Degeneracy, Neuromodulation, and Phase Response Properties in Model Pyloric Neurons

Master’s Thesis

Presented to

The Faculty of the Graduate School of Arts and Sciences
Brandeis University
Interdepartmental Program in Neuroscience
Dr. Eve Marder, Advisor

In Partial Fulfillment
of the Requirements for the Degree

Master of Science
in
Neuroscience

by
Noah Guzmán

May 2019
To Janelle, without whom I would be lost. To my parents, whose support and love knows no bounds. To my sister, who has taught me much about perseverance in the face of adversity. To Dr. Eve Marder, whose patience and wisdom will continue to guide me throughout life. To Dr. Leandro Alonso, whose mentorship has taught me more than any book ever could. To Alec Hoyland, for inspiring me to become a theorist. And to Becky, whose kindness and generosity have kept me afloat when I should have sunk.
ABSTRACT

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A thesis presented to the Interdepartmental Program in Neuroscience

Graduate School of the Arts and Sciences

Brandeis University

Waltham, Massachusetts

By Noah Guzmán

Degeneracy is a ubiquitous feature of many biological systems, especially neural circuits. Degenerate systems exhibit multifunctionality and robustness in the face of environmental perturbations. Currently no rigorous measures for quantifying the degeneracy of dynamical systems exist. Here, I introduce a measure of degeneracy for biophysical neuron models based on the theory of time delay embeddings that is also applicable in experimental settings. Additionally, I construct a new two-compartment model of the conditional burster AB of the crustacean pyloric network. This model was initially conceived to remedy shortcomings in single compartment models of AB based on the work of Liu et al. (1998); these models fail to exhibit the transition from a tonic spiking state to a bursting state in the presence of a neuromodulatory current, $I_{MI}$. I describe these deficiencies in this thesis. In order to compare the new two-compartment models to the single compartment ones, my colleagues and I began to analyze their respective phase response properties. Here, I report the emergence of fine structural features in the phase response curves of these models. These fine structures can in part be accounted for by the dynamical phenomena of spike addition and spike deletion during a burst. Moreover, I report the discovery of multi-stability in the single compartment bursting models.
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Chapter 1

Introduction

“... all the empiricism in the world can't salvage a bad idea.”

Robert Hogan, *Wittgenstein Was Right*

1.1 Central Pattern Generators and Network Principles

Central pattern-generating circuits (CPGs) are neural circuits that generate rhythmic movements or behaviors such as breathing, chewing, and walking [Marder and Bucher, 2007]. The use of CPGs as models for studying general properties of neural oscillators dates back to studies of the flight motor pattern in the locust [Marder and Calabrese, 1996] using the fictive motor patterns created *in vitro* preparations that mimick those seen *in vivo*.

It was Getting who first postulated that neural networks could be understood by reducing them to “building blocks” on the cellular, synaptic, and connectivity levels [Getting, 1989].

On the cellular level, the presence of electrophysiological signatures such as plateau potentials and post-inhibitory rebound govern the role of a single cell within a network.

The way a particular cell is incorporated into a network further depends upon the properties of its synaptic connections including whether the synapses are chemical or electrical, graded or binary.
At the connectivity level, the types of behaviors a network can produce will be constrained by the topology (my apologies to the mathematicians) of the connections, such as whether these connections are mutual or feed-forward.

Many rhythmic networks are driven by a subset of so-called pacemaker cells, cells with endogenous rhythmic activity that entrain the activity of the other cells in the network. This thesis will focus primarily on the cellular level of analysis, looking at the pacemaker AB of the crustacean pyloric network.

1.2 Anatomy and Physiology of the Stomatogastric System

The anatomy of the stomatogastric nervous system (STNS) was originally characterized to near completion by Maynard and Dando in the 1970s [Maynard and Dando, 1974].

The foregut of reptantian Crustacea (lobsters and crabs) may be divided into four distinct regions: the esophagus, the cardiac sac, the gastric mill, and the pylorus [Maynard and Dando, 1974]. This thesis will focus primarily on the motor rhythms generated in the pylorus, but to give context to these studies, I briefly cover the other regions as well.

- **Esophagus**: Food that has been processed by the animal’s mandibles and maxillipeds (external mouth parts) is passed through the esophagus toward the cardiac sac by a peristaltic wave of muscle contraction with a period of 5-10 seconds. Involved in generating this rhythm are networks of cells from the Commisural ganglia (CoG) and the oesophageal ganglia (OG) [Harris-Warrick et al., 1992, Ch. 1].

- **Cardiac Sac**: The cardiac sac functions as a storage area for food before it is passed to the gastric mill. Food is passed to the gastric mill by constriction of the cardiac sac having long irregular periods of up to several minutes. The network generating this rhythm is primarily located in the OGs, but under the right modulatory conditions, gastric and pyloric cells can also participate in driving the rhythm [Harris-Warrick et al., 1992, Ch. 1].

Before covering the gastric mill and pylorus, we must introduce the stomatogastric ganglion (STG) where the networks governing the gastric and pyloric rhythms are located. The STG contains
approximately 30 cell bodies, most being motor neurons which interact to produce the gastric and pyloric rhythms [Harris-Warrick et al., 1992, Ch. 1].

It should be noted that several modulatory neurons in the OGs innervate the STG and can heavily influence the gastric and pyloric rhythms. Most cells in the STG, as well as several cells in other ganglia, can be classified into distinct cell types based on their anatomy [Maynard and Dando, 1974], synaptic connectivity, and electrophysiological signatures [Harris-Warrick et al., 1992, Ch. 2]. Both networks are characterized by extensive electrical and chemical coupling between their respective cell types [Harris-Warrick et al., 1992, Ch. 1].

- **Gastric Mill**: The chewing of food by ossicles (tooth-like structures) takes place in the gastric mill, a region of the stomach. The movements of these ossicles can be split into two distinct gastric rhythms. The “squeeze” mode has a period of about 8-10 seconds while the “cut and grind” mode has a period of about 5-10 seconds [Heinzel, 1988]. Eleven neurons in the STG comprise part of the CPG of the gastric mill. The interneuron Int1 is key in coordinating the 10 other motor neurons of the CPG. Int1 also sends inhibitory feedback to the CoGs which exert higher order control over the gastric network [Harris-Warrick et al., 1992, Ch. 1].

- **Pylorus**: The pylorus acts as both a rhythmic pump for circulating digestive fluid and as a filter for sorting food particles. Approximately 14 neurons comprising 6 different cell types make up the pyloric CPG [Harris-Warrick et al., 1992, Ch. 1]. The conditional burster AB forms a peacemaking kernel with follower cell PD, and together they drive the 1.0-2.5 Hz pyloric rhythm [Harris-Warrick et al., 1992, Ch. 1]. AB, much like Int1, sends inhibitory feedback to the CoGs [Harris-Warrick et al., 1992, Ch. 1].

Chemical neurotransmission at pyloric and gastric synapses is always inhibitory and occurs exclusively via glutamate or acetylcholine (ACh) [Harris-Warrick et al., 1992, Ch. 1].

Here I identify a number of electrophysiological motifs in single STG neurons that are relevant for network behavior and are often found in cells in other pattern generating systems [Getting, 1989]. I will give a brief overview of the ionic mechanisms in STG cells governing these properties and how they contribute to network rhythms.
Figure 1.1: Schematic contextualizing the stomatogastric nervous system with other parts of the anatomy (adapted from [Stein, 2009]).
Figure 1.2: Extracellular recordings and circuit diagrams of gastric and pyloric cells (adapted from [Nusbaum et al., 2017]).
Figure 1.3: Exemplary STG neurons, including the muscles they innervate, their intracellularly recorded waveforms, and morphologies (adapted from [Otopalik and Marder, 2018]).
• **Plateau Potentials**: Cells displaying this electrophysiological motif appear to be bistable, with a more hyperpolarized “down-state” and a more depolarized “up-state”. The up-state may be a more depolarized resting potential or it may be oscillatory, resulting in spikes riding on top of a depolarized baseline potential [Harris-Warrick et al., 1992, Ch. 2].

Transient depolarizing inputs can switch the cell from the down-state to the up-state. The up-state may terminate independently, or if it is stable and there are no intrinsic dynamics which bring the cell back to the down-state automatically, a transient hyperpolarizing stimulus can cause the cell to switch back. Because transitions between up-states and down-states cause the cell to exhibit switch-like behavior, plateau potentials promote bursting. This may arise because the up-state is itself continuously spiking or because the more depolarized up state is closer to threshold and therefore more sensitive to synaptic input that can push it into firing [Harris-Warrick et al., 1992, Ch. 2].

• **Endogenous Bursting**: This is perhaps the most difficult motif to characterize because the ionic mechanisms are not well understood. Mechanisms underlying intrinsic bursting are best understood from the perspective of dynamical systems theory, which we will cover in later sections.

However, despite its complexity, it is simple to see that endogenous bursting is an important part of any network. Any endogenously bursting cell could function as a pacemaker cell to drive network oscillations at a particular frequency.

• **Adaptation**: Spike frequency adaptation occurs when the spike frequency during a burst or plateau decreases near the end of the burst or plateau. An analysis in the Lobula Giant Movement Detector (Peron et al., 2009) revealed that spike frequency adaptation endows cells with band-pass properties and thus a natural resonance frequency [Fox et al., 2017, Lampl and Yarom, 1997, Hutcheon and Yarom, 2000]. It has been shown that the resonance frequency of a driver neuron effects its phase relationships with other cells it is coupled to and in an oscillatory network can effect the network frequency [Rotstein, 2014, Rotstein, 2017, Tohidi and Nadim, 2009, Rotstein and Nadim, 2014].

• **Post Inhibitory Rebound**: Post inhibitory rebound occurs when a cell spikes or releases
a burst of spikes following release from an inhibitory stimulus. This phenomenon can play a role in bursting networks of inhibition coupled cells, where rhythms can be generated in the circuit due to cells continually being released and captured by inhibition [Harris-Warrick et al., 1992, Ch. 2].

- **Spike Latency**: This phenomenon occurs when, following a depolarizing stimulus, the neuron displays a delay before the onset of firing [Harris-Warrick et al., 1992, Ch. 2]. This can cause phase shifts in the cell when it is driven by an excitatory synapse, which may be beneficial in a network setting [Izhikevich, 2007].

The neuropil of the STG is dense and tangled due to the complex morphology of individual STG cells, with a high degree of animal-to-animal variability in neurite structure [Maynard and Dando, 1974]. Though it would seem that this sub-optimal morphology matters greatly for the electrical properties of STG cells, it has recently been shown that these neurons are electrotonically compact, allowing them to exhibit stereotyped electrophysiology despite lacking stereotyped morphology [Otopalik et al., 2017].

Having covered the properties of single cells that help give rise to rhythms in the STG, I now need to cover the synaptic properties of STG cells. As I have said before, all cells in the STG are inhibitory either employing fast glutamatergic or slow cholinergic synapses. The kinetics of these synapses can play a role in determining the network dynamics. Additionally, synaptic transmission may be both spike driven and graded in the STG [Graubard et al., 1983]. By not being limited to binary spike transmission, synapses achieve a greater dynamic range, allowing cells within a network to influence each other more easily.

Beyond chemo tonic transmission, there is also extensive electrical coupling in the STG [Harris-Warrick et al., 1992, Ch. 2]. Electrical coupling can link different cells such as AB and PD together into a functional unit, as well as linking cell types to themselves, leading to more prominent synchronization of activity.
Figure 1.4: Electrophysiological signatures in single cells and connectivity motifs important for central pattern generating networks (adapted from [Marder and Bucher, 2007]).
1.3 Neuromodulation

Depending on a cell type’s particular distribution of receptors, it may experience inhibitory, excitatory, or no effects from a given modulator. It is even possible for silent cells to be recruited by neuromodulators, which can impact network activity in the STG [Harris-Warrick et al., 1992, Ch. 3].

Neuromodulation, beyond simple inhibition or excitation of a cell, can fundamentally alter its electrophysiological motifs, thus changing the way that cell acts as a building block within a network. Perhaps the most well known phenomenon of neuromodulation in the STG is the fact that many neuromodulators converge onto the same inward modulatory current, $I_{MI}$ [Swensen and Marder, 2000, Swensen and Marder, 2001]. This current has a limited range of activity, so it can endow cells with switch-like properties. This is the modulatory phenomenon that I will focus on in this thesis.

Other modulators act on different ion channel species. to modify their range of activity or maximal conductance [Marder and Bucher, 2007]. By modifying ion channel properties directly, modulators alter the electrophysiological motifs of the cells they act on. Moreover, these effects on ion channels vary from cell type to cell type, giving neuromodulation greater control over each building block of the STG networks.

Recently, it has been shown that at least in the STG, there may be complex interactions between neuromodulators and global perturbations; some modulators can increase the robustness of STG rhythms to a particular perturbation, while other modulators make the rhythms more sensitive to the same perturbation [Haddad and Marder, 2018].
1.4 Theoretical Biophysics

1.4.1 The Hodgkin-Huxley Formalism

The crowning achievement of Hodgkin and Huxley (HH) in the 1950s was to show experimentally that a single neuron could be modeled as a variable resistor-capacitor (RC) circuit [Hodgkin and Huxley, 1952d, Hodgkin and Huxley, 1952b, Hodgkin et al., 1952, Hodgkin and Huxley, 1952a, Hodgkin and Huxley, 1952c].

The modern interpretation of HH-like models, today referred to as conductance-based models, is that each resistance represents an ion channel species, the resistance depending on the membrane voltage and powered by an electromotive force at the Nernst potential of the ion channel’s charge carrier.

Mathematically, the formalism is given by a system of differential equations describing the time evolution of the membrane potential and gating variables for each ion channel species. Let us now give a short derivation of the HH formalism.

The cell membrane of a neuron acts as capacitor of capacitance $C$. The voltage across the membrane is $V_m$. Then from the definition of capacitance and current, the current across the membrane capacitor is

$$I_C = \frac{dq}{dt} = \frac{d(CV_m)}{dt} = C\dot{V}_m$$

The current $I_i$ through an ion channel species $i$ is given by Ohm’s formula, with the maximal conductance $\bar{g}_i$, a quantity determined the density of the ion channel species in the membrane, is modified in a voltage dependent manner by the gating variables:

$$I_i(V_m) = \bar{g}_i m_i^p(V_m) h_i^q(V_m)[V_m - E_i]$$

where $m$ is the activation gate, $h$ is the inactivation gate, $p, q$ are exponential fits to data, and $E$ is the Nernst potential of ion channel’s charge carrier.

The dynamics of the gating variables are given by relaxation to a voltage dependent steady state.
It is this steady state, along with the voltage dependence of the characteristic time constant for each ion channel, that makes the gating variable dynamics voltage dependent in the first place:

\[ \dot{x}_i(V_m) = \frac{x_{i,\infty}(V_m) - x_i}{\tau_{x_i}(V_m)}, \quad x_i \in \{m_i, h_i\} \]

The steady-state \( x_{i,\infty} \) is typically a sigmoid function of the membrane potential, while the time constant \( \tau \) is either a sigmoid or Gaussian function of the membrane potential.

We can relate the capacitor current to the ionic currents via Kirchoff’s current law which, allowing for the possibility of an experimentally applied current \( I_{app} \), takes the form

\[ CV_m - I_{app} + \sum_i I_i(V_m) = 0 \]

In summary, conductance based models are defined by the following set of equations:

\[ CV_m = I_{app} - \sum_i I_i \]  \hspace{1cm} (1.1)

\[ I_i = \bar{g}_i m_i^p h_i^q (V_m - E_i) \]  \hspace{1cm} (1.2)

\[ \dot{x}_i = \frac{x_{i,\infty} - x_i}{\tau_{x_i}}, \quad x_i \in \{m_i, h_i\} \]  \hspace{1cm} (1.3)

where the subscript \( i \) runs over all the ion channel species being modeled and we have dropped the voltage dependence of the various terms for compactness.

In some models, there are ion channels such as BK channels whose current depends on intracellular calcium concentration. Such channels make it necessary to model the intracellular calcium concentration. To do this, the flux of the calcium concentration inside the cell is modeled similarly to an ionic current via

\[ \frac{d[Ca^{2+}]}{dt} = \frac{[Ca^{2+}]_{\infty} (I_{Ca}) - [Ca^{2+}]}{\tau_{Ca}} \]  \hspace{1cm} (1.4)

where \( \tau_{Ca} \) is a non-varying time constant for calcium buffering and the steady-state calcium con-
centration $[Ca^{2+}]_\infty$ depends on the calcium currents via:

$$[Ca^{2+}]_\infty(I_{Ca}) = [Ca^{2+}]_0 - f_{Ca} \sum_{i \in \{Ca\}} I_i$$  \hspace{1cm} (1.5)

The constant $f_{Ca}$ is a buffering factor which converts the calcium current into a calcium concentration, while $[Ca^{2+}]_0$ is the background (equilibrium) intracellular calcium concentration [Liu et al., 1998].

1.4.2 Modeling Cells of the STG

Passive single cell models of the STG date back the mid 1980s [Edwards and Mulloney, 1984, Hartline, 1987]. Single cell models with active conductances inspired by the STG did not come about until the work of Hartline [Hartline, 1989].


Explicit mathematical characterization of ion channel properties of an STG neuron was first accomplished for the LP cell by Jorge Golowasch [Golowasch and Marder, 1992a, Golowasch and Marder, 1992b, Golowasch et al., 1992]. Golowasch’s elucidation of the LP ionic currents led to the development of a mathematical model of the LP cell containing seven conductances [?].

Following Golowasch, a more complete characterization of the ionic currents in nonspecific cultured STG cells and a complementary ten conductance model was developed by Turrigiano [Turrigiano et al., 1995].

The single compartment conductance based model of a generic STG cell entered its most modern form with the work of Liu, who subsumed some of the conductances in Turrigiano’s model into one conductance, thereby reducing the dimensionality of the model to seven conductances [Liu et al., 1998].
Chapter 2

Methods

2.1 Single Compartment Models

Single compartment neuron models were constructed following [Liu et al., 1998] using Hodgkin-Huxley dynamics, equations (1.1) - (1.3). The model contains eight ionic conductances coupled through the membrane potential, seven of which have dynamical gating variables. The corresponding currents are

- $I_{Na}$, a fast sodium current
- $I_{CaT}$, a transient calcium current
- $I_{CaS}$, a slow calcium current
- $I_{A}$, a transient potassium current
- $I_{KCa}$, a calcium-dependent potassium current
- $I_{Kd}$, a delayed rectifier potassium current
- $I_{H}$, a hyperpolarization activated non-specific cation current
- $I_{L}$, a leak current
For the seven dynamical ionic conductances, the steady-state activation and inactivation functions are given by Boltzmann distributions:

\[ x_{i,\infty}(V_m) = \frac{1}{1 + \exp\left(\frac{V_m + V_h}{k}\right)} \quad (2.1) \]

where \( V_h \) is the half-activation potential \( x_{i,\infty}(V_h) = 0.5 \) and \( k \) controls the slope of the sigmoid. The time constants \( \tau_{x_i}(V_m) \) are given by similar functions. All such functions are given explicitly in the table below.

All models contain an Ohmic leak channel whose maximal conductance is not a function of the membrane potential, with current given by

\[ I_L = g_L(V_m - E_L) \quad (2.2) \]

One of the currents, a calcium-dependent potassium channel current \( I_{KCa} \), has a conductance with a steady-state activation function which varies with the intracellular calcium concentration. This dependence is modeled by a multiplicative factor as seen in the table below. The dynamics of the intracellular calcium concentration are given by equations (1.4) and (1.5).

Because the intracellular calcium concentration can vary drastically depending on the membrane potential dynamics, it is necessary to continually update the calcium reversal potential accordingly via the Nernst equation:

\[ E_{Ca}[\text{Ca}^{2+}] = \frac{RT}{zF} \ln \left( \frac{[\text{Ca}^{2+}]_{out}}{[\text{Ca}^{2+}]} \right) \quad (2.3) \]

where \( R \) is the ideal gas constant, \( T \) is the temperature in Kelvin, \( z = 2 \) is the valence of the calcium ion, \( F \) is Faraday’s constant, and \( [\text{Ca}^{2+}]_{out} = 3 \text{ mM} \) is the extracellular calcium concentration, which is taken to be constant throughout the simulation.

The system of ordinary differential equations (1.1) and (1.3) describing the model is numerically integrated using a fourth-order Runge-Kutta scheme (RK4) with a time step of \( \Delta t = 0.1 \text{ ms} \) unless otherwise indicated.


<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>E</th>
<th>$m_\infty$</th>
<th>$h_\infty$</th>
<th>$\tau_m$</th>
<th>$\tau_h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$</td>
<td>3</td>
<td>50</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 25.5}{-5.29}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 48.9}{51.8}\right)}$</td>
<td>$132 - \frac{126}{1 + \exp\left(\frac{V + 120}{-25.0}\right)}$</td>
<td>$\frac{105}{1 + \exp\left(\frac{V + 55}{-16.9}\right)}$</td>
</tr>
<tr>
<td>$I_{CaT}$</td>
<td>3</td>
<td></td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 27.1}{-7.2}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 32.1}{5.5}\right)}$</td>
<td>$21.7 - \frac{21.3}{1 + \exp\left(\frac{V + 68.1}{-20.5}\right)}$</td>
<td>$\frac{150}{1 + \exp\left(\frac{V + 55}{9}\right)} + \exp\left(\frac{V + 65}{-16}\right)$</td>
</tr>
<tr>
<td>$I_{CaS}$</td>
<td>3</td>
<td></td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 33}{-8.1}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 60}{6.2}\right)}$</td>
<td>$14 + \frac{7}{\exp\left(\frac{V + 27}{10}\right)} + \exp\left(\frac{V + 70}{-13}\right)$</td>
<td>$\frac{60}{1 + \exp\left(\frac{V + 55}{9}\right)} + \exp\left(\frac{V + 65}{-16}\right)$</td>
</tr>
<tr>
<td>$I_{A}$</td>
<td>3</td>
<td>-80</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 27.2}{-8.7}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 56.9}{4.9}\right)}$</td>
<td>$116 - \frac{104}{1 + \exp\left(\frac{V + 32.9}{-15.2}\right)}$</td>
<td>$38.6 - \frac{29.2}{1 + \exp\left(\frac{V + 38.9}{-26.5}\right)}$</td>
</tr>
<tr>
<td>$I_{KCa}$</td>
<td>4</td>
<td>-80</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 28.3}{-12.6}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 46}{-22.7}\right)}$</td>
<td>$903 - \frac{751}{1 + \exp\left(\frac{V + 38.9}{-26.5}\right)}$</td>
<td>$\frac{272}{1 + \exp\left(\frac{V + 42.2}{-8.73}\right)}$</td>
</tr>
<tr>
<td>$I_{Kd}$</td>
<td>4</td>
<td>-80</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 12.3}{-11.8}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 28.3}{19.2}\right)}$</td>
<td>$7.2 - \frac{6.4}{1 + \exp\left(\frac{V + 28.3}{19.2}\right)}$</td>
<td>$\frac{1499}{1 + \exp\left(\frac{V + 42.2}{-8.73}\right)}$</td>
</tr>
<tr>
<td>$I_{H}$</td>
<td>1</td>
<td>-20</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 70}{-6}\right)}$</td>
<td>$\frac{1}{1 + \exp\left(\frac{V + 42.2}{-8.73}\right)}$</td>
<td>$272 + \frac{1499}{1 + \exp\left(\frac{V + 42.2}{-8.73}\right)}$</td>
<td>$\frac{1499}{1 + \exp\left(\frac{V + 42.2}{-8.73}\right)}$</td>
</tr>
</tbody>
</table>

Figure 2.1: Mathematical formulation of the gating variable and time constant functions in the Liu model. The column $p$ corresponds to the exponents of the activation gates $m_i$. All inactivation gates $h_i$ have exponent $q = 1$. The column $E$ corresponds to the reversal potentials of each ionic current in mV. Adapted from [Liu et al., 1998].
Figure 2.2: Schematic representation of the single-compartment model. Arrows indicate the directions of each ionic current.

Figure 2.3: Activation and inactivation functions of the Liu model.
2.2 Multi-Compartment Models

Multi-compartment models were constructed in a similar manner to single compartment models. Following [Soto-Treviño et al., 2005], two-compartment models were constructed containing a somatic and an axonal compartment coupled by an Ohmic axial conductance of the form

$$I_{soma \rightarrow axon} = g_{axial}(V_{axon} - V_{soma}) \quad (2.4)$$

The magnitudes of the currents from one compartment to the other are identical with a sign reversal due to the switch in reversal potentials, i.e.

$$I_{axon \rightarrow soma} = g_{axial}(V_{soma} - V_{axon}) = -I_{soma \rightarrow axon} \quad (2.5)$$

All currents in the somatic compartment are identical to the currents in the single-compartment model of section 2.1, except that the fast sodium conductance was moved to the axonal compartment.
Figure 2.5: Characterizing the time scales and voltage dependence of the gating variables in the Liu model. The ordinate, the maximum value of that gating variable’s time constant, is plotted on a log scale. Notice that some gating variables, like the transient calcium inactivation variable ($h_{CaT}$) and the calcium-dependent potassium activation gating variable ($m_{KCa}$) have similar feedback relationships with the membrane potential and cluster together in this space, indicating that they perform degenerate functions.
to ensure that sodium spike initiation occurred only in the axon. The axonal compartment also contained a delayed rectifier potassium current ($I_{Kd}$) and a leak current ($I_L$) having the same mathematical description as their somatic compartment counterparts. Unlike the Soto-Trevino model, a persistent sodium current was not included in the somatic compartment.

Figure 2.6: Schematic representation of the two-compartment model. Arrows indicate the directions of each ionic current. The current $I_{axial}$ flows from one compartment to the other depending on the sign of the current as defined by $I_{axon\rightarrow soma} = -I_{soma\rightarrow axon}$.

2.3 Modeling Neuromodulation

Modeling of neuromodulation in the STG has focused primarily on the modulatory current $I_{MI}$, now understood to be the target of several modulatory substances including proctolin [Swensen and Marder, 2000].

It was Golowasch who first characterized the voltage dependence and timescale of activation for the proctolin induced current in LP [Golowasch and Marder, 1992b, Golowasch et al., 1992]. The mathematical model of the proctolin current developed by Golowasch was later employed by Sharp...
in his dynamic clamp studies [Sharp et al., 1993]. This model takes the form

\[ I_{MI} = m_{MI} \bar{g}_{MI} (V_m + 10) \]  

(2.6)

\[ \dot{m}_{MI} = \frac{m_{MI,\infty} - m_{MI}}{\tau_{MI}} \]  

(2.7)

\[ m_{MI,\infty} = \frac{1}{1 + \exp \left( \frac{V_m + 55}{-5} \right)} \]  

(2.8)

Swensen and Marder (2001) later developed a slightly modified model of \( I_{MI} \) with a more depolarized reversal potential and a more shallow concavity in the I-V curve, resulting in a current with overall lower magnitude. The data used to develop this model was collected primarily from LP cells as in the original work of Golowasch. This model takes the form

\[ I_{MI} = m_{MI} \bar{g}_{MI} (V_m + 22) \]  

(2.9)

\[ \dot{m}_{MI} = \frac{m_{MI,\infty} - m_{MI}}{\tau_{MI}} \]  

(2.10)

\[ m_{MI,\infty} = \frac{1}{1 + \exp \left( \frac{V_m + 21}{-8} \right)} \]  

(2.11)

In both the Golowasch and Swensen models, the modulatory time constant is \( \tau_{MI} = 6 \) ms.

Most recently, a third model of \( I_{MI} \) has been developed by [Zhao et al., 2010]. In this paper, the traditional \( I_{MI} \) I-V curve is split into two parts: a linear portion with negative slope and a piece-wise linear portion with positive slope. Both these linear approximations and the full nonlinear model were used to inject a simulated modulatory current into the pacemaker kernel of the pyloric network after it had been decentralized and gone quiescent. While both the negative linear approximation and the full nonlinear model were sufficient for rescuing bursting activity in the pacemaker, only the negative linear approximation was both necessary and sufficient. This means that an Ohmic leak-like current is all that is required to induce bursting in the silenced pyloric pacemaker. This model takes the form

\[ I_{MI} = -\bar{g}_{MI} (V_m + 68) \]  

(2.12)

In this thesis, all three models of neuromodulation are implemented in single compartment cells.
2.4 Landscape Optimization of Model Parameters

Finding parameters for a dynamical model that allow that model to recapitulate experimental observations is a daunting task. In the past, this was done by hand tuning the model’s parameters. But in high-dimensional models, it is rarely the case, if ever, that only one set of parameters will solve the model. So how can one optimize the parameters of a dynamical model to experimental data?

It was shown using STG models [Golowasch et al., 2002] that given a few sets of parameters which provide the desired behavior, merely taking the average of these parameters almost never gives a set of parameters which also recapitulate the data.

Rather than looking for a principled way of searching for new parameters, Prinz [Prinz et al., 2003a, Prinz et al., 2004] developed huge databases of pyloric network models by running simulations over the entire hyper-grid of parameter space. Novel and pioneering at the time, this method has since proved to be an inefficient way of finding solutions for a model.

Using multi-compartment models, [Keren et al., 2005] successfully employed genetic algorithms to discover parameters which matched the model’s activity to experimental observations. In an effort to compare many optimization methods, [Achard and Schutter, 2006] explored multiple methods such as gradient descent, simulated annealing, and genetic algorithms to optimize parameters for
conductance-based models.

All of these examples (with the notable exception of Prinz’s work), however, have focused on minimizing the error between quantitative aspects of the membrane potential waveforms of the models and experimental traces. In many systems, one is not interested in obtaining an exact match with the empirical waveform; the goal is rather to recapitulate more generic qualitative features of the experimental traces such as spike frequency, phase relationships, or response to perturbation.

Recent work in the Marder lab has focused on using evolutionary algorithms to optimize these more qualitative features of the model output in single cell and network models. Dr. Leandro Alonso has employed genetic algorithms [Eiben and Smith, 2015] to minimize these more complicated cost functions. The cost functions are single-objective, constructed as a sum of the squared errors between target quantities such as burst frequency and duty cycle, possibly over a range of experimental conditions. Most notably, this approach has been applied toward optimizing parameters of a pyloric network model so that the model recapitulates the experimentally observed response of the pyloric network to increasing temperature. Other work in the lab has employed alternative optimization algorithms such as particle-swarm optimization with the same focus on generic features of the waveform [Gorur-Shandilya et al., 2018].

One advantage to optimizing parameters based on generic features of the waveform is that the modeler is now loosening the constraints on the possible space of parameters, allowing for observation of a more rich set of model behaviors. When a cost function used in parameter optimization is too tightly constrained, it is possible that the modeler is throwing out the individual variability seen in real biological systems.

In this thesis, I employ genetic algorithms developed by Dr. Leandro Alonso for optimizing cost functions associated with the features of the model cells’ membrane potential and the method of constructing cost functions first introduced in [Alonso and Marder, 2019]. The construction of the cost functions is briefly covered below. Following [Alonso and Marder, 2019], I use a mutation rate of 5% and an elitism parameter of 1.2. The elitism parameter controls the bias in breeding probability for the fitter individuals, while the mutation rate controls the amount of random parameter variation
introduced during the evolution. The genetic algorithm was typically started with populations of 
$\sim$20-200 random seeds and evolved for $\sim$1000-5000 generations.

### 2.4.1 Constructing Cost Functions for Bursting Neurons

In order to construct cost functions for a particular type of membrane potential dynamics, we 
must define measures of the voltage trace that capture the essential features of the dynamics. For 
bursting neurons these are the *burst frequency* and the *duty cycle*.

We can find the start and end of a burst by defining a burst detection threshold $b_{th}$ and the spike 
detection threshold $s_{th}$. For our purposes thresholds of $b_{th} \sim 80 - 150$ ms and $s_{th} = 20 - 10$ mV 
suffices. Thus for any time $t$ of a recorded or simulated voltage trace, we define spike times $s_{t}$ as 
the time when the voltage trace first crosses the spike threshold. Thus, we define a time $t$ to be a 
spike time if

\[ [V_m(t-1) < s_{th}] \land [V_m(t) > s_{th}] \]

Supposing a particular voltage trace has $N$ spikes, these spike times in a vector, we can compute 
the $j^{th}$ inter-spike interval $ISI_j$ as

\[ ISI_j = s_{t_{j+1}} - s_{t_j} \quad \forall \quad j \leq N - 1 \]

Now we define the start time of the $k^{th}$ burst $b_{s_k}$ as the $k^{th}$ spike time for which the previous 
ISI greater than the burst detection threshold $b_{th}$ and which has a subsequent ISI less than the 
threshold,

\[ [ISI_{k-1} > b_{th}] \land [ISI_k < b_{th}] \]

For the corresponding burst end time $b_{e_k}$, we just use the opposite condition,

\[ [ISI_{k-1} < b_{th}] \land [ISI_k > b_{th}] \]

Now we can compute the $k^{th}$ **burst duration** $bd_k$ as

\[ bd_k = b_{e_k} - b_{s_k} \]
and the $k^{th}$ burst period $T_k$ as

$$T_k = bs_{k+1} - b_k$$

so that the *instantaneous burst frequency* of the $k^{th}$ burst is just the inverse of the period

$$f_k = 1/T_k$$

The *duty cycle* of the $k^{th}$ burst $dc_k$, defined as the fraction of the burst period for which the cell is actively spiking, is computed as the ratio of the burst duration to the burst period,

$$dc_k = bd_k/T_k$$

Given $M$ bursts in a voltage trace, we can define an average burst frequency $\overline{f_b}$ and an average duty cycle $\overline{dc}$ in the usual manner,

$$\overline{f_b} = \frac{1}{M} \sum_{k=1}^{M} f_k$$

$$\overline{dc} = \frac{1}{M} \sum_{k=1}^{M} dc_k$$

Using these metrics, we can construct a cost function for a bursting neuron. To obtain models that have voltage traces similar to those recorded in pyloric cells of the STG, we use a target average burst frequency of $f_{tg} = 1$ Hz and target average duty cycle $dc_{tg} = 0.2$. We can also introduce an error term to account for the number of times $\#_{sw}$ that the voltage crosses a slow-wave threshold $sw_{th}$. This slow-wave threshold helps to guarantee the presence of a slow-wave or plateau potential on top of which the spikes ride during a burst. Ideally, spikes that are part of a burst should only cross the slow-wave threshold once at the start of each burst, meaning that we want $\#_{sw} = \#_b$ where $\#_b$ is the number of bursts. We typically employed two slow wave thresholds, $sw_{th} = -51$ mV and $sw_{th} = -49$ mV, so if $\#_{sw}$ is the total number of crossings of both slow waves, we desire $\#_{sw}/2 = \#_b$. Taking the squared deviations from these target values for any vector of
model parameters \( g \), we obtain

\[
E_f = (f_t g - \bar{f}_b)^2 \tag{2.13}
\]

\[
E_{dc} = (dc_t g - \bar{d}c)^2 \tag{2.14}
\]

\[
E_{sw} = \left(\frac{\#_{sw}}{2} - \#_b\right)^2 \tag{2.15}
\]

We can scalarize the cost function by summing the individual error functions,

\[
E_{burst}(g) = \alpha E_f + \beta E_{dc} + \gamma E_{sw} \tag{2.16}
\]

The weights \((\alpha, \beta, \gamma)\) indicate the importance of each term in the cost function, that is, which feature of the waveform will most constrain the optimization. Though the choice of weights is somewhat arbitrary, we have found that \(\alpha = \gamma = 10\) and \(\beta = 100\) give good results. This is the function that is optimized using the genetic algorithm. The algorithm will typically start with a random population of parameter vectors, simulating voltage traces for each, computing the necessary metrics from the voltage traces, and then computing the cost function \(E_{burst}\) for each. The algorithm then uses the cost for each parameter vector to continue searching for parameters that minimize the cost function.

For the case of a two-compartment model, we will have two voltage traces, one for the soma and one for the axon. Because spikes tend to be greatly attenuated in the somatic compartment, one should compute the metrics defined above using the axonal voltage trace.

### 2.4.2 Constructing Cost Functions for Spiking Neurons

The process of constructing a cost function for a tonic spiking cell is essentially the same as that for a bursting neuron. The primary difference is that we desire an average target duty cycle of zero (since no bursting occurs) \(dc_t g = 0\) and we use the average spiking frequency rather than the burst frequency. The \(k^{th}\) instantaneous spike frequency is just the inverse of the \(k^{th}\) ISI,

\[
f_k = 1/ISI_k
\]
Figure 2.8: Schematic illustrating the procedure for computing the metrics used in the bursting cost function. The spike detection threshold is used to compute the spike times associated with a voltage trace. The slow wave threshold ensures that spikes do not repolarize too far below the slow wave plateau. The inter-spike interval (ISI) threshold facilitates the detection of bursts in the spike train by computing which spikes are burst starts (bs) or burst ends (be). Adapted from [Alonso and Marder, 2019].

The target spiking frequency is that of the LP neuron in the pyloric network, $f_{tg} = 5$ Hz. For the tonic spiking neurons, we used a slow-wave threshold of $sw_{th} = -50$ mV. We can also introduce a new error term to prevent unwanted phenomena such as damped oscillations or after-depolarization potentials following spikes. The metric $\#_{mid_i}$ measures the number of times the voltage trace crosses some threshold $mid_{th}$.

If, for example, the voltage trace undergoes damped oscillations following a spike, these oscillations will cross $mid_{th}$ many times. Since this is an undesirable feature of the waveform, we desire $\#_{mid_i} = \#_s$ where $\#_s$ is the number of spikes, so that each spike crosses the $i^{th}$ $mid_{th}$ only once. Using multiple $mid_{th}$ results in a more accurate voltage trace, so we use several $mid_{th}$ in an interval from -35 to -45 mV. Again taking the squared deviations from the target values, we have

$$E_f = (f_{tg} - \overline{f_s})^2$$  
(2.17)
$$E_{dc} = (dc_{tg} - \overline{dc})^2$$  
(2.18)
$$E_{sw} = (#_{sw})^2$$  
(2.19)
$$E_{mid} = \sum_i (\#_{mid_i} - \#_s)^2$$  
(2.20)
Scalarizing these multiple error terms into a single cost function gives

\[ E_{\text{spiker}}(g) = \alpha E_f + \beta E_{dc} + \gamma E_{sw} + \delta E_{\text{mid}} \] (2.21)

Again, the weights \((\alpha, \beta, \gamma, \delta)\) are somewhat arbitrary, but we have found \(\alpha = \beta = 1000\) and \(\gamma = \delta = 100\) give good results.

![Schematic illustrating the procedure for computing the metrics used in the spiking cost function. The \(\tau_i\) indicate the spike times found by the spike detection threshold. The slow wave thresholds control the shape of the waveform during spike repolarization (i.e. preventing ringing behavior). Adapted from [Alonso and Marder, 2019].](image)

**2.4.3 Searching for Neurons That Transition from Spiking to Bursting in the Presence of Modulators**

It is sometimes desirable to search for parameters which allow a model to exhibit a particular bifurcation structure or transitions between distinct excitable states. In later sections, I describe the physiologically relevant transition from a tonic spiking mode to a bursting mode in the presence of the neuromodulatory current \(I_{MI}\). To optimize models for this transition, I create a cost function which first evaluates the parameters using a spiking cost function with the modulatory conductance \(g_{MI}\) set to zero. Then I allow \(g_{MI}\) to take whatever random value the algorithm has assigned to that individual model and evaluate the parameters using a bursting cost function. This cost function will cause the genetic algorithm to search for parameters which are tonic spiking when no modulators are present (i.e. zero \(g_{MI}\)) and which transition to bursting in the presence of modulators (i.e. non-zero \(g_{MI}\)). The spiking and bursting cost functions are just those described above, giving

\[ E_{\text{stb}}(g) = E_{\text{spiker}}(g \mid g_{MI} = 0) + E_{\text{burster}}(g) \] (2.22)
Currentscapes, first introduced by [Alonso and Marder, 2019], provide a method of visualizing the contributions of each conductance to the total ionic current (and therefore, to the membrane potential) and how these contributions evolve in time.

Given a model with $M$ currents (including the possibility of an applied current), a time series of the $M$ currents with duration $n_{\text{secs}}$ simulated with time step $\Delta t$ can be represented by an $M \times N$ matrix $C$ where $N = n_{\text{secs}}/\Delta t$. Though we separate the analysis of inward (negative) and outward (positive) currents, the analysis is identical for each type of current. For simplicity, we will only cover the definition of the outward currents.

First, we construct the matrix of outward currents $C^+$ defined by

$$
C^+_{ij} = \begin{cases} 
C_{ij}, & C_{ij} > 0 \\
0, & C_{ij} < 0 
\end{cases}
$$

(2.23)

The time series of each outward current is one row of $C^+$, along with the rows of all zeros corresponding to the inward currents. Now we normalize each outward current at each time point by the total current at that time point. To do this, we store the total current at each time point in a normalization vector $n^+$ with elements $n^+_j$ given by summing $C^+$ over all rows at each time point:

$$
n^+_j = \sum_i C^+_{ij}
$$

(2.24)

Normalizing the currents at each time point, we obtain the matrix $\hat{C}^+$ defined by

$$
\hat{C}^+_{ij} = C^+_{ij}/n^+_j
$$

(2.25)

The columns of $\hat{C}^+$ represent each current’s fraction (share) of the total current at that time point. In order to visualize these current shares, we could plot a pie chart illustrating them for each time point, but it would then be difficult to see how the shares evolve in time.
What we do instead is use a linear version of a pie chart, where the share of each current is represented not by a portion of a circle but by a portion of a vertical bar. These types of plots are sometimes referred to as stacked area charts. We can then plot a time series of these vertical bars representing the evolution of the current shares. To do this, we construct the time series of these vertical bars as an $R \times N$ currentscape matrix $C^S$, where $R \approx 10^3$ is a resolution factor representing the height of the vertical bars at each time point.

We introduce the auxiliary variable $p_{ij} = R \cdot \hat{C}_{ij}^+$ ($\ast$ is just scalar multiplication), which represents the portion of the vertical bar (and therefore the share of the total current) occupied by the $i^{th}$ current. Now we can define the currentscape by

$$C^S_{ij} = k \mid \sum_{u}^{k} p_{uj} \leq i < p_{(u+1)j} + \sum_{u}^{k} p_{uj}$$  \hspace{1cm} (2.26)

Here, the integer $k \in [0, M]$ indexes the current types and by definition the represented share of the $0^{th}$ current must start at the top of each vertical bar, i.e. $\sum_{u}^{k=0} p_{uj} = 0$. To complete the currentscape, we plot the normalization vector $n^+$ above (below) the outward (inward) current shares as a filled-in curve on logarithmic scale.

### 2.6 Time-Delay Embeddings

Time-delay embeddings are tools originating in the theory of dynamical systems [Takens, 1981]. Loosely, a time-delay embedding is the trajectory of a dynamical system created using the time series of one variable and one or more of its “lagged” time series. These lagged time series are just versions of the original time series shifted backwards in time, much in the same way that one uses time shifted versions of signals to compute their autocorrelation or cross-correlation. Using a time-delay embedding of only one state variable of a deterministic higher-dimensional dynamical system, one can reconstruct the trajectories in the full state space. This is especially useful in experimental settings, where one only has access to one observable of a system such as the voltage. In principle, the experimentalist can use the time series of this single observable to reconstruct the dynamical attractor of the full system [Packard et al., 1980, Sauer et al., 1991].
Figure 2.10: An illustration of the conceptual basis of the currentscape plot. In (A), part of the time series of a bursting model neuron is shown. In (B), the currentscape for this same model is plotted below the voltage trace. The black filled-in curves correspond to the total outward and inward currents \((n^+, n^-)\), plotted on logarithmic scale. Dotted reference lines have been plotted at ± 5, 50, and 500 nA. Each color represents a different current type. In (C), the current shares at two time points \(T_1\) and \(T_2\) have been plotted as both pie charts and stacked area charts. The currentscape is the time series of these stacked area charts. Adapted from [Alonso and Marder, 2019].
Time-delay embeddings and their use to reconstruct attractors in complex dynamical systems are originally due to the work of Floris Takens [Takens, 1981]. Takens’ theorem ensures the existence of time-delay embeddings for a particular dynamical system. Below, I give a brief overview of the mathematical foundation and the practical algorithmic computations involved in constructing time-delay embeddings from a single observable of a system.

2.6.1 Takens’ Theorem

We begin with a formal definition of a time-delay embedding, sometimes called a delay-coordinate map. Then we provide a formal statement of Takens’ theorem which we restate in more colloquial language.

First, the rigorous definition of a time-delay embedding [Sauer et al., 1991]:

**Definition 1. (Delay-Coordinate Map)** If $\Phi^t : M \to M$ is a flow on a manifold $M \subset \mathbb{R}^d$, $\tau$ is a positive number (called the *delay*), and $h : M \to \mathbb{R}$ is a smooth function, define the delay-coordinate map $F(h, \Phi^t, \tau) : M \to \mathbb{R}^{n}$ for $x \in M$ by

$$F(h, \Phi^t, \tau)(x) = [h(x), h(\Phi^{-\tau}(x)), h(\Phi^{-2\tau}(x)), \ldots, h(\Phi^{-(n-1)\tau}(x))] \tag{2.27}$$

Now for the formal statement of Takens’ theorem [Takens, 1981]:

**Theorem 1. (Takens, 1981)** Let $M$ be a compact manifold of dimension $d$, $\Phi^t : M \to M$ be a $C^2$ flow on $M$, and $h : M \to \mathbb{R}$ a $C^2$ function. Then for generic pairs $(\Phi^t, h)$, the delay-coordinate map $F(h, \Phi^t, \tau) : M \to \mathbb{R}^{2d+1}$ is an embedding of $M$ in $\mathbb{R}^{2d+1}$.

It is helpful to think of the function $h$ as projection of a point in the state space onto one of its state variable axes (a so-called observation function, since each state variable is an observable of the system).

But what does this theorem say in terms that are more familiar to the average scientist? Suppose that a time series $\{x_t\}_{t=1, \ldots, N}$ with $N$ time points lies on a $d$-dimensional attractor of an $n^{th}$-order
deterministic dynamical system.

An experimentally convenient, though not unique, representation of this attractor is achieved by using \textit{time-delay coordinates} with delay $\tau$, where a point in the \textit{embedding space} (the state space of the $d$-dimensional dynamical system reconstructed using time-delay coordinates of only one of the state variables $x$) is given by the vector

$$x_t = [x_t, x_{t-\tau}, \ldots, x_{t-\left(d_E-1\right)\tau}]^T \quad (2.28)$$

As $t$ increases from one to $N$, the vectors $x_t$ trace out a trajectory in the embedding space. The integer $d_E$ is called the embedding dimension, and is just the dimension of the embedding space. What Takens’ theorem says is that the attractor of the original $d$-dimensional dynamical can be mapped one-to-one onto the attractor formed by the time-delayed trajectory in the embedding space; this mapping is guaranteed to exist and to preserve the geometry of the attractor when the embedding dimension is $d_E > 2d$.

Since the dimension $d$ of any attractor of an $n^{th}$-order dynamical system must be $d \leq n$, we can also say that $d_E > 2n$. But the theorem only tells us when the time-delay embedding is guaranteed to preserve, or \textit{unfold}, the geometry of the original system. Often, an embedding dimension much less than $2d$ suffices. In any case, the embedding dimension can give us information about the dimension of the original attractor.

\subsection*{2.6.2 Estimating the Optimal Delay}

How can we select the delay $\tau$ used in constructing the time-delay embeddings? If the unlagged time series $\{x\}_t$ and the lagged time series $\{x\}_{t-\tau}$ are too similar, then the time-delay embedding will not faithfully reconstruct the original attractor.

To see this, consider a dynamical system with state variables $(x, y)$ having a two-dimensional limit cycle. Suppose we try to reconstruct the limit cycle using a time-delay embedding of the time series of the single state variable $x$ with embedding dimension $d_E = 2$. If we make a choice of $\tau$ such that the unlagged and lagged time series are nearly identical, then instead of forming a limit cycle in the
Figure 2.11: An illustration of time delay embedding using the Lorenz system. (A) shows the full three-dimensional “butterfly” attractor of the Lorenz system. (B) shows the time series of one state variable in the Lorenz system, variable $x$. (C) Using only the time series $x(t)$ and two of its lagged versions, one can reconstruct the butterfly attractor. Adapted from [Sauer, 2006]
Following the method of [Fraser and Swinney, 1986], we use the mutual information to compute the optimal value of the delay $\tau$. The mutual information $H(X, Y)$ of two random variables $X$ and $Y$ gives a measure of dependence between the two variables, much like the Pearson correlation or cross-correlation. Unlike these other correlation measures, the mutual information is capable of capturing nonlinear dependencies between variables.

The general idea then is to take the mutual information between the unlagged time series $\{x_t\}$ and the lagged time series $\{x_{t-\tau}\}$ as a function of tau. Roughly, we can compute the mutual information as follows:

Treat the time series $\{x_t\}$ and $\{x_{t-\tau}\}$ as sequences of realizations of the random variables $X$ and $X_\tau$. Create one-dimensional histograms for the states $i \in X$ and $j \in X_\tau$, and a two-dimensional joint histogram of the co-occurring states $(i, j) \in X \times X_\tau$. These histograms give empirical probabilities $\mathbb{P}_X[i] = p_i$, $\mathbb{P}_{X_\tau}[j] = p_j$, and $\mathbb{P}_{X,X_\tau}[i,j] = p_{ij}$ respectively. Now we can compute the mutual information between the unlagged and lagged time series as

$$H_\tau(X, X_\tau) = \sum_{i \in X} \sum_{j \in X_\tau} p_{ij} \ln \left( \frac{p_{ij}}{p_i p_j} \right) \quad (2.29)$$

$$= \sum_{i \in X} \sum_{j \in X_\tau} p_{ij} (\ln p_{ij} - \ln p_i - \ln p_j) \quad (2.30)$$

Now we take $H_\tau(X, X_\tau)$ search for the first local minimum as function of $\tau$. The value of $\tau$ at this local minimum corresponds to a lag for which there is low dependence between the unlagged and lagged time series (they are “uncorrelated” so to speak). This $\tau$ is the optimal time delay.

### 2.6.3 Estimating the Embedding Dimension

To estimate the optimal embedding dimension for a dynamical system of dimension $d$, one could just use Takens’ theorem and set $d_E > 2d$. But in the case of an empirical time series, one cannot usually say what the dimension of the system is. And in any case, the cost of computation increases greatly as the dimension of the data increases. To provide a method of estimating the embedding
dimension that is both reliable for experimental data as well as computationally efficient, one must be able to determine the value of $d_E$ for which the original attractor is completely unfolded.

Just such a method was introduced by [Kennel et al., 1992]. The algorithm, known as the method of false nearest neighbors or FNN for short, does the following:

1. First, estimate the optimal lag using the technique of the previous section.

2. Now begin creating time delay embeddings starting at $d_E = 2$. For the time delay embedding with dimension $d$, find the nearest neighbor of each point in the embedding space and compute the distance between these points. Keeping track of these same points, compute the distance between them in dimension $d + 1$ embedding space.

3. If the increase in distance between any point and its nearest neighbor when going from embedding dimension $d$ to $d + 1$ is large, then these points are likely not true neighbors, their closeness in dimension $d$ being an artifact of the projection of the attractor into a lower dimension. These are called false nearest neighbors (FNNs).

4. As one criterion for deciding which points are FNNs, one must choose a threshold $R_{tol}$. If the difference in distance between two points in dimensions $d$ and $d + 1$ normalized by the distance in $d$ is greater than $R_{tol}$, the points may be FNNs. A second criterion increases the robustness of the method. As the embedding dimension increases and the attractor unfolds, even true nearest neighbors may end up far from each other if the attractor is large and data points are sparse. To control for this, normalize the distance between points in dimension $d + 1$ by the “radius” of the attractor $R_A$ and if this normalized distance is still greater than some threshold $A_{tol}$, then the points may be FNNs. Select points as FNNs if either test fails.

5. For the embedding of dimension $d$, compute the total percentage of FNNs in the embedding space. When the percentage drops below unity ($< 1\%$), select the value of $d_E$ at the first minimum of this percentage curve as the optimal embedding dimension.

The method’s primary weakness is its dependence on the parameters $R_{tol}$ and $A_{tol}$. For details on the parameter dependence and implementation, see the original Kennel et al. paper. In this thesis, I follow Kennel et al. in using $R_{tol} = 15$ and $A_{tol} = 2$.  

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2.7 Phase Response Curves

Neurons in circuits are continuously subjected to synaptic input. How each cell responds to this input will in part determine the overall activity of the entire circuit. One way of characterising how a cell responds to transient input is through a phase response curve (PRC) [Guckenheimer, 1975]. The usual assumption of a phase response analysis is that the cell’s membrane potential evolves on a stable limit cycle and this limit cycle is isolated in the state space (i.e. there are no other nearby stable attractors) [Winfree, 1974].

When a step current or synaptic current is transiently injected into the cell, its dynamics are perturbed off of the limit cycle momentarily before returning to it. Since the neuron’s voltage dynamics are periodic, one can assign a phase to any point on the voltage trace, where phase is
defined as the elapsed time measured from an arbitrary reference divided by the intrinsic period [Oprisan and Canavier, 2002]. For bursting neurons, it is customary to choose one burst as the reference burst and define the intrinsic period as the period of the reference burst.

The oscillatory neuron’s phase response is determined by injecting current at different phases of its limit cycle oscillation and determining how long it takes for the transient dynamics to “reset” back to the limit cycle. This is why PRCs are sometimes called phase resetting curves.

If the time of the reference burst start is $t_0$ and the time of the subsequent burst start in the unperturbed trace is $t_1$ we can compute the reference burst period as

$$T_0 = t_1 - t_0 \quad (2.31)$$

Now in practice, we treat the start of the reference burst as our reference time point. Then the phase $\phi$ of the system at any time $t_0 < t \leq t_1$ is computed from

$$\phi(t) = \frac{t - t_0}{T_0} \quad (2.32)$$

By definition, we set $\phi(t_0) = 0$. This results in a phase normalized to the burst period such that $\phi(t_1) = 1$ and $\phi$ is bounded above and below, i.e. $\phi \in [0, 1]$. Now phase response curves are usually plotted with the phase $\phi$ of injected current on the abscissa and the shift in the phase normalized to the reference period $\Delta \phi$ on the ordinate. We can compute this normalized phase shift as follows:

Let the time of the injected current be $t_i$. Then the phase of the injected current is $\phi(t_i) = (t_i - t_0)/T_0$. Find the start time $t_2$ of the first subsequent burst following the current injection. The period of the perturbed burst is then $T_1 = t_2 - t_0$. The phase shift is computed as

$$\Delta \phi = \frac{T_1 - T_0}{T_0} \quad (2.33)$$

This means that for a phase advance (perturbed burst starts earlier than unperturbed burst) we have $T_1 < T_0$ and therefore $\Delta \phi < 0$. For a phase delay (perturbed burst starts later than unperturbed burst) we have $T_1 > T_0$ and therefore $\Delta \phi > 0$. 

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In general, if the dynamical system is truly periodic, the phase shift is bounded above and below by \(-1 \leq \Delta \phi \leq 1\). However, if the dynamical system is not truly evolving on a limit cycle or there are other attractors nearby in state space, then exotic phenomena are possible. These phenomena include “burst skipping” where the system goes quiescent for an entire burst period following the current injection, resulting in \(|\Delta \phi| > 1\) (Fig. 2.14).

One can repeat these procedures with respect to subsequent bursts to compute the periods of later bursts \(T_2, T_3, \ldots, T_n\) (measured in reference to the preceding burst) giving the higher order phase response curves \(\Delta \phi_2, \Delta \phi_3, \ldots, \Delta \phi_n\).

![Figure 2.13: Schematic of the measures used to compute the PRC of a bursting neuron. Black is the control or reference trace and red is the perturbed trace. See text for the meaning of the notation.](image-url)
Figure 2.14: Burst skipping following injection of an excitatory current in a two-compartment model. Following the perturbation, the voltage trace goes quiescent for approximately two burst periods. (Top) Currentscape for somatic compartment, (Bottom) currentscape for axonal compartment. The phase $\phi$ indicates the phase of the current injection. Stimulus was a 2 nA step current with a duration of 50 ms.
Chapter 3

Results

3.1 Degeneracy in Single Compartment Models is Characterized by Low Dimensional Attractors

In order to rigorously characterize the degeneracy of the ionic currents in the single compartment model neurons, I set out to estimate the geometric dimension of the bursting attractors in the state space of these models. To estimate the dimension of these attractors, I constructed time delay embeddings for all state variables of 100 bursting model cells and computed their optimal embedding dimensions. These state variables include the membrane potential $V_m$, the activation and inactivation gates $m_i, h_i$, and the intracellular calcium concentration $[Ca^{2+}]$. Because the optimal embedding dimension of a lagged time series corresponds to the dimension in which the original geometric attractor in the full state space has been completely “unfolded”, we can use the embedding dimension as an estimate of the full attractor’s dimension.

Using the genetic algorithm described in section 2.4, I optimized the cost function described in subsection 2.4.1 to find $\sim$100 models exhibiting bursting activity at a frequency of $\sim$1 Hz. The parameter distributions for these models are illustrated in the figure below. These parameter distributions have sufficient variance to guarantee that the population of 100 bursters are representative of the whole parameter space.

These models were then simulated for 40 seconds of physiological time and the time series of their
state variables used to construct time delay embeddings. The optimal lags and the embedding dimensions for each model’s state variables were computed as described in section 2.6.

In this section, I also reproduce a simplified model of bursting introduced by [Franci et al., 2014]. This model, a three time scale bursting modification of the Fitz-Hugh Nagumo model, is used to investigate the possibility of observing STG-like neural dynamics in a low dimensional model as opposed to the high dimensionality of the single compartment Liu model.

![Parameter distributions of the bursting models. A majority of the conductances and the calcium buffering time constant are approximately uniformly distributed. Though $g_{KCa}$ and $g_{H}$ appear to be skewed, this is because these conductances generally cluster at lower values. All models were optimized with $g_{MI} = 0$.](image)

Figure 3.1: Parameter distributions of the bursting models. A majority of the conductances and the calcium buffering time constant are approximately uniformly distributed. Though $g_{KCa}$ and $g_{H}$ appear to be skewed, this is because these conductances generally cluster at lower values. All models were optimized with $g_{MI} = 0$.

### 3.1.1 Most State Variables Have Low Embedding Dimension

The distributions of the embedding dimensions for each dynamical variable in the 100 single compartment models are illustrated in the violin plots of Fig. 3.2 below. A majority of the state variables have embedding dimensions clustered below $d_E = 5$.

The distributions for some state variables such as the voltage and sodium activation gate have long
tails resulting in a large variance. What can we say about these variables? It is possible that for some types of bursting attractors, these variables are playing a unique role in the dynamics and are not strongly coupled to other state variables, so they must be embedded in a high dimensional space to completely unfold the attractor. The very high embedding dimensions observed for some variables may also be due to numerical constraints; though the numerically simulated trajectories are finely sampled ($\Delta t = 0.1$ ms), they are still not sampled with infinite precision, so higher embedding dimensions may be required to reconstruct the full attractor.

![Figure 3.2: Distributions of the embedding dimension for each state variable of the Liu model for all 100 models tested. Notice that the distributions tend to cluster below $d_E = 5$.](image)

In Fig. 3.3, I have grouped the embedding dimensions of all 13 state variables in all 100 models together and plotted their distribution. There is a large peak in the distribution for the bin centered on $d_E = 3$, which includes all $d_E \in \{2, 3, 4\}$. This result suggests that most of the bursting attractors are low-dimensional. In other words, although the total state space is 13 dimensional, the bursting attractor dynamics often (though not necessarily) take place in a low-dimensional subspace of the state space. How can we be sure that this statement is reasonable? Because an embedding is by
definition injective (one-to-one), Takens’ theorem guarantees that time delay embeddings, properly constructed, are injective; it is well known from the constant rank theorem (see any advanced calculus text) that no mapping from a space of dimension $m$ to a space of dimension $n$ where $n < m$ can be injective. What this means is that whatever optimal embedding dimension $d_E$ we compute, we must have $d_E \leq d$ where $d$ is the dimension of the original attractor.

One interpretation of this result is that many of the ionic currents are playing similar roles or are in some sense highly correlated [Kepler et al., 1992]. If ion channel gating variables have similar membrane potential feedback relationships and are active over similar voltage ranges and time scales, they will essentially be playing similar functions in the cell, each one tracking the other’s activity. These ion channels are said to be playing degenerate roles in the membrane potential dynamics. In the words of Tim O’Leary [O’Leary, 2018],

“A single channel type rarely has a monopoly on a specific physiological process. Strong overlap exists in the biophysical properties of different channels and in how channel types shape neural activity. This overlap is often termed degeneracy. For example, the activation potentials and time-constants of many currents have overlapping windows where multiple currents make very similar contributions to membrane properties. This raises the question of why a biological system would spend time and energy expressing more types of conductances than appear necessary for physiological function.”

In this way, by computing the embedding dimensions of the state variables and finding the mode of their distribution, we are in some sense quantifying the extent of degeneracy in the single compartment models. The lower the mode of the embedding dimension distribution, the more likely it is that many of the state variables of the system are highly correlated. This interpretation is especially pertinent given the recent results showing that dynamical systems with degenerate state variables exhibit long-range correlations in their time series [Delignières and Marmelat, 2013]. If we believe that the mechanisms in the models sufficiently recapitulate the mechanisms in the actual cells of the STG, then we have also quantified the degeneracy in the true biological system.

Though under normal conditions degeneracy is not immediately obvious in the STG, it is rapidly revealed under the influence of neuromodulators or global perturbations such as temperature varia-
tions. In the case of neuromodulation, different modulators can reveal the pluripotency of degenerate neurons, switching them between different activity states resulting in both single cell changes in excitability and qualitative changes in network rhythms [Briggman and Kristan, 2008, Kintos et al., 2016, Marder and Bucher, 2001]. Degeneracy is apparently a ubiquitous feature of networks such as the STG. Harris-Warrick and Marder [Harris-Warrick and Marder, 1991] refer to such circuits as polymorphic networks since they are capable of being reconfigured into multiple distinct activity states, making their behavior flexible and able to adapt to different biological contexts.

In the case of global perturbations, degeneracy imparts robustness to the STG. If any one of the many ion channel species loses function in the face of a particular perturbation, there is likely another ion channel species already playing a similar role. Ion channels which play similar roles can compensate for each other if one of the channels is lost or pathologically perturbed [O’Leary, 2018, Prinz, 2017]. This allows the important aspects of the STG’s rhythms, such as burst duty cycle, to be maintained even under environmental duress.

Figure 3.3: Embedding dimension distribution for all state variables lumped together. The mode of the distribution is in the bin centered at $d_E = 3$. 

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3.1.2 A Simplified Model Recapitulates Physiologically Relevant Dynamics

Given that the bursting attractors in the model STG cells are low dimensional, is it possible for more simple low dimensional neuron models to recapitulate physiologically relevant dynamics of the STG models? Recent studies by Alessio Franci and his colleagues indicate that the answer is yes [Franci et al., 2012, Franci et al., 2013, Franci et al., 2014, Franci and Sepulchre, 2014, Drion et al., 2012].

The model we will study was introduced and analyzed in [Franci et al., 2014]. Though I perform no new analysis of the model, I will reproduce some of the results of Franci et al.’s study and use these results as an organizing center for coming discussions of neuromodulation. The completeness of Franci et al.’s analysis can guide intuition about the more complex STG models, which are not amenable to such analytic study. The model is a variation of the classical FitzHugh-Nagumo model with an added ultraslow variable \( z \):

\[
\dot{V} = kV - \frac{V^3}{3} - (n + n_0)^2 + I - z \tag{3.1}
\]

\[
\dot{n} = \varepsilon_n(V)[n_\infty(V - V_0) - n] \tag{3.2}
\]

\[
\dot{z} = \varepsilon_z(V)[z_\infty(V - V_1) - z] \tag{3.3}
\]

where \( \varepsilon_z(V) \ll \varepsilon_n(V) \ll 1 \) \( \forall V \) are Gaussian time-constant functions and \( n_\infty, z_\infty \) are sigmoidal activation functions aggregating the slow time-constant \( (n) \) gating variables and the ultraslow time-constant \( (z) \) gating variables. Similarly, \( V \) aggregates the membrane potential and the fast time-constant gating variables. The parameter \( I \) is an external applied current.

The parameter \( k \) represents the gain of the positive-feedback in the fast-timescale while \( n_0 \) represents the balance between ionic currents providing positive-feedback (regenerative) and those providing negative-feedback (restorative).

For simple numerical simulations, we follow [Franci et al., 2014] and use the piecewise-linear ap-
proximation of (1) - (3)

\[ \dot{V} = kV - \frac{V^3}{3} - (n + n_0)^2 + I - z \]  
\[ \dot{n} = \varepsilon_n [\hat{n}_\infty (V - V_0) - n] \]  
\[ \dot{z} = \varepsilon_z [\hat{z}_\infty (V - V_1) - z] \]  

with

\[ \hat{n}_\infty (V - V_0) = \begin{cases} 
0.9(V - V_0), & V < V_0 \\
7(V - V_0), & V > V_0 
\end{cases} \]

and

\[ \hat{z}_\infty (V - V_0) = \begin{cases} 
0, & V < V_1 \\
100(V - V_1), & V > V_1 
\end{cases} \]

where

\[ I = 11/3, \quad \varepsilon_n = 0.02, \quad \varepsilon_z = 0.0001, \quad V_1 = -1.2 \]

We will use numerical simulations to examine how the bursting waveform of the model varies as a function of the fast gain parameter \( k \) and the half-activation potential \( V_0 \).

Figure 3.4: As the parameter \( n_0 \) governing the balance between resorptive and regenerative currents decreases, thereby favoring regenerative currents, the model transitions from tonic spiking to bursting.
Figure 3.5: Both increasing the fast gain parameter $k$ and decreasing the half-activation potential $V_0$ separately transition the model between different bursting waveforms, and therefore, bursting mechanisms.

The most important result of the modeling work done by Franci et al. is the elucidation of fundamental dynamical mechanisms underlying the transition from spiking to bursting. Additionally, the transition between different bursting waveforms is equally important. Because all parameters in the model have a rigorous physiological interpretation, it is possible to connect the results of this modeling work directly to experimental preparations of bursting neurons.

These phenomena (transition from spiking to bursting, transition between waveforms) are hallmarks of neuromodulation, often occurring when neuromodulators such as dopamine are applied to a single neuron or small network of neurons. Until recently, general principles regarding the mechanisms governing these changes to intrinsic excitability were unknown.

Regarding neuromodulation, the important take-away from the work here is this: transitions in intrinsic excitability can be explained by transitions in the balance between regenerative and restorative currents (the parameter $n_0$).

This insight allows us to view the seemingly disparate actions of different neuromodulators as having a common principle: changing the balance between positive and negative ionic feedback loops in the neuron.
3.2 Single Compartment Models Fail to Capture the Physiological Transition from Spiking to Bursting

In section 1.3, we saw that in a reduced neuron model, it was possible to track the switch from tonic spiking activity to bursting activity with only a single parameter. Though this toy model is incredibly valuable for organizing one’s thinking, it lacks the complexity imparted by having many different ion channels coupled together.

An open problem in neuromodulation within the STG is to understand how the modulatory current $I_M$ can induce a previously silent or spiking model to burst. It has been known since at least the 1980s that the pacemaker AB is a conditional burster, typically silent or tonic spiking without neuromodulatory input [Hooper and Marder, 1987]. Recent work [Zhao et al., 2010] illustrates that $I_M$ is both necessary and sufficient to induce bursting in in vivo AB cells. This transition from tonic spiking to bursting has also been observed in the pyloric cell LP [Harris-Warrick et al., 1992, Ch. 3], and is important in the functioning of thalamic relay cells [Sherman, 2001]. A primary goal of this thesis is to elucidate the properties of model pyloric cells which make them amenable to switching excitability states in the presence of an identified neuromodulatory current.

In this section I implement three different models of the modulatory current $I_M$ in single compartment models of the conditional burster AB optimized for tonic spiking behavior and search for models exhibiting a transition from tonic spiking to bursting for some $\bar{g}_M > 0$.

Using the genetic algorithm described in section 2.4, I optimized the cost function described in subsection 2.4.2 to find $\sim$200 models exhibiting tonic spiking activity at a frequency of $\sim$5 Hz. The parameter distributions for these models are illustrated in the figure below. As can be seen from the distributions, these models sample a wide range of the parameter space, so we can be sure that the effects of introducing a neuromodulatory current are not just due to a biased sampling of particular parameter sets.

To investigate the possibility of a bifurcation from a stable tonic spiking regime to a stable bursting regime in the presence of modulatory current, each of the models was simulated for 20 seconds of physiological time while steadily increasing $\bar{g}_M$ over the course of the simulation. The modulatory
conductance was increased linearly in time $t$ according to

$$\tilde{g}_{MI}(t) = \tilde{g}_{MI}^{\text{max}} \frac{t}{20}$$

(3.7)

where $\tilde{g}_{MI}^{\text{max}}$ is the highest value of the modulatory conductance at the end of the ramp. This value depended on the model of modulation being implemented, $\tilde{g}_{MI}^{\text{max}} = 2 \mu S$ for the Golowasch model, $\tilde{g}_{MI}^{\text{max}} = 1 \mu S$ for the Swensen model, and $\tilde{g}_{MI}^{\text{max}} = 0.5 \mu S$ for the Zhao model. These values were chosen heuristically by selecting the highest value of $\tilde{g}_{MI}^{\text{max}}$ for which none of the models blew up in finite time.

Using a time step of $\Delta t = 0.1$ ms, a 20 second simulation time corresponds to $20 \times 1000 / \Delta t = 2 \times 10^5$ values of $g_{MI}$ with a change in maximal conductance at each time step $\Delta \tilde{g}_{MI} \propto 10^{-5} \mu S$. This value is sufficiently small so that we do not have to worry about increasing $\tilde{g}_{MI}$ too quickly and overshooting some region of stable activity.

The membrane potential waveforms of each model were examined by eye to check for qualitative changes that could correspond to a bifurcation from tonic spiking to bursting.

### 3.2.1 No Road From Spiking to Bursting with Traditional Models of Neuro-modulation

Using two traditional models of the modulatory current $I_{MI}$, the Golowasch model and the Swensen model, none of the $\sim$200 tonic spiking single compartment models displayed activity which could be called bursting for any value of $\tilde{g}_{MI}$.

In both the Golowasch and Swensen models, three basic regimes of activity were observed. For the Golowasch model, these can be observed in Fig. 3.7. In Fig. 3.7 (A), we observe a regime in which the spike amplitude steadily decreases while the baseline membrane potential depolarizes significantly. In Fig. 3.7 (B) the cell develops fast subthreshold activity while again the baseline depolarizes significantly. In this regime, the cell eventually becomes quiescent at a depolarized potential, likely due to a depolarization block.

The third regime, illustrated in Fig. 3.7 (C), comes the closest to bursting. The baseline membrane
Figure 3.6: Parameter distributions of the tonic spiking models. A majority of the conductances and the calcium buffering time constant are approximately uniformly or normally distributed. All models were optimized with $g_{MI} = 0 \ \mu S.$
potential first hyperpolarizes before entering a state characterized by multiple spikes in quick succession (often triplets, though sometimes doublets or quadruplets) separated by a short “slow-wave”. No STG physiologist would consider these cells to be bursting, however, as they lack the characteristic plateau potential and are active on a much faster time scale than the pyloric pacemaker kernel (> 5 Hz).

In all regimes displayed by the cells implementing the Golowasch model, $I_{MI}$ quickly saturates for values of $g_{MI} > 1 \, \mu S$. Additionally, the currentscapes show that all regimes have a pattern of $I_A$, $I_H$, and $I_L$ decreasing their shares of the total current as the share of $I_{MI}$ increases, while the shares of $I_{Na}$, $I_{KCa}$, and $I_{CaS}$ increase; $I_{Kd}$ and $I_{CaT}$ maintain relatively stable shares throughout the simulation.

Cells implementing the Swensen model behaved in much the same way as when implementing the Golowasch model. The primary difference between these models is that in the Swensen model, $I_{MI}$ accounts for a lower share of the current at any given time and saturates at a slower rate. The typical spike triplets of Golowasch regime (C) are replaced by spike doublets in Swensen regime (B).
3.2.2 A Linearized Model of Neuromodulation Displays a Transition from Spiking to Pseudo-Bursting

In addition to the two traditional models of $I_{MI}$, I also implemented a newer model of $I_{MI}$ introduced by Zhao et al. and covered in section 2.3. This model approximates $I_{MI}$ by the linear portion of its I-V curve with negative slope (i.e. negative conductance). In this case, $I_{MI}$ functions as a negative leak current which is in opposition to the Golowasch and Swensen models, in which $I_{MI}$ functions as an inward nonlinear current.

Just as with the Swensen and Golowasch models, cells implementing the Zhao model displayed three regimes of activity. The first of these regimes, illustrated in Fig. 3.9, follows standard biophysical intuition about leak currents: the spike frequency decreases as $\bar{g}_{MI}$ increases until the cell goes quiescent at a hyperpolarized potential.

The second and third regimes are more interesting, and come the closest to true AB-like bursting, a state that I will refer to as pseudo-bursting. I call this state pseudo-bursting because although a well defined slow wave is present along with a plateau potential, the plateau is too narrow and the number of spikes per burst (always two) is too low to be considered pyloric-like. Additionally, the frequency of the pseudo-bursting is approximately 2.5 Hz, slightly higher than the standard 1 Hz of AB. Thus, these regimes cannot be said to recapitulate the physiology of the pyloric pacemaker.

In the second regime, the cell maintains a relatively stable spiking frequency before eventually entering an intermittent pseudo-bursting state in which pseudo-bursts are separated by one or more spikes. As $\bar{g}_{MI}$ continues to increase, the cell eventually goes quiescent as in the first regime.

The third regime is similar to the second except that before going quiescent, the cell enters what appears to be a stable pseudo-bursting state. In order to ensure that this activity pattern is indeed stable, I simulated several of these models with $\bar{g}_{MI}$ set to a value in the interval of the ramp corresponding to persistent pseudo-bursting. The results of two of these simulations are illustrated below, and barring any possible long time scale attractors (> 20 s), the pseudo-bursting in this regime is indeed stable.

These results are promising, and to some degree reaffirm the results of [Zhao et al., 2010]. However,
Figure 3.7: The effect of linearly increasing $\bar{g}_{MI}$ in models optimized for tonic spiking using the Golowasch model. During the 20 seconds of simulated physiological time, $\bar{g}_{MI}$ is ramped linearly from 0 $\mu$S to 2 $\mu$S. The models (A) - (C) represent three typical regimes that occur as $\bar{g}_{MI}$ is increased. All of the models were originally optimized for tonic spiking with $\bar{g}_{MI} = 0$ $\mu$S. In all models, although $\bar{g}_{MI}$ is increasing, the current $I_{MI}$ appears to saturate for $\bar{g}_{MI} > 1$ $\mu$S.
Figure 3.8: The effect of linearly increasing $\bar{g}_{M1}$ in models optimized for tonic spiking using the Swensen model. During the 20 seconds of simulated physiological time, $\bar{g}_{M1}$ is ramped linearly from 0 $\mu$S to 1 $\mu$S. The models (A) - (C) represent three typical regimes that occur as $\bar{g}_{M1}$ is increased. All of the models were optimized for tonic spiking with $\bar{g}_{M1} = 0$ $\mu$S.
as already discussed, the observed pseudo-bursting is not sufficiently similar to the bursting activity of pyloric cells for us to develop a theory of the physiological spiking to bursting transition. These differences are observed primarily in the low duty cycle and faster burst frequency.
3.2.3 Two-Compartment Models and Attempts to Optimize for The Transition

One possible reason that none of single compartment models exhibited a true transition from tonic spiking to bursting is that I did not sample enough regions of the parameter space. Perhaps some set of maximal conductances and other parameters actually does result in the desired transition. To account for this possibility, I attempted to optimize the single compartment models for the transition using the genetic algorithms and cost functions described previously.

Despite running the genetic algorithm many times, often for a large population (~1000) and for many generations (~10000) no parameters were discovered exhibiting a physiologically realistic transition from spiking to bursting. For the types of cost functions developed in this thesis, the score for a set of “good” parameters (ones resulting in biophysically realistic voltage traces) is usually $E(g) < 1$. But no set of parameters attained a cost of less than $E(g) = 1000$ in this case.

The failure of the single compartment cells to account for the spike to bursting transition with all three models of $I_{MI}$ led to the hypothesis that the separation of spike initiation and slow-wave generation mechanisms into different compartments may be important for observing the transition. This hypothesis resulted in the development of a two-compartment model.

This model contains a somatic compartment with the ionic currents responsible for generating the slow-wave and an axon with the ionic currents responsible for spike initiation. The model is loosely based on the two-compartment models developed in [Soto-Treviño et al., 2005] for simulating the pyloric pacemaker kernel. In that paper, the behavior of only one set of parameters was investigated. Five further sets of bursting parameters for the Soto-Trevino model were examined in the context of temperature perturbations in [Caplan et al., 2014].

To ensure that the two-compartment model I developed exhibited bursting behavior and to develop a population of models for future study, I used the optimization procedure previously described to find 22 sets of parameters which resulted in the two-compartment model having a bursting waveform. The currentscapes of four exemplar models are illustrated below.

So far, all attempts to optimize the two-compartment model for the tonic spiking to bursting transition have been unsuccessful, but I will continue to use the genetic algorithm to search for the
Figure 3.9: The effect of linearly increasing $\bar{g}_{MI}$ in models optimized for tonic spiking using the Zhao model. During the 20 seconds of simulated physiological time, $\bar{g}_{MI}$ is ramped linearly from 0 $\mu$S to 0.5 $\mu$S. The models (A) - (C) represent three typical regimes that occur as $\bar{g}_{MI}$ is increased. (B) shows intermittent pseudo-bursting, while (C) shows stable pseudo-bursting. All of the models were originally optimized for tonic spiking with $\bar{g}_{MI} = 0$ $\mu$S.
Figure 3.10: Stable pseudo-bursting in a tonic spiking model. (A) illustrates the tonic spiking state with $\bar{g}_{MI} = 0 \, \mu S$. (B) illustrates the stable pseudo-bursting state with $\bar{g}_{MI} = 0.12 \, \mu S$. Parameters are the same as for model (C) in the previous figure.
Figure 3.11: Stable pseudo-bursting in another tonic spiking model. (A) illustrates the tonic spiking state with $\tilde{g}_{MI} = 0 \mu S$. (B) illustrates the stable pseudo-bursting state with $\tilde{g}_{MI} = 0.11 \mu S$. 
Figure 3.12: Two different standard solutions discovered by the genetic algorithm using the spiking to bursting cost function. In both (A) and (B), the top trace indicates the behavior of the model with $g_{MI} = 0\ \mu S$, while the bottom trace indicates the behavior of the model with $g_{MI} > 0\ \mu S$. 
necessary parameters.
3.3 Phase Response Properties of Single and Two-Compartment Models

We were curious to see whether any major differences existed between the phase response curves of the single and two-compartment models. In the hopes of comparing the model PRCs to PRCs of actual STG cells, I have limited the magnitude and duration of the current injections employed in the model PRCs to ±1 nA and 100 ms, respectively. These are the values currently being used by experimentalists in the Marder lab for exploratory investigations of PRCs.

Both single and two-compartment models were simulated without any current injection for 40 seconds, with the first 20 seconds being discarded to get rid of transients. These traces were used as control traces for reference. A reference burst was chosen and its period was computed and divided into 250 points for current injection. A 250 point PRC gives a resolution in the phase of $d\phi = 0.004$, so all PRCs are finely sampled. In some cases, higher order PRCs (usually up to third order) were computed.

I would like to thank my colleagues Dr. Leandro Alonso and Pierre Losciuto for writing the initial versions of the phase response analysis code and for their continued efforts on these studies.

3.3.1 Fine Structure of the Phase Response Curves

Single Compartment PRCs Exhibit Structured Discontinuities

In many of the single compartment models, both excitatory and inhibitory PRCs displayed interesting structures resembling step functions at low values of the phase $\phi$. Careful observation reveals that these structures emerge when current is injected during the active spiking phase of the burst.

It is not immediately clear from just looking at the voltage traces for each current injection phase what determines the emergence of these fine structures in the PRC. Possible hypotheses such as the discontinuities corresponding to injection during a spike do not hold up, since there are almost always more spikes per burst than discontinuities in the PRC and $d\phi$ is sufficiently small to sample all spikes in the burst. Similar fine structures were observed in a nearly identical STG model [Prinz...
Figure 3.13: Two-compartment models with similar voltage traces but disparate currentscapes. (A) and (B) illustrate the voltage traces and currentscapes for two different two-compartment models. In both (A) and (B), the top currentscapes correspond to the somatic compartment, while the bottom currentscapes correspond to the axonal compartment.
Figure 3.14: Two-compartment models with similar voltage traces but disparate currentscapes. (A) and (B) illustrate the voltage traces and currentscapes for two different two-compartment models. In both (A) and (B), the top currentscapes correspond to the somatic compartment, while the bottom currentscapes correspond to the axonal compartment.
et al., 2003b] but were not further analyzed there.

Though the fine structures appear initially in the first order PRCs, they appear to propagate into the higher order PRCs as well. Additionally, new structures will emerge in the higher order PRCs at phases corresponding to current injection during the quiescent part of the burst. As will be discussed below, the discontinuities in the first order PRCs can be in part explained by various spike addition/deletion mechanisms, but the emergence of these fine structures at later phases of the is not as easy to account for. Initial investigations suggest that spike adding and deleting may occur in later bursts, but why this should be the case when no current is being injected during these bursts is not totally clear. It may be the case that the new bursting equilibria emerging after the perturbation are meta-stable, and the models return to the original attractors very slowly.

However, other possibilities exist. Some of the models exhibit sudden large phase advances due to the previous burst being truncated early or spiking at a much faster frequency. These phenomena have been described and analyzed previously in a Morris-Lecar type model [Agbanusi, 2008] and further analysis will be required to determine if similar mechanisms are at play in the Liu models.
Two-Compartment PRCs Exhibit Fewer First-Order Discontinuities

The two-compartment models generated first-order PRCs which more closely resembled PRCs constructed from recordings of true STG cells (Fig. 3.18). Both the two-compartment and experimental PRCs show a “scattering” of the phase response for perturbations delivered during the active phase of the burst. These scatterings also appear to be due to spike addition and deletion or changes of the within-burst firing rate, but they lack the structure seen in the single compartment phase response curves.

As previously stated, stimuli were always delivered to the somatic compartment to generate the phase response curves. Since the somatic compartment contains only slow regenerative (positive feedback) and fast restorative (negative feedback) ionic currents, this lack of fine structure in the phase response curves gives further credence to the hypothesis that the fine structure emerges due to the effects of fast regenerative currents. Though we have not tested this hypothesis, it seems likely that the two-compartment first-order PRCs would develop the fine structure seen in the single compartment first-order PRCS if the perturbations were delivered in the axonal compartment. Similar theories were suggested by [Maran et al., 2011], who examined phase response properties in a multi-compartment model of the AB-PD pacemaker kernel.

Unlike the first-order PRCs, the fine structure that emerges in the higher-order PRCs of the single compartment models also emerges in the higher-order PRCs of the two-compartment models. Moreover, this higher-order fine structure can be explained by spike addition and deletion just as for the single compartment models. Why this should be the case is not immediately clear.
Figure 3.15: A cell that initially shows fine structure in its first order excitatory PRC (A). The discontinuities propagate to later phases in the second order (B) and third order (C) PRCs.
Figure 3.16: A cell that initially shows no fine structure in its first order excitatory PRC (A). The discontinuities emerge in later phases in the second order (B) and third order (C) PRCs.
Figure 3.17: A cell that initially shows fine structure in its first order inhibitory PRC (A). The discontinuities propagate to later phases in the second order (B) and third order (C) PRCs.
Figure 3.18: The first order excitatory PRCs from one of the two-compartment models having a long burst duration (A) and an experimental preparation of a PD cell (B; adapted from [Prinz et al., 2003b]). Note the similarity between the “scattering” of the phase response at early phases of current injection.

Spike Adding Accounts for Discontinuous Phase Delays While Spike Deletion Accounts for Discontinuous Phase Advances

In the single compartment PRCs, the discontinuous positive jumps in $\Delta \phi$ can be at least partially explained by a phenomenon known as *spike adding*. Spike adding in a bursting cell occurs when the usual bursting attractor undergoes a bifurcation such that one or more spikes are added to the burst. In other words, the number of spikes per burst increases after the bifurcation [Nowacki et al., 2012].

When current of any sign is injected during some portions of the active phase of the burst, such
Figure 3.19: A two-compartment cell that initially shows no fine structure in its first order excitatory PRC (A). The discontinuities develop in later phases in the second order (B) and third order (C) PRCs.
Figure 3.20: A two-compartment cell that initially shows no fine structure in its first order inhibitory PRC (A). The discontinuities develop in later phases in the second order (B) and third order (C) PRCs.
a bifurcation can occur, and one or more spikes may be added to the burst. This spike adding typically lengthens the burst period, resulting in the delay of the subsequent burst ($\Delta \phi > 0$). As can be seen from the voltage traces in Fig. 3.22, each positive jump in $\Delta \phi$ in the PRC corresponds to the addition of one or more spikes.

One must be careful to distinguish between spike addition and spike deletion. Spike deletion is just the opposite of spike addition, wherein a bifurcation of the bursting attractor results in one or more spikes being deleted from the burst. The theory of spike addition and deletion is rich, but for the sake of space and time, it cannot be covered here. The interested reader should consult [Desroches and Kirk, 2018] and [Nowacki et al., 2012].

In many of the inhibitory PRCs, when current is injected during the active phase of the burst, two spikes may be deleted from the burst. At some later phase (still within the active phase of the burst), only one spike may be deleted. This transition from a double to single spike deletion manifests in the PRC as a positive jump in $\Delta \phi$, and thus can easily be confused with spike adding. However, it is important to remember that spike addition and deletion can only be discussed with respect to the reference burst since this is the burst being perturbed. The deletion of fewer spikes is still a spike deletion.

Though spike addition occurs in both excitatory and inhibitory PRCs, the phenomenon is primarily observed for excitatory current injections. Many of the inhibitory PRCs do not exhibit spike addition at all. This is not surprising, since injection of an excitatory current usually drives spiking or bursting in most neurons, while injection of an inhibitory current usually leads to hyperpolarization and reduced firing frequency.

Changes in the number of spikes per burst can account for the fine structure observed in the first-order PRCs for active phases of the burst. These results are in agreement with recent results from [Sherwood and Guckenheimer, 2010] who report similar discontinuities in the PRCs of a Hindmarsh-Rose bursting model and show that these discontinuities result from transient changes in the number of spikes per burst.

Examination of the voltage traces for each current injection phase indicates that the same mechanisms are partially responsible for the discontinuities seen at later phases of injection in higher-order
PRCs. Take the PRCs shown in Fig. 3.15. The fine structures observed in the first-order PRC (3.15.A) are due to spike addition. In the second and third-order PRCs (3.15.B-C), new fine structures emerge for phases of injection corresponding to quiescent parts of the burst \((\phi > 0.4)\), while the fine structures seen in the (3.15.A) remain.

Phase responses for later (higher-order) bursts, are always measured relative to the previous burst, so the fine structures in 3.15.B-C for \(\phi < 0.4\) are the same ones observed in the first-order PRC. They have been propagated through to later bursts (i.e. a delay in the first burst after injection results in a delay in all subsequent bursts). But, whereas the fine structures seen at early phases emerged due to spike addition and deletion in the reference burst, the fine structures that emerge at later phases \((\phi > 0.4)\) in the higher-order PRCs are due spike addition and deletion in bursts after the reference burst.

Spike addition and deletion were easy to explain for the reference burst: the injection of current during the active phase of the burst caused some spike adding/deleting bifurcation in the bursting attractor. But why would current injection during the quiescent phase of the control burst result in spike addition and deletion during later bursts, resulting in the fine structure emerging in the higher-order PRCs?

One possibility is that the perturbations during the quiescent phase of the burst kick the bursting trajectory into a region of phase space where a meta-stable bursting attractor lives. If this attractor has more or less spikes per burst than the original attractor, then as the trajectory passes slowly through this meta-stable state, later bursts may appear to undergo “spike addition/deletion”. Eventually the trajectory will return to the initial bursting attractor. Rephrased from a more biological perspective, the interactions of the ionic currents following the stimulus result in a transient but long time scale perturbation of the bursting voltage waveform. This would explain why in Fig. 3.15, the third-order PRC has the same structure as the second-order PRC: the trajectory has returned to the original attractor, so no new fine structure emerges; the fine structures that are present are merely propagated from the lower-order phase responses.
3.3.2 Multi-stability in Single Compartment Models

Perhaps unsurprisingly (due to the high dimensionality of the models), many of the single compartment models exhibited two stable bursting states. Multi-stability in bursting neuron models has been studied in detail previously, so this is not an entirely new phenomenon [Malashchenko et al., 2011, Franci et al., 2014]. However, to the best of my knowledge, bistability of two different bursting attractors has been observed only once before, in the aplysia R15 model [Newman and Butera, 2010]. In the present case, the multi-stability was revealed during construction of the phase response curves.

For some phases of the injected current, many single compartment model cells would switch to a qualitatively different bursting attractor. To visualize these attractor transitions, I discarded the first ten seconds of each simulation following the current injection to allow transient activity to die down; then I computed the vector of inter-spike intervals (ISI) for the voltage trace and plotted them vertically as a function of the injection phase \( \phi \). One can think of each vertical line in these plots as a birds eye view of the steady-state ISI distribution for the voltage trace at that injection phase.

Small values of the ISI indicate the intervals between spikes, while medium to large values of the ISI indicate the intervals between bursts. Thus, these plots can be used to visualize the structure of the bursting attractor as a function of the injection phase. If the plot appears as a series of unbroken horizontal lines, then the cell remains on the original bursting attractor throughout each phase of current injection. Any breaks in these lines, however, can indicate that the cell has switched to a different attractor.

Since ISI maps are a form of Poincare map, one can think of each vertical slice of these plots as a line through a Poincare section. The plots can then be interpreted as illustrating the evolution of the Poincare map as a function of the current injection phase.

Approximately 10% of the single compartment models examined so far display bistable bursting states, suggesting that the phenomenon is not restricted to some small region of parameter space. Many of these models show the same bistability in response to both excitatory and inhibitory
Figure 3.21: Spike addition in an excitatory phase response curve. (A) The perturbed traces (red) are plotted on top of the control traces (black) for increasing phase of current injection. The horizontal traces show only the initial burst (the one being perturbed). Each blue arrow indicates the addition of a single spike. These blue arrows correspond to the positive jumps in $\Delta \phi$ seen in the early part of the phase response curve in (B).
Figure 3.22: Spike deletion in an inhibitory phase response curve. (A) The perturbed traces (red) are plotted on top of the control traces (black) for increasing phase of current injection. The horizontal traces show only the initial burst (the one being perturbed). The first blue arrow (top) indicates the deletion of two spikes. This pattern continues until the next blue arrow, following which only one spike is deleted. These blue arrows correspond to the negative jumps in $\Delta \phi$ seen in the early part of the phase response curve in (B).
Figure 3.23: (A) shows the voltage traces for increasing (top to bottom) phases of excitatory current injection in a single-compartment model. The blue arrows indicate where the number of spikes in the reference burst changes, while green arrows indicate where the number of spikes in the subsequent burst changes. (B) illustrates how these changes in spike number are manifested as discontinuities in the first-order (top) and second-order (bottom) PRCS. Same parameters as Fig. 3.15.
perturbations (Fig. 3.25). In contrast, none of the two-compartment models examined so far exhibit multi-stability of any kind.

Though I have only examined a small population of the two-compartment models and cannot claim to have thoroughly explored their parameter space, it is nonetheless striking that multi-stability is so common in the single compartment models as compared to the two-compartment ones. One possibility is that the separation of time scales into two different compartments which are usually only weakly coupled in some way prevents the existence of multiple stable attractors in the same model.

For models exhibiting attractor switching to both excitatory and inhibitory stimuli, the transitions do not always occur at the same phase of current injection. However, the transitions are always to the same bursting attractors in both cases, suggesting that the models are indeed bistable rather than tristable or otherwise multi-stable.

Figure 3.24: Two types of bursting attractor maps. In (A), the model neuron returns to the same bursting attractor for all phases of the perturbation. In (B), the model neuron transitions to a different stable attractor at a point near $\phi = 0.5$, indicating multi-stability.
Figure 3.25: ISI maps of three single compartment models exhibiting attractor switching in response to both excitatory and inhibitory stimuli. (A) - (C) show the ISI maps of three different bistable single compartment models. (Left) The ISI maps in response to excitatory stimuli. (Right) The ISI maps in response to inhibitory stimuli. Note that the attractor transitions do not always occur at the same current injection phase for the two signs of stimuli.
Figure 3.26: (A) The ISI map of model (A) of the previous figure. Note the transition to a different bursting attractor near $\phi = 0.4$. (B) The voltage traces (black, control; red, perturbed) for increasing $\phi$. The transition seen in (A) can be seen in the voltage traces. (C) The first-order PRC for this model does not appear to differ greatly from those of models which are not multi-stable.
Chapter 4

Conclusion

Degeneracy is a ubiquitous feature of neural systems. In crustaceans, ion channel degeneracy endows the circuits of the STG with multifunctional capabilities as well as robustness in the face of global perturbations such as high extracellular potassium, pH variations, and temperature increases. Modulatory input from modulators such as RPCH and proctolin can switch these multifunctional networks between the states supported by their degenerate components.

Until now, no rigorous measure of degeneracy for neurons or circuits was available. In this thesis, I introduced a measure of degeneracy based on the theory of time delay embeddings. If one constructs time delay embeddings of the dynamical trajectories of many models or experimental preparations, one can estimate the level of degeneracy in the system by the most common embedding dimension computed in the attractor reconstruction. The lower this embedding dimension, the more degenerate the system.

Using genetic algorithms to optimize cost functions associated with qualitative features of a model cell’s membrane potential waveform allows one to find many (potentially thousands) of sets of conductances and other parameters that result in the desired voltage dynamics. In this manner, I generated several hundred bursting and tonic spiking single compartment models.

Given that none of the single compartment models were capable of recapitulating a physiologically realistic transition between tonic spiking and bursting states, a reasonable conclusion is that the bifurcation underlying this transition requires a more coarse separation of time scales in the model.
dynamics. The work of Franci et al. analyzing the three time scale bursting modification of the Fitz-Hugh Nagumo model indicates that the spiking to bursting transition is via a global transcritical bifurcation induced by shifting the balance between restorative and regenerative feedback between the membrane potential and ionic currents toward the regenerative currents. It remains unclear if one could find such a measure in the more biophysically realistic Liu model without reducing the models significantly.

Attempts to optimize the single compartment models to find parameters exhibiting the spiking the bursting transition did not produce satisfactory results. The optimization routine regularly returned solutions which either did not fire tonically without modulatory input or exhibited some form of pseudo-bursting with modulatory input. None of these solutions recapitulated the known physiology of pyloric cells.

Two-compartment models can provide the hypothesized need for a separation of time scales in the ionic current dynamics. In light of this, I developed a two compartment model of the pyloric pacemaker AB. Initial attempts to optimize this model for the spiking to bursting transition were unsuccessful. Pursuing more fruitful lines of inquiry, my colleagues and I sought to compare and contrast the phase response properties of the single and two compartment models with each other as well as those of real STG cells.

We observed the presence of fine structure in the phase response curves of these models and putatively in the \textit{in vivo} STG cells as well. Some of this fine structure can be explained by spike addition and deletion mechanisms resulting from the bifurcation of the bursting attractor during particular phases of the current injection. Additionally, I also observed for the first time, to the best of my knowledge, multi-stability of bursting attractors in the single compartment models. Though multi-stability of silent and bursting or tonic spiking and bursting states has been described in other bursting models, bistability between two distinct bursting states has not been previously described in the Liu models studied here.

After all this, we are left with a number of lingering questions:

1. What are consequences of the discontinuities in the PRCs of individual cells for network function?
2. Do multifunctional neural circuits exploit multi-stability in their component cells?

3. How can neurons avoid pathological multi-stability?

4. Can two-compartment models exhibit the transition from tonic spiking to bursting?

Future work will seek to address these questions in both the model and in vivo STG cells.
Appendix A

Model Parameters

Table A.1: Auxiliary parameters of the single and two-compartment models. The parameter $C$ is the capacitance used for the single compartment models $C$ (soma) is the capacitance used for the somatic compartment of the two-compartment models.

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Table A.9: Parameters for models in Fig. 3.15.

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Table A.10: Parameters for models in Fig. 3.16.

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Table A.12: Parameters for models in Fig. 3.18.

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Table A.13: Parameters for models in Fig. 3.19.

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Table A.17: Parameters for models in Fig. 3.25.

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