alpha-base-rate-ahpz *valence-ahpz *gamma-ahpz))) 
    (if (< tz *base-tahpz) *base-tahpz tz)))

::: T-Z-AMP
::: t-z-AHP-current(activation) - msec
(defun t-z-ahp (voltage) 
  (let ((b (alpha voltage *v-half-ahpz *alpha-base-rate-ahpz *valence-ahpz *gamma-ahpz)) 
     (a (beta voltage *v-half-ahpz *alpha-base-rate-ahpz *valence-ahpz *gamma-ahpz)) 
     (tz (/ 1.0 (+ a b)))) 
    (if (< tz *base-tahpz) *base-tahpz tz)))

::: MENU-FOR-AHP-CURRENT
(defun menu-for-a'hp-current () 
  (tv:choose-variable-values '(*gbar-ahp "AHP-current conductance [micro-S]" :number) 
    " Z Variable Kinetics 
    " (*v-half-ahpz "V/12 for Na 1 m" :number) (*alpha-base-rate-ahpz "Alpha-base value for Na 1 m at V1/2" :number) 
    :documentation "Increase speeds up gating particle") 
    (*valence-ahpz "Valence for Na 1 m" :number) (*gamma-ahpz "Gamma for Na 1 m" :number) 
    (*base-tahpz "Minimum value of time constant [msec]" :number) 
    " Y Variable Kinetics 
    " (*v-half-ahpy "V/12 for Na 1 h" :number) (*alpha-base-rate-ahpy "Alpha-base value for Na 1 h at V1/2" :number) 
    :documentation "Increase speeds up gating particle") 
    (*valence-ahpy "Valence for Na 1 h" :number) 
    " 279 280"
gamma-ahpy Gamma for Na I h

base-tahpy NNinimum value of time constant [msec1II

Variable Kinetics

tau-alpha-ahp "Forward time constant for Ca++-binding to W particle* :number

tau-beta-ahp "Backward time constant for Ca++-binding to W particle* :number

(setq *alpha-ahp (// 1.0 *tau-alpha-ahp)

*beta-ahp (// 1.0 *tau-beta-ahp))

 ARP-PLOT

(defun ahp-plot ()
 (setq *t-z-ahp* nil *t-y-ahp* nil *volts* nil zahp-inf* nil y-ahp-inf* nil *y-ahp-eff* nil

(menu-for-ahp-current)
 (do ((v -100.0 (+ v 0.5)) (0 v 50))

(setq *z-ahp-inf* (nconc *z-ahp-inf* (list (z-ahp-inf v))))

*volts* (nconc *volts* (list )))

W-ARP-PLOT

(defun w-ahp-plot ()
 (menu-for-ahp-current)
 (setq *w-ahp-inf* nil *caconc* nil *t-w-ahp* nil)
 (do ((ca 1.0e-6 (* ca 12 ))) (0 ca 10.0))

(setq w-ahp-inf* (nconc w-ahp-inf* (list (w-ahp-inf ca))))

*caconc* (nconc *caconc* (list ca)))

A-current ************

Zbics and Weight report that I-a activates in <10ms and decays over
several hundred ms (380ms 350 to -40ms) (32 degrees). However, 4-AP sensitive tail
currents which have

time constants of a few hundred ms in response to hyperpolarizing pulses to -54ms suddenly
disappear when the clamp is below -54ms, suggesting that the time constant for inactivation
is very rapid for potentials below -54ms, i.e. The failure to observe any 4-AP-sensitive
tail currents negative to -34ms suggests that the 4-AP-sensitive transient current

desactivates very rapidly upon hyperpolarization.

 MENU-FOR-a-CURRENT

(defun menu-for-a-current ()
 (tv:choose-variable-values

" X Variable Kinetics"

(vx-half-ax "V/12 for a x (sb+30,zw-45)* :number

(base-rate-ax "Alpha-base value for a x at V/12" :number)

(valence-ax "Valence for a x (sb+3.67,zw-8.5)* :number

(gamma-ax "Gamma for a x" :number)

(base-txa "Minimum value for time constant [ms]" :number

" Y Variable Kinetics"

(vy-half-ay "V/12 for a y (sb+70,zw-55)* :number

(base-rate-ay "Alpha-base value for a y at V/12" :number)

(valence-ay "Valence for a y (sb4.28,zw+8)* :number

(gamma-ay "Gamma for a y" :number)

(base-tya "Minimum value for time constant [ms]" :number


(defun x-a-inf (voltage)

(Segd and Barker; Segd, Rogawski, and Barker - z=3.67,xinf=30

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(let ((a (alpha voltage v-half-ax *base-rate-ax *valence-ax *gamma-ax))
      (b (beta voltage v-half-ax *base-rate-ax *valence-ax *gamma-ax))
      (c a a b)))

Y-A-INF

Y-a-inf is inactivation variable for A-current.
(defun y-a-inf (voltage)
  (let ((a (alpha voltage v-half-ay *base-rate-ay *valence-ay *gamma-ay))
        (b (beta voltage v-half-ay *base-rate-ay *valence-ay *gamma-ay))
        (tx (// *qten-factor-at-30 a )))
    (if (< tx (* qten-factor-at-30 (base-txa) tx)))))

T-X-A

tau-A-current(activation) - msec (estimate)
(defun t-x-a (voltage)
  (let ((a (alpha voltage v-half-ax *base-rate-ax *valence-ax *gamma-ax))
        (b (beta voltage v-half-ax *base-rate-ax *valence-ax *gamma-ax))
        (ty (// *qten-factor-at-30 ty )))
    (if (< ty (* qten-factor-at-30 (base-tya) ty)))))

T-Y-A

tau-A-current(inactivation) - msec
(defun t-y-a (voltage)
  (let ((a (alpha voltage v-half-ay *base-rate-ay *valence-ay *gamma-ay))
        (b (beta voltage v-half-ay *base-rate-ay *valence-ay *gamma-ay))
        (ty (// *qten-factor-at-30 (base-tya) ty)))
    (if (< ty (* qten-factor-at-30 (base-tya) ty)))))

A-PLOT

defvars-x-a-inf x-a-inf x-a-eff y-a-inf
(let ((v -100.0 (v 0.5)))
  (do ((v -100.0 (v 0.5)))
      (setq
        *y-a-inf* (list (y-a-inf v))
        *x-a-inf* (list (x-a-inf v))))
  (defun a-current (x-a y-a v)
    (* (g-a (aref SOMA gbar-a$) x-a y-a) v *e-k)))

G-A

(defun g-a (gbar-a x-a y-a)
  (gbar-a x-a x-a x-a y-a))


(defun x-a-eff (x-a)
  (x-a 3.0))

A-EFF

(defun y-a-eff (y-a)
  (y-a 1.0))

Persistant Slow Na current

For cat neocortical cells, Stafstrom, Schwindt, Chubb and Crill (1985) report Inap
Activates within 2 to 4 ms, over the range measured (~70 to ~30mv)
Activates at about 1-4mv above rest.

Max. conductance [microS], as measured by French and Gage.

(defvars-w-value (v-half-napx 40.0) (alpha-base-rate-napx 0.04)
  (beta-base-rate-napx 0.04) (valence-napx 6.0) (gamma-napx 0.30) (base-txnap 1.0))

---
(defun menu-for-NaP-current
  (tv:choose-variable-values
   '(*gbar-nap "Persistent Na current conductance [microS]" :number)
   " X Variable Kinetics"
   (*v-half-napx "V12 for Nap x" :number)
   (*alpha-base-rate-napx "Alpha/beta-base value for Nap x at V1/2" :number)
   (*valence-napx "Valence for Nap x" :number)
   (*gamma-napx "Gamma for Nap x" :number)
   (*base-txnapx "Base value for tau nap x" :number))
  (setq *beta-base-rate-napx *alpha-base-rate-napx)
  (aset *gbar-nap SOMA gbar-nap$))

(defun gbar-nap (area)
  (*gbar-nap-dens area 100))

(defun x-nap-inf (voltage)
  (let ((a (alpha voltage *v-half-napx *alpha-base-rate-napx *valence-napx *gamma-napx))
        (b (beta voltage *v-half-napx *alpha-base-rate-napx *valence-napx *gamma-napx))
        (tx (/ 1.0 a))
        (t (x(t a b))))
    (cond ((> voltage 0.0)
           (* qten-factor-at-22 1.0))
          ((> voltage -20.0)
           (* qten-factor-at-22 0.0))
          (t (* qten-factor-at-22 40.0))))

(defun t-x-nap (voltage)
  (let ((d (1.0 1.0 (- midpoint voltage) slope))
        (x (exp d)))
    (cond (< mid point 49.0)
          (> mid point 50.0)
          (= mid point 49.0)
          (= mid point 50.0)
          (> voltage 0.0)
          (< voltage 0.0)))

(defun nap-current (gbar-nap x-nap v)
  (* gbar-nap x-nap (- v *e-na)))

; Plot-Na
(defun plot-nap
  (defvars *x-nap-inf* *t-x-nap*)
  (defun plot-nap
    (do ((v -100.0 ( + v 50.0)))
        (setq *x-nap-inf* (nconc *x-nap-inf* (list (x-nap-inf v)))
              *t-x-nap* (nconc *t-x-nap* (list (t-x-nap v)))
              *volts* (nconc *volts* (list v)))
    ))

;; Fast Na-current ***********

;; Original estimates for the parameters of the three conductances are derived from single Na only spike record
;; (24 degrees C) and the Na only repetitive records (27 degrees C and 32 degrees C). All Qten's are derived
;; from a reference of 24 degrees C. Gating particle kinetics have a Qten of 3; conductance Qten's are set to
;; 1.5.

(defun gbar-na1-dens 40.0) ; conductance density, mS/cm^2
(defun gbar-na2-dens 1) ; conductance density, mS/cm^2
(defun gbar-na3-dens 35.0) ; conductance density, mS/cm^2
(defvar gbar-na-nnap 20.0) ; dendrite conductance density, mS/cm^2

(defun qten-th1 0.5) ; base-th1 (base-th1 2.0) (base-th2 3.0) (base-th3 0.40) (base-th3 0.30))
(defun menu-for-Na-current ()
  (tv:choose-variable-values
   (tv:define-variable-values
    (gbar-na-dens "Na 1 current conductance density (std =35) [mS/sq-cm]" :number)
    "M Variable Kinetics"
    (v-half-m1 "V/12 for Na 1 m" :number)
    (base-rate-m1 "Alpha-base value for Na 1 m at V1/2" :number)
    (valence-m1 "Valence for Na 1 m" :number)
    (gamma-m1 "Gamma for Na 1 m" :number)
    (base-tm1 "Minimum value of time constant [msec]" :number)
    "H Variable Kinetics"
    (v-half-h1 "V/12 for Na 1 h" :number)
    (base-rate-h1 "Alpha-base value for Na 1 h at V1/2" :number)
    (valence-h1 "Valence for Na 1 h" :number)
    (gamma-h1 "Gamma for Na 1 h" :number)
    (base-th1 "Minimum value of time constant [msec]" :number)
    (gbar-na2-dens "Na 2 current conductance density (std =1) [mS/sq-cm]" :number)
    "M Variable Kinetics"
    (v-half-m2 "V/12 for Na 2 m" :number)
    (base-rate-m2 "Alpha-base value for Na 2 m at V1/2" :number)
    (valence-m2 "Valence for Na 2 m" :number)
    (gamma-m2 "Gamma for Na 2 m" :number)
    (base-tm2 "Minimum value of time constant [msec]" :number)
    "H Variable Kinetics"
    (v-half-h2 "V/12 for Na 2 h" :number)
    (base-rate-h2 "Alpha-base value for Na 2 h at V1/2" :number)
    (valence-h2 "Valence for Na 2 h" :number)
    (gamma-h2 "Gamma for Na 2 h" :number)
    (base-th2 "Minimum value of time constant [msec]" :number)
    (gbar-na3-dens "Na 3 current conductance density (std =35) [mS/sq-cm]" :number)
    "M Variable Kinetics"
    (v-half-m3 "V/12 for Na 3 m" :number)
    (base-rate-m3 "Alpha-base value for Na 3 m at V1/2" :number)
    (valence-m3 "Valence for Na 3 m" :number)
    (gamma-m3 "Gamma for Na 3 m" :number)
    (base-tm3 "Minimum value of time constant [msec]" :number)
    "H Variable Kinetics"
    (v-half-h3 "V/12 for Na 3 h" :number)
    (base-rate-h3 "Alpha-base value for Na 3 h at V1/2" :number)
    (valence-h3 "Valence for Na 3 h" :number)
    (gamma-h3 "Gamma for Na 3 h" :number)
    (base-th3 "Minimum value of time constant [msec]" :number))
  )
)

;;; A-M-NA
(defun a-m-na (flag voltage)
  (cond ((and (= flag 1) (= na-choose 3)) (a-m-na-hippo voltage ))
        ((and (= flag 2) (= na-choose 3)) (a-m-na3-hippo voltage ))
        ((and (= flag 3) (= na-choose 3)) (a-m-na3-hippo voltage )))
)

;;; B-M-NA
(defun b-m-na (flag voltage)
  (cond ((and (= flag 1) (= na-choose 3)) (b-m-na1-hippo voltage ))
        ((and (= flag 2) (= na-choose 3)) (b-m-na3-hippo voltage ))
        ((and (= flag 3) (= na-choose 3)) (b-m-na3-hippo voltage ))
)

;;; A-H-NA

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(defun a-h-na (flag voltage)
  (cond ((and (= flag 1) (= *na-choose 3)) (a-h-na1-hippo voltage))
        ((and (= flag 2) (= *na-choose 3)) (a-h-na2-hippo voltage))
        ((and (= flag 3) (= *na-choose 3)) (a-h-na3-hippo voltage))))

;;; B-H-NA
(defun b-h-na (flag voltage)
  (cond ((and (= flag 1) (= *na-choose 3)) (b-h-na1-hippo voltage))
        ((and (= flag 2) (= *na-choose 3)) (b-h-na2-hippo voltage))
        ((and (= flag 3) (= *na-choose 3)) (b-h-na3-hippo voltage))))

;;; M-NA-INF
(defun m-na-inf (flag)
  (cond ((= 1 flag) (*a-m-nal ( *a-m-nal *b-m-nal)))
        ((= 2 flag) (*a-m-na2 (*a-m-na2 *b-m-na2)))
        ((= 3 flag) (*a-m-na3 (*a-m-na3 *b-m-na3)))))

;;; T-M-NA
(defun t-m-na (flag)
  (let ((tm)
        (cond ((= 1 flag) (*a-m-nal ( *a-m-nal *b-m-nal)))
              ((= 2 flag) (*a-m-na2 (*a-m-na2 *b-m-na2)))
              ((= 3 flag) (*a-m-na3 (*a-m-na3 *b-m-na3))))))

;;; H-NA-INF
(defun h-na-inf (flag)
  (cond ((= 1 flag) (*a-h-nal (*a-h-nal *b-h-nal)))
        ((= 2 flag) (*a-h-na2 (*a-h-na2 *b-h-na2)))
        ((= 3 flag) (*a-h-na3 (*a-h-na3 *b-h-na3))))

;;; T-H-NA
(defun t-h-na (flag)
  (let (th)
        (cond ((= 1 flag) (*a-h-nal (*a-h-nal *b-h-nal)))
              ((= 2 flag) (*a-h-na2 (*a-h-na2 *b-h-na2)))
              ((= 3 flag) (*a-h-na3 (*a-h-na3 *b-h-na3))))))

;;; GBAR-NA
(defun gbar-na (flag area)
  (cond ((= 1 flag) (*gbar-nal-dens area 1.0e3))
        ((= 2 flag) (*gbar-na2-dens area 1.0e3))
        ((= 3 flag) (*gbar-na3-dens area 1.0e3))))

;;; GBAR-NAD
(defun gbar-nad (area)
  (*gbar-nad-dens area 1.0e3))

;;; WHEN EDITING POWERS OF GATING PARTICLES, ALSO EDIT APPROPRIATE M-EFF AND H-EFF FUNCTIONS

;;; NA1-CURRENT
(defun n1-current (gbar-na m-na h-na v)
  (* (g-na1 gbar-na m-na h-na) (- v *e-na)))

;;; G-NA1
(defun g-na1 (gbar-na m-na h-na)
  (* gbar-na m-na h-na))

;;; M-EFF-NA1, H-EFF-NA1
(defun m-eff-na1 (m-na) (* m-na 1.0))
(defun h-eff-na1 (h-na) (* h-na 2.0))

;;; NA2-CURRENT
(defun n2-current (gbar-na m-na h-na v)
  (* (g-na2 gbar-na m-na h-na) (- v *e-na)))

;;; G-NA2
(defun g-na2 (gbar-na m-na h-na)
  (* gbar-na m-na h-na))

;;; M-EFF-NA2, H-EFF-NA2
(defun m-eff-na2 (m-na) (* m-na 1.0))
(defun h-eff-na2 (h-na) (* h-na 1.0))

;;; NA3-CURRENT
(defun n3-current (gbar-na m-na h-na v)
  (* (g-na3 gbar-na m-na h-na) (- v *e-na)))

;;; G-NA3

(defun g-na (gbar-na m-na h-na) (* gbar-na m-na m-na h-na h-na h-na))

;;; M-EFF-NAI, H-EFF-NAI
(defun m-eff-na3 (m-na) (* m-na 2.0))
(defun h-eff-na3 (h-na) (* h-na 3.0))

;;; Generic Na Kinetics ******* Basic functions are from Traub et al.
(defun *ref-na (10.0)
  (defvar faraday 9.65e4)
  (defvar temperature! 298.0)
  (defvar R 0.31)
  (^mol K)

;;; A-M-NAI-HIPPO
(defun a-m-na1-hippo (voltage)
  (alpha voltage v-half-m1 *base-rate-m1 *valence-m1 *gamma-m1))

;;; B-M-NAI-HIPPO
(defun b-m-na1-hippo (voltage)
  (beta voltage v-half-m1 *base-rate-m1 *valence-m1 *gamma-m1))

;;; A-H-NAI-HIPPO
(defun a-h-na1-hippo (voltage)
  (beta voltage v-half-h1 *base-rate-h1 *valence-h1 *gamma-h1))

;;; B-H-NAI-HIPPO
(defun b-h-na1-hippo (voltage)
  (alpha voltage v-half-h1 *base-rate-h1 *valence-h1 *gamma-h1))

;;; A-M-NA2-HIPPO
(defun a-m-na2-hippo (voltage)
  (alpha voltage v-half-m2 *base-rate-m2 *valence-m2 *gamma-m2))

;;; B-M-NA2-HIPPO
(defun b-m-na2-hippo (voltage)
  (beta voltage v-half-m2 *base-rate-m2 *valence-m2 *gamma-m2))

;;; A-H-NA2-HIPPO
(defun a-h-na2-hippo (voltage)
  (beta voltage v-half-h2 *base-rate-h2 *valence-h2 *gamma-h2))

;;; B-H-NA2-HIPPO
(defun b-h-na2-hippo (voltage)
  (alpha voltage v-half-h2 *base-rate-h2 *valence-h2 *gamma-h2))

;;; A-M-NA3-HIPPO
(defun a-m-na3-hippo (voltage)
  (alpha voltage v-half-m3 *base-rate-m3 *valence-m3 *gamma-m3))

;;; B-M-NA3-HIPPO
(defun b-m-na3-hippo (voltage)
  (beta voltage v-half-m3 *base-rate-m3 *valence-m3 *gamma-m3))

;;; A-H-NA3-HIPPO
(defun a-h-na3-hippo (voltage)
  (beta voltage v-half-h3 *base-rate-h3 *valence-h3 *gamma-h3))

;;; B-H-NA3-HIPPO
(defun b-h-na3-hippo (voltage)
  (alpha voltage v-half-h3 *base-rate-h3 *valence-h3 *gamma-h3))

;;; NAI- PLO T, NA2- PLO T, NA3- PLO T
(defvars ma-infl* st-his sh-infl* st-m1
  *ma-infl2* st-h2* sh-infl2* st-m2
  *ma-infl3* st-h3* sh-infl3* st-m3
  *voltage* *ga-na1-inf* *g-na2-inf* *g-na3-inf*
  *ma-eff1* sh-eff1* ma-eff2* sh-eff2* ma-eff3* sh-eff3*)

(defun na1-plot ()
  (menu-for-na-current)
  (setq *ma-infl* nil *st-his* nil sh-infl* nil *ma-infl2* nil sh-infl2* nil *ma-infl3* nil sh-infl3* nil)
  (do* ((v -100.0 (+ v .60)
        (m) (h))
       (v 50.0)
       (setq *ma-na1* (*m-na1 1 v) *sh-na1* (*sh-na1 1 v)
             *ma-h-na1* (*ma-h-na1 1 v) *sh-h-na1* (*sh-h-na1 1 v)
             *ma-infl* (nconc *ma-infl* (list v))
             *sh-infl* (nconc *sh-infl* (list v)))
        (m))
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(defun na2-plot ()
  (menu-for-na-current)
  (setq *m-inf2* nil *t-m2* nil *h-inf2* nil *t-h2* nil *9-na2-inf* nil *volts* nil *h-eff2* nil *-eff2* nil)
  (do* ((v -100.0 (+ v .50))
        (m) (h))
    (> 50.0)
    (setq *a-m-na2 (a-m-na 2 v) *b-m-na2 (b-m-na 2 v)
          *a-h-na2 (a-h-na 2 v) *b-h-na2 (b-h-na 2 v)
          *m (m-na-inf 2) *h (h-na-inf 2)
          *volts* (nconc *volts* (list M *m-inf2* (nconc *-inf2* (list m)) *h-inf2* (nconc *h-inf2* (list h))
                                  *m-eff2* (nconc *-eff2* (list -eff-na2 m))) *h-eff2* (nconc *h-eff2* (list (h-eff-na2 W)
                                        *9-na2-inf* (nconc *g-na2-inf* (list (g-W 20 (m-na-inf 2)(h-na-inf 2))))
                                  *t-m2* (nconc *t-m2* (list (t-m-na 2M *t-h2* (nconc *t-h2* (list (t-h-na ZMM
                                  ...)

SOMATIC AND DENDRITIC Ca-CURRENT**************

(defvar *gbar-Ca-dens. 50.0) ; conductance density, mS/cm-squared
(defvar *gbar-Cad-dens 20.0) ; dendrite conductance density, mS/cm-squared
(defvar *base-tsca 20) ; Minimum value of activation time constant [msec]
(defvar *v-half-s 24.0) ; V/2 for Ca s :number
(defvar *v-half-w 35.0) ; V/2 for Ca w :number
(defvar *base-rate-s 0.001) ; documentation "Increase makes gating particle faster"
(defvar *base-rate-w 0.001) ; " documentation "Increase makes gating particle faster"
(defvar *valence-s 12.0) ; Gamma for Ca s :number
(defvar *valence-w 12.0) ; " Gamma for Ca w :number
(defvar *gamma-s 0.5) ; " Gamma for Ca s :number
(defvar *gamma-w 0.2) ; " Gamma for Ca w :number

;; MENU-FOR-CA-CURRENT
(defun menu-for-ca-current ()
  (tv:choose-variable-values
   "((gbar-Ca-dens "Ca current conductance density [mS/cm^2]" :number)
    " Variable Kinetics"
    " "
    (v-half-s "V/12 for Ca s" :number)
    (base-rate-s "Alpha-base value for Ca s at V/12" :number)
    (valence-s "Valence for Ca s" :number)
    (gamma-s "Gamma for Ca s" :number)
    (base-tsca "Minimum value of activation time constant [msec]" :number))
    " Variable Kinetics"
    " "
    (v-half-w "V/12 for Ca w" :number)
    (base-rate-w "Alpha-base value for Ca w at V/12" :number)
    (valence-w "Valence for Ca w" :number)
    (gamma-w "Gamma for Ca w" :number)
    (base-twca "Minimum value of inactivation time constant [msec]" :number))))
  (setq *gbar-ca (gbar-ca (surf-area *soma-radius)))

;; KI-S-CA
(defun k1-s-ca (voltage)
  (alpha voltage "v-half-s" *base-rate-s" *valence-s" *gamma-s")

;; K2-S-CA
(defun k2-s-ca (voltage)
(beta voltage *v-half-s *base-rate-s *valence-s *gamma-s))

;;; A-W-CA
(defun a-w-ca (voltage)
  (beta voltage *v-half-w *base-rate-w *valence-w *gamma-w))

;;; B-W-CA
(defun b-w-ca (voltage)
  (alpha voltage *v-half-w *base-rate-w *valence-w *gamma-w))

;;; MENU-FOR-CAD-CURRENT
(defun menu-for-cad-current (dendrite-array segment)
  (let ((label (format nil "C4 current conductance density in -A segment -2d [mS//sq-cm]" (aref dendrite-array 0 label$)) (+ 1 segment))))
  (tv:choose-variable-values
   '(*gbar-cad-dens label :number))
  (aset (* (aref dendrite-array segment length$) 314159 (aref dendrite-array segment diameter$)
    1.0e-8 *gbar-cad-dens)
    dendrite-array segment gbar-ca$)))

;;; GBAR-CA
(defun gbar-ca (area)
  (totd C4-channel conductance (micro$) *gbar-ca-dens area 1.00))

;;; GBAR-CAD
(defun gbar-cad (area)
  I,-totd,*ndrite Ca-chann conductawe (Micros) *gbar-cad-dens area 1.00))

;;; S-CA-INF
(defun s-ca-inf (v)
  (if (< (k1-s-ca v) (k2-s-ca v))
    (* (k1-s-ca v) (k2-s-ca v)))))

;;; T-S-CA
(defun t-s-ca (v)
  (let ((tau (/ 1.0 (* (k1-s-ca v) (k2-s-ca v)))))
    (* qten-factor-at-32 (if (< tau *base-tsca) *base-tsca tau))))

;;; W-CA-INF
(defun w-ca-inf (v)
  (if (< (a-w-ca v) (b-w-ca v)))
    (* (a-w-ca v) (b-w-ca v))))

;;; T-W-CA
(defun t-w-ca (v)
  (let ((tau (/ 1.0 (* (a-w-ca v) (b-w-ca v)))))
    (* qten-factor-at-32 (if (< tau *base-twca) *base-twca tau))))

;;; CA-CURRENT
(defun ca-current (gbar-ca s-ca w-ca v)
  (g-ca gbar-ca s-ca w-ca v (e-ca)))

;;; G-CA
(defun g-ca (gbar-ca s-ca w-ca)
  (if (< w-ca 0.001) (setq w-ca 0.0)
    (* gbar-Ca s-ca s-ca s-ca w-ca w-ca wca-w-ca)))

;;; S-CA-EFF, W-CA-EFF
(defun s-ca-eff (s-ca)
  (if (< s-ca 0.001) 0.0
    (* s-ca 2.0)))))
(defun w-ca-eff (w-ca)
  (if (< w-ca 0.001) 0.0
    (* w-ca 4.0)))

;;; CA-PLOT
(defun ca-plot ()
  (menu-for-ca-current)
  (setq *volts* nil *w-ca-inf* nil *s-ca-inf* nil *w-ca-eff* nil *s-ca-eff* nil
    *x-s-ca-nil* nil *x-w-ca-nil* nil)
  (do ((v -100.0 (+ v 0.5)))
    ((> v 50))
    (setq *w-ca-inf* (nconc *w-ca-inf* (list (w-ca-inf v)))
      *w-ca-inf* (nconc *w-ca-inf* (list (s-ca-inf v)))
      *w-ca-eff* (nconc *w-ca-eff* (list (w-ca-eff v)))
      *s-ca-inf* (nconc *s-ca-inf* (list (t-s-ca-inf v)))
      *x-w-ca* (nconc *x-w-ca* (list (t-w-ca v)))
      *x-w-ca* (nconc *x-w-ca* (list (t-w-ca v)))
      *volts* (nconc *volts* (list v))))

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**Persistent Calcium Current**

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**Ca** slow current as reported by Johnston, Habits, and Wilson.

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From deriving the IV curves of JH&W, it is determined that this current is due to a non-inactivating inward current with a reversal potential around 0mV. Thus it is unclear as to what species are actually comprising this current.

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**E-CAS Empirically-derived reversal potential for the so-called slow "Ca" current.**

*(defvar *e-cas* 0)*

---

**X-CAS Time constant for activation - ranges between 50 and 100 ms.**

*(defun t-x-cas (voltage) (ignore voltage) 75.0)*

---

**X-CAS-INF Steady state value for the activation variable.**

*(defun x-cas-inf (voltage) (let ((midpoint -30.0)(steepness 360)) (1.0 (list (s-ca-inf v)(w-ca-inf v)))))*

---

**CAS-PLOT**

*(defun cas-current (x-cas voltage) (* gbar-cas x-cas (- voltage *e-cas)))*

---

**Ca++ Concentration and Ca++ Reversal Potential System**

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Initially we will use a simple description of Ca++ accumulation in a thin shell just underneath the cell membrane. This model will include the contribution of the total Ca++ currents (transient and slow), and the first order removal of Ca++ via some combination of diffusion and/or binding that is expressed with a single rate constant. This treatment is modeled after Trab and Linas.

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**New version with two concentric shells -**

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*Ca++ shell dot = (K * (sum of Ca++ currents)) - ((Ca++)sh1 - [Ca++ sh2] @ t-ca-conc) *Ca++ shell2 dot = ((Ca++)sh1 - [Ca++ sh2] @ t-ca-conc) - ([Ca++ sh2] @ t2-ca-conc)

---

*(defvar *faraday* 9.64864) ;Coulombs/mole *(defvar *R* 8.314) ;Gas constant -- (Volts*Coulombs)*(DegreesKelvin*mole) ;mM *(defvar *core-conc* 50.0e-6) ;mM *(defvar *ca-conc-shell1-rest* 50.0e-6) *(defvar *ca-conc-shell2-rest* 50.0e-6) *(defvars-w-value (*shell1-vol *shell-depth 13333 31415 .0e 12 *soma-radius *soma-radius *shell1-shell2-ratio)) ;volume of core in ml *(defvars-w-value (*shell2-vol *shell1-shell2-ratio)) ;volume of shell 1 *(defvars-w-value (*shell1-vol *shell1-shell2-ratio)) ;shell 1 volume in ml ;Fraction of soma shell assigned to shell 1

---

*(defun ca-conc-shell-dot (total-ca-current shell1-conc shell2-conc) ;New version for two shells. (* dt (+ (/ (- 1.0 total-ca-current 1.0e-6) 2.0 *faraday)))*)
*shell-depth 1.0e-4
*alpha-shell)

(*Ficks-shell-shell (- shell2-conc shell1-conc))
(*Ficks-shell-core (- core-conc shell2-conc))

(defun ca-conc-shell2-dot (shell1-conc shell2-conc)
  (*dt (*Ficks-shell-shell (- shell1-conc shell2-conc))
   (*Ficks-shell-core (- core-conc shell2-conc))
   (*shell-depth 1.0e-4)))))

(defun e-ca ()
  (.04299 (*temperature 273.0) (log (// ca-conc-extra (aref SOMA ca-conc-shell$)))))

;;; PLOT-IV
(defun plot-iv ()
  (setq *iv-current* nil *iv-voltage* nil)
  (menu-for-soma-geometry-and-passive-components)
  (menu-for-soma-currents)
  (do ((voltage 90.0 voltage 0.5)M0 voltage 50.0))
    (let ((voltage-index 1000 (fixr (* 10 voltage))))
      (setq *iv-current* (nconc *iv-current* (list (if *include-dr (dr-current (aref x-dr-inf-array voltage-index) 1.0 voltage 0) )
                                                  (if *include-c (c-current (aref y-c-inf-array voltage-index) voltage 0) )
                                                  (if *include-q (* (aref SOMA gbar-q$)(aref x-q-inf-array voltage-index)(- voltage *e-k) )
                                                  0.0))
                                                   (if *include-na1 (na1-current (aref SOMA gbar-na1$)(aref m-na1-inf-array voltage-index) (aref h-na1-inf-array voltage-index) voltage 0) )
                                                   (if *include-na2 (na2-current (aref SOMA gbar-na2$)(aref m-na2-inf-array voltage-index) (aref h-na2-inf-array voltage-index) voltage 0) )
                                                   (if *include-na3 (na3-current (aref SOMA gbar-na3$)(aref m-na3-inf-array voltage-index) (aref h-na3-inf-array voltage-index) voltage 0) )
                                                   (if *include-nap (nap-current (aref SOMA gbar-nap$) (aref x-nap-inf-array voltage-index) voltage 0 )
                                                     (if *include-ca (ca-current (aref SOMA gbar-ca$)(aref w-ca-inf-array voltage-index) voltage 0 )
                                                       (if *include-cas (cas-current (aref w-cas-inf-array voltage-index) voltage 0 )
                                                         (*current voltage 0 )
                                                         (if *include-shunt (* g-electrode voltage 0) )
                                                         (- *i-constant-injection))))
                                                   )
                                                   )
                                                   )
                                                   )
                                                   )
                                                   )
                                                   )
                                                   )
                                                   )
                                                   )
                                                   ))
  *iv-voltage* (nconc *iv-voltage* (list voltage) ) )))

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Bibliography


