ANALYSIS OF MODELS OF BURSTING ELECTRICAL ACTIVITY IN PANCREATIC BETA CELLS

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Abstract

Pancreatic $\beta$-cells are responsible for producing and secreting insulin, a hormone which is essential in the regulation of blood glucose level. In the presence of glucose, $\beta$-cells exhibit periodic bursting electrical activity (BEA) consisting of active and silent phases. During the active phase, the membrane potential of these cells oscillates rapidly, whereas the membrane potential changes slowly during the silent phase. The plateau fraction, which is the ratio of the active phase duration to the period of the bursting phenomenon, has been correlated to the insulin-glucose response of these cells.

There are a number of mathematical models describing BEA in pancreatic $\beta$-cells. In the first part of this thesis, the class of first-generation models which consist of three coupled first-order ordinary differential equations is analyzed. Numerical and analytical techniques are presented for determining the approximate plateau fractions from the model equations as a function of the glucose-dependent parameter.

A consistent nondimensionalization of the model equations is proposed which permits all of the models to be written in a standard form. The equations then are separated into a second-order fast subsystem and a first-order slow subsystem. A bifurcation analysis of the fast subsystem in which the slow variable is treated as the bifurcation parameter reveals that the transition from the active phase to the silent phase occurs near a homoclinic bifurcation. The use of several numerical and analytical methods is demonstrated for the determination of the approximate location of this bifurcation, which is needed in the computation of the approximate silent and active phase durations and, subsequently, the approximate plateau fractions.
Leading-order problems for the silent and active phases are obtained using a combination of singular perturbation and multiple scales analyses and averaging techniques. The corresponding leading-order silent and active phase durations and the resulting leading-order plateau fractions are reduced to quadrature. Finally, the approximations are compared with the respective exact (numerically computed) silent and active phase durations and plateau fractions over a range of the glucose-dependent parameter for which the models exhibit BEA.

In the remainder of this thesis, a detailed study of a polynomial analog model of BEA in pancreatic $\beta$-cells is carried out. Depending on the values of the model parameters, the model exhibits a wide variety of oscillatory solution behaviour, including types of bursting observed in excitable cells other than pancreatic $\beta$-cells.

A bifurcation map in the fast subsystem parameter space is produced by computing curves which represent codimension-2 bifurcations. These curves bound regions on the map within which bifurcation diagrams of the fast subsystem are qualitatively the same. The importance of the bifurcation map is that it shows the relationships between the various types of oscillatory behaviour and, hence, provides a basis for an extension of the classification of bursting oscillations. Since the analog model consists of polynomial functions, the curves on the bifurcation map can be derived analytically.
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Chapter 1

Introduction

Cells of the islets of Langerhans in the pancreas secrete several important hormones in order to maintain the glucose level in the blood within a narrow operating range. The two most important hormones are insulin, which is produced and secreted by $\beta$-cells, and glucagon, which is produced and secreted by $\alpha$-cells. Insulin helps to decrease the blood glucose level, whereas glucagon helps to increase the blood glucose level. The disease called diabetes mellitus is a result of the inability of the body to properly utilize and/or produce insulin. If left untreated, diabetes can lead to serious medical complications.

In a short preliminary paper in 1968 [24], Dean and Matthews provided evidence that the $\beta$-cell is electrically excitable. In their more detailed follow-up paper in 1970 [25], they reported that $\beta$-cells exhibit a characteristic periodic pattern of electrical activity in the presence of glucose, namely bursting electrical activity (BEA), an example of which is shown in Figure 1.1. Bursting electrical activity is a periodic phenomenon, during which the membrane potential of the cell undergoes silent and active phases. The silent phases are characterized by a slowly changing membrane potential and the active phases are characterized by a rapidly oscillating membrane potential. The term 'burst', referring to the repetitive spiking activity during the active phase, was coined by Dean and Matthews.

During subsequent studies, it was found that the bursting pattern depends highly on the concentration of external glucose. When the glucose concentration is low (<5 mM), the membrane potential remains at a resting value of approximately -68 mV [3]. When the glucose concentration is increased, the $\beta$-cell membrane exhibits BEA. As
Chapter 1. Introduction

Figure 1.1: Regular pattern of bursting electrical activity induced by 10 mM glucose in a mouse pancreatic $\beta$-cell. (Adapted from Ozawa and Sand [66].)

the concentration is increased further, the duration of the active phase relative to the burst period increases also. That is, the higher the glucose concentration, the longer the active phases become and the shorter the silent phases [6, 8, 15, 23, 62]. When the glucose concentration is raised beyond 16.6 mM, the bursts disappear and the membrane potential exhibits continuous spiking.

Insulin release induced by the presence of glucose occurs over the same concentration range [53]. Moreover, the rate of insulin release and the duration of the active phase are strongly correlated experimentally [4, 61, 63]. Therefore, in order to understand the regulation of insulin release, it is necessary to understand the electrophysiological properties of the $\beta$-cell. Since the landmark work by Dean and Matthews, this has been a subject of intense investigation.

The first biophysical model for BEA was proposed by Atwater et al. [6]. They believed that three types of ion channels in the membrane of the $\beta$-cell played an important role in producing the electrical activity and that the intracellular calcium concentration was the agent controlling the switch from the active phase to the silent phase and vice versa. Based on the ideas of Atwater et al., Chay and Keizer [18] developed the first mathematical model of BEA in 1983. Their model was a modification of the classical Hodgkin
and Huxley model [47] for electrical activity in the squid giant axon. Although little electrophysiological data, such as channel densities, activation curves, or time constants, were available at that time, their model was very successful in simulating BEA.

As new channels are discovered, or new data becomes available, the biophysical theories are modified, resulting in a wealth of mathematical models of BEA. In this thesis, we restrict our attention to deterministic models. These models are assumed to represent the average behaviour of a single β-cell clustered together in an islet or in a petri dish. For single isolated β-cells, the stochastic opening or closing of single channels has an important influence on the membrane potential. As a result, single isolated cells do not produce bursts [14]. However, β-cells are known to be in close electrical contact with their neighbours through gap junctions [53]. For tightly coupled clusters of cells, the electrical effects of single-channel events are shared by all the cells. When the cluster is large enough, the effects of single-channel openings are less of a factor, stochastic noise disappears, and the islet behaves deterministically. For models addressing the issues related to stochasticity and the effects of coupling through gap junctions, see [86, 87, 89].

On the basis of the underlying physiological assumptions, the deterministic models that have been reported in the literature can be divided into two major groups. The class of models which we call first-generation models [13, 14, 16, 17, 44, 54, 87], developed from 1983 to 1989, are based on the assumption that the slow variable in the system is the intracellular calcium concentration. The essential differences between these models are the specific ionic currents that are thought to be important for producing BEA.

Since 1989, there has been a development of second-generation models [15, 55, 88]. These models are characterized by the fact that they no longer depend on the assumption that a slowly varying intracellular calcium concentration is responsible for burst termination. In the first two models, advanced by Chay [15] and Keizer and Smolen [55], the slow process is replaced by the slow voltage-dependent inactivation of the calcium
current, based on a hypothesis put forward by Satin and Cook [83, 84]. In these models, the intracellular calcium concentration no longer oscillates slowly, but varies rapidly and in synchrony with the rapidly oscillating membrane potential. Recent experiments by Valdeolmillos et al. [91] and Santos et al. [81], in which the intracellular calcium concentration is measured using fluorescence techniques, indeed show that intracellular calcium does not accumulate slowly during the active phase, but rather rises rapidly at the onset of the active phase, and reaches a steady state level after the first few spikes. In [88], Smolen and Keizer note that the slow voltage-dependent inactivation hypothesis is not compatible with the available data. Instead, they propose that the slow process depends on ATP (adenosine triphosphate) or ADP (adenosine diphosphate) concentration.

The identity of the slow variable remains unknown. Similarly, the ionic currents playing an important role in producing BEA and related phenomena remain under investigation. For example, the implications of the hypothesis that a calcium release activated current (CRAC) is present in β-cells is examined in a very recent paper by Bertram et al. [11].

Rather than focusing on the controversies surrounding these models, the goal in this thesis is to present techniques to study problems associated with BEA, and to add to the mathematical understanding of BEA in pancreatic β-cells in particular, and the bursting phenomenon in general. In Section 1.1, we outline the organization of this thesis and introduce the major issues discussed in the following chapters. The necessary electrophysiological background for this thesis is provided in Section 1.2.

1.1 Thesis Outline

This thesis can be divided into two parts. In the first part, consisting of Chapters 2, 3, and 4, we concentrate on biophysical models of bursting electrical activity in pancreatic
Figure 1.2: Correlation of the rate of insulin release from isolated islets with the plateau fraction as functions of glucose concentration. (From Ozawa and Sand [66].)

β-cells and develop analytical techniques to study a physiologically important problem, namely the determination of the plateau fraction, which is the ratio of the active phase duration to the period of the bursting phenomenon. In the second part, consisting of Chapter 5, we study the bursting phenomenon in a much broader context, concentrating on the bifurcation behaviour of a polynomial analog model of bursting electrical activity.

The plateau fraction is physiologically relevant because it appears to be strongly correlated experimentally [4, 61, 63] to the rate of insulin release, as shown in Figure 1.2. This correlation suggests that the relative lengths of the active and silent phases are important in the regulation of insulin release. From a physiological point of view, viable models of pancreatic β-cells are those that not only reproduce the observed electrical activity, but also predict a plateau fraction as a function of the glucose-dependent parameter(s) which is in agreement with experimental observations. Himmel and Chay [44] obtained plots of the plateau fraction as a function of the glucose-dependent parameter by numerically integrating the model equations for various values of the parameter and
extracting the plateau fraction from the solution. Pernarowski [67] and Pernarowski et al. [70] developed an analytical, and much more efficient, method for determining the plateau fraction in the context of the Sherman-Rinzel-Keizer model [87], based on formal perturbation techniques. In [67], Pernarowski notes that the method can be applied to all models which can be written in the same (perturbed Liénard) form as the Sherman-Rinzel-Keizer model. The question that was not answered is whether other $\beta$-cell models also can be written in this form.

One of the aims of the research described in this thesis is to extend Pernarowski’s analysis to the majority of other models, i.e., to find a unified approach to calculating the plateau fraction. We restrict our attention to those first-generation $\beta$-cell models that consist of three ordinary differential equations. Although these models have been superseded, their analysis remains fruitful for two reasons. First, all models, including the most recent second-generation models, are based on the assumption that there is a slow variable in the system that controls the termination of the burst during BEA. The identification of the slow variable is extremely important from a biophysical point of view. However, we believe that from a mathematical point of view, whether the slow process is governed by the intracellular calcium concentration, the slow voltage-dependent inactivation of the calcium current, the ATP or ADP concentration, or some other variable is irrelevant. We believe that the analysis presented in this thesis can be generalized to other models of BEA. Second, the bursting phenomenon is observed not only in pancreatic $\beta$-cells, but also in the electrical behaviour of many nerve cells. Examples include hippocampal pyramidal neurons [50, 93], thalamic neurons [27], and AB neurons [41]. Furthermore, bursting has been observed in biochemical systems of enzyme reactions [26, 48], as well as in chemical systems, such as the Belousov-Zhabotinskii reaction [49]. Any new insights that can be gained from the analysis of the aforementioned models adds to the understanding of the bursting phenomenon in general.
In Chapter 2, we introduce all first-generation models of BEA consisting of three ordinary differential equations. Most of the discussion is centered around the development of the first mathematical model, due to Chay and Keizer [18], which consists of five first-order differential equations, and the subsequent reduction to a third-order system [19]. The reasons as to why the Chay-Keizer model gives rise to the bursting phenomenon were provided by Rinzel [76]. We summarize his analysis in this chapter since it is fundamental to the work presented in the remaining chapters. In addition to the Chay-Keizer model and the Sherman-Rinzel-Keizer model, the models being considered are due to Chay [13, 14], Chay and Cook [16], Chay and Kang [17], and Himmel and Chay [44]. Finally, we present a consistent nondimensionalization of the model equations so that all models can be written in the same standard form.

Before being able to determine the plateau fraction from the model equations, we need to know how to predict the beginnings and ends of the silent and active phases. Based on the bifurcation analysis of the model equations, the end of the silent phase and the beginning of the active phase are easily determined \textit{a priori}. However, predicting when the active phase ends and the silent phase begins is more difficult. In Chapter 3, we examine various numerical and analytical approaches to determine when the escape from the active phase occurs.

The results of Chapter 3 are used in Chapter 4, where we derive leading-order expressions for the silent and active phase durations and the plateau fraction, using perturbation analysis, including a multiple scales analysis of the active phase and averaging. The silent and active phase durations are shown to be in excellent agreement with the corresponding exact durations. The leading-order plateau fraction is shown to consistently overestimate the exact plateau fraction, due to neglecting the time spent in the transitions from the silent to the active phase and vice versa. We end the chapter and the part of the thesis concerned with the determination of the plateau fraction with a discussion of these
transitions.

In Chapter 5, we study bursting oscillations in a much broader context. To avoid the complex nonlinearities in the biophysical models, we use the polynomial model due to Pernarowski [68]. Depending on the parameter values, this model exhibits a wealth of different types of solution behaviour, including square-wave bursting which is the type of bursting observed in pancreatic \(\beta\)-cells. An examination of the bifurcation diagram corresponding to different types of solution behaviour reveals that the bifurcation diagrams themselves are undergoing bifurcations as parameters are varied. We create a bifurcation map in the fast subsystem parameter space, consisting of regions within which the bifurcation diagrams are qualitatively the same. The bifurcation map is significant in that it shows the relationships between the various types of solution behaviour and, hence, provides a basis for a comprehensive classification scheme of bursting oscillations.

Finally, in Chapter 6, we make some general remarks about the work presented in this thesis and discuss possibilities for future work.

1.2 The Mathematics of Cell Electrophysiology

All living cells are enclosed by a thin membrane, which is made up of phospholipid and protein molecules, as shown in Figure 1.3. The phospholipids provide the basic structure of the membrane and the proteins carry out specific functions.

Each phospholipid consists of a hydrophyllic (water-loving, polar) head and two hydrophobic (water-hating, nonpolar) fatty acid tails. To form the basic structure of the membrane, phospholipids line up spontaneously into two layers (bilayer) with the tails sandwiched between the heads (cf. Figure 1.3). Because of the special architecture of the bilayer, namely that the inside is strongly hydrophobic, the bilayer acts as an impermeable barrier to water-soluble molecules.
Figure 1.3: Three-dimensional view of a small section of a cell membrane. (From Alberts et al. [1], page 275.)

Embedded in the phospholipid bilayer are many different types of protein molecules (cf. Figure 1.3). These molecules carry out the specific functions of the membrane. Some proteins act as receptors for chemical signals, others are enzymes that catalyze reactions which are membrane-related, and still others act to transport specific molecules or ions into and out of the cell.

The ability of proteins to control the flow of ions (and, therefore, electrical current) is the underlying reason for the electrical activity exhibited by many types of cells. The proteins which are concerned with the movement of ions have three very important characteristics. First, they form tiny pores and, hence, these proteins are usually called channel proteins or ion channels. Second, these channel proteins exhibit ion selectivity. That is, each type of ion channel permits a specific ion to pass through it, for example, potassium ($K^+$) or sodium ($Na^+$). Third, the channels are not always open. They have switches, or gates, which open only when stimulated. The stimulation can be a change in membrane potential, in which case the channel is said to be voltage-gated. Alternatively, the stimulation can be the binding of a ‘messenger’ molecule to a membrane receptor or
Figure 1.4: Schematic drawing of a channel protein or ion channel in its open and closed states. The outside of the channel is hydrophobic and interacts with the phospholipid bilayer. The inside is hydrophilic and facilitates the passage of water-soluble ions. When the channel gate opens, the protein changes conformation to form a tiny aqueous pore. The pore is of atomic dimensions and it is here that the ion selectivity is determined. The location of the gate and the ion selectivity filter are shown here to be on the outside of the membrane. For most channels, this detailed information is still unknown. (From Alberts et al. [1], page 313.)

the binding of an ion (corresponding to the terms ligand-gated and ion-gated channel, respectively). Figure 1.4 shows a schematic drawing of a gated ion channel.

The driving force for ionic movement through open channels stems from the differences in the electric potential and the ionic concentrations across the cell membrane. The membrane potential is the voltage difference that exists across all biological membranes. It arises from an imbalance of electrical charges across the membrane, as well as ionic current flow through the membrane. In a resting cell, this imbalance is maintained by passive ionic diffusion through open channels and active, energy-consuming mechanisms such as ionic pumps.

Large concentration differences across the membrane constitute the second factor influencing the movement of ions. Typically, potassium ions are at a much higher concentration inside the cell relative to the outside, and sodium, chloride, and calcium ions
are at a much higher concentration outside the cell.

Thus, there are two forces acting on any ion, namely an electrostatic force due to the membrane potential and a diffusional force due to the concentration differences. The equivalent electric potential difference (the Nernst potential, \( V_{\text{ion}} \)) required to maintain the concentrations for a specific ion on the two sides of the membrane is given by the Nernst equation

\[
V_{\text{ion}} = \frac{RT}{FZ} \ln \frac{C_o}{C_i},
\]

where

\[
R = \text{universal gas constant (8.31 joules/mole/K)},
\]

\[
F = \text{Faraday's constant (96.487 coulombs/mmole)},
\]

\[
T = \text{absolute temperature (K)},
\]

\[
Z = \text{valence (charge) of the ion},
\]

\[
C_o, C_i = \text{outside and inside concentrations of the ion, respectively}.
\]

That is, if the membrane potential is \( V_{\text{ion}} \), then the electrical gradient just balances the concentration difference for that ion and there is no net flow of the ion across the membrane.

When the membrane is made more permeable to a given ion, the membrane potential tends to be driven towards the Nernst potential for that ion. As a result, practically any change in the membrane permeability, due to the opening of a channel in response to some stimulus, causes a change in the membrane potential. Resting membranes are typically permeable primarily to \( K^+ \) ions. Therefore, the resting potential equilibrates to a value near the Nernst potential for \( K^+ \), generally about -75 mV.

Precisely how the membrane potential varies with the flow of ionic currents can be simulated through the use of mathematical models. The importance of the classical work
Chapter 1. Introduction

of Hodgkin and Huxley [47] in this area cannot be overestimated. The underlying theory used to develop their model still is used extensively today.

In particular, the membrane can be thought of as a leaky capacitor. The membrane current $i_m$ thus is the sum of the capacitive current and all ionic currents, viz.,

$$i_m = C_m \frac{dV}{dT} + \sum I_{ion},$$

where $C_m$ is the more-or-less constant specific capacitance of the membrane, $V$ is the membrane potential, $T$ is the time, and $\sum I_{ion}$ is the sum of all ionic currents, depending on the types of channels present in the membrane. In the present context, we ignore the contributions due to electrogenic pumps.

Normally, $i_m$ is zero, due to Kirchhoff's law, which essentially restates the law of conservation for charge. That is, the capacitive and ionic currents are in balance,

$$C_m \frac{dV}{dT} = - \sum I_{ion}.$$  

(1.3)

The above expression forms the starting point for all mathematical models of membrane electrical activity following the Hodgkin-Huxley modelling theory. The models differ in the ionic currents included in $\sum I_{ion}$. An important assumption is that all ionic currents flow independently of each other. That is, each type of ion channel contributes a term to $\sum I_{ion}$. In practice, only the channels which are thought to be important in producing the desired electrical activity are included.

The net driving force (due to the electrical gradient and concentration difference) for each ionic type is proportional to the difference between the membrane potential and the Nernst potential of that ion, $V - V_{ion}$. The actual current carried by the ion not only depends on this driving force, but also on how easy or difficult it is for the ion to pass through the membrane. In particular, by Ohm's Law,

$$I_{ion} = \frac{V - V_{ion}}{R_{ion}},$$

(1.4)
where $R_{\text{ion}}$ is the resistance of the membrane to the ion. However, instead of resistance, physiologists prefer to use conductance, which is the reciprocal of resistance. Defining the conductance of the ion, $g_{\text{ion}}$, to be

$$g_{\text{ion}} = \frac{1}{R_{\text{ion}}},$$

(1.5) becomes

$$I_{\text{ion}} = g_{\text{ion}}(V - V_{\text{ion}}).$$

(1.6)

The conductance $g_{\text{ion}}$ in effect measures the ease with which the ion passes through the membrane or the permeability of the membrane to the ion. From experiments, it is known that $g_{\text{ion}}$ often depends on the state of the membrane (for example, the value of the membrane potential or whether ‘messenger’ molecules are bound to the membrane, etc.). For instance, for a voltage-gated channel, the conductance may increase (i.e., channel gates are switched to the open state) as the potential difference across the membrane decreases. Therefore, mathematical models also must include descriptions of the dependence of $g_{\text{ion}}$ on the state of the membrane.

There are two major difficulties with the Hodgkin-Huxley modelling theory that should be pointed out. First, it may not always be clear which ion channels are the important players in producing the desired electrical activity. In fact, it may well be that a particular ion channel hasn’t even been identified, let alone characterized as an important player. Second, the dependence of the conductance $g_{\text{ion}}$ on the state of the membrane may not be well understood. In the case of bursting electrical activity in pancreatic $\beta$-cells, the controversies surrounding these difficulties have led, and continue to do so, to many different biophysical theories and corresponding mathematical models, as will become evident in the next chapter.
Chapter 2

Description of the First-Generation Biophysical Models and Preliminary Analysis

In this chapter, we introduce the first-generation models of bursting electrical activity in pancreatic β-cells consisting of three ordinary differential equations. The biophysical theories upon which the models are based essentially differ in the types of channels that are thought to be important for producing the bursting activity and how these channels are thought to function. Therefore, the mathematical models mainly differ in those terms which represent the currents passing through the channels. However, all models have in common the assumption that there is a net efflux of Ca\(^{2+}\) from the cell during the silent phase and a gradual buildup of Ca\(^{2+}\) during the active phase.

In Section 2.1, we discuss the first model in detail. Although both the biophysical theory and corresponding mathematical model have been superseded, the discussion is useful, as it serves as a basis for understanding the bursting phenomenon in general. The remaining models of bursting electrical activity in pancreatic β-cells which are considered in this thesis are introduced in Section 2.2. In Section 2.3, we nondimensionalize the models so that they can be written in a standard form and reformulate the equations for the purpose of the upcoming analysis in the following chapters.
2.1 The First Mathematical Model for Bursting Electrical Activity in the Pancreatic Beta Cell

We begin by discussing the first biophysical model of bursting electrical activity in pancreatic β-cells, due to Atwater et al. [6] in Section 2.1.1. In Section 2.1.2, we discuss the corresponding first mathematical model, due to Chay and Keizer [18]. Since we extensively use Rinzel's fast/slow subsystem analysis [76] throughout this thesis, a summary of this analysis is provided in Section 2.1.3.

2.1.1 The Biophysical Model

By the late 1970's, there was a strong belief that three types of channels play an important role in the control of the electrical activity. These channels were a voltage-gated Ca$^{2+}$ channel [60], a voltage-gated K$^+$ channel [7, 42, 43], and a Ca$^{2+}$-activated K$^+$ channel [5, 75]. Based on these beliefs and the hypothesis that the calcium ion is a control agent for the membrane potential [5], Atwater et al. [6] proposed the first biophysical model explaining the bursting electrical activity.

In particular, Atwater et al. proposed that changes in the membrane potential which are induced by the presence of external glucose can be explained in terms of changes in the intracellular calcium concentration, [Ca$^{2+}$]. When no glucose is present, [Ca$^{2+}$] is maintained at a relatively high level. Thus, the Ca$^{2+}$-activated K$^+$ channel is open, resulting in a membrane potential near the Nernst potential for K$^+$. When glucose is present, the cell is induced to lower [Ca$^{2+}$] through the activation of energy-consuming processes. As [Ca$^{2+}$] is lowered, the Ca$^{2+}$-activated K$^+$ channel is inhibited, causing the membrane potential to increase. When [Ca$^{2+}$] is sufficiently reduced, the Ca$^{2+}$-activated K$^+$ channel has a low open probability and a rapid depolarization occurs. The voltage-gated K$^+$ and Ca$^{2+}$ channels are then activated, resulting in a burst of spikes or action
potentials. During the spiking activity, Ca$^{2+}$ flows into the cell. As [Ca$^{2+}$], increases, the Ca$^{2+}$-activated K$^+$ channel becomes active again, repolarizing the membrane and inhibiting a further influx of calcium. Once the cell has lowered [Ca$^{2+}$], the cycle starts again.

2.1.2 The Chay-Keizer Model

The model of Atwater et al. [6] describes how the interaction of membrane processes (ionic currents) and the changing intracellular calcium concentration can produce bursting electrical activity in a qualitative sense. To study this interaction quantitatively, Chay and Keizer [18] developed the first mathematical model in 1983.

Chay and Keizer included the four basic features of the biophysical model, namely the three ionic channels described in the previous section and the dynamic calcium concentration. Since much of the required electrophysiological data for β-cells was not available at that time, they used the classical Hodgkin and Huxley [47] model for electrical activity in the squid giant axon as a basis for their model. The most important modifications to the Hodgkin and Huxley model are the addition of the Ca$^{2+}$-activated K$^+$ channel, the replacement of the inward sodium current by an inward calcium current, and the addition of a dynamical equation for the intracellular calcium concentration.

Following the scheme introduced by Hodgkin and Huxley, the conductance of the voltage-gated K$^+$ channel is written as

$$g_K = \bar{g}_Kn^4, \quad (2.1)$$

where $\bar{g}_K$ is the maximum conductance of the channel and $n^4$ is the fraction of K$^+$ activation. Similarly, the conductance of the voltage-gated Ca$^{2+}$ channel is written as

$$g_{Ca} = \bar{g}_{Ca}m^2h, \quad (2.2)$$
where $\bar{g}_{Ca}$ is the maximum conductance, $m$ is the activation parameter of the channel, and $h$ is the inactivation parameter. These equations may be interpreted physically as follows. The $K^+$ channel is assumed to be open if four similar, but independent, channel subunits are in the active state. The probability that one subunit is active is $n$; the probability that four are active is $n^4$. Similarly, the $Ca^{2+}$ channel is assumed to be open if three similar channel subunits are active (with probability $m$) and a different subunit is not active (with probability $h$). Since $m$, $h$, and $n$ represent probabilities, their values range between 0 and 1.

To model the $Ca^{2+}$-activated $K^+$ channel, a scheme proposed by Plant [72] was adopted. This scheme assumes that $Ca^{2+}$ binds to the channel according to first-order Michaelis-Menten kinetics (i.e., one $Ca^{2+}$ ion bound to the channel will activate it). Thus, the conductance for this channel is written as

$$g_{K, Ca} = \bar{g}_{K, Ca} \frac{Ca_i/K_d}{1 + Ca_i/K_d},$$

where $\bar{g}_{K, Ca}$ is the maximum conductance of the channel, $Ca_i$ is the intracellular calcium concentration, and $K_d$ is the dissociation constant for $Ca^{2+}$ bound to the channel gate.

The flow of other ions is reflected in a leakage current of non-specific nature. The leakage current is assumed to have a constant, relatively small, conductance, $g_L$.

Based on (1.6) and (2.1)-(2.3), the ionic currents thus are

$$I_Ca(V) = \bar{g}_{Ca}n^3h(V - V_{Ca}),$$

$$I_K(V) = \bar{g}_Kn^4(V - V_K),$$

$$I_{K, Ca}(V, Ca_i) = \bar{g}_{K, Ca} \frac{Ca_i}{K_d + Ca_i}(V - V_K),$$

$$I_L(V) = \bar{g}_L(V - V_L),$$

where $I_Ca$, $I_K$, $I_{K, Ca}$, and $I_L$ are the currents flowing through the voltage-gated $Ca^{2+}$ and $K^+$ channels, the $Ca^{2+}$-activated $K^+$ channel, and the leakage channel, respectively.
$V_{Ca}$, $V_K$, and $V_L$ are the Nernst potentials for calcium, potassium, and the leakage, respectively.

From equation (1.3), the rate of change for the membrane potential $V$ then satisfies

$$4\pi r^2 C_m \frac{dV}{dT} = -[I_{Ca}(V) + I_K(V) + I_{K, Ca}(V, Ca_i) + I_L(V)],$$

(2.8)

where $r$ is the radius of a single $\beta$-cell. The factor $4\pi r^2$, representing the cell surface area, needs to be included because conductances typically are given in Siemens for the entire $\beta$-cell rather than Siemens/unit area.

The activation and inactivation variables $m$, $h$, and $n$, satisfy the relaxation equations introduced by Hodgkin and Huxley, namely,

$$\frac{dm}{dT} = \frac{m_\infty(V) - m}{\tau_m(V)},$$

(2.9)

$$\frac{dh}{dT} = \frac{h_\infty(V) - h}{\tau_h(V)},$$

(2.10)

$$\frac{dn}{dT} = \frac{n_\infty(V) - n}{\tau_n(V)}.$$  

(2.11)

The voltage dependencies of the steady-state functions $m_\infty$, $h_\infty$, and $n_\infty$, and the functions $\tau_m$, $\tau_h$, and $\tau_n$ corresponding to the time constants have exactly the same form as in the Hodgkin and Huxley model, but they are shifted along the voltage axis.

So far, the Chay-Keizer model consists of four equations (2.8)-(2.11). However, because of the proposed importance of the changes in the intracellular calcium concentration, a fifth equation is required. The rate of change of the intracellular calcium is essentially the difference between influx and efflux of calcium. The influx of calcium is due to the voltage-gated Ca$^{2+}$ channel ($I_{Ca}$). Since little information about the metabolism of calcium was known at the time, the efflux of calcium was modelled as $-k_{Ca}Ca_i$, where $k_{Ca}$ represents the glucose-dependent rate constant for the removal of $Ca_i$. The higher
the concentration of glucose, the higher the value of $k_{Ca}$. The equation for $Ca_i$ thus is

\[ \frac{dCa_i}{dT} = f \left[ \frac{-3}{4\pi r^3 F} I_{Ca} (V) - k_{Ca} Ca_i \right], \]  

(2.12)

where $F$ is Faraday’s constant and $f$ is the ratio of free to bound intracellular calcium ions. The inclusion of $f$ reflects the fact that the majority of calcium ions entering the cell are immediately absorbed by high affinity binding sites and that the bound calcium ions do not take part in the processes leading to the electrical bursting activity. It is worth noting at this point that, strictly speaking, $Ca_i$ therefore represents the intracellular concentration of \textit{free} calcium ions, rather than the total intracellular calcium concentration. Finally, the factor of $\frac{3}{4\pi r^3}$ accounts for the cell volume and converts ionic charge to concentration.

Equations (2.8)-(2.12) define the five-dimensional model for the bursting electrical activity as presented in [18]. Chay and Keizer present a reduced model in [19], where the activation and inactivation variables of the voltage-gated $Ca^{2+}$ channel, $m$ and $h$ in (2.2), are replaced by their respective steady-state values ($m_\infty (V)$ and $h_\infty (V)$) and the relaxation equations for these variables, (2.9) and (2.10), are omitted. With some minor changes to the parameter values, the reduced model produces essentially the same results. Therefore, for the remainder of this thesis, we use the reduced Chay-Keizer model, instead of the original five-dimensional one.

The definitions of the steady-state functions $m_\infty (V)$, $h_\infty (V)$, and $n_\infty (V)$, and the function $\tau_n (V)$ completes the description of the reduced Chay-Keizer model. They are

\[ y_\infty (V) = \frac{\alpha_y (V)}{\alpha_y (V) + \beta_y (V)}, \]  

(2.13)

for $y = m, h,$ and $n$, where

\[ \alpha_m (V) = \frac{B_m (V_m - V)}{\exp \left[ \frac{1}{S_m (V_m - V)} \right] - 1}, \]  

(2.14)
\[ \beta_m(V) = 4.0 \exp \left[ \frac{1}{S_a} (V_a - V) \right], \quad (2.15) \]
\[ \alpha_h(V) = 0.07 \exp \left[ \frac{1}{S_h} (V_h - V) \right], \quad (2.16) \]
\[ \beta_h(V) = \frac{1}{\exp \left[ \frac{1}{S_b} (V_b - V) \right] + 1}, \quad (2.17) \]
\[ \alpha_n(V) = \frac{B_n(V_n - V)}{\exp \left[ \frac{1}{S_n} (V_n - V) \right] - 1}, \quad (2.18) \]
\[ \beta_n(V) = 0.125 \exp \left[ \frac{1}{S_c} (V_c - V) \right], \quad (2.19) \]

and
\[ \tau_n(V) = \frac{\tau}{\alpha_n(V) + \beta_n(V)}. \quad (2.20) \]

The graphs of the functions \( m_\infty, h_\infty, n_\infty, \) and \( \tau_n \) are shown in Figure 2.1. We observe that the steady-state functions for the activation variables \( m \) and \( n \) increase with \( V \), whereas the steady-state function for the inactivation variable \( h \) decreases with \( V \). The values of all parameters present in the model can be found in Appendix A.

The reduced Chay-Keizer model can be integrated using a standard computer code for stiff differential equations (e.g., LSODE from ODEPACK [45]). Figure 2.2 illustrates the numerical solution computed using the parameter values listed in Table A.1 in Appendix A. It is clear that the solution of the mathematical model mimics the bursting electrical activity observed experimentally (cf. Figure 1.1). The model also is compatible with the biophysical explanation of bursting proposed by Atwater et al. [6].

In particular, when \( k_{Ca} \) is low (representing a low concentration of external glucose), there is little removal of \( Ca_i \). Thus, \( Ca_i \) remains relatively high and the membrane potential remains near \( V_K \), the Nernst potential for \( K^+ \), due to the dominant \( I_{K,Ca} \). For higher values of \( k_{Ca} \), \( Ca_i \) is gradually reduced, \( I_{K,Ca} \) becomes less dominant and the membrane potential increases. When \( I_{K,Ca} \) is negligible, \( I_K \) and \( I_{Ca} \) are activated,
resulting in the spiking activity. During the spiking, $I_{Ca}$ causes $Ca_i$ to increase. Thus, $I_{K,Ca}$ is slowly activated again, eventually reducing the membrane potential back to $V_K$. When this occurs, $I_{Ca}$ and $I_K$ have been inactivated. That is, $Ca_i$ no longer increases, and the cycle starts again.

2.1.3 Rinzel's Fast/Slow Subsystem Analysis

Even though the Chay-Keizer models put the biophysical model by Atwater et al. [6] on a precise mathematical footing, insights as to why the system of equations should give rise to the bursting phenomenon were still lacking. Rinzel [76] provided these insights with his lucid analysis in 1985.
Figure 2.2: Numerical solution of the reduced Chay-Keizer model. (a) Membrane potential $V$. (b) Intracellular calcium concentration $Ca_i$. 
The key idea in Rinzel's treatment of the system is to identify a fast and a slow subsystem. Due to the smallness of the parameter $f$ in (2.12), the time course of $Ca_i$ is much slower than that of the remaining variables, $V$ and $n$. In fact, the dynamics of $Ca_i$ determine the time scale of the slow overall periodic behaviour (on the order of seconds). For this reason, the third equation of the reduced Chay-Keizer model, (2.12), is defined to be the slow subsystem. The remaining two equations, (2.8) and (2.11), define the fast subsystem. This subsystem is responsible for generating the spikes during the active phase, which occur on a much faster time scale.

The slow behaviour of $Ca_i$ is exploited by performing a bifurcation analysis of the fast subsystem, treating $Ca_i$ as the bifurcation parameter. Once the bifurcation structure of the fast subsystem is understood, the dynamics of $Ca_i$ are included in order to account for the overall bursting behaviour. The first step in the bifurcation analysis is to determine the steady states. Setting $n = n_{\infty}(V)$ in (2.8) and using (2.4)-(2.7), we thus require

$$I_{ss}(V; Ca_i) = \bar{g}_{Ca}m_{\infty}^2(V)h_{\infty}(V)(V - V_{Ca}) + \bar{g}_{K}n_{\infty}^{4}(V)(V - V_{K})$$
$$+ \bar{g}_{K, Ca} \frac{Ca_i}{K_d + Ca_i} (V - V_{K}) + \bar{g}_{L}(V - V_{L}) = 0.$$  \hspace{1cm} (2.21)

Note that we denote $Ca_i$ as a parameter in $I_{ss}$ by use of the semicolon.

Figure 2.3a shows the behaviour of $I_{ss}$ as a function of $V$ for several biophysical values of $Ca_i$. For low values of $Ca_i$, there is one steady state ($I_{ss} = 0$) at a high value of $V$. Similarly, for high values of $Ca_i$, there is one steady state at a low value of $V$. For intermediate values of $Ca_i$, there are three steady states. Figure 2.3b shows the location of the steady states plotted in $(V, Ca_i)$ space.

The stability of these steady states can be determined numerically. Rinzel used AUTO [28] to obtain the bifurcation diagram and the results are reproduced in Figure 2.4 for illustrative purposes. The low $V$ steady states, or the steady states on the left branch of the $I_{ss} = 0$ curve, are stable nodes (indicated by a solid curve). The steady states on
Figure 2.3: $I_{ss}(V; Ca_i)$ and the curve of steady states of the fast subsystem for the reduced Chay-Keizer model. (a) $I_{ss}(V; Ca_i)/4\pi r^2$ as a function of $V$ for $Ca_i = 0, 1, 2,$ and $3 \mu M$. The arrow indicates the direction of increasing $Ca_i$. (b) Curve of steady states of the fast subsystem.
Figure 2.4: Bifurcation diagram, generated with AUTO, of the fast subsystem of the reduced Chay-Keizer model. Stable steady states are indicated by a solid curve; unstable steady states by dashes. Saddle-node bifurcations (SN) occur at the local extrema of the $I_{ss} = 0$ curve. Immediately above the Hopf bifurcation (HB) point, the unstable steady states are surrounded by stable periodic orbits. The maximum and minimum values of the periodic orbits are indicated by the solid curve surrounding the right branch of the $I_{ss} = 0$ curve. The branch of periodic orbits terminates at a homoclinic bifurcation (HC).

The middle branch are saddle points and, hence, unstable (dashed curve). The steady states on the right branch are spirals, except near the local maximum of the $I_{ss} = 0$ curve, where the steady states are unstable nodes. Saddle-node bifurcations, at which nodes become saddles and vice versa, occur at the local extrema of the $I_{ss} = 0$ curve and are labelled by SN. For high values of $Ca_i$, the spirals on the left branch are unstable (dashed curve); they become stable at a Hopf bifurcation, labelled by HB. The Hopf bifurcation is supercritical and, hence, stable periodic orbits surrounding the unstable spirals emanate from the HB point. The maxima and minima of the orbits are plotted as a solid curve surrounding the right branch. This branch of periodic orbits terminates at
a homoclinic bifurcation, labelled by HC. At this point, the periodic orbit has become a
homoclinic orbit, with infinite period, connecting the saddle point on the middle branch
of the $I_{ss} = 0$ curve to itself.

Thus, for values of $Ca_i$ between the local minimum of the $I_{ss} = 0$ curve and the
homoclinic bifurcation, the fast subsystem exhibits bistability. The low $V$ steady state is
stable, whereas the high $V$ steady state is unstable, but surrounded by a stable periodic
orbit. This bistability is the key to explaining the bursting behaviour. Recall that
during the bursting activity, the membrane potential switches between a low voltage
state (the silent phase) and a high voltage oscillation (the active phase). The mechanism
for switching between the silent and active phases becomes clear when the dynamics of
$Ca_i$ are included in the analysis. Figure 2.5 shows the bifurcation diagram of Figure 2.4
together with the nullcline ($\dot{Ca}_i = 0$) for $Ca_i$ and the projection of the numerical solution
from Figure 2.2 superimposed. When the system is in the low $V$ steady state to the
left of the $\dot{Ca}_i$ nullcline, where $\dot{Ca}_i < 0$, $Ca_i$ decreases and $V$ increases. When the
local minimum of the $I_{ss} = 0$ curve is reached, the solution trajectory switches to the
oscillation about the high $V$ steady state to the right of the $\dot{Ca}_i$ nullcline. Here $\dot{Ca}_i$
is positive, so that $Ca_i$ increases until the homoclinic bifurcation is reached. At this
point, the trajectory switches back to the low $V$ steady state. It is worth pointing out
that for the full system of equations, there is one unstable steady state, occurring at the
intersection of $I_{ss} = 0$ and the $\dot{Ca}_i$ nullcline, and a stable limit cycle, namely the periodic
bursting solution.

2.2 Further Developments

In this section, we introduce the remaining first-generation models for bursting electrical
activity which consist of three ordinary differential equations. These are the models due
Figure 2.5: As Figure 2.4, with the $\dot{Ca}_i$ nullcline and the projection of the numerical solution of Figure 2.2 superimposed. $\dot{Ca}_i < 0$ to the left of the $\dot{Ca}_i$ nullcline; $\dot{Ca}_i > 0$ to the right.

to Chay [13, 14], Chay and Cook [16], Chay and Kang [17], Himmel and Chay [44], and Sherman, Rinzel, and Keizer [87].

Table 2.1 outlines the different currents included in each particular model and compares some salient features of the models, namely the form of the various currents included, whether a leakage current is present or not and whether the Nernst potential for the Ca$_{2+}$ ion depends explicitly on its concentration difference or not (cf. equation (1.1)). As will become apparent in Section 2.3 and Chapter 3, the most important distinction between the models from an analytical point of view is the value of the integer exponent of the activation variable $n$ in the voltage-gated K$^+$ channel (cf. Table 2.1). We note that the first three models, namely the reduced Chay-Keizer, Chay (1986), and Himmel-Chay models, have values of the exponent greater than one, whereas the remaining models,
namely the Chay-Kang, Sherman-Rinzel-Keizer, and Chay-Cook models, have an exponent equal to one.

Table 2.1 and the discussions below reflect the controversies surrounding the currents thought to play an important role in the bursting electrical activity at the time when these models were developed. Some controversies have already been resolved, while others remain under investigation. Rather than focusing on these controversies, the purpose of this section is to briefly introduce the different forms of the equation for the membrane potential $V$ and the hypotheses underlying the different forms. The complete definition of each model can be found in Appendix A.

2.2.1 The Chay (1986) Model

During the early 1980's, researchers began applying the relatively new patch-clamping technique to study the function of single ion channels in pancreatic $\beta$-cells. Two separate $K^+$ channels were identified, namely a low-conductance and a high-conductance $K^+$ channel.

Experiments by Ashcroft et al. [3], Cook and Hales [21], and Findlay et al. [32] showed that the low-conductance $K^+$ channel is directly inhibited by a metabolite of glucose, namely ATP. Ashcroft et al. [3] showed that the current due to this channel dominates in the absence of bursting and is responsible for the resting potential of the membrane in the absence of glucose.

Experiments by Cook et al. [22] and Findlay et al. [33] showed that the high-conductance $K^+$ channel can be activated by both membrane depolarization and intracellular $Ca^{2+}$ ions. Based on these results, it was suggested that the two separate $K^+$ channels as used in the Chay-Keizer models, namely the voltage-gated $K^+$ channel and the $Ca^{2+}$-activated $K^+$ channel, are in fact the same channel.

Chay [13] subsequently modified the reduced Chay-Keizer model and demonstrated
### Table 2.1: Comparison of the first-generation models consisting of three ordinary differential equations

The table indicates the forms of the conductances of the Ca\(^{2+}\) and K\(^+\) currents included in the equation for the membrane potential \(V\) (cf. (2.8)), whether a leakage current is included or not, and whether the Nernst potential for calcium is allowed to vary with \(Ca_i\) or not. The models are 1: Reduced Chay-Keizer [19]; 2: Chay (1986) [13]; 3: Himmel-Chay [44]; 4: Chay-Kang [17]; 5: Sherman-Rinzel-Keizer [87]; 6: Chay-Cook [16].

<table>
<thead>
<tr>
<th>Model</th>
<th>Ca(^{2+}) channels</th>
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that a single $K^+$ channel, namely a $K^+$ channel activated by both membrane depolarization and intracellular $Ca^{2+}$ ions, along with a voltage-gated $Ca^{2+}$ channel also can account for the bursting activity observed in $\beta$-cells. Chay omitted the modelling of the low-conductance ATP-inhibited $K^+$ channel since the current due to this channel is negligible during bursting.

The modified equation for the membrane potential $V$ (cf. (2.8)) is

$$4\pi r^2 C_m \frac{dV}{dT} = - \left[ I_{Ca}(V, Ca_i) + I_{K(V, Ca)}(V, Ca_i) + I_L(V) \right], \quad (2.22)$$

where $I_{Ca}$ represents the voltage-gated $Ca^{2+}$ current, $I_{K(V, Ca)}$ represents the current flowing through the voltage-gated, $Ca^{2+}$-sensitive $K^+$ channel, and $I_L$ represents the leakage current as in the Chay-Keizer models.

The $I_{Ca}$ and $I_{K(V, Ca)}$ currents are modelled by

$$I_{Ca}(V, Ca_i) = \bar{g}_{Ca} m^2(V)(V - V_{Ca}), \quad (2.23)$$

$$I_{K(V, Ca)}(V, Ca_i) = \bar{g}_{K(V, Ca)} n^2(V - V_K), \quad (2.24)$$

and the $I_L(V)$ current is as defined by (2.7). The function $m_\infty(V)$ represents the open probability of the $Ca^{2+}$ channel and $n$ represents the probability of opening the $K^+$ channel. The reason for raising $m_\infty$ to the power of 2, rather than 3 as in the Chay-Keizer models, is that it is the lowest power giving rise to spiking. The reason for raising $n$ to the power of 2, instead of 4 as in the Chay-Keizer models, is based on the observations in [22, 33] that the slopes of the probability curves for opening are not very steep. That is, a power of 2 fits the curves better than a power of 4. The inactivation variable $h$ (or $h_\infty$) for the $Ca^{2+}$ current (cf. (2.2)) has been omitted in light of experimental results by Satin and Cook [82] which showed that inactivation is never complete and is not reproduced by Hodgkin-Huxley type kinetics. In addition, the Nernst potential for $Ca^{2+}$, $V_{Ca}$, is allowed to vary with the intracellular calcium concentration, rather than being
kept at a constant value as in the Chay-Keizer models. Finally, the calcium dependence of $I_K(V,Ca)$ comes in through the steady-state value of $n$, $n_{\infty}(V,Ca_i)$, and the relaxation function $\tau_n(V,Ca_i)$. The complete model can be found in Appendix A.

### 2.2.2 The Himmel-Chay Model

In 1987, Himmel and Chay \cite{44} developed a model to test the hypothesis that the current through the low-conductance ATP-inhibited K$^+$ channel \cite{3,21,32} dominates when the glucose concentration is low, while the current through the high-conductance K$^+$ channel(s) dominates the silent phase during bursting.

The model is very similar to the reduced Chay-Keizer model, with the following exceptions. First, Himmel and Chay add a term which represents the current flowing through the low-conductance ATP-inhibited K$^+$ channel to the equation for the membrane potential $V$ (cf. (2.8)). Since it is assumed that the conductance of this channel is negligible when the glucose concentration is high enough so that the membrane potential exhibits the bursting phenomenon, we omit this extra current. Second, the activation variable $n$ is raised to the power of 3 instead of 4 and the value of the maximum conductance $g_K$ is decreased. Himmel and Chay conclude that since there are no appreciable differences in the results, this aspect of the model must not be very important. Finally, the Nernst potential $V_{Ca}$ is allowed to vary with the intracellular calcium concentration, as for the Chay (1986) model. The result of this change is that the amplitude of $Ca_i$ is smaller and in better agreement with experiment.

For a precise definition of the equations and the values of all parameters, the reader is referred to Appendix A.
2.2.3 The Chay (1987) and Chay-Kang Models

Up until now, the mathematical models and, in particular, the functions related to the activation and inactivation variables, were all based on the Hodgkin and Huxley model for the squid giant axon [47]. Since little was known about the properties of the ion channels in β-cells, the functions describing the channel kinetics (\(m_\infty\), \(h_\infty\), etc.) were taken directly from the Hodgkin and Huxley model and shifted along the voltage axis until the new model exhibited the bursting phenomenon.

In 1986, Rorsman and Trube [80] published voltage-clamp data that allowed mathematical modellers to represent the properties of the voltage-gated K\(^+\) and Ca\(^{2+}\) channels more realistically. Rorsman and Trube found that the outward current appears to be carried mainly through a K\(^+\) channel that is insensitive to Ca\(^{2+}\) ions and that the inward current is carried mainly through a voltage-gated Ca\(^{2+}\) channel. This current seems to be inactivated slowly by an inhibitory effect of intracellular Ca\(^{2+}\) itself (the slow inactivation also was observed by Satin and Cook [82]).

The first mathematical models incorporating the data from Rorsman and Trube were those by Chay [14] and Chay and Kang [17]. The two models are practically identical and we consider only the Chay-Kang model. The equation for the membrane potential \(V\) is

\[
4\pi r^2 C_m \frac{dV}{dT} = - \left[ I_{Ca(V,Ca)}(V,Ca_i) + I_K(V) + I_L(V) \right],
\]

where \(I_{Ca(V,Ca)}\) represents the voltage-gated Ca\(^{2+}\) current that is slowly inactivated by Ca\(^{2+}\), \(I_K\) represents the voltage-gated K\(^+\) current, and \(I_L\) represents the usual leakage current, defined by (2.7). Chay and Kang omitted the term representing the Ca\(^{2+}\)-activated K\(^+\) current (cf. (2.6)) based on the observation that Ca\(^{2+}\)-activated K\(^+\) channels are open very rarely under physiological voltages and intracellular calcium concentrations [22, 33]. The calcium feedback mechanism is replaced by the Ca\(^{2+}\)-inactivation of the calcium
channels.

The $I_{Ca(V, Ca)}$ and $I_K$ currents are modelled by

$$I_{Ca(V, Ca)}(V, Ca_i) = \bar{g}_{Ca(V, Ca)} m_\infty(V) h_\infty(V, Ca_i)(V - V_{Ca}),$$

(2.26)

$$I_K(V) = \bar{g}_K n(V - V_K),$$

(2.27)

where $m_\infty$, $h_\infty$, and $n$ have the usual meaning. Note that all activation and inactivation variables, in particular, the activation variable $n$, appear linearly. Furthermore, the voltage-clamp data of Rorsman and Trube are represented by the much simpler definitions of $m_\infty$, $h_\infty$, $n_\infty$, and $\tau_n$ (see Appendix A).

### 2.2.4 The Sherman-Rinzel-Keizer Model

In 1988, Sherman, Rinzel, and Keizer [87] modified the channel kinetics of the voltage-gated K$^+$ and Ca$^{2+}$ channels in the reduced Chay-Keizer model to incorporate the voltage-clamp data of Rorsman and Trube [80]. Therefore, the equation for the membrane potential $V$ almost is identical to that of the reduced Chay-Keizer model, except that the leakage current has been omitted. The model still is based on the premise that the calcium feedback mechanism is provided by the Ca$^{2+}$-activation of a K$^+$ channel, rather than by the Ca$^{2+}$-inactivation of the Ca$^{2+}$ channels as suggested by Rorsman and Trube.

We mention that the model was not developed to incorporate all of the observations of Rorsman and Trube. Instead, it was developed to provide a more realistic basis than the reduced Chay-Keizer model for a subsequent extension which includes stochastic Ca$^{2+}$-activated K$^+$ channels to study the effect of channel sharing and explain the irregular electrical behaviour of single cells and small clusters. We do not consider the stochastic version of the model in this thesis.
The equation for the membrane potential $V$ in the deterministic version of the Sherman-Rinzel-Keizer model is

$$4\pi r^2 C_m \frac{dV}{dT} = -[I_{Ca}(V) + I_K(V) + I_{K, Ca}(V, Ca)]$$

(2.28)

where $I_{Ca}$ and $I_K$ are defined by

$$I_{Ca}(V) = \bar{g}_{Ca} m_{\infty}(V) h(V)(V - V_{Ca}),$$

(2.29)

$$I_K(V) = \bar{g}_K n(V - V_K),$$

(2.30)

and $I_{K, Ca}$ by (2.6). In comparison with the reduced Chay-Keizer model (cf. (2.8)), we note that the leakage current has been omitted. Furthermore, the activation function $m_{\infty}$ and the activation variable $n$ both appear linearly (cf. (2.4) and (2.5)). Finally, as for the Chay-Kang model, the definitions of $m_{\infty}$, $h_{\infty}$, $n_{\infty}$, and $\tau_n$ are much simpler (see Appendix A).

### 2.2.5 The Chay-Cook Model

In 1988, Chay and Cook [16] developed a unified model that can give rise to two types of bursting, namely the so-called square-wave bursting (as is observed in pancreatic $\beta$-cells) and parabolic bursting (as is observed in the Aplysia abdominal ganglion R15 cell [73]). Parabolic bursting differs from square-wave bursting in that the spike frequency increases towards the middle of a burst and then decreases again. The name parabolic refers to the plot of instantaneous spike period versus spike number, which appears as a concave-upward parabola. For the purpose of this thesis, the set of parameters that produces square-wave bursting is used.

The model is very similar to the Chay-Kang model, except that the voltage-gated, Ca$^{2+}$-inhibited Ca$^{2+}$ current has been split into two separate currents. That is, the
equation for the membrane potential $V$ is given by

$$4\pi r^2 C_m \frac{dV}{dT} = - \left[ I_{Ca}(V) + I_{Ca(V,Ca)}(V,Ca_i) + I_K(V) + I_L(V) \right], \quad (2.31)$$

where $I_{Ca}$ represents the voltage-gated component of the Ca$^{2+}$ current, $I_{Ca(V,Ca)}$ represents the Ca$^{2+}$-inhibited component of the Ca$^{2+}$ current, $I_K$ represents the voltage-gated K$^+$ channel, and $I_L$ represents the leakage current as usual. As for the Chay-Kang model, the calcium feedback mechanism is provided by the Ca$^{2+}$-inhibited component of the Ca$^{2+}$ current, $I_{Ca(V,Ca)}$. The $I_{Ca}$ and $I_{Ca(V,Ca)}$ currents are modelled by

$$I_{Ca}(V) = \bar{g}_{Ca} m_\infty(V)(V - V_{Ca}), \quad (2.32)$$

$$I_{Ca(V,Ca)}(V,Ca_i) = \bar{g}_{Ca(V,Ca)} s_\infty(V,Ca_i)(V - V_{Ca}). \quad (2.33)$$

For precise functional definitions, see Appendix A.

### 2.3 Nondimensionalization and Problem Reformulation

We first nondimensionalize the equations and scale the variables so that they are $O(1)$. In order to write all models in a standard form, a consistent nondimensionalization of the model equations is required. The following is the basis for the nondimensionalization of all models:

$$v = \frac{-V}{V_K}, \quad w = (\gamma_K)^\frac{1}{\rho} n, \quad z = \ln \frac{C_{a_i}}{\lambda}, \quad t = \frac{T}{\bar{\tau}_n},$$

$$\gamma_i = \frac{\bar{g}_i \bar{\tau}_n}{4\pi r^2 C_m}, \quad v_i = \frac{-V_i}{V_K}, \quad s_i = \frac{-S_i}{V_K}, \quad b_i = -B_i V_K,$$

$$\lambda = \frac{\tau}{\bar{\tau}_n}, \quad \epsilon = f k_{Ca} \bar{\tau}_n, \quad \beta = \frac{-3V_K C_m}{r F k_{Ca} \bar{\tau}_n \lambda},$$

where $p$ is the integer exponent of the activation variable $n$ for the voltage-gated K$^+$ channel, $\lambda$ is a parameter with the dimension of $\mu M$ (there is at least one such parameter in each model, usually the dissociation constant $K_d$), and $\bar{\tau}_n$ is approximately the
maximum value of $\tau_i(V)$ over the physiological range of $V$. The subscripts $i$ take on the appropriate symbols, such as $K, Ca, L$, etc., depending on the particular model being nondimensionalized. Letting $v = -V/V_K$ ensures that the nondimensional membrane potential has a value near $-1$ in the silent phase, since at that time $V$ is nearly the Nernst potential for potassium, $V_K$. Note that $v$ takes on negative values to maintain the same orientation of the nondimensional (mathematical) and dimensional (physical) membrane potential. The nondimensionalization of $n$ is such that $w$ attains a maximum of approximately 1 during the active phase. The nondimensionalization of time $T$ ensures that the maximum relaxation time associated with the $w$ variable is approximately equal to 1. For the nondimensionalization of $Ca_i$, it is not sufficient to simply take the ratio of $Ca_i$ with any parameter $\mathcal{X}$ having the dimension of $\mu M$. For some models, notably the Chay (1986) model, the only choice for $\mathcal{X}$ is a parameter several orders of magnitude larger than $Ca_i$ (for example, the extracellular calcium concentration, about 1000 times larger than the intracellular concentration). The form of the differential equation for $Ca_i$ leads to the choice $z = \ln \frac{Ca_i}{\mathcal{X}}$.

This general nondimensionalization is complete for all models, except the two models which allow the calcium Nernst potential to vary with the intracellular $Ca^{2+}$ concentration, namely the Chay (1986) and the Himmel-Chay models. Two or three additional nondimensional parameters are required for these cases. The reader is referred to Appendix A for details.

With this general nondimensionalization, all first-generation $\beta$-cell models which are summarized in Table 2.1 can be written in the standard form

\begin{align}
\frac{dv}{dt} = & \ i_{Ca}(v,z) - w^p(v + 1) - g(z)(v + 1) + l(v), \quad (2.34) \\
\frac{dw}{dt} = & \ \tilde{w}_\infty(v,z) - w \frac{\tilde{w}_\infty(v,z)}{\tilde{r}_w(v,z)} , \quad (2.35) \\
\frac{dz}{dt} = & \ \varepsilon [\beta e^{-z} i_{Ca}(v,z) - 1] , \quad (2.36)
\end{align}
where \( i_{Ca}(v, z) \) represents the \( Ca^{2+} \) current(s), \( w^p(v + 1) \) represents the voltage-gated \( K^+ \) current (also activated by \( Ca^{2+} \) in the case of the Chay (1986) model), \( g(z)(v + 1) \) represents the \( Ca^{2+} \)-activated \( K^+ \) current, and \( l(v) \) represents the leakage current. Note from Table 2.1 that \( g(z) \) and \( l(v) \) can be zero, depending on the particular model. The functions \( \bar{w}_{\infty}(v, z) \) and \( \bar{\tau}_{w}(v, z) \) are the nondimensionalized \( n_{\infty}(V, Ca_i) \) and \( \tau_{n}(V, Ca_i) \), respectively. The parameter \( \varepsilon \) is small, approximately \( 10^{-3} \) to \( 10^{-5} \), depending on the specific model. The parameter \( \beta \) is (inversely) related to the blood glucose level. Finally, \( p \) is an integer, ranging from 1 to 4, again, depending on the particular model. Although \( p \) looks innocuous, it plays an important role in the analysis, as we will see shortly.

Next, we simplify the equation for \( v \) by using the transformation \( u = \ln(v + 1) \). Since \( v \) is always \( > -1 \) with the nondimensionalization described above, this transformation is well-defined. The general nondimensional model then can be rewritten in the generic form

\[
\begin{align*}
\dot{u} &= A(u, z) - w^p, \\
\dot{w} &= \frac{w_{\infty}(u, z) - w}{\tau_{w}(u, z)}, \\
\dot{z} &= \varepsilon \left[ \beta e^{-z} h(u, z) - 1 \right],
\end{align*}
\]

where

\[
\begin{align*}
A(u, z) &= e^{-u}[i_{Ca}(v(u), z) + l(v(u))] - g(z), \\
w_{\infty}(u, z) &= \bar{w}_{\infty}(v(u), z), \\
\tau_{w}(u, z) &= \bar{\tau}_{w}(v(u), z), \\
h(u, z) &= i_{Ca}(v(u), z).
\end{align*}
\]

Finally, we combine the first two differential equations, (2.37) and (2.38), into a single second-order equation by eliminating \( w \). This is achieved by differentiating (2.37) with
respect to \( t \) and using equations (2.37)-(2.39). The resulting system is

\[
\begin{align*}
\ddot{u} + E(u, \dot{u}, z) + F(u, z)\dot{u} + G(u, z) &= \varepsilon H(u, z), \\
\dot{z} &= \varepsilon K(u, z),
\end{align*}
\]

(2.44)

(2.45)

where

\[
E(u, \dot{u}, z) = \frac{p \nu_\infty(u, z)}{\tau_w(u, z)} [A(u, z) - \dot{u}]^{p-1},
\]

(2.46)

\[
F(u, z) = \left[ -\frac{p}{\tau_w(u, z)} \frac{\partial A(u, z)}{\partial u} \right] \dot{u},
\]

(2.47)

\[
G(u, z) = -\frac{p}{\tau_w(u, z)} A(u, z),
\]

(2.48)

\[
H(u, z) = \frac{\partial A(u, z)}{\partial z} K(u, z),
\]

(2.49)

\[
K(u, z) = \beta e^{-z} h(u, z) - 1.
\]

(2.50)

We note that for those models for which \( p = 1 \), the term involving \( \dot{u} \) in (2.46) reduces to unity, so that \( E(u, \dot{u}, z) \) no longer depends on \( \dot{u} \). For these models then, the only damping term in (2.44) is the \( F(u, z)\dot{u} \) term, which makes the analysis in Chapter 3 slightly easier than for the remaining models.

More generally, since \( \varepsilon \) is a small parameter, \( z \) changes on a much slower time scale than \( u \) and \( \dot{u} \). Hence, the slow subsystem consists of (2.45). The fast subsystem is given by (2.44), with \( \varepsilon = 0 \) and \( z \) treated as a parameter, i.e.,

\[
\ddot{u} + E(u, \dot{u}; z) + F(u; z)\dot{u} + G(u; z) = 0.
\]

(2.51)

From (2.51), we deduce that the fast subsystem nullcline is given by

\[
\bar{G}(u; z) = 0,
\]

(2.52)

where we define

\[
\bar{G}(u; z) = G(u; z) + E(u, 0; z).
\]

(2.53)
Using the parameter values listed in Appendix A, the bifurcation diagrams of (2.51) have the same qualitative features for all of the models under consideration, as shown in Figure 2.6. The fast subsystem nullcline $\tilde{G} = 0$ has a cubic-like shape in all cases. Steady states on the left branch are always stable nodes; steady states on the middle branch are saddle points; steady states on the right branch are either spiral sources or spiral sinks, except near the local maximum of the $\tilde{G} = 0$ nullcline, where the steady states are nodes. In Figure 2.6a, the stability of the spirals changes only once, at a supercritical Hopf bifurcation lying below the local minimum of the $\tilde{G} = 0$ nullcline. The branch of periodic orbits emanating from the Hopf point terminates at a homoclinic bifurcation on the middle branch. In Figure 2.6b, there are two supercritical Hopf bifurcations. The lower Hopf bifurcation (HB1) lies below the local minimum of the $\tilde{G} = 0$ nullcline, whereas the upper Hopf bifurcation (HB2) lies in the region of bistability, near the local maximum of the $\tilde{G} = 0$ nullcline. The branches of periodic orbits emanating from both Hopf points terminate at homoclinic bifurcations (HC1 and HC2, respectively) on the middle branch. For models of this type, the upper Hopf bifurcation and corresponding homoclinic bifurcation do not play a role in the bursting behaviour, since $x$ never attains a high enough value to be affected by these bifurcations. The appearance of a second Hopf bifurcation on the right branch is the result of a codimension-2 Takens-Bogdanov bifurcation, which we investigate in more detail in Chapter 5.

In Chapter 3, we investigate methods to determine the location of the homoclinic bifurcations for all models. In Chapter 4, we use the approximations from Chapter 3 as a starting point for computing approximate plateau fractions.
Figure 2.6: Illustration of the two types of bifurcation diagrams exhibited by the fast subsystem, (2.51), of the nondimensional $\beta$-cell models. (a) Bifurcation diagram for the reduced Chay-Keizer and Himmel-Chay models. (b) Bifurcation diagram for the Chay (1986), Chay-Kang, Sherman-Rinzel-Keizer, and Chay-Cook models.
Chapter 3

Escape from the Active Phase

In this chapter, we investigate various methods for approximating the value of \( z = z_{esc} \) at which the solution trajectory of the full system of equations, (2.44)-(2.45), escapes from the active phase and returns to the silent phase. The reason for doing so is as follows. In Chapter 4, we derive leading-order approximations of the silent and active phase durations and, subsequently, a leading-order approximation of the plateau fraction. We thus need to know when the silent phase starts and ends and, similarly, when the active phase starts and ends.

Figure 3.1 shows the projection of the numerical solution to the full system of equations onto the bifurcation diagram of the fast subsystem, (2.51). We introduce \((u_m, z_m)\) and \((u_M, z_M)\) to denote the local minimum and maximum of the \( \tilde{G} = 0 \) nullcline, respectively. We observe that the solution trajectory undergoes the transition from the silent to the active phase near \((u_m, z_m)\). This point is easy to calculate. Therefore, we know approximately when the silent phase ends and the active phase begins. However, determining \textit{a priori} when the solution undergoes the transition from the active phase back to the silent phase, i.e., when the active phase ends and the silent phase begins, is more difficult and the subject of this chapter.

We define \( z_{esc} \) to be the value of \( z \) at which the solution trajectory projected onto \((u, z)\) space intersects the middle branch of the \( \tilde{G} = 0 \) nullcline (cf. Figure 3.1). Evaluations of \( z_{esc} \) indicate that it depends on the value of the glucose-dependent parameter \( \beta \). Since we are interested in the plateau fraction as a function of \( \beta \) in Chapter 4, ideally, we also
wish to determine the dependence of $z_{\text{esc}}$ on $\beta$.

To obtain an approximation of $z_{\text{esc}}$, we consider the fast subsystem. From Figure 3.1, we observe that the solution trajectory of the full system of equations undergoes the transition from the active phase back to the silent phase near the homoclinic bifurcation of the fast subsystem. Therefore, letting $z_{HC}$ be the value of $z$ at which the homoclinic bifurcation of interest occurs, namely HC in Figure 2.6a or HC1 in Figure 2.6b, we may use $z_{\text{esc}} \approx z_{HC}$. Since the glucose-dependent parameter $\beta$ only appears in the slow subsystem, none of the methods described below can be used to determine the dependence of $z_{\text{esc}}$ on $\beta$. However, the results in Chapter 4 are not affected significantly by using the constant approximation of $z_{\text{esc}}$ obtained in this chapter.
In Section 3.1, we describe how the bifurcation analysis of (2.51) with the AUTO software package can be used to approximate $z_{HC}$. In Section 3.2, we use bisection approaches which are based on the bifurcation of the solution behaviour of (2.51) in the $(u, \dot{u})$ phase plane as $z$ is varied. In addition to these numerical methods, we discuss two analytical methods. In Section 3.3, we compute the leading-order approximation of $z_{HC}$ using the Melnikov [64] integral. However, this method yields sufficiently accurate results for only two of the six models under consideration in this thesis. To obtain higher-order corrections to the Melnikov results, we use a version of the Fredholm alternative in Section 3.4. Finally, a comparison of the various approaches and a discussion of their advantages and disadvantages is provided in Section 3.5.

3.1 Approximation of $z_{esc}$ with the AUTO Software Package

In this section, we use the AUTO [28] software package to approximate $z_{HC}$ and, subsequently, $z_{esc}$. When AUTO computes branches of periodic orbits emanating from a Hopf point (cf. Figure 2.6), it also determines the period of the respective periodic orbits. The period increases as the bifurcation parameter $z$ increases, until it is infinite at the homoclinic bifurcation. Although numerical difficulties at values of $z$ near the homoclinic bifurcation prevent the exact determination of $z_{HC}$, we can obtain a very accurate approximation of $z_{HC}$, $z_{AUTO}$, by continuing the computation of a branch of periodic orbits until the period is sufficiently large.

For the first-generation models under consideration, approximations were sought by requiring that the period at $z = z_{AUTO}$ was at least 1000. The results of this approach are summarized in Table 3.1.
Chapter 3. *Escape from the Active Phase*

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</tbody>
</table>

Table 3.1: Approximate values of $z_{HC}$ and, subsequently, $z_{esc}$ obtained with AUTO ($z_{AUTO}$), bisection ($z_{BIS}$), Melnikov's method ($z_{MEL}$), and the Fredholm alternative method ($z_0$ and $z_0 + \delta z_1$), for all first-generation models under consideration in this thesis. To facilitate comparison of the methods, the values have been normalized with $z_m$ corresponding to 0 and $\tilde{z}_{esc}$ corresponding to 1. As in Figure 3.1, $z_m$ is the value of $z$ at the local minimum of the $\tilde{G} = 0$ nullcline, and $\tilde{z}_{esc}$ is the approximate median of exact values of $z_{esc}$ obtained for values of $\beta$ near $\beta_{HC}$ (cf. Figure 4.1 in Chapter 4). The models are 1: Reduced Chay-Keizer; 2: Chay (1986); 3: Himmel-Chay; 4: Chay-Kang; 5: Sherman-Rinzel-Keizer; 6: Chay-Cook.

3.2 Approximation of $z_{esc}$ with Bisection Techniques

In this section, we focus on the dependence of the solution trajectories of (2.51) on the value of the parameter $z$ in the $(u, \dot{u})$ phase plane. We discuss two bisection techniques based on the bifurcation of the solution behaviour at $z = z_{HC}$. Even though both methods are less efficient and more cumbersome than the use of AUTO, we include a discussion of them, as this provides valuable insights for the techniques described later.

We note that the $(u, \dot{u})$ phase plane is perpendicular to the $(u, z)$ plane shown in Figure 3.1. For each value of $z$ between $z_m$ and $z_M$, there are three fixed points, corresponding to the three branches of the $\tilde{G} = 0$ nullcline. The left fixed point is a stable node, the middle fixed point is a saddle, and the right point is, in general, a spiral. We are interested in the behaviour of solution trajectories of (2.51) in relation to these fixed points for different values of $z$. 
Figure 3.2 shows trajectories obtained numerically for a value of \( z = z_1 < z_{HC} \) and a value of \( z = z_2 > z_{HC} \). It is evident that trajectories starting near the right fixed point approach a stable periodic orbit when \( z < z_{HC} \), whereas trajectories with the same initial conditions eventually approach the left fixed point when \( z > z_{HC} \).

We now use a standard bisection procedure, starting with \( z_1 \) and \( z_2 \), to zero in on the exact value of \( z_{HC} \). The resulting approximations of \( z_{HC} \) and, subsequently, \( z_{esc} \) are referred to as \( z_{BIS} \), and are summarized in Table 3.1. As expected, \( z_{BIS} \) is in close agreement with \( z_{AUTO} \).

Alternatively, we can examine the relative position of the stable and unstable orbits of the saddle point, or the middle fixed point, in the \((u, \dot{u})\) phase plane of (2.51). Stable and unstable orbits can be computed with the software package DSTOOL [39]. The results corresponding to Figures 3.2a and b are shown in Figure 3.3. It is clear that for the case \( z = z_1 < z_{HC} \), the right stable orbit lies on the outside of the right unstable orbit, whereas for the case \( z = z_2 > z_{HC} \), the situation is reversed. When \( z = z_{HC} \), the two orbits join, creating the homoclinic orbit which connects the saddle point to itself. Starting with \( z_1 \) and \( z_2 \), the same standard bisection approach as above then can be used in conjunction with DSTOOL to approximate \( z_{HC} \) and, subsequently, \( z_{esc} \). The applicability of this method was verified for the Sherman-Rinzel-Keizer model and the resulting approximation was within \( 10^{-4} \) of \( z_{BIS} \). Since the resulting approximations for the remaining models are expected to be essentially identical to \( z_{BIS} \) as well, this method has not been implemented for the remaining models.
Figure 3.2: Solution trajectories of the fast subsystem, (2.51), for (a) $z = z_1 < z_{HC}$ and (b) $z = z_2 > z_{HC}$. The bullets indicate the location of the three fixed points of (2.51), corresponding to the three branches of the $\mathcal{G} = 0$ nullcline. For both cases, the left fixed point is a stable node, the middle fixed point is a saddle, and the right fixed point is a spiral source.
Figure 3.3: Phase portraits of the fast subsystem, (2.51), calculated with DSTOOL, showing the stable (solid curves) and unstable orbits (dashed curves) of the saddle point. (a) The right stable orbit lies outside the right unstable orbit for \( z = z_1 < z_{HC} \). (b) The right stable orbit lies inside the right unstable orbit for \( z = z_2 > z_{HC} \).
3.3 Approximation of $z_{esc}$ with Melnikov’s Method

In this section, we use an analytical method due to Melnikov [64] to determine the leading-order approximation of $z_{HC}$. The method is based on the perturbation analysis of a near-integrable system. The unperturbed system is assumed to be integrable and to possess a separatrix solution, smoothly joining the stable and unstable orbits for a hyperbolic saddle point. When the system is perturbed, the separatrix breaks and, in general, the stable and unstable orbits no longer smoothly join. For autonomous perturbations, the stable orbit either lies completely inside the unstable orbit or vice versa. In [64], Melnikov derived an integral to calculate the distance between the stable and the unstable orbits. The sign of this integral determines the relative orientation of the orbits. In our case, the relative orientation depends on the bifurcation parameter $z$ (cf. Figure 3.3). The relative orientation changes, to leading order, at $z = z_{MEL}$, corresponding to the homoclinic orbit of the fast subsystem at $z = z_{HC}$.

In order to apply Melnikov’s method, it is necessary to rewrite the fast subsystem equation (2.51) as a perturbed integrable system. From (2.46), we see that the factor involving $\dot{u}$ in the $E(u, \dot{u}; z)$ term is unity for models with $p = 1$. That is, only the $F(u; z)\dot{u}$ term is responsible for any damping in the system. For the Sherman-Rinzel-Keizer model, Pernarowski [67] and Pernarowski et al. [69, 70] showed that this damping term is numerically small relative to the remaining terms, so that (2.51) is in perturbed Liénard form. Writing (2.51) in precisely this form allowed Pernarowski [67] and Pernarowski et al. [70] to apply Melnikov’s method and obtain a good approximation of the location of the homoclinic bifurcation.

In general, it is not necessary that (2.51) is written in perturbed Liénard form. It is sufficient to write (2.51) as a perturbed Hamiltonian system, which we do for all models in Section 3.3.1. Having obtained a near-integrable system for all models, we then apply
Melnikov's method in Section 3.3.2.

3.3.1 Reformulation of the Fast Subsystem as a Near-Integrable System

In this section, we show that the fast subsystem, (2.51), of all models can be rewritten as a perturbed Hamiltonian system. We initially follow the argument used by Pernarowski [67] and Pernarowski et al. [70] for the Sherman-Rinzel-Keizer model to show that the damping term is numerically small relative to the remaining terms. Attempting to extend the same kind of reasoning to the models with \( p \neq 1 \) reveals a minor flaw in the argument presented in [67]. The same flaw is not presented in [70]. However, the discussion there may be misleading. In this section then, we also present a revised argument.

We begin with the models for which \( p = 1 \), namely the Chay-Kang, Sherman-Rinzel-Keizer, and Chay-Cook models. As mentioned earlier, the \( E(u, \dot{u}; z) \) term does not depend on \( \dot{u} \) for these models, so the \( F(u; z) \dot{u} \) term is the only dissipative term. For this special case, we write (2.51) as

\[
\ddot{u} + F(u; z)\dot{u} + \bar{G}(u; z) = 0, \tag{3.1}
\]

where

\[
\bar{G}(u; z) = \frac{1}{\tau_w(u; z)} [\omega(u; z) - A(u; z)] \tag{3.2}
\]

from (2.46) and (2.48) and \( F(u; z) \) is defined by (2.47).

Figure 3.4 shows the graphs of \( \int_0^t \bar{G}(u(s), z(s))ds \) versus \( \dot{u} \) from the solution of the full system of equations, (2.44)-(2.45), for several oscillations in the active phase. We observe that the curves deviate little from a straight line with slope \(-1\). In fact, this behaviour persists over the entire active phase, with the small drift of the loops being due to the slowly varying oscillations as \( z \) changes. We note that for the computations shown in Figure 3.4, \( t = 0 \) occurs in the middle of a silent phase and, thus, reflect the accumulation due to the \( \bar{G}(u, z) \) term during the remainder of the silent phase as well as
Figure 3.4: Comparison of $\int_0^t \tilde{G}(u,z)dt$ versus $\dot{u}$ over several oscillations in the active phase, for (a) Chay-Kang model; (b) Sherman-Rinzel-Keizer model; (c) Chay-Cook model. In each case, the curve deviates little from the straight line with slope $-1$ throughout the entire active phase.
during the first portion of the active phase. That is, we may vertically shift all curves to the origin, and the active phase then can be approximated by

\[ \dot{u} + \int_0^t \tilde{G}(u(s); z(s)) ds \approx 0, \quad (3.3) \]

implying that the cumulative effect of the damping term is small in the active phase.

In [67], Pernarowski differentiates (3.3) with respect to \( t \), giving \( \ddot{u} + \tilde{G}(u; z) \approx 0 \), and concludes that the local effect of the \( F(u; z)\dot{u} \) term in (3.1) also must be small. Below we show that this argument is false. The subtleties of the argument are circumvented in a subsequent paper by Pernarowski et al. [70], where they mention that the observation of the active phase approximation in (3.3) motivated them to compare the (local) magnitude of the damping term with the remaining terms for the Sherman-Rinzel-Keizer model. This comparison showed that the damping term is indeed small. Motivated similarly, we find that \( F(u; z)\dot{u} \) is numerically small relative to the remaining terms in (3.1) for all models with \( p = 1 \), so that (3.1) is in perturbed Liénard form for these models as well.

We now examine (2.51) for the models for which \( p \neq 1 \), namely the reduced Chay-Keizer, Chay (1986), and Himmel-Chay models. For these models, both the \( E(u, \dot{u}; z) \) and \( F(u; z)\dot{u} \) terms contribute to the dissipation in the system. Based on the definition of \( \tilde{G}(u; z) \) in (2.53), we hypothesize that the \( E(u, \dot{u}; z) \) term must be split into separate components. Writing the Taylor series expansion of \( E(u, \dot{u}; z) \) about \( \dot{u} = 0 \), we obtain

\[ E(u, \dot{u}; z) = E(u, 0; z) + \frac{\partial E}{\partial \dot{u}}(u, 0; z)\dot{u} + \ldots \quad (3.4) \]

Numerical experiments reveal that the first two terms in (3.4) are the most important ones. Replacing \( E(u, \dot{u}; z) \) in (2.44)-(2.45) by the first term of the Taylor series does not give a bursting solution. Bursting is recovered when the second term of (3.4) is included as well, and the solution already is in good agreement with the solution of the full system of equations, as shown in Figure 3.5. Adding subsequent terms of (3.4) merely improves
Figure 3.5: Comparison of the solutions $u(t)$ of the full system of equations (solid curve), (2.44)-(2.45), and the same system of equations where $E(u, \dot{u}, z)$ has been replaced by the first two terms of its Taylor series about $\dot{u} = 0$ (dashed curve).

the agreement. We group $E(u, 0; z)$ with $G(u; z)$ and $\frac{\partial E}{\partial u}(u, 0; z)\dot{u}$ with $F(u; z)\dot{u}$ in (2.51).

The question remains where the other terms in (3.4) belong.

We investigate two possibilities. The first is to include the remaining terms in (3.4) with $G(u; z)$, i.e., to write (2.51) as

$$\ddot{u} + \left[F(u; z) + \frac{\partial E}{\partial u}(u, 0; z)\right] \dot{u} + \dot{G}(u, \dot{u}; z) = 0,$$

(3.5)

where

$$\dot{G}(u, \dot{u}; z) = G(u; z) + E(u, \dot{u}; z) - \frac{\partial E}{\partial u}(u, 0; z)\dot{u}$$

(3.6)

includes all terms of the Taylor series except the main damping term $\frac{\partial E}{\partial u}(u, 0; z)\dot{u}$. Figure 3.6 shows the plots of $\int_0^t \dot{G}(u(s), \dot{u}(s), z(s)) ds$ versus $\dot{u}$. As for the models with $p = 1$, the relationship is approximately linear with slope $-1$, so that we can infer that the cumulative effect of the middle term in (3.5) is small in the active phase. However,
Figure 3.6: Comparison of $\int_0^t \dot{G}(u, z) dt$ versus $\dot{u}$ over several oscillations in the active phase, for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model. As in Figure 3.4, the curve lies along the straight line with slope $-1$ throughout the entire active phase.
the examination of the local magnitude of this term relative to \( \dot{u} \) and \( \ddot{G} \) reveals that, in fact, it is \( O(1) \). That is, (3.5) is not in perturbed form and, therefore, of no use for the application of Melnikov's method. The reason why this \( O(1) \) term essentially has no cumulative effect in the active phase is that it is roughly symmetric about zero during each oscillation. That is, any positive cumulative effect during the first half of the oscillation is cancelled by the negative cumulative effect during the second half of the oscillation.

The second possibility is to include the remaining terms in (3.4) with \( F(u; z)\dot{u} \), i.e., to write (2.51) as

\[
\ddot{u} + [F(u; z)\dot{u} + E(u, \dot{u}; z) - E(u, 0; z)] + \ddot{G}(u; z) = 0, \tag{3.7}
\]

where \( \ddot{G} \) is defined by (2.53). Figure 3.7 shows the plots of \( \int_0^t \ddot{G}(u(s), z(s))ds \) versus \( \dot{u} \).

We observe that during each oscillation, the relationship again is approximately linear with slope \(-1\), but that there is a small drift. The small drift remains when \( z \) is held constant. That is, there is a cumulative effect due to the damping term in (3.7). However, an examination of the local magnitude of this term reveals that it is small relative to \( \dot{u} \) and \( \ddot{G}(u; z) \) in the active phase and that (3.7), in fact, is written in perturbed form. The cumulative effect of the damping term is due to the fact that, even though it is small, it is not symmetric about zero and there is no cancellation as in the previous case.

We note that (3.7) includes all cases, \( p = 1, 2, 3, 4 \), and as such, we use this form of the fast subsystem equation for the derivation of the Melnikov integral. In light of the smallness of the damping term, we infer the existence of an artificial small parameter, \( \delta \), so that the damping term is \( O(\delta) \) and rewrite (3.7) as

\[
\ddot{u} + \delta \ddot{F}(u, \dot{u}; z) + \ddot{G}(u; z) = 0, \tag{3.8}
\]

where

\[
\ddot{F}(u, \dot{u}; z) = \frac{1}{\delta} [F(u; z)\dot{u} + E(u, \dot{u}; z) - E(u, 0; z)] \tag{3.9}
\]
Figure 3.7: Comparison of $\int_0^t \tilde{G}(u, z) dt$ versus $\dot{u}$ over several oscillations in the active phase, for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model. In each case, the relationship is approximately linear with slope $-1$ in each cycle, but there is a small overall drift upwards during the active phase.
<table>
<thead>
<tr>
<th>Model</th>
<th>$\varepsilon$</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Chay-Keizer</td>
<td>0.00126</td>
<td>$\approx$ 0.060</td>
</tr>
<tr>
<td>Chay (1986)</td>
<td>0.000024</td>
<td>$\approx$ 0.025</td>
</tr>
<tr>
<td>Himmel-Chay</td>
<td>0.00108</td>
<td>$\approx$ 0.030</td>
</tr>
<tr>
<td>Chay-Kang</td>
<td>0.00054</td>
<td>$\approx$ 0.012</td>
</tr>
<tr>
<td>Sherman-Rinzel-Keizer</td>
<td>0.00066</td>
<td>$\approx$ 0.080</td>
</tr>
<tr>
<td>Chay-Cook</td>
<td>0.00072</td>
<td>$\approx$ 0.015</td>
</tr>
</tbody>
</table>

Table 3.2: Comparison of $\varepsilon$ and $\delta$, showing that $\delta >> \varepsilon > 0$.

and $\tilde{G}$ is defined by (2.53). With this formulation, the fast subsystem nullcline still is given by $\dot{C} = 0$. Furthermore, (3.8) can be referred to as a strongly nonlinear oscillator, i.e., as $\delta \to 0$, (3.8) remains nonlinear. In fact, when $\delta = 0$, (3.8) describes a Hamiltonian system (cf. Section 3.3.2). However, we keep $\delta$ fixed in this thesis.

We will see below that we do not need to know the value of the artificial small parameter $\delta$ explicitly. However, to obtain an estimate of the size of $\delta$, we define [70]

$$\delta = \sup_{z_m < z < z_{HC}} \left\{ \max \left| \frac{\tilde{F}(u; z)}{\dot{u}} \right| \right\}, \quad (3.10)$$

where the maximum is evaluated over at least one oscillation of the periodic orbit. Numerical evaluations of the value of $\delta$ are summarized in Table 3.2 and compared to the size of $\varepsilon$. We observe that $\delta >> \varepsilon > 0$ for all models, verifying that we may indeed keep the damping term $\delta \tilde{F}(u; z)\dot{u}$, while ignoring the $\varepsilon H(u, z)$ term in (2.44).

### 3.3.2 Derivation and Evaluation of the Melnikov Integral

We first investigate the nature of the solution of the unperturbed version of (3.8), namely the Hamiltonian equation

$$\ddot{u} + \tilde{G}(u; z) = 0. \tag{3.11}$$
Like the corresponding fast subsystem, the fixed points of (3.11) are given by $\tilde{G}(u; z) = 0$. For values of $z$ between $z_m$ and $z_M$, (3.11) has three fixed points and its corresponding phase portrait is shown in Figure 3.8. We introduce the following notation. The hyperbolic fixed point, or the saddle point, occurs at $(u, \dot{u}) = (a_s(z), 0)$, where $a_s(z)$ is defined by the middle root of

$$
\tilde{G}(a_s; z) = 0, \tag{3.12}
$$

and the separatrix, $(u_0(t; z), \dot{u}_0(t; z))$, crosses the $u$-axis at $u = b_s(z)$ to the right of $a_s$ and at $u = c_s(z)$ to the left of $a_s$.

When the perturbation due to the $\delta \tilde{F}(u, \dot{u}; z)$ term is added back into the system, the separatrix itself is perturbed and breaks into a stable and unstable orbit. For values of $z$ below $z_{HC}$, the unstable and unstable orbits separate so that the stable orbit lies outside the unstable orbit, whereas for values of $z$ above $z_{HC}$, the relative orientation of these
orbits is reversed (cf. Figure 3.3). The separatrix is perturbed but persists at $z = z_{HC}$.

We now adapt the derivation of the Melnikov integral for a two-dimensional autonomous system of equations perturbed by a time-periodic function (cf. Lichtenberg and Lieberman [58]). When the perturbation is non-autonomous, the Melnikov integral is used to predict the onset of chaotic motion, at some time $t_0$. In (3.8), the perturbation is autonomous, and as such, the stable and unstable orbits either do not intersect or are entirely coincident [37]. Rather than obtaining a Melnikov distance function which depends on a time $t_0$ then, we obtain a number. However, the number depends on the parameter $z$.

Letting $(x, y) = (u, \dot{u})$, (3.8) can be rewritten as

\begin{align*}
\dot{x} &= y, \quad (3.13) \\
\dot{y} &= -\tilde{G}(x; z) - \delta \tilde{F}(x, y; z). \quad (3.14)
\end{align*}

Perturbing the stable and unstable orbits, $(x^s(t; z), y^s(t; z))$ and $(x^u(t; z), y^u(t; z))$, respectively, off the separatrix, $(x_0(t; z), y_0(t; z))$, we write

\begin{align*}
x^{s,u}(t; z) &= x_0(t; z) + \delta x^{s,u}_1(t; z) + O(\delta^2), \quad (3.15) \\
y^{s,u}(t; z) &= y_0(t; z) + \delta y^{s,u}_1(t; z) + O(\delta^2). \quad (3.16)
\end{align*}

Substituting (3.15)-(3.16) into (3.13)-(3.14), expanding $\tilde{F}(x, y; z)$ and $\tilde{G}(x; z)$ about $(x, y) = (x_0(t; z), y_0(t; z))$, and collecting like powers of $\delta$ yields the integrable leading-order equations

\begin{align*}
\dot{x}_0 &= y_0, \quad (3.17) \\
\dot{y}_0 &= -\tilde{G}(x_0; z), \quad (3.18)
\end{align*}
Figure 3.9: Geometrical representation of the Melnikov distance. The dashed curve is the separatrix of the unperturbed fast subsystem, as in Figure 3.8. There is a saddle point at $(x, y) = (a_s, 0)$. The solid curves are the stable and unstable orbits of the fast subsystem. The vectors $\vec{d}$ and $\vec{N}$ represent the difference between the stable and unstable orbits and the normal to the separatrix, respectively. (Adapted from [70].)

defining the separatrix shown in Figure 3.8, where $(x_0, y_0)$ replaces $(u_0, \dot{u}_0)$. The first-order equations are given by

$$
\frac{dx_1^{s,u}}{dt} = y_1, \quad (3.19)
$$

$$
\frac{dy_1^{s,u}}{dt} = -\tilde{G}_x(x_0; z)x_1^{s,u} - \tilde{F}(x_0, y_0; z). \quad (3.20)
$$

The stable and unstable solutions of (3.19)-(3.20) differ by

$$
\vec{d}(t; z) = \begin{pmatrix} x^s - x^u \\ y^s - y^u \end{pmatrix} = \delta \begin{pmatrix} x_1^s - x_1^u \\ y_1^s - y_1^u \end{pmatrix} + O(\delta^2), \quad (3.21)
$$

and the *Melnikov distance* $D(t; z)$ then is defined to be the projection of $\vec{d}$ along a normal $\vec{N}$ to the separatrix $(x_0, y_0)$. The geometrical representation of the Melnikov distance is shown in Figure 3.9. From (3.17)-(3.18), we take
\[ \vec{N} = \begin{pmatrix} \vec{G}(x_0; z) \\ y_0 \end{pmatrix}, \quad (3.22) \]

so that

\[ D(t; z) = \vec{N} \cdot \vec{d} \]

\[ = \delta \left[ y_0 (y_1^n - y_1^1) + \vec{G}(x_0; z) (x_1^s - x_1^u) \right] + O(\delta^2) \]

\[ = \delta \left[ \left( y_0 y_1^s + \vec{G}(x_0; z)x_1^s \right) - \left( y_0 y_1^u + \vec{G}(x_0; z)x_1^u \right) \right] + O(\delta^2). \quad (3.23) \]

To find an explicit expression for \( D \), we write

\[ D = \delta D_1 + O(\delta^2) = \delta [D_1^s - D_1^u] + O(\delta^2), \quad (3.24) \]

where

\[ D_1^{s,u} = y_0 y_1^{s,u} + \vec{G}(x_0; z)x_1^{s,u}. \quad (3.25) \]

Differentiating (3.25) with respect to time, we obtain

\[ \dot{D}_1^{s,u} = y_0 \dot{y}_1^{s,u} + \vec{G}(x_0; z)\dot{x}_1^{s,u} + y_0 y_1^{s,u} + \vec{G}_z(x_0; z)\dot{x}_0 x_1^{s,u}. \quad (3.26) \]

Using (3.17)-(3.18) and (3.19)-(3.20) in (3.26) gives

\[ \dot{D}_1^{s,u} = -\tilde{F}(x_0, y_0; z)y_0. \quad (3.27) \]

Integrating (3.27) then yields

\[ D_1^s(\infty; z) - D_1^s(t_0; z) = -\int_{t_0}^{\infty} \tilde{F}(x_0, y_0; z)y_0 dt, \quad (3.28) \]

\[ D_1^u(t_0; z) - D_1^u(-\infty; z) = -\int_{-\infty}^{t_0} \tilde{F}(x_0, y_0; z)y_0 dt, \quad (3.29) \]

for the stable and unstable orbits, respectively. We point out that since we are interested in the value of \( \varepsilon_{HC} \) at which there is a homoclinic orbit surrounding the right fixed point, we restrict \( x_0(t) \geq a_s \) in (3.28)-(3.29).
In light of (3.12) and (3.17)-(3.18), we have

\[ \lim_{t \to \pm \infty} x_0(t; z) = a_s(z), \quad (3.30) \]
\[ \lim_{t \to \pm \infty} y_0(t; z) = 0, \quad (3.31) \]

Using these limits in (3.25), we thus have

\[ D(\infty; z) = D(-\infty; z) = 0, \quad (3.32) \]

so that from (3.24) and (3.28)-(3.29), we obtain the Melnikov integral up to \( O(\delta^2) \),

\[ D(z) = \delta \int_{-\infty}^{\infty} \tilde{F}(x_0, y_0; z) y_0 \, dt, \]
\[ = \delta \int_{-\infty}^{\infty} \tilde{F}(u, \dot{u}; z) \dot{u} \, dt, \quad (3.33) \]

where we have returned to \( u \) and \( \dot{u} \) variables and omitted the subscripts. However, we remember that the integral is to be evaluated around the right loop of the separatrix solution of (3.11) (cf. Figure 3.8).

We now show that it is not necessary to determine the dependence of \( u \) and \( \dot{u} \) on \( t \) explicitly by converting the improper integral in \( t \) to a line integral in \( u \). Integrating (3.11) from \( u = a_s \) to \( u \) and using the fact that \( \dot{u} = 0 \) when \( u = a_s \), we have

\[ \frac{1}{2} \dot{u}^2 + \int_{a_s}^{u} \tilde{G}(\tilde{u}; z) d\tilde{u} = 0. \quad (3.34) \]

Hence,

\[ \dot{u} = \pm \sqrt{-2V(u; a_s)}, \quad (3.35) \]

where

\[ V(u; a_s) = \int_{a_s}^{u} \tilde{G}(\tilde{u}; z) d\tilde{u}. \quad (3.36) \]

We note that (3.35) implies that the separatrix is symmetrical about \( \dot{u} = 0 \) (cf. Figure 3.8). Since \( \dot{u} = 0 \) when \( u = b_s, b_s \) thus is given by

\[ V(b_s; a_s) = 0. \quad (3.37) \]
Using (3.30) and (3.35) in (3.33), we have

\[
D(z) = \delta \int_{a_s}^{b_s} \tilde{F}(u, \dot{u}; z) du
= \delta \left[ \int_{a_s}^{b_s} \tilde{F}(u, +\sqrt{-2V(u; a_s); z}) du + \int_{b_s}^{a_s} \tilde{F}(u, -\sqrt{-2V(u; a_s); z}) du \right].
\] (3.38)

Finally, using the symmetry of the separatrix and the definition of (3.9) in (3.38), we obtain the \(\delta\)-independent Melnikov distance,

\[
D(z) = 2 \int_{a_s}^{b_s} F(u; z) \sqrt{-2V(u; a_s)} du
+ \int_{a_s}^{b_s} \left[ E(u, +\sqrt{-2V(u; a_s); z}) - E(u, -\sqrt{-2V(u; a_s); z}) \right] du.
\] (3.39)

Since \(E(u, 0; z)\) is even in \(\dot{u}\) it does not contribute to the Melnikov integral. Furthermore, \(D(z)\) reduces to \(2 \int_{a_s}^{b_s} F(u; z) \sqrt{-2V(u; a_s)} du\) for models with \(p = 1\), since \(E(u, \dot{u}; z)\) does not depend on \(\dot{u}\) for these models.

Even though (3.39) is an analytical expression for the Melnikov distance, the non-linearities in \(\tilde{F}\) and \(V\) force us to evaluate \(D(z)\) numerically. The algorithm to evaluate \(D(z)\) for each value of the parameter \(z\) is as follows:

1. Solve (3.12) to determine \(a_s(z)\). We use a standard root solver (such as the RTSAFE routine from [74]) consisting of a combination of Newton's method and bisection to guarantee a solution.

2. Solve (3.37) to determine \(b_s(z)\), using the same root solver as above.

3. Compute \(D(z)\) from (3.39), using a standard numerical quadrature routine from QUADPACK [71]. Note that each evaluation of the integrand of \(D(z)\) requires the computation of \(V(u; a_s(z))\), which is another quadrature.

Figure 3.10 shows two typical graphs of the Melnikov distance as a function of \(z\), computed according to the algorithm described above. In Figure 3.10a, the Melnikov
distance changes sign once, at $z_{MEL}$ given by $D(z_{MEL}) = 0$, corresponding to models for which the fast subsystem undergoes exactly one homoclinic bifurcation (cf. Figure 2.6a).

In Figure 3.10b, the Melnikov distance changes sign twice, corresponding to a bifurcation diagram where there are two homoclinic bifurcations (cf. Figure 2.6b). In this case, it is the first change of sign that is of interest to us. We note that for $z < z_{MEL}$, the Melnikov distance is positive, corresponding to the case where the stable orbit lies on the outside relative to the unstable orbit, so that stable periodic orbits surrounding the right fixed point are possible. The relative orientation of the orbits reverses near $z = z_{MEL}$. That is, $z_{MEL}$ is the leading-order approximation of $z_{HC}$ and, subsequently, $z_{esc}$.

The values of $z_{MEL}$ are determined by a bisection procedure on $D(z)$ for each of the biophysical models, using an accuracy of at least $10^{-6}$ in each step of the algorithm described above and for the bisection. The results are presented in Table 3.1 and are in good agreement with typical $z_{esc}$ values for the Chay-Kang and Sherman-Rinzel-Keizer models. However, the results for the remaining models, especially the Chay (1986) model, can benefit from a higher-order correction, which is the subject of the section below.
3.4 Approximation of $z_{esc}$ with the Fredholm Alternative

In this section, we determine the first-order correction to the leading-order value of $z_{HC}$ obtained with Melnikov's method above. We note that Melnikov's method can be used to derive the integrals required in each term of the $\delta$-power series expansion of the distance between the stable and unstable orbits and, thus, it also can be used to derive the first-order correction to $z_{MEL}$. Instead, we demonstrate the use of a method based on a version of the Fredholm alternative due to Chow, Hale, and Mallet-Paret [20]. In the case of perturbed Hamiltonian systems, the Fredholm alternative method is well-known to be equivalent to Melnikov's method [51], in that it yields the same integrals. A clear introduction to the Fredholm alternative is given in [52].

In Section 3.4.1, we derive leading-order and first-order problems. From the leading-order problem, we recover the Melnikov integral of the previous section, as expected. The first-order problem determines the required correction. We solve the equations numerically in Section 3.4.2. The results indicate that the first-order correction is equal to zero for models with $p = 1$. The reason for this is exposed in Section 3.4.3.

3.4.1 Derivation of the Equations

We rewrite the fast subsystem, (3.8), as

$$\ddot{u} + \tilde{G}(u; z) = -\delta \tilde{F}'(u; \dot{u}; z)$$  \hspace{1cm} (3.40)

and seek an asymptotic solution of (3.40). Letting

$$u(t) = u_0(t) + \delta u_1(t) + \delta^2 u_2(t) + O(\delta^3),$$
$$z = z_0 + \delta z_1 + \delta^2 z_2 + O(\delta^3),$$

substituting (3.41)-(3.42) into (3.40), expanding $\tilde{F}$ and $\tilde{G}$ about $(u, \dot{u}; z) = (u_0, \dot{u}_0; z_0)$, and collecting terms of equal magnitude gives an infinite sequence of equations.
The leading-order equation is

\[ \ddot{u}_0 + \dot{G}(u_0; z_0) = 0. \] (3.43)

We thus have recovered the integrable Hamiltonian system defined by (3.11). Similarly, the first-order equation is

\[ \ddot{u}_1 + \dot{G}_u(u_0; z_0)u_1 = -\dot{F}(u_0, \dot{u}_0; z_0) - \dot{G}_z(u_0; z_0)z_1. \] (3.44)

Although we determine the location of the homoclinic orbit up to first order only, we also require the second-order equation, which is

\[ \ddot{u}_2 + \dot{G}_u(u_0; z_0)u_2 = -\dot{G}_z(u_0; z_0)z_2 \]
\[ - \frac{1}{2} \left[ \dot{G}_{u u}(u_0; z_0)u_1^2 + 2\dot{G}_{u z}(u_0; z_0)u_1 z_1 + \dot{G}_{z z}(u_0; z_0)z_1^2 \right] \]
\[ - \left[ \dot{F}_u(u_0, \dot{u}_0; z_0)u_1 + \dot{F}_u(u_0, \dot{u}_0; z_0)\dot{u}_1 + \dot{F}_z(u_0, \dot{u}_0; z_0)z_1 \right]. \] (3.45)

From (3.44) and (3.45), we observe that \( u_n \), for \( n \geq 1 \), satisfies the general equation of the form

\[ \ddot{u}_n + \dot{G}_u(u_0, z_0)u_n = T_n(u_0, u_1, ..., u_{n-1}, \dot{u}_0, \dot{u}_1, ..., \dot{u}_n; z_0, z_1, ..., z_{n-1}), \] (3.46)

where \( T_n \) is determined by \( \dot{F} \) and \( \dot{G} \) and their derivatives. We define the differential operator \( L \) by

\[ Lu = \ddot{u} + \dot{G}_u(u_0; z_0)u, \quad -\infty < t < \infty, \] (3.47)

so that (3.46) can be rewritten as

\[ Lu_n = T_n. \] (3.48)

According to the version of the Fredholm alternative for solutions bounded on \( R \) due to Chow et al. [20], solutions to (3.48) exist if and only if

\[ (T_n, v) = 0 \] (3.49)
for all \( v \) for which \( L^*v = 0 \), where \( L^* \) is the adjoint of \( L \) and \( \langle u, v \rangle \) is the inner product defined by

\[
\langle u, v \rangle = \int_{-\infty}^{\infty} u(t)v(t)dt.
\]

(3.50)

In other words, solutions exist if and only if \( T_n \) is orthogonal to any \( v \) in the nullspace of \( L^* \). Since \( L \) is self adjoint, we require a \( v \) so that

\[
Lv = v + \tilde{G}_u(u_0; z_0)v = 0.
\]

(3.51)

By differentiating (3.43) with respect to \( t \), it is clear that \( \dot{u}_0 \) is always a solution of the homogeneous equation (3.51). From (3.49) and (3.50), solutions to (3.48) thus exist if and only if

\[
\int_{-\infty}^{\infty} T_n(t)\dot{u}_0(t)dt = 0.
\]

(3.52)

We now proceed by investigating how the Melnikov integral condition can be recovered from the above systems of equations. As mentioned in the previous section, the Hamiltonian system, (3.43), has a separatrix for every value of \( z_0 \) between \( z_m \) and \( z_M \). It therefore is not sufficient to simply consider this system of equations by itself. To obtain a restriction on the values of \( z_0 \), it is necessary also to consider the solvability condition for the \( u_1 \) equation. Applying (3.52) to (3.44), the required solvability condition is

\[
\int_{-\infty}^{\infty} [\ddot{F}(u_0, \dot{u}_0; z_0) + \tilde{G}_z(u_0; z_0)z_1] \dot{u}_0 dt = 0,
\]

(3.53)

which is an integral equation with both \( z_0 \) and \( z_1 \) unknown. However, since \( \tilde{G}_z(u_0; z_0)z_1 \) does not depend explicitly on \( \dot{u}_0 \), the contribution of this term to the integral is zero, and (3.53) reduces to

\[
\int_{-\infty}^{\infty} \ddot{F}(u_0, \dot{u}_0; z_0)\dot{u}_0 dt = 0.
\]

(3.54)

Thus, we obtain exactly the same integral condition as was obtained using the Melnikov distance approach by setting \( D(z) = 0 \) in (3.33), which has a solution for precisely one
value of \( z_0 \). In fact, \( z_0 \equiv z_{MEL} \). However, we retain the \( z_0 \) notation to distinguish between the different methods used to determine these two values of \( z \).

Similarly, to determine the value of \( z_1 \), it is necessary to consider the solvability condition for the \( u_2 \) equation. Applying (3.52) to (3.45), and remembering that there is no net contribution to the integral by terms which depend on \( u_0 \) and \( z_0 \) only, we require

\[
\int_{-\infty}^{\infty} M(u_0, u_1, \dot{u}_0, \dot{u}_1; z_0, z_1) \dot{u}_0 dt = 0,
\]

where

\[
M(u_0, u_1, \dot{u}_0, \dot{u}_1; z_0, z_1)
= \frac{1}{2} \left[ \tilde{G}_{uu}(u_0; z_0) u_1^2 + 2 \tilde{G}_{uz}(u_0; z_0) u_1 z_1 + \tilde{G}_{zz}(u_0; z_0) z_1^2 \right]
+ \left[ \tilde{F}_u(u_0, \dot{u}_0; z_0) u_1 + \tilde{F}_z(u_0, \dot{u}_0; z_0) \dot{u}_1 + \tilde{F}_{zz}(u_0, \dot{u}_0; z_0) \dot{u}_1 \right].
\]

We have just discussed the conditions that need to be satisfied to uniquely determine \( z_0 \) and \( z_1 \). Similarly, of course, we need conditions to uniquely determine \( u_0 \) and \( u_1 \). Recall that we are interested in a solution of (3.40) which is homoclinic to the saddle point on the \( \tilde{G} = 0 \) nullcline at \( a_s(z) \), for some value of \( z \). Therefore, we require

\[
\lim_{t \to \pm \infty} u(t) = a_s(z).
\]

Using (3.12), and (3.41)-(3.42) in (3.57), the boundary conditions at infinity are

\[
\lim_{t \to \pm \infty} u_0(t) = a_s(z_0) = a_s^0,
\]

\[
\lim_{t \to \pm \infty} u_1(t) = \frac{d a_s(z_0)}{dz} z_1 \frac{\tilde{G}_{zz}(a_s^0, z_0)}{\tilde{G}_{u}(a_s^0, z_0)},
\]

for the leading-order and first-order problems, respectively. Since the equation for each \( u_n \) is a second-order equation, these conditions seem sufficient on first glance. However, as discussed above, \( \dot{u}_0 \) always is a solution of the homogeneous equation (3.51). As such,
any multiple of $\dot{u}_0$ can be added to the solution $u_n$ of (3.46), for $n \geq 1$. To fix the multiplicative constant, an additional condition is required. To obtain this condition, we use the fact that the homoclinic orbit must pass through $\dot{u} = 0$ for some $t$ between $-\infty$ and $\infty$. Without loss of generality, we take

$$\dot{u}(0) = 0,$$

yielding

$$\dot{u}_n(0) = 0,$$

for all values of $n$.

We now return to the integral defined by (3.55). This integral cannot be converted to an integral in the phase plane (cf. Section 3.3) since it is not possible to obtain a solution for $u_1$ and $\dot{u}_1$ as functions of $u_0$ and $\dot{u}_0$. Because $\dot{u}_0$ is a solution of the homogeneous equation of (3.44), in theory, it is possible to write down an analytical solution for $u_1$ and $\dot{u}_1$ as functions of $t$, using reduction of order and the method of variation of coefficients [12]. However, numerical methods then must be used to evaluate $u_1(t)$ and $\dot{u}_1(t)$ in (3.55). We prefer to obtain a numerical solution directly, discussed in the next section.

### 3.4.2 Numerical Solution

We pose the problem as a boundary-value problem (BVP) on the domain $t_L \leq t \leq t_R$, where $t_L$ and $t_R$ are as large as allowed by available computer resources, and use the COLSYS code written by Ascher et al. [2].

We start by setting up the BVP for determining the value of $z_0$. Although $z_0$ is of course more easily determined by converting (3.54) into a line integral in $u$, as was done in Section 3.3, solving this problem numerically is an important step towards determining $z_1$ below. Naturally, we require the leading-order equation, (3.43). The corresponding
boundary conditions for $u_0$ from (3.58) become $u_0(t_L) = u_0(t_R) = a_0^0$, where $a_0^0$ is an unknown constant. To let COLSYS determine the value of $a_0$, we introduce the differential equation $\dot{a}_0^0 = 0$, with the corresponding condition $\tilde{G}(a_0^0, z_0) = 0$ at either the left or right boundary. To uniquely determine $z_0$, we include the solvability condition (3.54) as follows. We define

$$h(t) = \int_{-\infty}^{t} \tilde{F}(u_0(\tau), \dot{u}_0(\tau); z_0) \dot{u}_0(\tau) d\tau,$$

(3.62)

and use the Fundamental Theorem of Calculus to introduce an artificial differential equation for $h(t)$, with corresponding boundary conditions, $h(t_L) = h(t_R) = 0$.

To summarize, we thus arrive at the following system of equations

$$\ddot{u}_0 + \tilde{G}(u_0; z_0) = 0,$$

(3.63)

$$\dot{z}_0 = 0,$$

(3.64)

$$\dot{a}_0^0 = 0,$$

(3.65)

$$\dot{h} = \tilde{F}(u_0, \dot{u}_0; z_0) \dot{u}_0,$$

(3.66)

for the five unknowns $u_0, \dot{u}_0, z_0, a_0^0, h$. The required five boundary conditions are

$$u_0(t_L) = u_0(t_R) = a_0^0,$$

(3.67)

$$\tilde{G}(a_0^0; z_0) = 0,$$

at $t = t_L,$

(3.68)

$$h(t_L) = h(t_R) = 0.$$

(3.69)

This system of equations uniquely determines the value of $z_0$, with essentially identical results obtained from COLSYS (within the requested accuracy of $10^{-6}$) and from the Melnikov distance approach in Section 3.3 (see Table 3.1).

To determine $z_1$, we include the first-order equation, (3.44), and the corresponding boundary conditions for $u_1$, (3.59). Since we now explicitly include the equation for $u_1$, we omit (3.66) and (3.69) and replace them by the solvability condition for $z_1$, (3.55).
We define

\[ k(t) = \int_{-\infty}^{t} M(u_0(\tau), u_1(\tau), \dot{u}_0(\tau), \dot{u}_1(\tau); z_0(\tau), z_1(\tau)) \dot{u}_0(\tau) d\tau \]  

(3.70)

and, as before, use the Fundamental Theorem of Calculus to introduce a differential equation for \( k(t) \), with the two boundary conditions \( k(t_L) = k(t_R) = 0 \). The net result is an addition of three equations, but only two boundary conditions. We now recall that any multiple of \( \dot{u}_0 \) can be added to the solution for \( u_1 \), as it is a solution of the homogeneous equation for \( u_1 \). To uniquely determine the multiplicative constant, we use the additional condition (3.61).

To summarize, we thus have the following system of eight equations,

\[
\begin{align*}
\ddot{u}_0 + \ddot{G}(u_0; z_0) &= 0, \\
\dot{z}_0 &= 0, \\
\dot{a}^0_s &= 0, \\
\ddot{u}_1 + \ddot{G}_u(u_0; z_0)u_1 &= -\ddot{F}(u_0, \dot{u}_0; z_0) - \ddot{G}_z(u_0; z_0)z_1, \\
\dot{z}_1 &= 0, \\
\dot{k} &= M(u_0, u_1, \dot{u}_0, \dot{u}_1; z_0, z_1)\dot{u}_0,
\end{align*}
\]

(3.71)
(3.72)
(3.73)
(3.74)
(3.75)
(3.76)

for the eight unknowns \( u_0, \dot{u}_0, z_0, a^0_s, u_1, \dot{u}_1, z_1, \) and \( k \). The corresponding eight boundary conditions are

\[
\begin{align*}
u_0(t_L) &= u_0(t_R) = a^0_s, \\
\tilde{G}(a^0_s; z_0) &= 0, & \text{at } t = t_L, \\
\dot{u}_1(0) &= 0, \\
u_1(t_L) &= u_1(t_R) = -z_1\frac{\tilde{G}(a^0_s; z_0)}{\tilde{G}_u(a^0_s; z_0)}, \\
k(t_L) &= k(t_R) = 0.
\end{align*}
\]

(3.77)
(3.78)
(3.79)
(3.80)
(3.81)
This system of equations uniquely determines the value of $z_1$.

The results obtained are presented in Table 3.1. We see that for the models with $p \neq 1$, namely the reduced Chay-Keizer, Chay (1986), and Himmel-Chay models, the first-order correction does indeed improve the leading-order results, as expected, so that $z_0 + \delta z_1$ (see Table 3.2 for values of $\delta$) agrees much better with typical values of $z_{esc}$ than $z_0 = z_{MEL}$ alone. For the models with $p = 1$, namely the Chay-Kang, Sherman-Rinzel-Keizer, and Chay-Cook models, $z_1 = 0$ within the requested accuracy. We shall see in the next section that this is not coincidental and that, in fact, $z_1$ is identically equal to zero.

The leading-order results already were in excellent agreement with typical values of $z_{esc}$ for the Chay-Kang and Sherman-Rinzel-Keizer models and these are not changed with the addition of $\delta z_1 = 0$. Unfortunately, the results also remain unchanged for the Chay-Cook model. To explain the remaining discrepancy for this model, we return to the investigations in Section 3.3.1. We hypothesize that the damping term $\delta \tilde{F}(u, \dot{u}; z)$ in (3.9) is not small enough for this model. To test this hypothesis, we replace $\delta \tilde{F}(u, \dot{u}; z)$ by $\frac{1}{4} \delta \tilde{F}(u, \dot{u}; z)$. The corresponding modified exact value of $z_{esc}$ for a typical value of $\beta$ is approximately -0.694, yielding a normalized $z_{MEL} = z_0$ value of 1.06419, which is better than the 0.90639 of Table 3.1, as expected.

### 3.4.3 Why The First-Order Correction is Zero for Models with $p = 1$

In this section, we consider the symmetry of the leading-order and first-order solutions for $u$, $u_0$, and $u_1$, respectively, and examine the effect on the solvability condition for $u_2$ to show that $z_1 \equiv 0$ for models with $p = 1$. For these models, we can rewrite (3.40) as

$$\ddot{u} + \tilde{G}(u; z) = -\delta \tilde{F}(u; z)\dot{u},$$

(3.82)
where

$$\hat{F}(u; z) = \frac{1}{\delta} F(u; z)$$

(3.83)

from (3.9), since \(E(u, \dot{u}; z) - E(u, 0; z) \equiv 0\) from (2.46).

The corresponding leading-order equation for \(u\), (3.43), does not depend on \(\hat{F}\), so that the separatrix solution is not affected. Changing \(t\) to \(-t\) in the leading-order problem, (3.43), it is clear that \(u_0\) is even in \(t\) and, hence, \(\dot{u}_0\) is odd in \(t\).

Due to (3.82), the first-order equation for \(u\), (3.44), can be rewritten as

$$\ddot{u}_1 + \dot{G}_u(u_0; z_0)u_1 = -\hat{F}(u_0; z_0)\dot{u}_0 - \dot{G}_z(u_0; z_0)z_1.$$  \hspace{1cm} (3.84)

Letting \(\tilde{Y}(t)\) be the bounded solution of

$$\ddot{Y} + \tilde{G}_u(u_0; z_0)\dot{Y} = -\hat{F}(u_0; z_0)\dot{u}_0$$  \hspace{1cm} (3.85)

and \(\tilde{Y}(t)\) be the bounded solution of

$$\ddot{Y} + \tilde{G}_u(u_0; z_0)\dot{Y} = -\tilde{G}_z(u_0; z_0),$$  \hspace{1cm} (3.86)

we have

$$u_1 = \tilde{Y} + z_1\dot{Y}.$$  \hspace{1cm} (3.87)

Since \(u_0\) is even and \(\dot{u}_0\) is odd in \(t\), it is clear from (3.85) that \(\tilde{Y}\) is odd in \(t\) and, hence, \(\dot{Y}\) is even. Similarly, \(\tilde{Y}\) is even in \(t\) from (3.86) and, hence, \(\dot{Y}\) is odd. Furthermore, 

$$\dot{Y} = \frac{\partial u_0}{\partial z_0}.$$  \hspace{1cm} To see this, we differentiate (3.43) with respect to \(z_0\) to obtain

$$\frac{\partial \ddot{u}_0}{\partial z_0} + \dot{G}_u(u_0; z_0)\frac{\partial u_0}{\partial z_0} = -\tilde{G}_z(u_0; z_0).$$  \hspace{1cm} (3.88)

That is, \(\frac{\partial u_0}{\partial z_0}\) is a particular solution of (3.86), which is bounded because a separatrix solution exists for all \(z_0\) between \(z_m\) and \(z_M\). The complete solution \(\dot{Y} = \frac{\partial u_0}{\partial z_0}\) then follows by requiring that \(\dot{Y}(t)\) is bounded [20] and \(\dot{Y}(0) = 0\) from (3.61).
Due to (3.82), the second-order equation for \( u \), (3.45), can be rewritten as

\[
\ddot{u}_2 + \tilde{G}_u(u_0; z_0)u_2 = -\tilde{G}_z(u_0; z_0)z_2
\]

\[
- \frac{1}{2} \left[ \tilde{G}_{uu}(u_0; z_0)u_1^2 + 2\tilde{G}_{uz}(u_0; z_0)u_1z_1 + \tilde{G}_{zz}(u_0; z_0)z_1^2 \right]
\]

\[
- \left[ \hat{F}_u(u_0; z_0)\dot{u}_0u_1 + \hat{F}(u_0; z_0)\dot{u}_1 + \hat{F}_z(u_0; z_0)\dot{u}_0z_1 \right],
\]  

(3.89)

yielding the modified solvability condition

\[
\int_{-\infty}^{\infty} \dot{M}(u_0, u_1, \dot{u}_0, \dot{u}_1; z_0, z_1)\dot{u}_0dt = 0,
\]  

(3.90)

for \( u_2 \), where

\[
\dot{M}(u_0, u_1, \dot{u}_0, \dot{u}_1; z_0, z_1)
\]

\[
= \frac{1}{2} \left[ \tilde{G}_{uu}(u_0; z_0)u_1^2 + 2\tilde{G}_{uz}(u_0; z_0)u_1z_1 + \tilde{G}_{zz}(u_0; z_0)z_1^2 \right]
\]

\[
+ \left[ \hat{F}_u(u_0; z_0)\dot{u}_0u_1 + \hat{F}(u_0; z_0)\dot{u}_1 + \hat{F}_z(u_0; z_0)\dot{u}_0z_1 \right],
\]  

(3.91)

similar to (3.55)-(3.56).

Using (3.87) in (3.91) gives

\[
\dot{M} = \dot{M}_a z_1^2 + \dot{M}_b z_1 + \dot{M}_c,
\]  

(3.92)

where

\[
\dot{M}_a = \frac{1}{2} \tilde{G}_{uu}(u_0; z_0)\dot{Y} + \tilde{G}_{uz}(u_0; z_0)\dot{Y} + \frac{1}{2} \tilde{G}_{zz}(u_0; z_0),
\]  

(3.93)

\[
\dot{M}_b = \tilde{G}_{uu}(u_0; z_0)\dot{Y} + \tilde{G}_{uz}(u_0; z_0)\dot{Y}
\]

\[
+ \hat{F}_u(u_0; z_0)\dot{u}_0\dot{Y} + \hat{F}(u_0; z_0)\dot{Y} + \hat{F}_z(u_0; z_0)\dot{u}_0,
\]  

(3.94)

\[
\dot{M}_c = \frac{1}{2} \tilde{G}_{uu}(u_0; z_0)\dot{Y}^2 + \tilde{G}_u(u_0; z_0)\dot{u}_0\dot{Y} + \hat{F}(u_0; z_0)\dot{Y}.
\]  

(3.95)

Apparently, (3.92) is quadratic in \( z_1 \). However, \( \dot{M}_a \) is orthogonal to \( \dot{u}_0 \), i.e.,

\[
\int_{-\infty}^{\infty} \dot{M}_a \dot{u}_0dt = 0,
\]  

(3.96)
so that from (3.90) and (3.92), \( z_1 \) is uniquely defined by

\[
z_1 = - \frac{\int_{-\infty}^{\infty} \hat{M} \dot{u}_0 dt}{\int_{-\infty}^{\infty} \hat{M} \dot{u}_0 dt}.
\] (3.97)

We note that since \( \hat{M} \) does not depend on \( \hat{F} \), the same reduction holds for models with \( p \neq 1 \) as well, so that \( z_1 \) also is uniquely defined for those models.

To prove (3.96), we differentiate (3.88) with respect to \( z_0 \), giving

\[
\frac{\partial^2 \hat{u}_0}{\partial z_0^2} + \hat{G}_u(u_0; z_0) \frac{\partial^2 u_0}{\partial z_0^2} = - \left[ \hat{G}_{uu}(u_0; z_0) \left( \frac{\partial u_0}{\partial z_0} \right)^2 + 2\hat{G}_{uz}(u_0; z_0) \frac{\partial u_0}{\partial z_0} + \hat{G}_{zz}(u_0; z_0) \right]
\]

\[
= - \left[ \hat{G}_{uu}(u_0; z_0) \dot{Y}^2 + 2\hat{G}_{uz}(u_0; z_0) \dot{Y} + \hat{G}_{zz}(u_0; z_0) \right]
\]

\[
= -2\hat{M}_a. \quad (3.98)
\]

Since \( \frac{\partial^2 u_0}{\partial z_0^2} \) is bounded, the right-hand side of (3.98) is orthogonal to \( \dot{u}_0 \) and, hence, (3.96) follows.

Using the symmetry of \( u_0, \dot{u}_0, \dot{Y}, \) and \( \dot{Y} \) in (3.95), we find \( \hat{M}_c \) is even, so that the numerator in (3.97) vanishes. Similarly, it is clear that every term in \( \hat{M}_c \) is odd and contributes to the integral in the denominator, so that it is non-zero in general. Therefore, \( z_1 \equiv 0 \) for all models with \( p = 1 \).

### 3.5 Comparison of the Different Methods

In this chapter, we have investigated several methods for approximating \( z_{HC} \), which is the value of \( z \) at which the fast subsystem, (2.51), exhibits the homoclinic bifurcation of interest. The approximate value of \( z_{HC} \) in turn approximates \( z_{esc} \), which is the value of \( z \) at which the numerical solution of the full system of equations undergoes the transition from the active phase back to the silent phase.
Chapter 3. *Escape from the Active Phase*

We demonstrated the use of two numerical methods to determine approximations to $z_{HC}$, as well as Melnikov’s method and the Fredholm alternative method. The latter two methods are analytical, but need to be combined with some numerical calculations in order to yield explicit approximations. We mention again that the dependence of $z_{esc}$ on the glucose-dependent parameter $\beta$ cannot be determined with any of these methods since $\beta$ does not appear in the fast subsystem. That is, all methods have resulted in a constant, approximate value for $z_{esc}$.

The results from the two numerical methods, namely the use of AUTO to approximate the homoclinic orbit by a periodic orbit with very large period and bisection based on the bifurcation of the solution behaviour of the fast subsystem in the $(u, \dot{u})$ phase plane as $z$ is varied, are in excellent agreement with typical exact values of $z_{esc}$ for all models. Since consistently accurate results can be obtained very quickly, we conclude that these methods are the methods of choice when one is interested in the location of the homoclinic bifurcation for a given set of parameters in the fast subsystem, as is the case in this thesis. In Chapter 4, we thus use $z_{esc} \approx z_{AUTO} \approx z_{BIS}$.

In general, however, the numerical methods are inefficient for determining the dependence of the location of the homoclinic orbit on the values of the fast subsystem parameters. In that case, approximating $z_{HC}$ with the leading-order Melnikov method or, equivalently, the leading-order Fredholm alternative method, is very efficient, since the corresponding leading-order improper integral in $t$ can be converted into a line integral in the $(u, \dot{u})$ phase plane. Since for the purposes of the next chapter we are interested in the dependence of $z_{HC}$ on the parameter $\beta$ only, which does not appear in the fast subsystem and, therefore, does not affect the analytical approximations of $z_{HC}$, the advantage of using this method is not fully demonstrated here. However, we demonstrate its efficient use in Chapter 5. We note that the drawback of this method is twofold. First, the fast subsystem needs to be written in perturbed form. We were able to do so for all models
under consideration in this thesis, but there is no guarantee that this also is the case for other models. Second, the methods are asymptotic methods which do not always provide accurate results, and higher-order corrections may be required.

Higher-order corrections of the leading-order approximations of $z_{HC}$ can be obtained using either Melnikov's method or the Fredholm alternative method. However, the corresponding higher-order improper integrals no longer can be converted to simple line integrals in the $(u, \dot{u})$ phase plane. We posed the problem of obtaining the first-order correction as a boundary-value problem and solved it with COLSYS. The disadvantage of this approach is that it is computationally intensive and, in fact, less practical than using the AUTO and DSTOOL software packages.
Chapter 4

Determination of the Plateau Fraction

In this chapter, we investigate the dependence of the plateau fraction, which was defined as the ratio of the active phase duration to the burst period, on the glucose-dependent parameter $\beta$. One can obtain an exact graph of the plateau fraction as a function of $\beta$ by numerically integrating the full system of equations, (2.44)-(2.45), over a range of $\beta$ values and extracting the plateau fraction from the solution for each value of $\beta$. The problem with this approach is that it takes a relatively large amount of computer time to obtain an accurate graph. Moreover, this approach does not provide any physiological insight into the dependence of the plateau fraction on $\beta$, let alone any other model parameters. Instead, we derive an expression for the leading-order approximation of the plateau fraction using asymptotic methods, assuming that the durations that the solution spends in the transitions between the active and silent phases are very short. We extend the techniques of Pernarowski [67] and Pernarowski et al. [70], which were applied to the Sherman-Rinzel-Keizer model, to all models under consideration.

In Section 4.1, we decide on a range of values for $\beta$ over which to compute the plateau fractions. The exact silent and active phase durations and the plateau fraction are defined in Section 4.2. In Section 4.3, we derive a leading-order approximation for the silent phase duration, $T_s^{(0)}$, and compare the results to the silent phase duration obtained numerically. A leading-order approximation of the active phase duration, $T_a^{(0)}$, is derived in Section 4.4, and also compared to the numerical results. In Section 4.5, we discuss the resulting leading-order approximation of the plateau fraction, $\rho_f^{(0)}$. Finally,
the assumption that the transition phases are very short is re-examined in Section 4.6.

4.1 Range of Values of $\beta$

To decide on a range of values for $\beta$ over which to compute the plateau fractions, we examine the effects of varying $\beta$ on the solution of the full system of equations, (2.44)-
(2.45). From (2.50), we note that $K(u, z)$ depends on $\beta$. Varying the value of $\beta$ affects
the location of the $z$-nullcline, given by $K(u, z) = 0$ from (2.45), and, subsequently, the
location and stability of the fixed point of the full system of equations.

For high values of $\beta$, corresponding to low values of the dimensional $k_{Ca}$ parameter,
the $z$-nullcline intersects the $\tilde{G} = 0$ nullcline on the left branch. For these cases, the fixed
point of (2.44)- (2.45) is stable. As a consequence, the solution of (2.44)- (2.45) remains
in the silent phase and exhibits no bursting behaviour.

Decreasing $\beta$ shifts the $z$-nullcline and, therefore, the fixed point of the full system
of equations to the right. Bursting behaviour becomes possible when this fixed point
occurs on the middle branch of the fast subsystem nullcline and the fixed point of the
full system of equations becomes unstable. We use (2.50) to compute the critical value
of $\beta$,

$$\beta_m = \frac{1}{e^{-z_m h(u_m, z_m)}}, \tag{4.1}$$

where $(u_m, z_m)$ represents the local minimum of the fast subsystem nullcline. For $\beta = \beta_m$,
the $z$-nullcline intersects the $\tilde{G} = 0$ nullcline at $(u_m, z_m)$, as shown in Figure 4.1. We
note that if $\beta$ is just slightly smaller than $\beta_m$, the $z$-nullcline lies entirely to the left of
the branches of periodic orbits emanating from the Hopf bifurcation. That is, $z$ strictly
increases during the active phase.

Decreasing $\beta$ further eventually causes part of the $z$-nullcline to lie inside the branches
of periodic orbits, so that $z$ no longer strictly increases during the active phase. When
Figure 4.1: Dependence of the $\dot{z}$-nullcline on $\beta$. For $\beta = \beta_m$, the $\dot{z}$-nullcline intersects the $\mathcal{G} = 0$ nullcline at its local minimum, $(u_m, z_m)$. For $\beta_{HC}$, the $\dot{z}$-nullcline intersects the $\mathcal{G} = 0$ nullcline at approximately $(u_{HC}, z_{HC})$. Note that $\beta_{HC} < \beta_m$, i.e., the $\dot{z}$-nullcline moves to the left as $\beta$ increases.

$\beta$ is small enough, the decrease in $z$ balances the increase in $z$ during one oscillation, resulting in continuous spiking and no escape from the active phase back to the silent phase. We restrict our analysis to the values of $\beta$ for which an escape from the active phase is assured. We therefore choose the minimum value of $\beta$ to be

$$\beta_{HC} = \frac{1}{e^{z^{(0)}_{HC}} h(u^{(0)}_{HC}, z^{(0)}_{HC})},$$

(4.2)

where $z^{(0)}_{HC}$ is the best approximation of $z_{HC}$ obtained in Chapter 3, namely $z_{AUTO}$ or $z_{BIS}$, and $u^{(0)}_{HC}$ satisfies $\mathcal{G}(u^{(0)}_{HC}, z^{(0)}_{HC}) = 0$ on the middle branch. For $\beta = \beta_{HC}$, the $\dot{z}$-nullcline thus intersects the $\mathcal{G} = 0$ nullcline at approximately $(u_{HC}, z_{HC})$, as shown in Figure 4.1.
4.2 Definition of the Exact Silent and Active Phase Durations and the Plateau Fraction

We now define the exact silent and active phase durations, as well as the plateau fraction. Figure 4.2 shows the bifurcation diagram of (2.51) for a typical $\beta$-cell model, with the projection of the numerical solution of (2.44)-(2.45) onto the $(u, z)$ plane superimposed. Based on this figure, we identify four phases, namely the silent and active phases and two transition phases. *Capture* refers to the transition from the silent to the active phase and *escape* refers to the transition from the active phase back to the silent phase.

During the silent phase, the solution trajectory closely follows the left branch of the $\tilde{G} = 0$ nullcline. We define the *exact silent phase duration* to be

$$T_s = t_{\text{cap}} - t_{\text{sil}},$$

where $t_{\text{cap}} > t_{\text{sil}}$, and $t_{\text{cap}}$ and $t_{\text{sil}}$ are defined as follows. $t_{\text{sil}}$ is the time at which the solution trajectory crosses the left branch of the $\tilde{G} = 0$ nullcline after escaping from the active phase. More precisely, $t_{\text{sil}}$ is the time at which $u = u_{\text{sil}}$ and $z = z_{\text{sil}}$, where $u_{\text{sil}}$ and $z_{\text{sil}}$ are related through $\tilde{G}(u_{\text{sil}}, z_{\text{sil}}) = 0$ on the left branch. Similarly, $t_{\text{cap}}$ is the time at which the solution trajectory passes below the local minimum of the fast subsystem nullcline. In particular, at $t = t_{\text{cap}}$, $u = u_{\text{cap}} = u_m$, and $z = z_{\text{cap}}$.

During the active phase, the solution trajectory exhibits oscillations surrounding the right branch. Let $t_i$ be the time at which $u$ reaches a local maximum during the $i^{\text{th}}$ spike. We then can define the *exact active phase duration* to be

$$T_a = t_{N_\beta} - t_1,$$

where $t_{N_\beta} > t_1$, $N_\beta$ is the number of spikes per burst and $t_1$ is the time at which $u$ reaches the first local maximum. To compute $T_a$ accurately, the solution of (2.44)-(2.45) must be reported at small step sizes. We have used step sizes of 0.001 for all of the models.
Figure 4.2: Typical bifurcation diagram of the fast subsystem, (2.51), with the projection of the numerical solution of the full system of equations, (2.44)-(2.45), superimposed. Results are shown for the Himmel-Chay model. Corresponding graphs for the remaining models under consideration in this thesis are qualitatively identical. The labels $(u_m, z_m)$ and $(u_M, z_M)$ indicate the local minimum and maximum of the $\tilde{G}$ nullcline, respectively. The silent phase is defined to begin when the solution trajectory crosses the left branch of the $\tilde{G} = 0$ nullcline at $(u_{sil}, z_{sil})$ and defined to terminate when the solution trajectory passes below the local minimum of the $\tilde{G} = 0$ nullcline at $(u_{cap}, z_{cap})$. The active phase is defined to begin when $u$ reaches its first local maximum after the silent phase, at label 1, and ends when $u$ reaches its last local maximum before returning to the silent phase, at label $N_\beta$. The transition phases between the active and silent phases are referred to as capture and escape, as labelled. Also shown is $(u_{esc}, z_{esc})$, at which the active phase undergoes the transition from the active phase back to the silent phase.
The number of spikes per burst, $N_\beta$, is dependent on $\beta$, as shown in Figure 4.3. We can explain the decrease of $N_\beta$ with $\beta$ as follows. Since $\dot{z} > 0$ in the active phase, (2.45) and (2.50) imply that an increase in $\beta$ corresponds to an increase in $\dot{z}$ during the active phase. That is, $z = z_{\text{esc}}$ is approached more rapidly, resulting in a reduction in the number of spikes per burst, as observed. We note that a theoretical treatment of the transition from $n$ to $n+1$ spikes per burst as parameters are varied is provided in [90].

The silent and active phases are separated by two transition phases, during which the solution trajectory switches from one to the other. The transitions occur very fast, and we ignore the time that the solution spends in the transition phases in our approximation of the plateau fraction. Letting $T_b$ be the burst period, we thus can define the exact plateau fraction, $\rho_f$, to be

$$\rho_f = \frac{T_a}{T_b} \approx \frac{T_a}{T_a + T_s}. \quad (4.5)$$

Graphs of the exact silent and active phase durations, burst period, and plateau fraction as a function of $\beta$ are presented in the following sections, where comparisons between the exact and corresponding leading-order quantities are made for all models under consideration.

### 4.3 Leading-Order Approximation of the Silent Phase Duration

To derive the leading-order approximation for the silent phase duration, $T_s^{(0)}$, we examine the full system of equations, (2.44)-(2.45). From (2.45), the change in $z$ is $O(\varepsilon)$. From Figure 4.2, we note that $du/dz = O(1)$ during the silent phase. Thus the change in $u$ also must be $O(\varepsilon)$ during the silent phase. For this reason, we introduce a new slow time, $\tilde{t}$, and new dependent variables, $U$ and $Z$, as follows:

$$\tilde{t} = \varepsilon t, \quad (4.6)$$

$$U(\tilde{t};\varepsilon) = u(t;\varepsilon), \quad (4.7)$$
Figure 4.3: Dependence of the number of spikes per burst, \( N_\beta \), on \( \beta \), for \( \beta_{HC} \leq \beta \leq \beta_m \). All other parameter values are as listed in Appendix A. Results are shown for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model; (d) Chay-Kang model; (e) Sherman-Rinzel-Keizer model; (f) Chay-Cook model.
so that both $U$ and $Z$ both undergo $O(1)$ changes on the $\tilde{t}$ time scale. Substituting (4.6)-(4.8) into (2.44)-(2.45), we obtain

$$\varepsilon^2 U'' + E(U, \varepsilon U', Z) + \varepsilon F(U, Z)U' + G(U, Z) = \varepsilon H(U, Z),$$

(4.9)

$$Z' = K(U, Z),$$

(4.10)

where $'$ denotes differentiation with respect to $\tilde{t}$.

System (4.9)-(4.10) is a singular perturbation problem. We seek an outer solution by substituting the expansions

$$U(\tilde{t}; \varepsilon) \sim U_0(\tilde{t}) + \varepsilon U_1(\tilde{t}) + \ldots,$$

$$Z(\tilde{t}; \varepsilon) \sim Z_0(\tilde{t}) + \varepsilon Z_1(\tilde{t}) + \ldots,$$

into (4.9)-(4.10), expanding $E$, $F$, $G$, $H$, and $K$ using the Taylor series about the leading-order solution $(U, U', Z) = (U_0, U_0', Z_0)$, and expanding $E(U_0, \varepsilon U_0', Z_0)$ using the binomial series. Collecting the leading-order terms yields

$$\tilde{G}(U_0, Z_0) = 0,$$

(4.11)

$$Z_0' = K(U_0, Z_0),$$

(4.12)

where $\tilde{G}$ is as defined by (2.53). The solution of the leading-order silent phase equations, (4.11)-(4.12), thus follows the $\tilde{G} = 0$ nullcline, as expected from Figure 4.2, with the change in $Z_0$ governed by (4.12). The accuracy of the time dependence of the leading-order problem is confirmed in Figure 4.4. The solution of the leading-order silent phase problem terminates when $(u, z) = (u_m, z_m)$. We see that the duration of the transition from the silent phase to the active phase, starting when $u = u_m$ and terminating when $u$ reaches its first local maximum, appears to be significant. We examine the transition durations in more detail in Section 4.5.
Figure 4.4: Comparison of the solution of the full system of equations (solid curves), (2.44)-(2.45), and the solution of the leading-order silent phase problem (dashed curves), given by (4.11) and (4.13). The initial conditions are \( (u, z) = (u_{sil}, z_{sil}) \). Results are shown for the Chay-Kang model for \( \beta = 8.5301e^{-2} \). All other parameter values are as listed in Appendix A. Corresponding graphs for the remaining models under consideration in this thesis are qualitatively the same.
Chapter 4. Determination of the Plateau Fraction

To obtain the leading-order silent phase duration, $T_s^{(0)}$, we differentiate (4.11) and use (4.12) to substitute for $Z_0'$. The resulting differential equation for $U_0$ is

$$U_0' = \frac{K(U_0, Z_0)}{-\tilde{G}_u(U_0, Z_0)/\tilde{G}_z(U_0, Z_0)}, \quad (4.13)$$

Finally, we separate variables in (4.13), integrate, and return to the original variables $t$ and $u$ via (4.6)-(4.7) to give

$$T_s^{(0)} = \frac{1}{\varepsilon} \int_{u_{sil}^{(0)}}^{u_{cap}} \frac{du}{N(u)}, \quad (4.14)$$

where

$$N(u) = \frac{K(u, \mathcal{G}(u))}{-\tilde{G}_u(u, \mathcal{G}(u))/\tilde{G}_z(u, \mathcal{G}(u))}, \quad (4.15)$$

and $\mathcal{G}(u)$ satisfies $\tilde{G}(u, \mathcal{G}(u)) = 0$.

The limits of integration in (4.14) are chosen as follows. According to the definition of the exact silent phase duration in (4.3), the limits of integration for $u$ should be from $u_{sil}$ to $u_{cap}$. The upper limit of integration presents no problems, as it is a straightforward exercise to compute the local extrema of the fast subsystem nullcline and obtain $u_{cap} = u_m$ (cf. Figure 4.2). However, $u_{sil}$ cannot be determined a priori since it depends on where the solution escapes the active phase. We define the leading-order approximation of $u_{sil}$ to be $u_{sil}^{(0)}$, satisfying $\tilde{G}(u_{sil}^{(0)}, z_{esc}^{(0)}) = 0$ on the left branch, where $z_{esc}^{(0)}$ is the best approximation of $z_{esc}$, the value of $z$ at which the solution of the full system of equations undergoes the transition from the active phase back to the silent phase, determined in Chapter 3.

Due to the complicated functional form of $N(u)$, $T_s^{(0)}$ must be evaluated numerically. We use a standard numerical quadrature routine from QUADPACK [71]. In general, for each evaluation of the integrand in (4.14), a standard root finding procedure must be used to determine $z = \mathcal{G}(u)$. Rather than integrating (4.13), it seems just as (dis)advantageous to integrate (4.12) and use the root finding procedure to determine $u$ as a function of
$z$ instead. However, for four of the models under consideration, namely the reduced Chay-Keizer, Chay-Kang, Sherman-Rinzel-Keizer, and Chay-Cook models, $z = G(u)$ can be found explicitly. For these models, $N(u)$ can be reduced to

$$N(u) = \frac{K(u, G(u))}{G'(u)},$$

greatly simplifying the computations. None of the models permit a solution for $u$ as a function of $z$.

In Figure 4.5, the exact and approximate silent phase durations as a function of $\beta$ are compared for all six models under consideration. The jaggedness of the exact silent phase duration curves is due to the discontinuities in the $N_\beta$ curves illustrated in Figure 4.3. The agreement is very good for all models (although one may argue that the results for the Himmel-Chay model are not quite as good as for the remaining models). We explain the general increase in the silent phase duration with $\beta$ as follows. Using (2.50) in (4.15), we differentiate (4.14) with respect to $\beta$ to obtain

$$\frac{dT_u^{(0)}}{d\beta} = \frac{1}{\epsilon} \int_{u^{(0)}_{sil}}^{u_{m}} \frac{e^{-g(u)}h(u, G(u))}{[\beta e^{-g(u)}h(u, G(u)) - 1]^2} du > 0,$$

since $\tilde{G}_u(u, G(u))/\tilde{G}_z(u, G(u)) = -dz/du > 0$ on the left branch of the $\tilde{G} = 0$ nullcline, and $h(u, G(u)) > 0$. Alternatively, we recall that $\dot{z} < 0$ during the silent phase. From (2.39), an increase in $\beta$ thus implies slower dynamics for $z$ and, hence, an increase in the silent phase duration.

### 4.4 Leading-Order Approximation of the Active Phase Duration

To derive a leading-order approximation of the active phase duration, it is necessary to first derive appropriately scaled equations. As the solution enters the active phase, the change in $u$ is no longer $O(\epsilon)$, but $O(1)$. Due to the existence of oscillations on the $O(1)$ time scale, the $\bar{u}$ term is also important. Therefore, (2.44)-(2.45) are appropriately
Figure 4.5: Comparison of the exact silent phase duration (jagged curve), $T_s$, and the leading-order silent phase duration (smooth curve), $T_s^{(0)}$, as a function of $\beta$, for $\beta_{HC} \leq \beta \leq \beta_m$. All other parameter values are as listed in Appendix A. Results are shown for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model; (d) Chay-Kang model; (e) Sherman-Rinzel-Keizer model; (f) Chay-Cook model.
scaled for the active phase. However, from the analysis in the previous chapter, we know that the active phase problem can be viewed as a slowly varying oscillator problem. The oscillations in $u$ occur on a fast, $O(1)$, time scale, but the slow evolution of $z$ and, hence, the slow variation of the oscillations occurs on a much slower, $O(\epsilon)$, time scale. Therefore, it is natural to use a multiple scales analysis [9, 56] of the active phase, taking both time scales into account simultaneously.

Kuzmak [57] and Luke [59] developed a multiple scales perturbation method for strongly nonlinear oscillators to determine solutions which are valid for times up to $O(1/\epsilon)$. In light of the reformulated fast subsystem equation, (3.5), and its unperturbed version, (3.11), the active phase indeed can be viewed as a strongly nonlinear oscillator so that we can formally apply the Kuzmak-Luke method.

Let

$$u(t; \epsilon) = U(\tau, \tilde{t}; \epsilon) \sim u_0(\tau, \tilde{t}) + \epsilon u_1(\tau, \tilde{t}) + \ldots,$$

(4.18)

$$z(t; \epsilon) = Z(\tau, \tilde{t}; \epsilon) \sim z_0(\tau, \tilde{t}) + \epsilon z_1(\tau, \tilde{t}) + \ldots,$$

(4.19)

where the slow time $\tilde{t}$ and the fast strained time $\tau$ are defined by

$$\tilde{t} = \epsilon t$$

(4.20)

and

$$\frac{d\tau}{dt} = \omega(\tilde{t}),$$

(4.21)

respectively. The frequency function $\omega(\tilde{t})$ is to be determined by the requirement that $u_0$ be periodic in $\tau$ with a period which does not depend on $\tilde{t}$. Furthermore, $u_i(\tau, \tilde{t})$ and $z_i(\tau, \tilde{t})$ are assumed to be periodic in $\tau$, for $i = 0, 1, 2, \ldots$. Even though the exact solutions $u$ and $z$ are functions of $t$ alone, we seek solutions which are functions of both $\tilde{t}$ and $\tau$ treated as independent variables. Using the chain rule for partial differentiation,
the time derivatives of \( u \) are

\[
\frac{\partial u}{\partial t} = \omega \frac{\partial U}{\partial \tau} + \varepsilon \left( \frac{\partial u_0}{\partial \tau} + \frac{\partial u_0}{\partial \tau} + \frac{\partial u_1}{\partial \tau} \right) + O(\varepsilon^2),
\]

(4.22)

and

\[
\frac{\partial^2 u}{\partial t^2} = \omega^2 \frac{\partial^2 U}{\partial \tau^2} + 2\varepsilon \omega \frac{\partial^2 U}{\partial \tau \partial \tau} + \varepsilon \frac{\partial u_1}{\partial \tau} + \frac{\partial u_0}{\partial \tau} + \varepsilon^2 \frac{\partial^2 U}{\partial \tau \partial \tau} + 2\varepsilon \omega \frac{\partial u_1}{\partial \tau} + \frac{\partial u_0}{\partial \tau} + O(\varepsilon^2),
\]

(4.23)

with similar expressions for the time derivatives of \( z \). Expanding \( E(u, \dot{u}, z) \) and \( F(u, z) \) about \((u_0, \omega \frac{\partial u_0}{\partial \tau}, z_0)\) and \((u_0, z_0)\), respectively, gives

\[
E(u, \dot{u}, z) = E^{(0)} + \varepsilon \left( E_1^{(0)} u_1 + E_1^{(0)} \left[ \frac{\partial u_1}{\partial \tau} + \frac{\partial u_0}{\partial \tau} \right] + E_2^{(0)} z_1 \right) + O(\varepsilon^2),
\]

(4.24)

\[
F(u, z) = F^{(0)} + \varepsilon \left( F_1^{(0)} u_1 + F_1^{(0)} z_1 \right) + O(\varepsilon^2),
\]

(4.25)

where the superscript \((0)\) means evaluated at \((u_0, \omega \frac{\partial u_0}{\partial \tau}, z_0)\) or \((u_0, z_0)\), as appropriate.

Substituting (4.22)-(4.23), (4.24)-(4.25), and corresponding expansions for \( G, H, \) and \( K \) into (2.44)-(2.45), yields the leading-order equations

\[
\omega^2 \frac{\partial^2 u_0}{\partial \tau^2} + E(u_0, \omega \frac{\partial u_0}{\partial \tau}, z_0) + \omega F(u_0, z_0) \frac{\partial u_0}{\partial \tau} + G(u_0, z_0) = 0, \quad (4.26)
\]

\[
\frac{\partial z_0}{\partial \tau} = 0, \quad (4.27)
\]

and the first-order equations

\[
\omega^2 \frac{\partial^2 u_1}{\partial \tau^2} + \omega \left[ E_1^{(0)} F^{(0)} \right] \frac{\partial u_1}{\partial \tau} + \left[ E_1^{(0)} + \omega \frac{\partial u_0}{\partial \tau} F_1^{(0)} + G_1^{(0)} \right] u_1 =
\]

\[
H^{(0)} - 2\omega \frac{\partial u_0}{\partial \tau \partial \tau} - \frac{\partial u_0}{\partial \tau \partial \tau} - \left[ E_2^{(0)} + F^{(0)} \right] \frac{\partial u_0}{\partial \tau} - \left[ E_2^{(0)} + \omega \frac{\partial u_0}{\partial \tau} F_2^{(0)} + G_2^{(0)} \right] z_1, \quad (4.28)
\]

\[
\omega \frac{\partial z_1}{\partial \tau} + \frac{\partial z_0}{\partial \tau} = K(u_0, z_0). \quad (4.29)
\]
From (4.27), we note that \( z_0 \) is a function of \( \tilde{t} \) only. With the restriction imposed on the glucose-dependent parameter \( \beta \) in the introduction to this chapter, \( z_0 \) increases monotonically during the active phase. We thus can write \( \tilde{t} \) as a function of \( z_0 \) and infer the existence of some function \( \omega_0 \) so that

\[
\omega(\tilde{t}) = \omega_0(z_0).
\] (4.30)

The change of variables

\[
\tau = \omega s,
\]
(4.31)

\[
u_0(\tau, \tilde{t}) = U_0(s, \tilde{t}),
\]
(4.32)

transforms (4.26) into

\[
\frac{\partial^2 U_0}{\partial s^2} + E(U_0, \frac{\partial U_0}{\partial s}, z_0) + F(U_0, z_0) \frac{\partial U_0}{\partial s} + G(U_0, z_0) = 0.
\] (4.33)

For a fixed value of \( z_0 \) between \( z_m \) and \( z_{HC} \), (4.33) is equivalent to (2.51) and known to have a periodic solution \( U_0 \) in \( s \) from the results in Chapter 3. Letting the period be \( T_0(z_0) \) and

\[
\omega_0(z_0) = \frac{1}{T_0(z_0)},
\] (4.34)

(4.31) implies \( \tau = s/T_0(z_0) \). That is, (4.26) has a periodic solution \( u_0 \) in \( \tau \), with constant period 1, as required.

Next, we integrate (4.29) with respect to \( \tau \), from \( \tau = 0 \) to \( \tau = 1 \). Since \( z_1 \) is assumed to be periodic in \( \tau \) as well, the contribution due to the first term is zero. We thus obtain the equation governing the slow evolution of \( z_0 \),

\[
\frac{\partial z_0}{\partial \tilde{t}} = \bar{K}(z_0(\tilde{t})) = \beta e^{-z_0(\tilde{t})} h(z_0(\tilde{t})) - 1,
\] (4.35)

where we have used (2.50) to rewrite \( K \) and

\[
\bar{h}(z_0(\tilde{t})) = \int_0^1 h(u_0(\tau, \tilde{t}), z_0(\tau, \tilde{t})) d\tau
\] (4.36)
is the average value of $h$ over one oscillation of the periodic solution.

Returning to the original variables $u, z,$ and $t$, the leading-order active phase problem thus is given by (2.51) and

$$\frac{dz}{dt} = \varepsilon \left[ \beta e^{-\gamma h(z)} - 1 \right], \quad (4.37)$$

where

$$h(z) = \frac{1}{T_0(z)} \int_0^{T_0(z)} h(u(t), z) dt. \quad (4.38)$$

For any value of $z$ between $z_m$ and $z_{HC}^{(0)}$, the period $T_0(z)$ can be obtained easily from the periodic solution of (2.51). To determine $\tilde{h}(z)$, we define

$$\tilde{h}(t, z) = \int_0^t h(u(t), z) dt \quad (4.39)$$

and use the Fundamental Theorem of Calculus to introduce the differential equation

$$\frac{d\tilde{h}}{dt} = h(u(t), z). \quad (4.40)$$

We solve (2.51) and (4.40) simultaneously, and take

$$\tilde{h}(z) = \lim_{t \to \infty} \frac{\tilde{h}(t + T_0(z), z) - \tilde{h}(t, z)}{T_0(z)}. \quad (4.41)$$

The period $T_0(z)$ and averaged calcium current $\tilde{h}(z)$ so obtained are shown in Figures 4.6a and b, respectively. We note that as $z$ approaches $z_{HC}^{(0)}$, $T_0(z)$ increases significantly, as expected, since the larger $z$ becomes, the closer the trajectory passes to the saddle points on the middle branch of the $G = 0$ nullcline. Because $h(u, z)$ is smallest for values of $u$ near the middle branch, $\tilde{h}(z)$ decreases significantly as $z$ approaches $z_{HC}^{(0)}$.

In order to obtain a numerical solution of the leading-order active phase problem, ideally, $\tilde{h}(z)$ should be known for every value of $z$ between $z_m$ and $z_{HC}^{(0)}$. However, as we have just seen, obtaining an accurate value for $\tilde{h}(z)$ is computationally expensive, and as such, we look for a more efficient, yet accurate, approximation scheme. Whereas
Figure 4.6: (a) Period $T_0(z)$ of the periodic solution of (2.51). (b) Averaged calcium current $\tilde{I}(z)$ over one oscillation of the periodic solution. Results are shown for the Sherman-Rinzel-Keizer model, for $z_m \leq z \leq z_{HC}^{(0)}$ and $\beta = 2.7179e^{-2}$. All other parameter values are as listed in Appendix A. Corresponding graphs for the remaining models under consideration in this thesis are qualitatively identical.
Pernarowski [67] and Pernarowski et al. [70] use a quadratic approximation of the form

\[ \tilde{h}(z) \approx h_2 z^2 + h_1 z + h_0, \]  

(4.42)
based on a least squares fit over 15 evenly spaced values of \( z \), we choose to compute \( \tilde{h}(z) \) for 50 evenly spaced values of \( z \) between \( z_m \) and \( z_{HC}^{(0)} \), and use a simple linear interpolation to approximate \( \tilde{h}(z) \) for any other value of \( z \). A linear approximation scheme is deemed sufficient based on the observation that the typical graph of \( \tilde{h}(z) \) in Figure 4.6b, created with the same 50 data points, is smooth.

In Figure 4.7 then, the numerical solution of the leading-order active phase problem, given by (2.51) and (4.37) with \( \tilde{h}(z) \) approximated as just described, is compared to the numerical solution of the full system of equations, (2.44)-(2.45). From Figure 4.7a, we observe that the two solutions are in excellent agreement over the first half of the active phase. As \( t \) increases, the oscillations become increasingly out of phase. We note that the oscillations are never out of phase by more than half a period for any of the models under consideration in this thesis.

To obtain the leading-order active phase duration, \( T_a^{(0)} \), we separate variables in (4.37) and integrate, yielding

\[ T_a^{(0)} = \frac{1}{\epsilon} \int_{z_m}^{z_{HC}^{(0)}} \frac{dz}{\beta e^{-z \tilde{h}(z)} - 1}. \]  

(4.43)
The limits of integration are chosen as follows. According to the exact definition of the active phase duration in (4.4), the lower limit of integration should correspond as closely as possible to the value of \( z \) at the time when \( u \) reaches a local maximum during the first spike in the active phase. Since the solution trajectory leaves the silent phase near the local minimum of the \( \tilde{G} = 0 \) nullcline and the value of \( z \) does not change significantly during the transition from the silent to the active phase, we take \( z = z_m \). Similarly, the upper limit of integration should correspond to the value of \( z \) at the time when \( u \) reaches a local maximum during the last spike in the active phase. Since \( z \) does not change
Figure 4.7: Comparison of the solution of the full system of equations (solid curves), (2.44)-(2.45), and the solution of the leading-order active phase problem (dashed curves), given by (4.33) and (4.35). Initial conditions are on the limit cycle solution of (2.51) at $z = z_m$. Results are shown for the Chay-Kang model for $\beta = 8.5301e^{-2}$. All other parameter values are as listed in Appendix A. Corresponding graphs for the remaining models under consideration in this thesis are qualitatively the same.
Chapter 4. Determination of the Plateau Fraction

significantly during the last spike, we take \( z = z_{\text{sec}}^{(0)} \). For an efficient computation of \( T_a^{(0)} \), \( \bar{h}(z) \) again should be approximated as described above.

The exact and approximate active phase durations as a function of \( \beta \) are compared in Figure 4.8. As for the silent phase durations, the agreement is very good for all models. The decreases in the active phase duration as a function of \( \beta \) can be explained as follows. Differentiating (4.43) with respect to \( \beta \), we obtain

\[
\frac{dT_a^{(0)}}{d\beta} = -\frac{1}{\varepsilon} \int_{z_m}^{z_{\text{sec}}^{(0)}} \frac{e^{-z \bar{h}(z)}}{[\beta e^{-z \bar{h}(z)} - 1]^2} dz < 0, \tag{4.44}
\]

since \( \bar{h}(z) > 0 \). Alternatively, we recall that \( \dot{z} > 0 \) during the active phase. Therefore, from (2.39), an increase in \( \beta \) implies faster dynamics for \( z \) and, hence, a decrease in the active phase duration, as observed.

4.5 Leading-Order Approximation of the Plateau Fraction

From (4.5), we define the leading-order plateau fraction, \( \rho_f^{(0)} \), to be

\[
\rho_f^{(0)} = \frac{T_a^{(0)} + T_s^{(0)}}{T_a^{(0)} + T_s^{(0)}}. \tag{4.45}
\]

The exact and leading-order plateau fractions as a function of \( \beta \) are compared in Figure 4.9. For all models, the leading-order results overestimate the exact plateau fractions. Since \( T_s^{(0)} \) and \( T_a^{(0)} \) are in excellent agreement with \( T_s \) and \( T_a \), respectively, the discrepancy must be due to the omission of the duration of the transition phases in the denominator of (4.45). As observed in Figure 4.4, the duration of the transition from the silent to the active phase may be significant. The same is true for the transition from the active phase back to the silent phase (cf. Figure 4.7).

The time spent in the transition phases, \( T_b - (T_s + T_a) \), as a percentage of the burst period, \( T_b \), is shown in Figure 4.10. We observe that, in general, the transition phase
Figure 4.8: Comparison of the exact active phase duration (jagged curve), $T_a$, and the leading-order active phase duration (smooth curve), $T_a^{(0)}$, as a function of $\beta$, for $\beta_{HC} \leq \beta \leq \beta_m$. All other parameter values are as listed in Appendix A. Results are shown for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model; (d) Chay-Kang model; (e) Sherman-Rinzel-Keizer model; (f) Chay-Cook model.
Figure 4.9: Comparison of the exact plateau fraction (jagged curve), $\rho_f$, and the leading-order plateau fraction (smooth curve), $\rho_f^{(0)}$, as a function of $\beta$, for $\beta_{HC} \leq \beta \leq \beta_m$. All other parameter values are as listed in Appendix A. Results are shown for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model; (d) Chay-Kang model; (e) Sherman-Rinzel-Keizer model; (f) Chay-Cook model.
Figure 4.10: Transition phase duration, $T_b - (T_s + T_a)$, as a percentage of the burst period, $T_b$, for $\beta_{HC} \leq \beta \leq \beta_m$. All other parameter values are as listed in Appendix A. Results are shown for the (a) reduced Chay-Keizer model; (b) Chay (1986) model; (c) Himmel-Chay model; (d) Chay-Kang model; (e) Sherman-Rinzel-Keizer model; (f) Chay-Cook model.
duration is small, but not insignificant. We explain the increase in the percentage with \( \beta \) as follows. For \( \beta \) near \( \beta_m \), there are significantly fewer spikes per burst (cf. Figure 4.3) and the active phase is much shorter (cf. Figure 4.8). More importantly though, the fixed point for the full system of equations, (2.44)-(2.45), lies close to the local minimum, \((u_m, z_m)\), of the \( \tilde{G} = 0 \) nullcline. Therefore, the solution trajectory travels near this fixed point in its transition from the silent phase to the active phase, resulting in a significant increase in the duration of this transition phase. This is reflected in Figure 4.10. We note that the time spent in the two transition phases in roughly equal for all values of \( \beta \), except for values of \( \beta \) near \( \beta_m \). Finally, we observe that the percentage of time spent in the transition phases is much higher for the Chay (1986) model than for the remaining models. We attribute this to the fact that the number of spikes per burst is much less than for the other models (cf. Figure 4.3), even for the smaller values of \( \beta \) near \( \beta_{HC} \).

We return to Figure 4.9 and observe that the plateau fraction decreases with \( \beta \). As for the silent and active phase durations, we can explain this trend by differentiating (4.45) with respect to \( \beta \) and using the signs derived in (4.17) and (4.44) to obtain

\[
\frac{d \rho_{P}^{(0)}}{d \beta} = - \frac{T_a^{(0)} \frac{dT_a^{(0)}}{d \beta} - T_s^{(0)} \frac{dT_s^{(0)}}{d \beta}}{[T_a^{(0)} + T_s^{(0)}]^2} < 0, \tag{4.46}
\]

as observed.

\section*{4.6 Examination of the Transition Phases}

We saw in the previous section that the transition phase durations are not insignificant, especially when \( \beta \) is near \( \beta_m \), and it thus is desirable to obtain leading-order approximations of these durations. In this section, we follow the approach of Pernarowski [67] and Pernarowski \textit{et al.} [70] to derive the equations of two surfaces which correctly describe each of the transition phases in \((u, \dot{u})\) space. However, as we will see below, the equations
cannot be used to derive a leading-order approximation of the transition phase durations.

We return to the general nondimensional model, (2.37)-(2.39), and briefly summarize the argument used by Pernarowski *et al.* in their derivation of the surfaces just mentioned for the Sherman-Rinzel-Keizer model. During both transition phases, $z$ changes little and can be regarded as constant, namely $z \approx z_m$ during the transition from the silent to the active phase (capture) and $z \approx z^{(0)}_{\text{esc}}$ during the transition from the active phase back to the silent phase (escape). Furthermore, they argue that $w$ is near $w_\infty(u, z)$ and that $\tau_w(u, z)$ is $O(1)$ throughout both transition phases.

Using the same argument for all models under consideration, the leading-order problem for the capture phase thus is

\begin{align*}
\dot{u} &= A(u; z_m) - w_\infty^p(u; z_m), \\
\dot{w} &= 0, \\
\dot{z} &= 0.
\end{align*}

The equations describing the escape phase are exactly the same, except $z_m$ is replaced by $z^{(0)}_{\text{esc}}$. Projecting the solution of the full system of equations, (2.44)-(2.45), onto the $(u, \dot{u})$ plane, and superimposing the curves defined by (4.47), as shown in Figure 4.11, confirms the accuracy of (4.47) in $(u, \dot{u})$ space.

However, (4.47) cannot be used to determine $u$ as a function of $t$, nor can it be used to reduce the transition phase duration to quadrature, similar to what was done for the silent and active phase durations. The reason is that we wish to start and end the integrations on or very near the $\bar{G} = 0$ nullcline. However, $\bar{G} = 0$ is equivalent to $A(u, z) - w_\infty^p(u, z) = 0$ via (2.46)-(2.48) and (2.53). That is, (4.47) induces non-integrable singularities at the endpoints.

In order to resolve this issue and successfully obtain the leading-order transition phase durations, we expect that it is necessary to perform a higher-order analysis, requiring
Figure 4.11: Projection of the numerical solution of the full system of equations, (2.44)-(2.45), onto the $(u, \dot{u})$ plane (solid curve) with the leading-order approximations of the transition phases, (4.47), superimposed. For the upper dashed curve, corresponding to the escape, $z = z_m$ and for the lower dashed curve, corresponding to the capture, $z = z_c^{(0)}$. Results are shown for the reduced Chay-Keizer model. Corresponding graphs for the remaining models under consideration in this thesis are qualitatively identical.

the method of matched asymptotic expansions [9] (where asymptotic solutions in the transition phases are matched to the asymptotic solutions in the silent and active phases to obtain a global, uniformly valid solution for the entire bursting phenomenon). Furthermore, the slow passage through a limit point (in our case the local minimum of the $\tilde{G} = 0$ nullcline) has been analyzed for several problems, including bursting phenomena [31, 40, 48]. We expect that a similar analysis would be useful in eliciting the dependence of the duration of the transition from the silent to the active phase on the $\beta$ parameter, and help explain the significant increase in this duration as $\beta$ approaches $\beta_m$ (cf. Section 4.5). However, we do not pursue these avenues of research further.
Chapter 5

Multiple Bifurcations in a Polynomial Analog Model

In this chapter, we study bursting oscillations in a much broader context. To avoid the complex nonlinearities in the biophysical models, we concentrate on a simplified model exhibiting the bursting phenomenon, namely the polynomial model introduced by Pernarowski [68]. Pernarowski’s model is analogous to the biophysical models of bursting electrical activity in pancreatic beta cells, in the same way that the Fitzhugh-Nagumo model [34] of nerve membrane is analogous to the Hodgkin-Huxley model [47] describing the electrical impulses in the squid giant axon.

Depending on the parameter values, Pernarowski’s model exhibits a wealth of oscillatory behaviour, including square-wave bursting which is the type of bursting observed in pancreatic β-cells. In [68], Pernarowski used a local stability analysis of the fixed points of the fast subsystem, a Hopf bifurcation analysis, and Melnikov’s method in connection with homoclinic bifurcations to determine the region in parameter space where the model equations exhibit square-wave bursting oscillations. We ask the question: Given any set of parameter values, can we predict the bifurcation structure of the fast subsystem and, hence, anticipate what kind of oscillatory behaviour the full system of equations will produce?

In answering this question, we create a bifurcation map in parameter space, consisting of regions within which the bifurcation diagrams of the fast subsystem are qualitatively the same. The bifurcation map is significant in determining the relationship between the various types of oscillatory behaviour and, hence, provides a basis for an extension of the
classification schemes of bursting oscillations by Rinzel [77] and Bertram et al. [10].

In Section 5.1, we introduce Pernarowski's model and various types of solution behaviour. Some preliminary analysis is contained in Section 5.2, where we use the symmetry of the model equations to simplify the bifurcation map and in Section 5.3, where we perform a standard fixed point analysis of the fast subsystem.

The details of the development of the bifurcation map are presented in Sections 5.4–5.7. We develop analytical constraints on the various bifurcations exhibited by the fast subsystem of the polynomial model. The constraints correspond to curves on the bifurcation map bounding the different regions. Hopf bifurcation constraints are developed in Section 5.4 and homoclinic bifurcation constraints are developed in Section 5.5. Constraints associated with another type of bifurcation exhibited by the polynomial analog model, namely the saddle-node of periodic bifurcation, introduced below, are investigated in Section 5.6. In that section, we need to resort to numerical software to complete the bifurcation map. The complete bifurcation map is presented in Section 5.7. We note that each type of bifurcation diagram predicted by the analysis is shown in the figures in Appendix B.

In the development of the bifurcation map, which is very qualitative in nature, we lose some pertinent quantitative information. To recover some of this information, we examine two-parameter bifurcation diagrams in Section 5.8. A second reason for presenting this type of diagram is because of the surprising discovery that it is essentially identical to the two-parameter bifurcation diagram generated for the biophysically based Chay-Cook model in [10]. That is, the polynomial analog model not only superficially mimics various types of solution behaviour of models of excitable cells, but also possesses the rich bifurcation structure of such models. We discuss the implications of this discovery for the classification of bursting oscillations in Section 5.9.

Finally, knowledge of the bifurcation structure of the fast subsystem, in general,
is sufficient for predicting the type of oscillatory behaviour of the solution of the full system of equations. However, this is not true near the boundaries of the regions on the bifurcation map. The dependence of the type of oscillatory behaviour exhibited by the full system of equations on the size of the asymptotic parameter \( \varepsilon \) governing the dynamics of the slow subsystem is examined briefly in Section 5.10.

5.1 Pernarowski’s Analog Model and Various Solution Behaviours

Pernarowski’s analog model \([68]\) is given by

\[
\ddot{u} + F(u)\dot{u} + G(u, c) = -\varepsilon H(u, c),
\]

\[
\dot{c} = \varepsilon H(u, c),
\]

where

\[
F(u) = a \left[(u - \hat{u})^2 - \eta^2\right],
\]

\[
G(u, c) = c + u^3 - 3(u + 1),
\]

\[
H(u, c) = \beta(u - \tilde{u}) - c.
\]

We note the similarity of (5.1)-(5.2) to the transformed biophysical models of bursting electrical activity in pancreatic \( \beta \)-cells in Chapter 2 (cf. (2.44)-(2.45)). Based on this similarity, the variable \( u \) may be interpreted as the membrane potential of an excitable cell. Since the parameter \( \varepsilon \) is small \((0 < \varepsilon << 1)\), (5.2) models the dynamics of a slowly changing quantity. In the case of pancreatic \( \beta \)-cells, \( c \) may be interpreted as the intracellular calcium concentration or some other slow variable.

As in Chapter 3, we divide (5.1)-(5.2) into slow and fast subsystems. The slow subsystem is given by (5.2) and the fast subsystem by

\[
\ddot{u} + F(u)\dot{u} + G(u; c) = 0,
\]
Figure 5.1: The $G = 0$ nullcline of the fast subsystem, (5.6). The local minimum is at $(u_m, c_m) = (-1, 1)$ and the local maximum is at $(u_M, c_M) = (1, 5)$. Fixed points lying between $u = -2$ and $u = 2$ are in the region of bistability. The $G = 0$ nullcline is a reflection of itself through the point $(0, 3)$ (cf. Section 5.2).

where the use of the semicolon in $G$ indicates that $c$ is treated as the bifurcation parameter. The fast subsystem nullcline is given by $G = 0$, which traces out a cubic in $(u, c)$ space, as shown in Figure 5.1. Since $G$ does not depend on any model parameters, the nullcline and its local extrema remain fixed. We introduce $(u_m, c_m) = (-1, 1)$ and $(u_M, c_M) = (1, 5)$ to denote the local minimum and maximum of the nullcline, respectively. We refer to the region lying between $c_m$ and $c_M$ as the region of bistability. For most choices of the parameter values, the fast subsystem indeed exhibits bistability in this region, although parameter values can be found for which this is not the case. The value of $u$ defining the region of bistability on the right branch of the $G = 0$ nullcline is given by the largest root of $G(u, c_m) = 0$, which is $u = 2$. Similarly, the value of $u$ defining the region of bistability on the left branch is given by the smallest root of $G(u, c_M) = 0$, which is $u = -2$, as indicated in Figure 5.1.

The stability of the fixed points of the fast subsystem and, hence, the behaviour of the
solution of the full system of equations, (5.1)-(5.2), is determined by the damping term, \( F(u) \dot{u} \). Hence, depending on the values of the parameters in \( F \), the model exhibits a wide variety of oscillatory behaviour. Numerical solutions of (5.1)-(5.2) and the bifurcation diagrams of (5.6) for three sets of parameter values are shown in Figures 5.2-5.4.

Figure 5.2 shows square-wave bursting similar to that observed in the electrical activity of pancreatic \( \beta \)-cells. The bifurcation diagram of this burster exhibits a supercritical Hopf bifurcation (HB) on the right branch of the \( G = 0 \) nullcline. Periodic orbits emanating from the Hopf point are stable and increase in size as \( c \) increases, until they disappear at a homoclinic bifurcation (HC), as in Chapter 2.

Tapered bursting is shown in Figure 5.3 and is similar to the electrical activity observed in the pyramidal cells of the cat hippocampus [50]. Compared to the bifurcation diagram of the square-wave burster, a second supercritical Hopf bifurcation has appeared on the right branch of the \( G = 0 \) nullcline. As \( c \) increases, the periodic orbits emanating from the lower Hopf point (not shown) first increase in size and then decrease. The periodic orbits disappear through the upper Hopf bifurcation, rather than through a homoclinic bifurcation.

A third type of bursting is shown in Figure 5.4. In this case, the individual spikes do not ride on a plateau, as for the previous bursters, but undershoot the value of \( u \) in the silent phase. This type of bursting was named nearly-parabolic bursting by Pernarowski [68]. However, the name is slightly misleading, as parabolic bursting is a different type of bursting, requiring at least two slow variables [73, 78]. Instead, we refer to this type of bursting as bursting with an undershoot. As for the square-wave burster in Figure 5.2, the bifurcation diagram for this burster also exhibits one Hopf bifurcation on the right branch of the \( G = 0 \) nullcline. But in this case, the Hopf bifurcation is subcritical, rather than supercritical. Periodic orbits emanating from the Hopf point are unstable at first, but become stable at a saddle-node of periodic bifurcation (SNP). In
Figure 5.2: Square-wave bursting, as observed in pancreatic $\beta$-cells ($\eta = 0.7$, $\tilde{u} = 1.6$, $a = 0.25$, $\beta = 4$, $\tilde{u} = -0.954$, and $\epsilon = 0.0025$). (a) Numerical solution of the full system of equations, (5.1)-(5.2). (b) Bifurcation diagram of the fast subsystem, (5.6), with the projections of the solution from (a) superimposed. As in Chapter 2, solid lines indicate stability, dashed lines indicate instability, SN denotes a saddle-node bifurcation, HB denotes a Hopf bifurcation, and HC denotes a homoclinic bifurcation.
Figure 5.3: Tapered bursting ($\eta = 0.7$, $\hat{u} = 2.1$, and remaining parameter values as in Figure 5.2). (a) Numerical solution of the full system of equations, (5.1)-(5.2). (b) Bifurcation diagram of the fast subsystem, (5.6), with the projection of the solution from (a) superimposed. Not shown is a supercritical Hopf bifurcation on the right branch of the $G = 0$ nullcline at $(u, c) \approx (2.8, -10.55)$. 
Figure 5.4: Bursting with an undershoot ($\eta = 1.2$, $\dot{u} = 1.0$, and remaining parameter values as in Figure 5.2). (a) Numerical solution of the full system of equations, (5.1)-(5.2). (b) Bifurcation diagram of the fast subsystem, (5.6), with the projection of the solution from (a) superimposed. Unstable periodic orbits become stable at the saddle-node of periodics (SNP).
addition, the periodic orbits grow very quickly in size, and surround all three fixed points when \( c > c_m \). The periodic orbits disappear through a homoclinic bifurcation. We study these large periodic orbits and corresponding homoclinic bifurcations in more detail in the following sections. At this point, it suffices to mention that the undershoot observed in the numerical solution of (5.1)-(5.2) is simply the result of the fact that in the region of bistability, the fast subsystem exhibits periodic orbits with minimum \( u \) values smaller than the \( u \) values on the left branch of the \( G = 0 \) nullcline.

We note that the values of all parameters except \( \eta \) and \( \hat{u} \) were kept constant to produce the three different types of oscillatory behaviour in Figures 5.2-5.4. Depending on the values of these parameters, the bifurcation diagram of the fast subsystem may or may not exhibit Hopf, homoclinic, and saddle-node of periodics bifurcations. Furthermore, Hopf bifurcations may be supercritical or subcritical, and homoclinic bifurcations may correspond to a homoclinic orbit surrounding the fixed point on the right branch of the \( G = 0 \) nullcline only, or to a homoclinic orbit surrounding all three fixed points, and so on. That is, as the parameters are varied, the bifurcation diagram itself is undergoing bifurcations. It is these bifurcations that are of interest in this chapter.

The Hopf, homoclinic, saddle-node, and saddle-node of periodics bifurcations exhibited in Figures 5.2-5.4 are classified as codimension-1 bifurcations. The *codimension* of a bifurcation is the smallest dimension of a parameter space which contains the bifurcation in a consistent way [37].

More precisely then, the codimension-1 bifurcations themselves are undergoing bifurcations as \( \eta \) and \( \hat{u} \) are varied. For example, supercritical Hopf bifurcations become subcritical at a codimension-2 *degenerate Hopf bifurcation* (DHB). Similarly, stable homoclinic orbits become unstable at a codimension-2 *neutral saddle loop bifurcation* (NSL). The codimension-2 bifurcations associated with the Hopf, homoclinic, and saddle-node of periodics bifurcations are studied in Sections 5.4-5.6. Each codimension-2 bifurcation
gives rise to a curve in \((\eta, \hat{u})\) space. These curves in turn bound regions within which the bifurcation diagrams of the fast subsystem, (5.6), are qualitatively the same. Before studying the codimension-2 bifurcations, we perform preliminary symmetry and fixed point analyses in the next two sections.

5.2 Symmetry Considerations

In this section, we briefly examine the symmetries contained in the polynomial model. We use the symmetry in \( F \) to reduce the bifurcation map to the first quadrant of the \((\eta, \hat{u})\) plane. The symmetries will be explored further in Sections 5.4-5.6.

From (5.4), we deduce that

\[
G(u, c) = -G(-u, 6 - c), \quad (5.7)
\]

so that the \( G = 0 \) nullcline is a reflection of itself through the point \((u, c) = (0, 3)\), as indicated in Figure 5.1.

From (5.3), we deduce that

\[
F(u; \hat{u}, \eta) = F(u; \hat{u}, -\eta), \quad (5.8)
\]

\[
F(u; \hat{u}, \eta) = F(-u; -\hat{u}, \eta). \quad (5.9)
\]

Since the parameter \( \eta \) appears in \( F \) only, it is clear from (5.8) that changing \( \eta \) to \(-\eta\) has no effect on (5.1)-(5.2). Therefore, we eliminate the left half-plane of the bifurcation map and consider values of \( \eta \geq 0 \) only. Even though changing \( u \) to \(-u\) and \( \hat{u} \) to \(-\hat{u}\) does not affect \( F \) (cf. (5.9)), this transformation does affect the bifurcation diagram, in that the bifurcations occurring on the right branch of the \( G = 0 \) nullcline now occur on the left branch and vice versa. Curves of codimension-2 bifurcations thus originate in both the upper and lower half-planes. In fact, each curve in the first quadrant of the bifurcation map is reflected across \( \hat{u} = 0 \). As such, we only show the first quadrant of the bifurcation
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5.3 Preliminary Dynamical Systems Analysis

We apply standard dynamical systems methods (see for example [37, 46]) to the fast subsystem, (5.6), to determine the stability of the fixed points on the $G = 0$ nullcline. Even though the analysis is elementary, we include it here as a prerequisite for the following sections and derive some quantities that are referred to later. We note again that the location of the fixed points is independent of the parameter values in this simple polynomial model. However, the stability of the fixed points on the $G = 0$ nullcline is affected by the model parameters in the damping term, determined by $F$.

Writing (5.6) as a system of two first-order differential equations by letting $\vec{x} = (x_1, x_2) = (u, \dot{u})$, we obtain

$$\frac{d\vec{x}}{dt} = \vec{f}(\vec{x}; c), \quad (5.10)$$

where

$$\vec{f}(\vec{x}; c) = \begin{pmatrix} f_1(\vec{x}; c) \\ f_2(\vec{x}; c) \end{pmatrix} = \begin{pmatrix} x_2 \\ -G(x_1; c) - F(x_1)x_2 \end{pmatrix}. \quad (5.11)$$

Fixed points of (5.10) are of the form $\vec{x}_c = (x_1, 0)$, where $x_1$ is a root of $G(x_1; c) = 0$. The Jacobian matrix of (5.11) at the fixed point $\vec{x} = \vec{x}_c$ is

$$D\vec{f}(\vec{x}_c; c) = \left. \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \end{pmatrix} \right|_{\vec{x}=\vec{x}_c} = \begin{pmatrix} 0 & 1 \\ -G_u(x_1; c) & -F(x_1) \end{pmatrix}, \quad (5.12)$$

with determinant and trace given by

$$\text{Det} D\vec{f}(\vec{x}_c; c) = G_u(x_1; c) = 3(x_1^2 - 1), \quad (5.13)$$

$$\text{Tr} D\vec{f}(\vec{x}_c; c) = -F(x_1), \quad (5.14)$$
respectively.

The stability of the fixed points is deduced from the eigenvalues of $D\tilde{f}(\tilde{x}_c; c)$, given by

$$\mu_{1,2} = \frac{\text{Tr}D\tilde{f}}{2} \pm \frac{1}{2}\sqrt{\text{Tr}^2D\tilde{f} - 4\text{Det}D\tilde{f}}.$$  \hspace{1cm} (5.15)

If the determinant is negative, the eigenvalues $\mu_{1,2}$ are real and opposite in sign, and hence the fixed point is a saddle. Along the middle branch of the $G = 0$ nullcline, $\tilde{x}_1$ is between $u_m = -1$ and $u_M = 1$ (cf. Figure 5.1), so that the determinant is negative from (5.13). Thus, all fixed points along the middle branch are saddles. Similarly, the determinant is positive along the left and right branches of the $G = 0$ nullcline. In this case, the fixed points are either nodes or spirals, depending on the relative magnitude of the trace and the determinant. If the discriminant in (5.15) is positive, the fixed points are nodes. Otherwise the fixed points are spirals. Their stability in turn is determined by the sign of the trace. Stability is obtained if the trace is negative, and instability if the trace is positive.

5.4 Constraints on the Hopf Bifurcations

In this section, we examine the codimension-2 bifurcations associated with Hopf bifurcations. Hopf bifurcations occur when stable spirals become unstable spirals and vice versa. Based on the analysis in the previous section, Hopf bifurcations thus occur when the determinant in (5.13) is positive and the trace in (5.14) is zero. Written in term of $u$ and $c$, we require

$$G(u; c) = 0,$$  \hspace{1cm} (5.16)

$$G_u(u; c) = 3(u^2 - 1) > 0,$$  \hspace{1cm} (5.17)

$$F(u) = 0.$$  \hspace{1cm} (5.18)
Chapter 5. Multiple Bifurcations in a Polynomial Analog Model

The first condition simply states that there needs to be a fixed point. The remaining conditions together ensure that the fixed point is indeed a Hopf point. In particular, (5.17) implies that the Hopf bifurcation(s) may occur anywhere on the left or right branch of the $G = 0$ nullcline, since $u < u_m = -1$ on the left branch and $u > u_M = 1$ on the right branch. Finally, since $F$ is quadratic in $u$ (cf. equation (5.3)), (5.18) implies at most two Hopf bifurcations.

The symmetry about $\hat{u} = 0$ introduced in Section 5.2 is explored further here. Using (5.7)-(5.9) in (5.16) and (5.18) implies

$$G(-u; 6 - c) = 0,$$

$$F(-u; -\hat{u}, \eta) = 0,$$

so that if there is a Hopf bifurcation at $(u, c) = (u_{HB}, c_{HB})$, then there is also a Hopf bifurcation at $(u, c) = (-u_{HB}, 6 - c_{HB})$ when the sign of $\hat{u}$ is reversed. As a result, we expect codimension-2 curves associated with Hopf bifurcations on the right branch of the $G = 0$ nullcline to have a reflection, representing the codimension-2 curves associated with the corresponding Hopf bifurcation on the left branch, about $\hat{u} = 0$.

From now on, we refer to Hopf bifurcations on the right branch of the $G = 0$ nullcline as right Hopf bifurcations. Similarly, Hopf bifurcations on the left branch of the $G = 0$ nullcline are referred to as left Hopf bifurcations.

We examine the codimension-2 bifurcations affecting the number of Hopf bifurcations in more detail in Section 5.4.1 and investigate the codimension-2 bifurcations affecting the location of the corresponding Hopf points relative to the local extrema of the $G = 0$ nullcline in Section 5.4.2. In Section 5.4.3, we are concerned with the stability of the periodic orbits emanating from the Hopf points. We note that some of this work has been done previously by Pernarowski in [68]. We extend his work here by allowing left Hopf bifurcations and by allowing Hopf points to coalesce.
5.4.1 Number of Hopf Bifurcations

In Figures 5.2-5.4 we observed that the fast subsystem, (5.6), can exhibit one or two right Hopf bifurcations, depending on the values of $\eta$ and $\hat{u}$. For certain values of the parameters, it is also possible that there are no Hopf bifurcations. To determine the number of Hopf bifurcations, we examine $F(u)$ in more detail. From (5.3), we note that the graph of $F$ is a parabola (opening upward when $a$ is positive) and always has two roots, except when $\eta = 0$, in which case there is a double root at $u = \hat{u}$. We discuss this special case a little later. For positive values of $\eta$, the left and right roots are given by

$$u_L = \hat{u} - \eta,$$  \hspace{1cm} (5.21)

$$u_R = \hat{u} + \eta,$$  \hspace{1cm} (5.22)

respectively.

We are interested in the location of the two roots relative to the $u$ values at the local extrema of the $G = 0$ nullcline, $u_m = -1$ and $u_M = 1$ (cf. Figure 5.1), and wish to determine the effect of changing $\eta$ and $\hat{u}$. If $\eta$ and $\hat{u}$ are small, both roots lie between $u_m$ and $u_M$. That is, $F$ is zero along the middle branch of the $G = 0$ nullcline, where all fixed points are saddles. In this case, there can be no Hopf bifurcations.

Varying the value of $\hat{u}$ causes a horizontal shift in the graph and roots of $F(u)$. Increasing $\hat{u}$ causes the roots to be shifted to the right. When $u_R$ is to the right of $u_M$, but $u_L$ is still between $u_m$ and $u_M$, $F$ has one zero on the right branch and, thus, there is one corresponding right Hopf bifurcation. When $\hat{u}$ is increased further, so that $u_L$ is to the right of $u_M$ as well, $F$ has two roots on the right branch, corresponding to two right Hopf bifurcations. Similarly, left Hopf bifurcations emerge when the roots are shifted to the left of $u_m$ by a decrease in $\hat{u}$.

Varying the value of $\eta$ causes a vertical shift in the graph of $F(u)$. Increasing $\eta$ causes a vertical downward shift, resulting in an increase in the distance between the left and
right roots of $F$. For $\eta$ large enough, it is thus possible that $u_L$ lies to the left of $u_m$ and $u_R$ to the right of $u_M$, corresponding to one right and one left Hopf bifurcation.

The four curves representing the emergence of Hopf bifurcations at the local extrema (saddle-nodes) of the $G = 0$ nullcline, corresponding to $u_R = u_M$, $u_L = u_M$, $u_R = u_m$, and $u_L = u_m$, respectively, are

$$\hat{u} = 1 + \eta, \quad \hat{u} = 1 - \eta, \quad \hat{u} = -1 + \eta, \quad \hat{u} = -1 - \eta.$$  \hspace{1cm} (5.23) - (5.26)

These codimension-2 bifurcations are known as *Takens-Bogdanov bifurcations* (TB) (see [35, 36, 38] and references therein). We note that the curves defined by (5.23) and (5.26) are reflections of each other across $\hat{u} = 0$, as are the curves defined by (5.24)-(5.25), as expected from the symmetry discussion earlier.

The four curves are referred to as the minor TB (right), major TB (right), major TB (left), and minor TB (right) curves, respectively. The right and left descriptions refer to whether the emergence of the Hopf bifurcation occurs on the right or left branch of the $G = 0$ nullcline, and the major and minor descriptions refer to the first (major) or second (minor) Takens-Bogdanov bifurcation on the respective branch. The minor TB (right) curve and the portions of the major TB (right) and major TB (left) curves lying in the first quadrant of the bifurcation map are shown in Figure 5.5, and the number of Hopf bifurcations on the right and left branches of the $G = 0$ nullcline is indicated in each region defined by the curves.

In addition to the Takens-Bogdanov bifurcation, there is a second codimension-2 bifurcation through which Hopf bifurcations can (dis)appear, due to the double root of $F$, which corresponds to the coalescence of two Hopf points. From (5.3), $F(u)$ has a
5.4.2 Location of the Hopf Points

In this section, we are concerned with the location of the Hopf points relative to the \( c \) values at the local extrema of the \( G(u, c) = 0 \) nullcline, \( c_m = 1 \) and \( c_M = 5 \) (cf. Figure 5.1). The vertical location of the Hopf points can dramatically affect the solution behaviour, as shown in Figure 5.6. Figure 5.6b shows a bifurcation diagram similar to
Figure 5.6: Parabolic-amplitude bursting ($\eta = 0.47$, $\dot{u} = 1.3$, and remaining parameter values as in Figure 5.2). (a) Numerical solution of the full system of equations, (5.1)-(5.2). (b) Bifurcation diagram of the fast subsystem, (5.6).
the one shown in Figure 5.2b, but in which the Hopf point has moved up along the right branch of the $G = 0$ nullcline so that it lies in the region of bistability, between $c_m$ and $c_M$ (cf. Figure 5.1). The corresponding oscillatory behaviour produced by (5.1)-(5.2) is shown in Figure 5.6a. Rather than a square-wave burster as in Figure 5.2, we now have a burster where the amplitude of the spikes during the active phase changes dramatically. Pernarowski [68] refers to this type of bursting as *parabolic amplitude bursting*.

We distinguish between bifurcation diagrams such as shown in Figures 5.2b and 5.6b by imposing the constraint that a Hopf point lies either inside or outside the region of bistability. From Figure 5.1, there is a bifurcation in the location of the Hopf point when the corresponding root of $F$ occurs at $u = -2$ or $u = 2$.

The curves corresponding to $u_R = 2$, $u_L = 2$, $u_R = -2$, and $u_L = -2$ are given by the following equations,

\[
\begin{align*}
\dot{u} &= 2 + \eta, \\
\dot{u} &= 2 - \eta, \\
\dot{u} &= -2 + \eta, \\
\dot{u} &= -2 - \eta,
\end{align*}
\]

and are referred to as the minor HBL (right), major HBL (right), major HBL (left), and minor HBL (left) curves, respectively. Moving across the major HBL (right) curve on the bifurcation map corresponds to moving the major Hopf point on the right branch of the $G = 0$ nullcline into or out of the region of bistability in the bifurcation diagram of the fast subsystem, and so on. The curves are superimposed onto Figure 5.5 in Figure 5.7, and the locations of the Hopf points (if there are any) are indicated in each region. As in the previous section, the symmetry about $\dot{u} = 0$ is evident in the pair of curves defined by (5.27) and (5.30), and the pair defined by (5.28) and (5.29).
Figure 5.7: As Figure 5.5, with the minor HBL (right), major HBL (right), and major HBL (left) curves, representing bifurcations in the location of the respective Hopf point (relative to the c values at the local extrema of the $G = 0$ nullcline), superimposed.

5.4.3 Criticality of the Hopf Bifurcations

In Figures 5.2-5.4, we observed that Hopf bifurcations can be either supercritical or subcritical. That is, the periodic orbits emanating from a Hopf point can be either stable or unstable, respectively. In this section, we compute the curves which represent codimension-2 degenerate Hopf bifurcations (DHB), distinguishing regions on the bifurcation map in which the bifurcation diagrams exhibit either supercritical or subcritical Hopf bifurcations.

We first apply the center manifold theorem (see for example [37]) to (5.10). We assume that (5.10) has a Hopf point at $\tilde{x} = (x_{HB},0)$ and $c = c_{HB}$. Letting $\tilde{y} = (y_1, y_2) = (x_1 - x_{HB}, x_2)$ and writing the Taylor expansions for $G(x_1; c)$ and $F(x_1)$ about $u = x_1 = x_{HB}$
and $c = c_{HB}$, we obtain

$$\frac{d\vec{y}}{dt} = B\vec{y} + \vec{g}(\vec{y}),$$

(5.31)

where

$$B = \begin{bmatrix} 0 & 1 \\ -G_u(x_{HB}; c_{HB}) & 0 \end{bmatrix},$$

(5.32)

$$\vec{g}(\vec{y}) = \begin{pmatrix} g_1(\vec{y}) \\ g_2(\vec{y}) \end{pmatrix},$$

(5.33)

$$g_1(\vec{y}) = 0,$$

(5.34)

$$g_2(\vec{y}) = -\frac{1}{2}G_{uu}y_1^2 - \frac{1}{6}G_{uuu}y_1^3 - \vec{F}_u y_1 y_2 - \frac{1}{2} \vec{F}_{uu} y_1^2 y_2,$$

(5.35)

and the bar over the $G$ and $F$ denotes evaluation at $u = x_1 = x_{HB}, c = c_{HB}$. The eigenvalues of $B$ are $\pm \omega i$, where $\omega = \sqrt{G_u}$. The eigenvector corresponding to the $\omega i$ eigenvalue is

$$\begin{pmatrix} 1 \\ 0 \end{pmatrix} + i \begin{pmatrix} 0 \\ \omega \end{pmatrix}.$$  

(5.36)

We use the two components of this eigenvector as two new basis vectors, and make the transformation

$$y_1(1, 0) + y_2(0, 1) = z_1(0, \omega) + z_2(1, 0).$$

(5.37)

Letting $\vec{z} = (z_1, z_2)$, we write (5.31) in the standard form

$$\begin{pmatrix} \dot{z}_1 \\ \dot{z}_2 \end{pmatrix} = \begin{bmatrix} 0 & -\omega \\ \omega & 0 \end{bmatrix} \begin{pmatrix} h_1(\vec{z}) \\ h_2(\vec{z}) \end{pmatrix},$$

(5.38)

where

$$h_1(\vec{z}) = \frac{1}{\omega} g_2(\vec{y}) = -\frac{1}{2\omega} G_{uu} z_2^2 - \frac{1}{6\omega} G_{uuu} z_2^3 - \vec{F}_u z_1 z_2 - \frac{1}{2} \vec{F}_{uu} z_1^2 z_2^2,$$

(5.39)

$$h_2(\vec{z}) = g_1(\vec{y}) = 0.$$  

(5.40)
Using results in [37], the stability of the periodic orbits emanating from the Hopf point is determined by the sign of $a_{HB}$, where

$$a_{HB} = \frac{1}{16} \left[ \frac{\partial^3 h_1}{\partial z_1^3} + \frac{\partial^3 h_1}{\partial z_1 \partial z_2^2} \right] + \frac{1}{16\omega} \left[ \frac{\partial^2 h_1}{\partial z_1 \partial z_2} \left( \frac{\partial^2 h_1}{\partial z_1^2} + \frac{\partial^2 h_1}{\partial z_2^2} \right) \right],$$

and all derivatives of $h_1$ are evaluated at $\vec{z} = (0, 0)$. Using (5.3)-(5.4), $x_{HB} = \hat{u} \pm \eta$ from (5.21)-(5.22), and (5.39)-(5.40) in (5.41), we obtain

$$a_{HB} = \frac{1}{16\omega^2} \left[ \bar{F}_u \bar{G}_{uu} - \bar{G}_u \bar{F}_u \right] = 6a \left[ x_H^2 - 2x_H \hat{u} + 1 \right] = 6a \left[ \eta^2 - \hat{u}^2 + 1 \right].$$

If $a_{HB} < 0$, the Hopf bifurcation is supercritical and if $a_{HB} > 0$, the Hopf bifurcation is subcritical. We are interested in the degenerate case, $a_{HB} = 0$. Setting $a_{HB} = 0$ in (5.42), we obtain the two curves representing degenerate Hopf bifurcations in $(\eta, \hat{u})$ space,

$$\hat{u} = \pm \sqrt{1 + \eta^2},$$

again reflecting the symmetry about $\hat{u} = 0$.

The curves are referred to as the DHB (right) and DHB (left) curves, respectively. The DHB (right) curve is plotted in Figure 5.8. The DHB (left) curve is the reflection of the DHB (right) curve across $\hat{u} = 0$, and lies entirely in the fourth quadrant. In the region lying between the two DHB curves, all Hopf bifurcations are subcritical. In the regions lying outside these curves, all Hopf bifurcations are supercritical. It is interesting to note that the minor TB curves (cf. Figure 5.5), representing the emergence of a second right or left Hopf bifurcation, lie in the regions of supercriticality. That is, for bifurcation diagrams exhibiting two Hopf bifurcations on one branch, the periodic orbits emanating from the corresponding Hopf points are always stable.
Figure 5.8: As Figure 5.7, with the DHB (right) curve, representing a degenerate right Hopf bifurcation, superimposed.

5.5 Constraints on the Homoclinic Bifurcations

In this section, we examine the codimension-2 bifurcations associated with homoclinic bifurcations. We note that homoclinic bifurcations are sometimes referred to as *saddle loops* (SL) [36, 38], and some of the terminology used later will reflect this.

As in Chapter 3, the analysis of homoclinic bifurcations is based on Melnikov's method [64]. In Chapter 3, we were only interested in a homoclinic orbit surrounding fixed points on the right branch of the $G = 0$ nullcline. In this chapter, we also are interested in homoclinic orbits surrounding fixed points on the left branch of the $G = 0$ nullcline, as well as large homoclinic orbits surrounding three fixed points.

From now on, we refer to the homoclinic orbits surrounding fixed points on the right branch as *right homoclinic orbits*. Similarly, homoclinic orbits surrounding fixed points on the left branch are referred to as *left homoclinic orbits* and homoclinic orbits surrounding...
three fixed points are referred to as large homoclinic orbits. Large homoclinic orbits can be associated with a Hopf bifurcation on the right or left branch of the $G = 0$ nullcline. When we need to distinguish between these, we refer to large right or large left homoclinic orbits, respectively. In the same vein, we refer to right, left, large (right), and large (left) periodic orbits.

The existence of a homoclinic orbit is inferred from a change in the relative position of the stable and unstable orbits of the saddle point in the $(u, \dot{u})$ phase plane as the bifurcation parameter $c$ is varied. The situation for a right homoclinic orbit is as shown in Figure 3.3. For a low value of $c$ the right stable orbit lies outside the right unstable orbit and there is a right periodic orbit. For a high value of $c$ the stable orbit lies inside the unstable orbit and there are no periodic orbits. There is a right homoclinic orbit at the value of $c$ when the relative position of the orbits reverses and the stable and unstable orbits coincide. The situation for a left homoclinic orbit is similar, but in this case the relative position of the left stable and unstable orbits reverses. The situation for a large homoclinic orbit is shown in Figure 5.9. In this case, the orbits of interest are the large ones, connecting to the saddle point in the upper half plane. For a low value of $c$ the large stable orbit lies inside the large unstable orbit and there is a large periodic orbit. For a high value of $c$ the stable orbit lies outside the unstable orbit and there are no periodic orbits. The large periodic orbits cease to exist when the large stable and unstable orbits coincide, creating a large homoclinic orbit connecting the saddle point to itself.

The Melnikov distance functions, representing the distance between the stable and unstable orbits at a given value of $c$, are derived in Section 5.5.1. Since the definitions of $F(u)$ and $G(u, c)$ are simple, we can determine the Melnikov distance functions analytically. We use the Melnikov distance functions to derive the equations of the codimension-2 curves in the remaining sections. In Section 5.5.2, we distinguish between regions on the bifurcation map where bifurcation diagrams exhibit right, left, or large periodic orbits.
Figure 5.9: Phase portraits of the fast subsystem, (5.6), calculated with DSTOOL, showing the stable (solid curves) and unstable orbits (dashed curves) of the saddle point and illustrating the existence of a large homoclinic orbit. (a) For $c = 2.8$, the large stable orbit lies inside the large unstable orbit and there is a large stable periodic orbit surrounding all three fixed points. (b) For $c = 3.0$, the large stable orbit lies outside the large unstable orbit and there are no periodic orbits. The remaining parameter values are $\eta = 2.0$, $\hat{u} = 1.1$, and $a = 0.25$. 
In Section 5.5.3, we determine the conditions required to obtain a double homoclinic orbit, that is, a right and left homoclinic orbit at the same time. In Section 5.5.4, we are concerned with the stability of the periodic orbits near homoclinic bifurcations. Finally, we examine the conditions required for two homoclinic bifurcations to coalesce and disappear in Section 5.5.5.

5.5.1 The Melnikov Distance Functions

In this section, we derive the Melnikov distance functions measuring the separation between the stable and unstable orbits of the saddle point in the \((u, \dot{u})\) phase plane of the fast subsystem, (5.6), at a given value of \(c\) between \(c_m\) and \(c_M\). The derivation is essentially identical to the derivation outlined in Chapter 3, and we omit most of the details here.

In [68], Pernarowski showed that the value of \(F(u)\dot{u}\) is numerically small relative to \(\dot{u}\) and \(G(u, c)\) in the active phase near the homoclinic bifurcation. We thus can treat the \(F(u)\dot{u}\) term as a perturbation to the Hamiltonian system

\[
\dot{u} + G(u; c) = 0,
\]

so that Melnikov’s method can be applied to the fast subsystem, (5.6). As in the case of the biophysical models for bursting electrical activity in pancreatic \(\beta\)-cells, the unperturbed system has three fixed points for every value of \(c\) between \(c_m\) and \(c_M\), and its phase portrait at a typical value of \(c\) is as in Figure 3.8. The saddle point occurs at \((u, \dot{u}) = (a_s, 0)\), and the separatrix crosses the \(u\)-axis at \((b_s, 0)\) and \((c_s, 0)\), where the values of \(a_s\), \(b_s\), and \(c_s\) depend on \(c\).

From Chapter 3, the Melnikov distance function is given by

\[
D(c) = \int_{-\infty}^{\infty} F(u(t))\dot{u}(t)^2 dt,
\]

(5.45)
where \((u, \dot{u})\) needs to be evaluated along the separatrix solution of (5.44). To convert the integral in (5.45) to a line integral in \(u\), we first integrate (5.44) along the separatrix from \(a_s\) to \(u\), and use the fact that \(\dot{u} = 0\) when \(u = a_s\), to give

\[
\dot{u} = \pm \sqrt{-2V(u; a_s(c))},
\]

(5.46)

where

\[
V(u; a_s(c)) = \int_{a_s(c)}^{u} G(\bar{u}; c) \, d\bar{u},
\]

(5.47)

as before. However, whereas in Chapter 3 we had to resort to a numerical evaluation of \(V\), the simple definition of \(G\) allows us to determine \(V\) exactly. Using (5.4) in (5.47), we obtain

\[
V(u; a_s(c)) = \frac{1}{4} (u - a_s) \left[ 4c + (u^2 + a_s^2)(u + a_s) - 6(u + a_s) - 12 \right].
\]

(5.48)

Even though \(a_s\) can be expressed as a function of \(c\) explicitly, for convenience, we choose to express \(c\) as a function of \(a_s\) instead. Since \(a_s\) is given by \(G(a_s, c) = 0\), we have

\[
c = 3(a_s + 1) - a_s^3 \text{ from (5.4). Then}
\]

\[
V(u; a_s) = \frac{1}{4} (u - a_s) \left[ u^3 + a_s u^2 + (a_s^2 - 6)u - 3a_s^3 - 6a_s \right]
\]

\[
= \frac{1}{4} (u - a_s)^2 \left[ u^2 + 2a_s u + 3a_s^2 - 6 \right].
\]

(5.49)

Since \(\dot{u} = 0\) when \(u = b_s\) and \(u = c_s\) as well, it follows from (5.46) that \(b_s\) and \(c_s\) are given by \(V(b_s; a_s) = 0\) and \(V(c_s; a_s) = 0\), respectively. It is clear from (5.49) that \(V(u; a_s)\) has a double root at \(a_s\). The remaining two roots give \(b_s\) and \(c_s\). Requiring \(c_s < a_s < b_s\), we obtain

\[
b_s = -a_s + \sqrt{6 - 2a_s^2},
\]

(5.50)

\[
c_s = -a_s - \sqrt{6 - 2a_s^2}.
\]

(5.51)
We now have all the information to convert the integral in (5.45) to a line integral in $u$. We obtain three different Melnikov distance functions, $D_R$, $D_L$, and $D_S$, depending on whether we are interested in right, left, or large homoclinic orbits, respectively.

When we wish to examine a right homoclinic orbit, we need to evaluate the integral in (5.45) along the right loop of the separatrix solution of (5.44) (cf. Figure 3.8). Using (5.3), (5.46), and (5.49) in (5.45) gives the right Melnikov distance function,

$$D_R(a_s) = 2 \int_{a_s}^{b_s} F(u) \sqrt{ -2V(u; a_s) } du$$

$$= 2 \int_{a_s}^{b_s} F(u) \sqrt{ -\frac{1}{2} (u - a_s)^2 (u^2 + 2a_s u + 3a_s^2 - 6) } du$$

$$= \sqrt{2} \int_{a_s}^{b_s} F(u) \sqrt{ -(u^2 + 2a_s u + 3a_s^2 - 6) } du$$

$$= \sqrt{2a} \int_{a_s}^{b_s} \left[ (u - \hat{u})^2 - \eta^2 \right] (u - a_s) \sqrt{ -(u^2 + 2a_s u + 3a_s^2 - 6) } du.$$

(5.52)

Using standard tables of integrals and (5.50) in (5.53), we find

$$D_R(a_s) = a \left[ e_{R2}(a_s) (\hat{u}^2 - \eta^2) + e_{R1}(a_s) \hat{u} + e_{R0}(a_s) \right],$$

(5.54)

where

$$e_{R0}(a_s) = -\frac{12}{5} \sqrt{3} (a_s^4 - 2a_s^2 - 4) \sqrt{1 - a_s^2} + 6\sqrt{2} a_s (a_s^2 - 3) \Phi(a_s),$$

(5.55)

$$e_{R1}(a_s) = 6\sqrt{3} a_s (3 - a_s^2) \sqrt{1 - a_s^2} + 3\sqrt{2} (a_s^2 - 3) (a_s^2 + 1) \Phi(a_s),$$

(5.56)

$$e_{R2}(a_s) = 4\sqrt{3} \left[ 1 - a_s^2 + 2\sqrt{2} a_s (a_s^2 - 3) \right] \Phi(a_s),$$

(5.57)

$$\Phi(a_s) = \cos^{-1} \left( \frac{2a_s}{\sqrt{6 - 2a_s^2}} \right).$$

(5.58)

Similarly, when we wish to study a left homoclinic orbit, we need to evaluate the integral in (5.45) along the left loop of the separatrix solution of (5.44) (cf. Figure 3.8). Using (5.3), (5.46), and (5.49) in (5.45) then gives the left Melnikov distance function,

$$D_L(a_s) = -\sqrt{2a} \int_{a_s}^{a_s^*} \left[ (u - \hat{u})^2 - \eta^2 \right] (u - a_s) \sqrt{ -(u^2 + 2a_s u + 3a_s^2 - 6) } du.$$

(5.59)
The minus sign is due to the fact that \( |u - a_s| = -(u - a_s) \) along the left loop of the separatrix (cf. equation (5.52)). Using (5.51) in (5.59), we find

\[
D_L(a_s) = a \left[ e_{L2}(a_s)(\dot{u}^2 - \eta^2) + e_{L1}(a_s)\dot{u} + e_{L0}(a_s) \right],
\]

where

\[
e_{L0}(a_s) = -\frac{12}{5} \sqrt{3} (a_s^4 - 2a_s^2 - 4) \sqrt{1 - a_s^2} - 6\sqrt{2} a_s (a_s^2 - 3) \Psi(a_s),
\]
\[
e_{L1}(a_s) = 6\sqrt{3} a_s (3 - a_s^2) \sqrt{1 - a_s^2} - 3\sqrt{2} (a_s^2 - 3) (a_s^2 + 1) \Psi(a_s),
\]
\[
e_{L2}(a_s) = 4\sqrt{3} \sqrt{1 - a_s^2} - 2\sqrt{2} a_s (a_s^2 - 3) \Psi(a_s),
\]
\[
\Psi(a_s) = \cos^{-1} \left( \frac{-2a_s}{\sqrt{6 - 2a_s^2}} \right).
\]

Finally, when we are interested in a large homoclinic orbit, we need to evaluate the integral in (5.45) along both loops of the separatrix solution of (5.44) (cf. Figure 3.8). The corresponding large Melnikov distance function, \( D_S \), is simply the sum of \( D_R \) and \( D_L \). That is,

\[
D_S(a_s) = a \left[ e_{S2}(a_s)(\dot{u}^2 - \eta^2) + e_{S1}(a_s)\dot{u} + e_{S0}(a_s) \right],
\]

where

\[
e_{S0}(a_s) = e_{R0}(a_s) + e_{L0}(a_s),
\]
\[
e_{S1}(a_s) = e_{R1}(a_s) + e_{L1}(a_s),
\]
\[
e_{S2}(a_s) = e_{R2}(a_s) + e_{L2}(a_s).
\]

We now return to the discussion of the symmetry induced by changing \( \dot{u} \) to \( -\dot{u} \). From (5.55)-(5.58) and (5.61)-(5.64), we find

\[
e_{R0}(a_s) = e_{L0}(-a_s),
\]
\[
e_{R1}(a_s) = -e_{L1}(-a_s),
\]
\[
e_{R2}(a_s) = e_{L2}(-a_s).
\]
Then (5.54) and (5.60) imply

\[ D_R(a; \hat{u}, \eta) = D_L(-a; -\hat{u}, \eta). \quad (5.69) \]

From (5.7), we have

\[ a^3(c) = -a^3(6 - c), \quad (5.70) \]

which together with (5.69) implies that if there is a right homoclinic orbit at \((u_{HC}, c_{HC})\), then there must be a left homoclinic orbit at \((-u_{HC}, 6 - c_{HC})\). Therefore, we expect the codimension-2 curves associated with homoclinic bifurcations discussed below to exhibit the same symmetry about \(\hat{u} = 0\) as the codimension-2 curves associated with Hopf bifurcations.

### 5.5.2 Homoclinic Orbits at the Local Extrema of the \(G = 0\) Nullcline

In this section, we distinguish between regions on the bifurcation map where the bifurcation diagrams of the fast subsystem exhibit right, left, or large periodic orbits. We defer the investigation into the existence of corresponding homoclinic orbits to Section 5.5.5.

Right periodic orbits undergo the transition to large right periodic orbits and vice versa when the corresponding homoclinic orbits contact the local minimum of the \(G = 0\) nullcline (cf. Figures 5.2 and 5.4). A right homoclinic orbit occurs at the local minimum of the \(G = 0\) nullcline when \(D_R(u_m) = 0\). Recalling that \(u_m = -1\) and using (5.54), we thus require

\[ e_{R2}(-1)(\hat{u}^2 - \eta^2) + e_{R1}(-1)\hat{u} + e_{R0}(-1) = 0. \quad (5.71) \]

Using (5.55)-(5.58), we find

\[ e_{R0}(-1) = 12\sqrt{2}\pi, \quad (5.72) \]
\[ e_{R1}(-1) = -12\sqrt{2}\pi, \quad (5.73) \]
\[ e_{R2}(-1) = 4\sqrt{2}\pi, \quad (5.74) \]
so that (5.71) reduces to
\[ \eta^2 - \left( \dot{u} - \frac{3}{2} \right)^2 = \frac{3}{4}. \]  
(5.75)

This curve defines a hyperbola in \((\eta, \dot{u})\) space, representing a codimension-2 saddle-node loop bifurcation (SNL) [36, 38, 85] at the local minimum of the \(G = 0\) nullcline.

Similarly, left periodic orbits become large left periodic orbits and vice versa when the corresponding homoclinic orbits connect to the local maximum of the \(G = 0\) nullcline. A left homoclinic orbit occurs at the local maximum of the \(G = 0\) nullcline when \(D_L(u_M) = 0\). Recalling that \(u_M = 1\) and using (5.60), we thus require
\[ e_{L_2}(1)(\dot{u}^2 - \eta^2) + e_{L_1}(1)\dot{u} + e_{L_0}(1) = 0. \]  
(5.76)

Using (5.61)-(5.64), we find
\[ e_{L_0}(1) = 12\sqrt{2}\pi, \]  
(5.77)
\[ e_{L_1}(1) = 12\sqrt{2}\pi, \]  
(5.78)
\[ e_{L_2}(1) = 4\sqrt{2}\pi, \]  
(5.79)

so that (5.76) reduces to
\[ \eta^2 - \left( \dot{u} + \frac{3}{2} \right)^2 = \frac{3}{4}. \]  
(5.80)

This curve is the reflection of the hyperbola defined by (5.75) across \(\dot{u} = 0\) and represents the saddle-node loop bifurcation at the local maximum of the \(G = 0\) nullcline.

It is well-known that the transition from a right or left homoclinic orbit to a large homoclinic orbit is not immediate [10, 30]. Corresponding to each of the saddle-node loop bifurcations just discussed, there is a second saddle-node loop bifurcation at which the large homoclinic orbits contact the local extrema of the \(G = 0\) nullcline, so that there is a pair of saddle-node loop bifurcations near each of the local extrema. For parameter values between those at which two corresponding saddle-node loop bifurcations occur,
Chapter 5. Multiple Bifurcations in a Polynomial Analog Model

Figure 5.10: Illustration of a series of SNIC bifurcations at the local minimum of the $G = 0$ nullcline, $c = 1$, resulting in the deformation of a right homoclinic orbit into a large homoclinic orbit. At $c = 1$, the fast subsystem has two fixed points. The fixed point at $u = u_m = -1$ is the saddle-node and the fixed point at $u = 2$ is a spiral source. The direction of the large arrow indicates increasing values of $\eta$, which are 0.88, 1.0, 1.1, and 1.2, respectively. The parameters $\hat{\mu}$ and $a$ were held constant at 1.6 and 0.25, respectively.

The homoclinic orbit deforms continuously, as shown in Figure 5.10. The deformation is the result of a series of codimension-1 saddle-node on an invariant circle bifurcations (SNIC) [30]. How fast the deformation occurs depends on the value of the parameter $a$. The smaller $a$, the faster the deformation occurs and the smaller the distance in parameter space between the two saddle-node loop bifurcations. In the degenerate case, $a = 0$, the two saddle-node loop bifurcations merge.

We now attempt to derive the equation of the curves in parameter space which represent the saddle-node loop bifurcations corresponding to the connection of the large homoclinic orbits to the local extrema of the $G = 0$ nullcline. Large homoclinic orbits
Figure 5.11: As Figure 5.8, with the SNL (right) and SNL (left) curves, representing homoclinic bifurcations at the local extrema of the $G = 0$ nullcline, superimposed.

occur at the local minimum of the $G = 0$ nullcline when $D_S(u_m) = D_S(-1) = 0$. We recall that $D_S = D_L + D_R$. From (5.61)-(5.64), we find

$$e_{L0}(-1) = e_{L1}(-1) = e_{L2}(-1) = 0,$$

so that $D_L(-1) \equiv 0$ for all values of the parameters from (5.60). The condition $D_S(-1) = 0$ thus reduces to $D_R(-1) = 0$, giving the same result as in (5.75). Similarly, large homoclinic orbits occur at the local maximum of the $G = 0$ nullcline when $D_S(u_M) = D_S(1) = 0$, which reduces to $D_L(1) = 0$, giving the same results as in (5.80). We therefore conclude that the Melnikov theory predicts the location of the saddle-node loop bifurcations in the degenerate case $a = 0$.

The two hyperbolae given in (5.75) and (5.80) are referred to as the SNL (right) and SNL (left) curves, respectively, and are plotted in Figure 5.11. To the left of the SNL (right) and SNL (left) curves, bifurcation diagrams of the fast subsystem exhibit
right and left periodic orbits, respectively. To the right of these curves, the bifurcation
diagrams exhibit large right and large left periodic orbits, respectively, as indicated in
Figure 5.11. Near the two hyperbolae, we keep in mind that there is a small region where
homoclinic orbits contact the saddle-nodes at the local extrema of the $G = 0$ nullcline.
We can think of this region as a boundary layer, where the thickness of the layer depends
on the value of $a$, as well as $\eta$ and $\dot{u}$. The boundary layer is non-existent in the case
$a = 0$.

5.5.3 Double Homoclinic Orbits

In the region on the bifurcation map where bifurcation diagrams exhibit one right and one
left Hopf bifurcation, there is the possibility of having a codimension-2 double homoclinic
bifurcation, also known as a double saddle loop bifurcation (DSL) [36]. At this bifurcation,
right and left periodic orbits are homoclinic to the same saddle point on the middle branch
of the $G = 0$ nullcline, resulting in a figure eight.

The necessary conditions for this situation are

\[ D_R(a_3^1, 1) = 0, \quad (5.82) \]

\[ D_L(a_3^2) = 0, \quad (5.83) \]

\[ a_{3,1} = a_{3,2}. \quad (5.84) \]

From (5.54) and (5.82), we obtain

\[ \dot{u}^2 - \eta^2 = -\frac{e_{R1}\dot{u} - e_{R0}}{e_{R2}}. \quad (5.85) \]

Substituting (5.85) in (5.60) and (5.83), we obtain an equation for $\dot{u}$ in terms of $a_3$.
Solving for $\dot{u}$ and subsequently for $\eta$ from (5.85), we obtain the following parametric
equations ($a_3$ being the parameter),

\[ \dot{u} = \frac{e_{R0}e_{L2} - e_{L0}e_{R2}}{e_{L1}e_{R2} - e_{R1}e_{L2}^2}, \quad (5.86) \]
Figure 5.12: As Figure 5.11, with the DSL curve, representing simultaneous right and left homoclinic bifurcations, superimposed. The curve is parameterized by $a_s$, for $u_m \leq a_s \leq u_M$, as indicated.

$$\eta = \sqrt{\dot{u}^2 + \frac{e_{R1}}{e_R} \dot{u} + \frac{e_{R0}}{e_R}}, \quad (5.87)$$

where we remember that $e_{R0}$, etc., are functions of $a_s$.

The curve defined by (5.86)-(5.87) and $u_m < a_s < u_M$ is referred to as the DSL curve, and is shown in Figure 5.12. We note that the DSL curve precisely divides the region on the bifurcation map in question, namely the small triangular region bounded by the $\eta$-axis, the major TB (left) curve (cf. Figure 5.5), and the SNL (right) curve (cf. Figure 5.11). The DSL curve is symmetric about $\dot{u} = 0$, crossing the $\eta$-axis at $a_s = 0$, as expected from the symmetry of the $G = 0$ nullcline about $(u, c) = (0, 3)$. Staying in the triangular region, bifurcation diagrams of the fast subsystem exhibit the left homoclinic orbit below the right homoclinic orbit when parameter values are chosen to the left of the DSL curve. The relative position of the two homoclinic orbits reverses when parameter...
5.5.4 Neutral Homoclinic Orbits

In this section, we distinguish between bifurcation diagrams in which the periodic orbits near a homoclinic bifurcation are stable and those in which the periodic orbits are unstable, as shown in Figure 5.13. The stability of periodic orbits near homoclinic bifurcations is determined by the trace of the Jacobian matrix at the saddle point. If the trace is positive, the periodic orbits are stable, whereas if the trace is negative, the periodic orbits are unstable [36, 38]. We compute curves in the fast parameter space along which
the trace of the Jacobian matrix changes sign with a simple zero, representing *neutral homoclinic orbits*, also known as *neutral saddle loops* (NSL).

In light of (5.14), the required conditions for a neutral right homoclinic orbit are

\[ F(a_s) = 0, \quad (5.88) \]
\[ D_R(a_s) = 0. \quad (5.89) \]

Using (5.3), (5.88) can be written as

\[ \dot{u}^2 - \eta^2 = 2a_s \dot{u} - a_s^2. \quad (5.90) \]

Substituting (5.90) into (5.54) and (5.89), we obtain an equation for \( \dot{u} \) in terms of \( a_s \). Solving for \( \dot{u} \) and subsequently for \( \eta \) from (5.90), we find the following parametric equations (again with \( a_s \) being the parameter),

\[ \dot{u} = \frac{e_{R2}a_s^2 - e_{R0}}{2a_s e_{R2} + e_{R1}}, \quad (5.91) \]
\[ \eta = |a_s - \dot{u}|, \quad (5.92) \]

where we remember that \( e_{R0}, e_{R1}, \) and \( e_{R2} \) are functions of \( a_s \).

The conditions for a neutral left homoclinic orbit are as (5.88)-(5.89), but rather than \( D_R(a_s) = 0 \), we require \( D_L(a_s) = 0 \). The resulting parametric equations are exactly the same as (5.91) and (5.92), but \( e_{R0} \) is replaced by \( e_{L0}, e_{R1} \) by \( e_{L1}, \) and \( e_{R2} \) by \( e_{L2} \). Similarly, the parametric equations for the case of a neutral large homoclinic orbit are also the same as (5.91) and (5.92), but \( e_{R0} \) is replaced by \( e_{S0}, e_{R1} \) by \( e_{S1}, \) and \( e_{R2} \) by \( e_{S2} \).

The curve defined by (5.91)-(5.92) and \( u_m < a_s < u_M \) is referred to as the NSL (right) curve, and its analogs for the left and large homoclinic orbits are referred to as the NSL (left) and NSL (large) curves, respectively. The curves are added to the bifurcation map in Figure 5.14. We make the following observations about the new curves. The NSL (right) lies entirely in the first quadrant of the bifurcation map. The NSL (left) curve
Figure 5.14: As Figure 5.12, with the NSL (right), NSL (left), and NSL (large) curves, representing neutral homoclinic bifurcations, superimposed. The curves are parameterized by \( a_s \), as indicated.

is the reflection of the NSL (right) curve across \( \hat{u} = 0 \) and lies entirely in the fourth quadrant. The NSL (large) curve meets the NSL (right) curve on the SNL (right) curve (cf. Figure 5.11) at \((\eta, \hat{u}) = (\frac{7}{5}, \frac{2}{5})\) when \( a_s = u_m \). This point has special significance, as will be discussed in Section 5.8 below. As \( a_s \) increases, the curve remains in the first quadrant of the map, until there is a discontinuity at \( a_s = 0 \), at which point it reappears in the fourth quadrant. As \( a_s \) increases further, the curve traces the reflection of the corresponding portion in the first quadrant and meets the NSL (left) curve on the SNL (left) curve at \((\eta, \hat{u}) = (\frac{7}{5}, -\frac{2}{5})\) when \( a_s = u_M \) (not shown). For parameter values between the NSL curves, the bifurcation diagrams of the fast subsystem exhibit unstable homoclinic orbits, whereas the homoclinic orbits are stable for parameter values lying outside the NSL curves.
5.5.5 Coalescing Homoclinic Orbits

From Figures 5.2 and 5.3, we observed that the bifurcation diagram of the fast subsystem may or may not exhibit right homoclinic orbits when there are right periodic orbits. Similarly, the existence of left and large homoclinic orbits is not necessarily implied by the existence of corresponding periodic orbits. In this section, we distinguish between bifurcation diagrams exhibiting homoclinic orbits and those that do not.

Figure 5.15 shows bifurcation diagrams of the fast subsystem for two sets of parameters. In both cases, there are two right Hopf bifurcations and corresponding right periodic orbits. However, in Figure 5.15a there are two right homoclinic orbits, whereas in Figure 5.15b the homoclinic orbits have disappeared. Based on these observations, we look for a curve on the bifurcation map along which two right homoclinic orbits coalesce. The right Melnikov distance functions, $D_R(a_s)$, for the two cases just described are plotted in Figure 5.15c. We recall that $D_R(a_s) = 0$ gives the leading-order value of $a_s$ at which a right homoclinic orbit occurs. Thus, it is clear that right coalescing homoclinic orbits, or right coalescing saddle loops (CSL), must occur when the conditions

\[ D_R(a_s) = 0, \quad (5.93) \]

\[ \frac{dD_R(a_s)}{da_s} = 0, \quad (5.94) \]

hold. Technically, we also require \( \frac{d^2D_R(a_s)}{da_s^2} \neq 0 \), but we do not insist on this condition in the derivation below, since it is generically satisfied.

We solve (5.93) and (5.94) simultaneously. From (5.54), we obtain

\[ \frac{dD_R(a_s)}{da_s} = \epsilon'_R(\epsilon_R(a_s))(\hat{u}^2 - \eta^2) + \epsilon'_R(a_s)^2 + \epsilon'_R(\epsilon_R(a_s))\hat{u} + \epsilon'_R(\epsilon_R(a_s)), \quad (5.95) \]

where $\epsilon'_R(\epsilon_R(a_s))$, $\epsilon'_R(\epsilon_R(a_s))$, and $\epsilon'_R(\epsilon_R(a_s))$ are the derivatives of $\epsilon_R(a_s)$, $\epsilon_R(a_s)$, and $\epsilon_R(a_s)$.
respectively, easily obtained from (5.55)-(5.58). Using (5.54) and (5.93), we obtain

\[ \dot{u}^2 - \eta^2 = -\frac{e_{R1} \dot{u} + e_{R0}}{e_{R2}}. \]  

(5.96)

Substituting (5.96) into (5.94) and (5.95), we again obtain an equation for \( \dot{u} \). Solving for \( \dot{u} \) and subsequently for \( \eta \) from (5.96), we obtain the following parametric equations for \( \dot{u} \) and \( \eta \),

\[ \dot{u} = \frac{e_{R0} e_{R2} - e_{R0} e'_{R2}}{e_{R1} e'_{R2} - e'_{R1} e_{R2}}. \]  

(5.97)
Figure 5.16: As Figure 5.14, with the curves of coalescing homoclinic orbits, CSL (right), CSL (left), and CSL (large), superimposed. The curves are parameterized by $a_s$, as indicated.

\[ \eta = \sqrt{\dot{u}^2 + \frac{e_{R1}}{e_{R2}} \dot{u} + \frac{e_{R0}}{e_{R2}}}. \] (5.98)

The conditions for left and large coalescing homoclinic orbits are as in (5.93)-(5.94), with $D_R$ replaced by $D_L$ and $D_S$, respectively. The resulting parametric equations for these two cases are as in (5.97)-(5.98), with $e_{R0}$, $e_{R1}$, and $e_{R2}$ replaced accordingly.

The curve defined by (5.97)-(5.98) and $u_m < a_s < u_M$ is referred to as the CSL (right) curve, and its analogs for the left and large homoclinic orbits are referred to as the CSL (left) and CSL (large) curves, respectively. The curves are added to the bifurcation map in Figure 5.16.

The portion of the CSL (right) curve in the first quadrant of the bifurcation map lies entirely in the region where bifurcation diagrams exhibit two right Hopf bifurcations and the corresponding periodic orbits are small instead of large. That is, this portion of
the curve represents the situation inferred in Figure 5.15, as expected. The remaining portion of the curve lies in the fourth quadrant, opposite the CSL (left, large) curve across \( \dot{u} = 0 \). We discuss the meaning of this portion a little later.

The CSL (large) curve is symmetric about \( a_s = 0 \) on \( \dot{u} = 0 \), and follows the SNL (right) and SNL (left) curves very closely (cf. Figure 5.11), except for values of \( a_s \) near zero. For \( a_s \) near zero, the curve deviates significantly to the left of the SNL curves. We now have an apparent paradox, in that we deduced earlier that large periodic orbits exist only to the right of the SNL curves, up to some thin boundary layer. Yet the curve of coalescing large homoclinic orbits lies well to the left of these curves. We use DSTOOL and AUTO to resolve the paradox numerically.

We focus our attention on the same triangular region as discussed in connection with the DSL curve (cf. Section 5.5.3), namely the region bounded by the \( \eta \) axis, the major TB (left) curve, and the SNL (right) curve. In this region, each bifurcation diagram is guaranteed to exhibit both right and left periodic orbits, with corresponding right and left homoclinic orbits. In order for there to be a curve of coalescing large homoclinic orbits in this region, large periodic orbits also must exist. DSTOOL indeed confirms this for \( \eta = 1.64, \dot{u} = 0 \), and \( a = 0.25 \), as shown in Figure 5.17.

A regular one-parameter continuation with AUTO, using \( c \) as the bifurcation parameter and keeping \( \eta \) and \( \dot{u} \) fixed at 1.64 and 0, respectively, fails to reveal these large periodic orbits. We hypothesize that any branch of periodic orbits must be detached from the main bifurcation diagram, which AUTO, therefore, cannot find directly. We make use of a two-parameter continuation, discussed in more detail in Section 5.8 below, to find an initial condition on the detached branch from which start the required one-parameter continuation.

Bifurcation diagrams so obtained are shown in Figure 5.18. Figure 5.18a shows an open, detached branch of large periodic orbits terminating at large homoclinic bifurcations
Figure 5.17: Phase portrait of the fast subsystem, (5.6), at $c = 3$, showing that a large periodic orbit can exist in addition to right and left periodic orbits for certain values of the model parameters. The right and left periodic orbits are both unstable and the large periodic orbit is stable. The remaining parameter values are $\eta = 1.64$, $\dot{u} = 0$, and $a = 0.25$.

at both endpoints, for parameter values just to the left of the SNL (right) curve. When $\eta$ is decreased, corresponding to moving leftward on the bifurcation map, the detached branch shrinks in size, and the large homoclinic orbits approach each other, as shown in Figure 5.18b. Figure 5.18c shows that when $\eta$ is decreased further, the large homoclinic orbits coalesce as predicted by the CSL (large) curve, resulting in a closed, but still detached branch of periodic orbits. For even smaller values of $\eta$, the closed branch further shrinks in size and disappears when the two saddle-node of periodics bifurcations at the top and bottom of this branch coalesce, leaving only the main branch of the bifurcation diagram. The coalescence of the SNP bifurcations is significant and discussed in more detail in Section 5.6 below. We note that the relative position of the right and left homoclinic orbits is reversed in Figures 5.18a and 5.18b. This reversal is the result of
Figure 5.18: Bifurcation diagrams illustrating the existence of a branch of large periodic orbits which is detached from the main branch for certain values of the parameters. (a) $\eta = 1.64$. (b) $\eta = 1.54919$. (c) $\eta = 1.5255$. The other parameters are $\dot{u} = 0$ and $a = 0.02$. Areas enclosed by the boxes are enlarged in the figures to the right of the bifurcation diagrams in (b) and (c).
crossing the DSL curve (cf. Section 5.5.3) as \( \eta \) is decreased.

We now briefly investigate the dependence of the CSL curves on the parameter \( a_s \), as indicated in Figure 5.16. The CSL (right) curve starts at \( (\eta, \dot{\eta}) = (0, 1) \) when \( a_s = u_M \). As \( a_s \) decreases, both \( \eta \) and \( \dot{\eta} \) approach infinity, and the curve approaches the upper half of the SNL (right) curve. However, as \( a_s \) approaches \( u_m \), there is a discontinuity and the curve unexpectedly reappears in the fourth quadrant, virtually indistinguishable from the lower half of the SNL (right) curve there. When \( a_s = u_m \), the curve ends at the intersection of the SNL (right) and SNL (left) curves, at \( (\eta, \dot{\eta}) = (\sqrt{3}, 0) \). Similarly, the reflection of the CSL (right) curve, namely the CSL (left) curve, lies mostly in the fourth quadrant, but appears in the first quadrant for values of \( a_s \) very close to \( u_M \) and is virtually indistinguishable from the SNL (left) curve here. The CSL (large) curve is virtually indistinguishable from the SNL curves for all values of \( a_s \), except values of \( a_s \) close to zero, as noted above. For values of \( a_s \) between 0 and \( u_m \), the curve lies mainly in the first quadrant near the upper half of the SNL (right) curve, whereas for values of \( a_s \) between 0 and \( u_M \), the curve lies mainly in the fourth quadrant near the lower half of the SNL (left) curve. When \( a_s \) approaches \( u_m \) or \( u_M \), there is a discontinuity at both ends of the curve. They reappear in the opposite quadrants, essentially at the same location as the 'tails' of the CSL (right) and CSL (left) curves.

We interpret the bifurcations represented by these unexpected portions of the CSL curves with the aid of Figure 5.19. Figure 5.19a shows the bifurcation diagram of the fast subsystem for parameter values just above the CSL (left,large) curve which, for our purposes, is equivalent to the SNL (left) curve in the bottom right corner of the bifurcation map. We note that are left and right Hopf bifurcations, with corresponding left and large right homoclinic orbits, respectively. According to the analysis in Section 5.5.2, the left homoclinic orbit undergoes the transition to a large left homoclinic orbit when moving inside the SNL (left) curve. Considering this codimension-2 bifurcation alone, we thus
Figure 5.19: Bifurcation diagrams illustrating that large left and large right homoclinic orbits do not coexist. (a) Bifurcation diagram for $\eta = 2.2$, $\hat{u} = 0.46$. There are right and left Hopf bifurcations, with corresponding large right and (small) left homoclinic orbits. (b) Bifurcation diagram for $\eta = 2.0$, $\hat{u} = 0.4$. There no longer are any homoclinic orbits. For both diagrams, $a = 0.25$.

should expect bifurcation diagrams to exhibit both large left and large right homoclinic orbits. However, this is not the case, as shown in Figure 5.19b. The bifurcation diagram in this figure still exhibits left and right Hopf bifurcations, but there no longer are any homoclinic orbits. Moving across these curves has caused the left and large right homoclinic orbits to contact the local maximum of the $G = 0$ nullcline at $u = a_s = u_M$ essentially simultaneously, corresponding to coalescing left homoclinic orbits and coalescing large homoclinic orbits, as predicted.
Based on the interpretation of all portions of the CSL curves, we now can infer the number of homoclinic orbits in each region of the bifurcation map, as indicated in Figure 5.16.

5.6 Constraints on the Saddle-Node of Periodics Bifurcations

In this section, we examine the codimension-2 bifurcations associated with the saddle-node of periodics bifurcation. We can deduce the emergence of some SNP bifurcations by examining the criticality of a Hopf bifurcation and the stability of the corresponding homoclinic bifurcation (if it exists), and use AUTO to continue the study of the coalescing SNP bifurcations mentioned in the previous section.

From Figures 5.8 and 5.14, we observe that the DHB (right) curve, representing degenerate Hopf bifurcations, lies above the NSL curves, representing neutral homoclinic orbits. Furthermore, the regions in which Hopf bifurcations are subcritical and homoclinic orbits are stable overlap. The existence of subcritical Hopf bifurcations and stable homoclinic orbits at the same time necessarily implies the existence of at least one saddle-node of periodics (cf. Figure 5.4). That is, the DHB (right) and NSL curves also represent the emergence of an SNP bifurcation. The curves are redrawn in Figure 5.20 and the number of saddle-node of periodics is indicated in the regions bounded by these curves.

Below the NSL curves, there are either no or two saddle-node of periodics bifurcations. To divide this region, we return to the observation in the previous section that the detached branch of periodic orbits, exhibited by bifurcation diagrams in the region just below where the NSL curves meet, disappears through the coalescence of two SNP bifurcations (cf. Figure 5.18). Based on this observation, we infer the existence of the codimension-2 CSNP curve, for coalescing SNP bifurcations, which precisely divides this region in two. Points on this curve were computed with AUTO for several values of $\hat{u}$. 
Figure 5.20: As Figure 5.16, with the CSNP curve, representing coalescing SNP bifurcations on the detached branch of periodic solutions (cf. Figure 5.18), superimposed. Also highlighted are the DHB (right), NSL (right), and NSL (large) curves, which represent degenerate Hopf bifurcations on the right branch of the $G = 0$ nullcline, and neutral right and large homoclinic orbits, respectively, as well as the emergence of a saddle-node of periodics.

We note that this curve is the only curve for which we do not have an analytic equation.

Finally, we need to slightly adjust the qualitative features of the periodic orbits indicated in Figure 5.11. In the region between the CSNP and SNL (right) curves, large periodic orbits exist in addition to the right and left periodic orbits. We note that the large periodic orbits are not associated with a right or left Hopf bifurcation.

5.7 The Complete Bifurcation Map

At this point, all constraints on the codimension-1 bifurcations have been derived. The complete bifurcation map is shown in Figures 5.21 and 5.22. Based on the superposition of the qualitative features of the Hopf, homoclinic, and SNP bifurcations indicated on
Chapter 5. *Multiple Bifurcations in a Polynomial Analog Model*

Figure 5.21: The complete bifurcation map. Corresponding bifurcation diagrams are shown in the figures in Appendix B. The qualitative features of the Hopf, homoclinic, and SNP bifurcations exhibited by the bifurcation diagrams in each labelled region are summarized in Table 5.1. The regions not labelled in the box surrounding the CSNP curve are shown in Figure 5.22. The horizontal lines at $\hat{u} = 0.8$ and 1.5 are discussed in Section 5.8.
Chapter 5. Multiple Bifurcations in a Polynomial Analog Model

Figure 5.22: Enlarged view of a section of the bifurcation map (cf. Figure 5.20), identifying regions F1-F4. Corresponding bifurcation diagrams are shown in the figures in Appendix B. The qualitative features of the Hopf, homoclinic, and SNP bifurcations and the nature of the detached branch of periodic orbits exhibited by the bifurcation diagrams in these regions are summarized in Table 5.2 and its caption.

The intermediate versions of the map, we can deduce the qualitative structure of the bifurcation diagram in each region. We thus have answered the question posed in the introduction to this chapter, namely, can we deduce the bifurcation structure of the fast subsystem given the values of the two parameters $\hat{u}$ and $\eta$?

The qualitative features of the Hopf, homoclinic, and SNP bifurcations exhibited by the bifurcation diagrams in the regions identified in Figure 5.21 are summarized in Table 5.1. In regions F1-F4, identified in Figure 5.22, all bifurcation diagrams exhibit right and left subcritical Hopf bifurcations in the region of bistability, with corresponding unstable right and left homoclinic orbits, respectively. The relative position of the right and left homoclinic orbits is summarized in Table 5.2, as well as the nature of the detached branch of large periodic orbits. We mention again that an example of each type of bifurcation diagram is included in Appendix B.

The regions are roughly grouped according to the number of Hopf bifurcations exhibited by the bifurcation diagrams and whether corresponding homoclinic orbits are small.
<table>
<thead>
<tr>
<th>Region</th>
<th>Type of HB</th>
<th>Sub- or super-critical</th>
<th>Does HB lie in region of bistability?</th>
<th>Nature of corresponding HC</th>
<th>Number of SNP’s</th>
<th>Diagram shown in Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B1</td>
<td>major right</td>
<td>sub</td>
<td>yes</td>
<td>small unstable</td>
<td>0</td>
<td>5.13b</td>
</tr>
<tr>
<td>B2</td>
<td>major right</td>
<td>sub</td>
<td>yes</td>
<td>small stable</td>
<td>1</td>
<td>5.13a</td>
</tr>
<tr>
<td>B3</td>
<td>major right</td>
<td>sub</td>
<td>no</td>
<td>small stable</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>major right</td>
<td>super</td>
<td>no</td>
<td>small stable</td>
<td>0</td>
<td>5.2</td>
</tr>
<tr>
<td>B5</td>
<td>major right</td>
<td>super</td>
<td>yes</td>
<td>small stable</td>
<td>0</td>
<td>5.6</td>
</tr>
<tr>
<td>C1</td>
<td>major right</td>
<td>super</td>
<td>no</td>
<td>large stable</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>major right</td>
<td>super</td>
<td>no</td>
<td>small stable</td>
<td>0</td>
<td>5.15a</td>
</tr>
<tr>
<td>C3</td>
<td>major right</td>
<td>super</td>
<td>yes</td>
<td>small stable</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>major right</td>
<td>super</td>
<td>yes</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C5</td>
<td>major right</td>
<td>super</td>
<td>no</td>
<td>–</td>
<td>0</td>
<td>5.3, 5.15b</td>
</tr>
<tr>
<td>C6</td>
<td>major right</td>
<td>super</td>
<td>no</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>major right</td>
<td>sub</td>
<td>no</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>D2</td>
<td>major right</td>
<td>sub</td>
<td>no</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>D3</td>
<td>major right</td>
<td>sub</td>
<td>yes</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>D4</td>
<td>major right</td>
<td>sub</td>
<td>yes</td>
<td>large unstable</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>D5</td>
<td>major right</td>
<td>sub</td>
<td>no</td>
<td>large unstable</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>E1</td>
<td>major right</td>
<td>sub</td>
<td>no</td>
<td>large unstable</td>
<td>2</td>
<td>5.13d</td>
</tr>
<tr>
<td>E2</td>
<td>major right</td>
<td>sub</td>
<td>yes</td>
<td>large unstable</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>E3</td>
<td>major right</td>
<td>sub</td>
<td>yes</td>
<td>large stable</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td>major right</td>
<td>sub</td>
<td>no</td>
<td>large stable</td>
<td>1</td>
<td>5.4, 5.13c</td>
</tr>
<tr>
<td>E5</td>
<td>major right</td>
<td>super</td>
<td>no</td>
<td>large stable</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1: Summary of the qualitative features of the Hopf, homoclinic, and SNP bifurcations exhibited by bifurcation diagrams of the fast subsystem in the labelled regions on the complete bifurcation map in Figure 5.21.
Table 5.2: Summary of the qualitative features of the homoclinic and SNP bifurcations and the nature of the detached branches of periodic orbits exhibited by bifurcation diagrams in regions F1-F4 on the bifurcation map. In each region, there is a major right and left subcritical Hopf bifurcation (in the region of bistability) with corresponding right and left homoclinic bifurcations.

<table>
<thead>
<tr>
<th>Region</th>
<th>Relative location of the left and right homoclinic orbits</th>
<th>Nature of the detached branch of periodic orbits</th>
<th>Number of SNP’s</th>
<th>Diagram shown in Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>left below right</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>left below right</td>
<td>closed branch, no large homoclinic orbits</td>
<td>2</td>
<td>5.18c</td>
</tr>
<tr>
<td>F3</td>
<td>left below right</td>
<td>open branch, with two large unstable homoclinic orbits</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>right below left</td>
<td>open branch, with two large unstable homoclinic orbits</td>
<td>2</td>
<td>5.18a</td>
</tr>
</tbody>
</table>

or large. For example, bifurcation diagrams in regions B1-B5 all exhibit a major right Hopf bifurcation, and corresponding branches of periodic orbits terminate at a small right homoclinic orbit. Across the SNL (right) curve, bifurcation diagrams in regions E1-E5 also exhibit a major right Hopf bifurcation, but branches of periodic orbits terminate at large right homoclinic orbits. Within each group, moving from one region to a neighbouring region across a codimension-2 curve generally corresponds to changing just one qualitative feature of the bifurcation diagram. For example, moving from C5 to C6 across the minor HBL (right) curve corresponds to changing the location of the minor right Hopf bifurcation from being inside the region of stability to being outside, and so on. In light of the results in Section 5.6, moving across the DHB or NSL curves corresponds to changing two qualitative features of the bifurcation diagram, namely the
criticality of a Hopf bifurcation or the stability of a homoclinic orbit, respectively, and the number of SNP bifurcations.

5.8 Two-Parameter Bifurcation Diagrams

Up until now, we have concerned ourselves with the qualitative features of bifurcation diagrams only. However, quantitative information pertaining to the exact locations of the four types of codimension-1 bifurcations exhibited by the fast subsystem, namely the saddle-node, Hopf, homoclinic, and saddle-node of periodics bifurcations, cannot be obtained from the bifurcation map.

In this section, we generate two-parameter bifurcation diagrams to assist us in obtaining more quantitative information, without resorting to the one-parameter bifurcation diagrams. We can think of the two-parameter bifurcation diagrams as being a step in between the very quantitative one-parameter bifurcation diagrams and the very qualitative bifurcation map, as follows. One-parameter bifurcation diagrams indicate the location of the fixed points and their stability, and show the locations of the codimension-1 bifurcations. Two-parameter bifurcation diagrams show how the locations of the codimension-1 bifurcations depend on a second parameter. Curves on the two-parameter bifurcation diagrams are thus curves of codimension-1 bifurcations. We can infer codimension-2 bifurcations (the locations of which we indicate with a bullet in the figures below) from the two-parameter bifurcation diagram. The bifurcation map in turn consists of curves of codimension-2 bifurcations.

One of the parameters in the two-parameter bifurcation diagrams is $c$, our primary bifurcation parameter. The other parameter can be either $\eta$ or $\hat{u}$, and we choose the former, as the results then can be most easily compared to the results obtained by Bertram et al. [10] in Section 5.9 below. In Section 5.8.1, we examine two-parameter
Figure 5.23: Two-parameter bifurcation diagram generated with AUTO for $\hat{u} = 1.5$ and $a = 0.25$.

bifurcation diagrams computed with AUTO and relate them to the bifurcation map. However, equations for all curves in these diagrams, except those representing the SNP bifurcations, can be derived analytically based on the results in Sections 5.4 and 5.5. We do this in Section 5.8.2, and also compare the analytical and numerical two-parameter bifurcation diagrams.

5.8.1 Numerical Two-Parameter Bifurcation Diagrams

Figure 5.23 shows the two-parameter bifurcation diagram computed with AUTO for $\hat{u} = 1.5$. The curves of left SN’s and right SN’s represent the location of the left and right saddle-nodes at the local extrema of the $G = 0$ nullcline, respectively. Since the location
of the saddle-nodes does not depend on the model parameters, these curves are vertical lines at \( c = c_m = 1 \) and \( c = c_M = 5 \). The curves of major right HB’s, minor right HB’s, and left HB’s represent the locations of the respective Hopf bifurcations. For example, for \( \eta = 0.25 \), there are two right Hopf bifurcations, namely a major one at \( c \approx 2.9 \) and a minor one at \( c \approx 4.8 \). Similarly, the curves of right HC’s, left HC’s, and large HC’s represent the locations of the respective homoclinic orbits and the curve of SNP’s represents the location of the saddle-node of periodics. We note that homoclinic bifurcations only occur at values of \( c \) in the region of bistability and, hence, the corresponding curves in the two-parameter bifurcation diagram remain between \( c = 1 \) and \( c = 5 \). In contrast, the curves of HB’s and SNP’s continue outside this region, reflecting the fact that Hopf and SNP bifurcation can occur at any value of \( c \).

We relate the two-parameter bifurcation diagram in Figure 5.23 to a horizontal cut through the bifurcation map at \( \hat{u} = 1.5 \) (cf. Figure 5.21) as follows. Each intersection of the horizontal line with a curve on the bifurcation map corresponds to a codimension-2 bifurcation, reflected by a bullet in the two-parameter bifurcation diagram. For example, the intersection with the CSL (right) curve corresponds to the emergence or disappearance of two right homoclinic orbits. In the two-parameter bifurcation diagram, this event is reflected by the bullet at the local minimum of the curve of right HC’s.

As mentioned in Section 5.5.2, the transitions from small to large homoclinic orbits at the local extrema of the \( G = 0 \) nullcline or saddle-nodes are not immediate, but occur over a range of parameter values in conjunction with SNIC bifurcations. This is clearly evident in Figure 5.23, where the curves of right and left HC’s and the curve of large HC’s join the curves of right and left SN’s at different values of \( \eta \). The analysis in Section 5.5.2 failed to yield curves on the bifurcation map corresponding to the codimension-2 SNL bifurcations at which large homoclinic orbits contact saddle-nodes. This failure is reflected in the two-parameter bifurcation diagram by the omission of bullets at the points where the curve
of large HC's joins the curves of right and left SN's.

Finally, we observe that the curve of SNP's emanates from the bullet corresponding to the codimension-2 NSL (large) bifurcation, as expected from Figure 5.20 and the discussion in Section 5.6. The bullet corresponding to the DHB (right) bifurcation is not shown but occurs at \( c \approx -7.21 \). Another curve of SNP's emerges from this point, also as expected.

We now examine the dependence of the two-parameter bifurcation diagram on \( \hat{u} \).

Returning to the bifurcation map, we observe two points at which curves meet in a cusp-like fashion, namely \((\eta, \hat{u}) = (0, 1)\) and \((\eta, \hat{u}) = (\frac{7}{5}, \frac{2}{3})\). We discuss the changes in the two-parameter bifurcation diagram as they relate to these points.

As \( \hat{u} \) decreases from \( \hat{u} = 1.5 \), the minor TB (right) bullet moves down along the curve of right SN's towards \( \eta = 0 \), and is exchanged for a major TB (right) bullet when \( \hat{u} = 1 \), as expected from the TB (right) curves on the bifurcation map. Similarly, the DHB (right) bullet (not shown in Figure 5.23) moves down along the curve of right HB's, and is exchanged for an NSL (right) bullet when \( \hat{u} = 1 \). For \( \hat{u} < 1 \), the curve of SNP's originally emanating from the DHB (right) bullet emanates from the NSL (right) bullet instead. In addition, both CSL (right) and CHB (right) bullets move towards the minor TB (right) bullet as \( \hat{u} \) decreases and vanish when \( \hat{u} = 1 \). Figure 5.24a shows the resulting two-parameter bifurcation diagram for \( \hat{u} = 0.8 \).

As \( \hat{u} \) decreases further, the NSL (right) and NSL (large) bullets approach each other, until they meet on the curve of left SN's when \((\eta, \hat{u}) = (\frac{7}{5}, \frac{2}{3})\). At this point, the two curves of SNP's join, and immediately detach from the curves of HC's for values of \( \hat{u} < \frac{2}{5} \). This detachment is clearly shown in the two-parameter bifurcation diagram for \( \hat{u} = 0 \) in Figure 5.24b. We can identify a local minimum on the curve of SNP's, corresponding to the coalescence of two saddle nodes of periodics, reflected by the CSNP bullet. Similarly, the curve of large HC's now also clearly has a local minimum, corresponding to
Figure 5.24: Two-parameter bifurcation diagrams generated with AUTO for (a) $\dot{u} = 0.8$ and (b) $\dot{u} = 0$. In both cases, $a = 0.25$. 
the coalescence of two large homoclinic orbits, and reflected by the CSL (large) bullet. Finally, double homoclinic orbits are indicated by the DSL bullet at the intersection of the curves of right and left HC's. We note that Figure 5.24b exhibits symmetry about $c = 3$ in light of the discussion in Section 5.2. Furthermore, small imperfections in the curves of HC's are the result of AUTO having some difficulties with the computations.

5.8.2 Analytical Two-Parameter Bifurcation Diagrams

In this section, we derive the equations of the curves of HB's and HC's based on the results of Sections 5.4 and 5.5, and compare the analytical two-parameter bifurcation diagram so obtained with the numerical version.

For the curves of HB's, we use (5.3)-(5.4) to rewrite (5.16) and (5.18) as

$$c = 3(u + 1) - u^3, \quad (5.99)$$
$$\eta = \left| \dot{u} - u \right|, \quad (5.100)$$

so that $c$ and $\eta$ are parameterized by $u$. Values of $u \geq u_M$ generate the curves of right HB's, whereas values of $u \leq u_m$ generate the curve of left HB's.

For the curve of right HC's, we require $D_R(a_s) = 0$. Using (5.54) to isolate $\eta$ and $u = a_s$ in (5.99), we again obtain parametric equations for $c$ and $\eta$,

$$c = 3(a_s + 1) - a_s^3, \quad (5.101)$$
$$\eta = \sqrt{\dot{u}^2 + \frac{e_{R1}(a_s)}{e_{R2}(a_s)}\dot{u} + \frac{e_{R0}(a_s)}{e_{R2}(a_s)}}, \quad (5.102)$$

where now $a_s$ is the parameter, for $u_m \leq a_s \leq u_M$. The curves of left and large HC's are given by (5.101)-(5.102) with the $e_R$'s replaced by $e_L$'s and $e_S$'s, respectively.

The curves defined by (5.99)-(5.100) and (5.101)-(5.102) and the trivial curves of right and left SN's are plotted in Figure 5.25a for $\dot{u} = 1.5$. Figure 5.25b shows the comparison of the analytical two-parameter bifurcation diagram with the numerical versions generated
Figure 5.25: (a) Analytical two-parameter bifurcation diagram for $\dot{u} = 1.5$. (b) Comparison with AUTO results (solid curves) for $a = 0.25$, $a = 0.15$, $a = 0.05$, and $a = 0.01$. The arrow indicates the direction of increasing $a$. 
with AUTO for several values of the parameter $a$. We observe that the agreement between the respective curves of right and left HB’s is exact for all values of $a$. The agreement between the respective curves of right and left HC’s also is very good. However, the agreement between the respective curves of large HC’s is highly dependent on the value of $a$. The smaller the value of $a$, the better the agreement.

From (5.3), (5.6), and (5.44) we see that the value of $a$ affects the size of the perturbation to the Hamiltonian system. Recalling that the curves of HC’s are derived from Melnikov’s method, which is a leading-order method based on the perturbation of the Hamiltonian system, the dependence of the agreement between the analytical and numerical results on $a$ is not surprising. What is interesting, however, is the observation that the value of $a$ hardly affects the curves of right and left HC’s, but significantly affects the curve of large HC’s. The reason why this is so lies in the effect of the size of the perturbation on the deviation of the relevant stable and unstable orbits of the saddle point from the separatrix of the Hamiltonian system (cf. Figure 3.8). For the curve of right (left) HC’s, the relevant orbits are the right (left) stable and unstable orbits which are hardly affected by the size of the perturbation (cf. Figure 3.3). In contrast, for the curve of large HC’s, the relevant orbits are the large ones and these are significantly affected by the size of the perturbation term (cf. Figure 5.9).

Finally, we note that decreasing the value of $\dot{u}$ also decreases the size of the perturbation term. That is, the analytical and numerical two-parameter bifurcation diagrams for $\dot{u} = 0.8$ and $\dot{u} = 0$ correspond very closely even for relatively large values of $a$.

5.9 On the Classification of Bursting Oscillations

The classification of bursting oscillations was begun by Rinzel [77], who identified three types of bursting oscillations. Rinzel’s scheme is based on an examination of the spike
frequency profile during the active phase and a characterization of the initiation and termination of the active phase in terms of a one-parameter bifurcation diagram.

In [10], Bertram et al. elaborate on and extend Rinzel's classification scheme. Their scheme is put into the context of a sequence of horizontal traversals through a two-parameter bifurcation diagram. For example, in Figure 5.23, a horizontal bar at $\eta = 0.75$ starting at the curve of left SN's and terminating at the curve of right HC's corresponds to a bursting solution in which the active phase starts at a saddle-node and terminates due to the passage through a right homoclinic bifurcation.

The two-parameter diagram shown in [10] is generated with the biophysically based Chay-Cook model. Surprisingly, this two-parameter bifurcation diagram is qualitatively identical to the one shown in Figure 5.23, except that the secondary parameters on the vertical axes, $\mu$ and $\eta$, respectively, are inversely related. In the Chay-Cook model, $\mu$ affects the time constant of the relaxation equation for the activation variable $n$ (cf. (2.11)). Drawing an analogy between the two parameters, we may interpret $\eta$ in the same way.

From the similarity of the two-parameter bifurcation diagrams generated with the Chay-Cook and polynomial models, we conclude that the polynomial analog model not only superficially mimics various types of solution behaviour of models of excitable cells, but also possesses the rich bifurcation structure of such models. Therefore, we suggest that the classification scheme of Bertram et al. can be taken a step further by considering bifurcation maps. In particular, such maps provide information about the relationships among the various types of oscillatory behaviour as evident from the bifurcation diagrams in the different regions.

In terms of the bifurcation map for the polynomial model, the types of bursting behaviour classified by Bertram et al. only form a subset of the set of possible types of oscillatory behaviour. In particular, none of the behaviour implied by bifurcation
diagrams in the lower portion of the bifurcation map have been classified.

The question of precisely how the classification of Bertram et al. can be extended further based on the different qualitative features of the bifurcation diagrams in each of the regions on a bifurcation map is not pursued in this thesis, but is left as an opportunity for future work.

5.10 Effect of $\varepsilon$ on the Solution Behaviour of the Full System of Equations

In this final section, we briefly examine the effect of $\varepsilon$ on the solution behaviour of the full system of equations, (5.1)-(5.2). The reason for initiating this study is based on an observation made during the analysis of one of the biophysical models of bursting electrical activity in pancreatic $\beta$-cells studied in the previous chapters, namely the Chay (1986) model. When the values of the parameters given in [13] are used, square-wave bursting is obtained, as for the other biophysical models under consideration in this thesis. However, Melnikov's method fails to determine the location of any homoclinic bifurcation, since the Melnikov distance for this model is positive for all values of the bifurcation parameter $z$ between $z_m$ and $z_M$.

Upon further investigation with AUTO, we find that the fast subsystem of the Chay (1986) model has the bifurcation structure of a tapered burster (cf. Figure 5.3), rather than the expected bifurcation structure of a square-wave burster (cf. Figure 2.6). We point out that the positive Melnikov distance for all values of $z$ between $z_m$ and $z_M$ is in accordance with the bifurcation structure of a tapered burster. Thus, the failure to determine the location of the homoclinic bifurcation is not the result of incorrectly applying Melnikov's method, but rather, it is the result of inappropriately applying the method to a fast subsystem which exhibits no homoclinic orbits. We note that for the purposes of Chapters 2-4, we have adjusted the values of the parameters slightly so that
the bifurcation diagram of the fast subsystem is as shown in Figure 2.6b, as indicated in Appendix A.2.

We now have an apparent paradox, in that the fast subsystem of the Chay (1986) model is that of a tapered burster, yet the numerical solution of the full system of equations exhibits square-wave bursting. The same phenomenon is easily reproduced with the polynomial analog model, as shown in Figure 5.26. However, when the value of the parameter $\varepsilon$ is decreased, the numerical solution indeed exhibits tapered bursting, as shown in Figure 5.27. From (5.2), we observe that $\varepsilon$ governs the rate at which the slow variable $c$ changes. For the smaller value of $\varepsilon$, the dynamics of $c$ are sufficiently slow that the solution trajectory remains close to the envelope of periodic orbits and, thus, can 'sneak through' the small opening close to the middle branch of the $G = 0$ nullcline and the left branch of periodic orbits and reach the upper Hopf point, as expected.

We believe that the nongeneric behaviour observed above is typical near boundaries of regions on the bifurcation map. That is, although the bifurcation diagrams of the fast subsystem do change as predicted by the codimension-2 curves on the map, the transitions in the corresponding numerical solutions of the full system of equations are $\varepsilon$-dependent.

Wiggins [92] includes a word of caution on the interpretation and application of bifurcation diagrams relating to the same type of phenomenon. Dynamical systems having parameters that change in time, no matter how slowly, and that pass through bifurcation values may exhibit behaviour that is different from the situation where the parameters are constant. For references to detailed analyses of such problems, see [92].
Figure 5.26: Illustration of an apparent paradox: the bifurcation diagram of the fast subsystem is that of a tapered burster, yet the numerical solution of the full system of equations exhibits square-wave bursting. The bifurcation diagram shown is for $\eta = 0.7$, $\dot{u} = 1.95$, and $a = 0.25$, lying in region C5 of the bifurcation map, just above the CSL (right) curve. The projection of the numerical solution of the full system of equations, (5.1)-(5.2), is superimposed for $\varepsilon = 0.0025$. The values of the remaining parameters are as in Figure 5.2.
Figure 5.27: Resolution of the apparent paradox. When the value of \( \varepsilon \) is decreased to \( \varepsilon = 0.001 \), the numerical solution of the full system of equations exhibits tapered bursting, as expected from the bifurcation diagram of the fast subsystem. All other parameters are as in Figure 5.26.
Chapter 6

Conclusions and Discussion

In this thesis, we have presented a variety of mathematical methods and techniques to study models of bursting oscillations. In particular, we have focused on models of bursting electrical activity (BEA) in the membrane potential of pancreatic $\beta$-cells and a polynomial analog model of the bursting phenomenon.

In the first part of this thesis, consisting of Chapters 2, 3, and 4, we investigated the determination of the plateau fraction for several models of BEA in pancreatic $\beta$-cells. The plateau fraction is physiologically important because it appears to be strongly correlated to the rate of insulin release. We have extended the techniques of Pernarowski [67] and Pernarowski et al. [69, 70], developed in the context of the Sherman-Rinzel-Keizer model, to a class of first-generation models which describe BEA in pancreatic $\beta$-cells and which consist of three ordinary differential equations. These models have in common the assumption that intracellular Ca$^{2+}$ concentration is the agent controlling the initiation and termination of the active phase during the bursting activity.

Although these models have been superseded by more recent second-generation models, the methods and techniques developed remain useful, since all these subsequent models of BEA also are based on the assumption that there is a slow variable in the system that controls the initiation and termination of the active phase. From a mathematical point of view, the identity of the slow variable is irrelevant and, therefore, we believe that the analyses presented in this thesis can be generalized to other models of BEA (see below).
In Chapter 2, we proposed a consistent nondimensionalization of the model equations which carried all of the models into a standard form. These equations then were reformulated to facilitate the analysis in subsequent chapters. In particular, the equations were rewritten as a second-order fast subsystem coupled to a first-order slow subsystem. Based on the form of the fast subsystem equation, we discovered that from an analytical point of view, the most important distinction between the models is the value of the integer exponent $p$ of the activation variable $n$ in the voltage-gated $K^+$ current. The value of $p$ affects the form of the damping terms (see below), however, it does not affect the qualitative bifurcation structure of the fast subsystem. The bifurcation diagrams of the fast subsystem, using the slow variable $z$ as the bifurcation parameter, were shown to have at least one Hopf bifurcation and one corresponding homoclinic bifurcation.

To determine the approximations of the plateau fractions from the model equations, we needed to be able to predict when the silent and active phases begin and end. Projecting the numerical solution of the full system of equations onto the bifurcation diagram of the fast subsystem revealed that the transition from the silent to the active phase occurs near the local minimum of the fast subsystem nullcline, which is easy to determine. However, the transition from the active to the silent phase occurs near a homoclinic bifurcation and its location is much more difficult to determine.

In Chapter 3 then, we approximated $z_{esc}$, which is the value of $z$ at which the numerical solution of the full system undergoes the transition from the active phase back to the silent phase, by $z_{HC}$, which is the value of $z$ at which the fast subsystem exhibits the homoclinic bifurcation of interest. The value of $z_{HC}$ in turn was approximated by using two numerical methods and two analytically based methods which required some numerical computations.

The two numerical methods were the use of AUTO to approximate the homoclinic orbit by a periodic orbit with very large period and bisection based on the bifurcation of
the behaviour of the solution trajectories in the phase plane of the fast subsystem. Both methods consistently provided approximations of \( z_{HC} \) which were very close to typical exact \( z_{esc} \) values.

The two analytically based methods we used were Melnikov’s method and the Fredholm alternative method. We reformulated the fast subsystem equation as a perturbed Hamiltonian system. For perturbed Hamiltonian systems, the two methods yield the same results, since the methods produce the same sequence of improper integrals. The methods were extremely efficient for determining the leading-order approximation of \( z_{HC} \) since the corresponding leading-order improper integral could be converted into a line integral in the phase plane of the fast subsystem. However, they provided accurate leading-order approximations of \( z_{HC} \) for only two of the six models under consideration, namely the Chay-Kang and Sherman-Rinzel-Keizer models. For the remaining four models, a higher-order correction was required.

The problem of obtaining a first-order correction to the leading-order approximations of \( z_{HC} \) was posed as a boundary-value problem which was solved numerically with COLSYS. The resulting first-order correction significantly improved the leading-order approximations of \( z_{HC} \) for the three models with \( p \neq 1 \), namely the reduced Chay-Keizer, Chay (1986), and Himmel-Chay models. The first-order correction for models with \( p = 1 \), namely the Chay-Kang, Sherman-Rinzel-Keizer, and Chay-Cook models, was shown to be identically equal to zero. We expect that a few higher-order corrections to further improve the approximations of \( z_{HC} \) for all models can be obtained in the same way. However, obtaining higher-order corrections is computationally very expensive and, therefore, not very practical in light of the availability of software packages such as AUTO.

We concluded that for the approximation of \( z_{HC} \) and, subsequently, \( z_{esc} \), which were required for a fixed set of fast subsystem parameters, the numerical methods are the methods of choice, especially the use of AUTO, since they efficiently provided the most
accurate approximations of $z_{esc}$.

Although the two analytically based methods for approximating $z_{HC}$ were not as successful as the numerical methods in terms of efficiency and accuracy, they did give rise to an interesting observation. In order to apply Melnikov's method and the Fredholm alternative method, we rewrote the fast subsystem equation of Chapter 2, (2.51), as a perturbed Hamiltonian system in Chapter 3, (3.8). The relative ease with which this reformulation could be done depended on the form of the damping terms $E(u, \dot{u}; z)$ and $F(u; z)$ in (2.51) and especially on the value of the parameter $p$. The modified damping term $\delta \tilde{F}(u, \dot{u}; z)$ in (3.8) was shown to be numerically small relative to the remaining terms for all models under consideration. This result was essential for the extension of the analysis of the Sherman-Rinzel-Keizer model by Pernarowski [67] and Pernarowski et al. [70] to these models. The question remains why this modified damping term is small for all models and whether this observation is generic. The finding that this damping term is not sufficiently small for the Chay-Cook model to yield an accurate leading-order approximation of $z_{HC}$ by Melnikov's method and the Fredholm alternative method provides a starting point for future research in this direction.

All four methods for approximating $z_{HC}$ were based on an analysis of the fast subsystem. Since the glucose-dependent parameter $\beta$ appears only in the slow subsystem, these methods have provided approximations for $z_{HC}$ and, subsequently, $z_{esc}$ which are independent of $\beta$. In order to elicit the dependence of $z_{esc}$ on $\beta$, the effects of the slowly varying bifurcation parameter $z$ must be included. In [79], Robinson shows how Melnikov's method can be extended so that it applies to perturbed systems of equations in which the parameters vary slowly with time. Robinson considers systems for which the perturbation is of the same order as the time scale on which the parameters vary. For the models of bursting electrical activity under consideration in this thesis, the parameter or slow variable $z$ changes on a time scale of $O(\varepsilon)$, whereas the perturbation in (3.8) is $O(\xi)$. 
In light of Table 3.2, $\delta >> \epsilon > 0$, and so Robinson's method is not directly applicable. The adaptation of Robinson's method to the type of models studied provides another opportunity for future work.

In Chapter 4, we investigated the dependence of the approximate plateau fraction on the glucose-dependent parameter $\beta$. To determine the leading-order plateau fraction, we required the leading-order silent and active phase durations. To obtain the leading-order silent phase duration, we first rescaled the equations to the slow time scale and obtained a singular perturbation problem. The leading-order solution of this problem yielded a leading-order silent phase duration in excellent agreement with the exact silent phase duration for each biophysical model considered here. To obtain the leading-order active phase duration, we used a multiple scales analysis and averaging of the active phase problem. The resulting approximations were shown to be in excellent agreement with the exact numerical results as well.

The subsequent leading-order approximations of the plateau fraction were shown to consistently overestimate the exact plateau fractions. This discrepancy is due to the omission of the duration of the transition phases in the leading-order burst period, thereby reducing the denominator in the plateau fraction. Finally, we derived the equations of two surfaces that correctly describe each of the transition phases in $(u, \dot{u})$ space. However, the equations could not be used to derive a leading-order approximation of the transition phase durations due to the occurrence of singularities in the corresponding quadratures.

We expect that to successfully obtain the leading-order transition phase durations, it is necessary to perform a higher-order analysis, requiring the method of matched asymptotic expansions. In addition, we believe that an analysis of the slow passage through a limit point (the local minimum of the fast subsystem nullcline), similar to that in [31, 40, 48], will be useful in eliciting the dependence of the duration of the transition from the silent to the active phase on the parameter $\beta$ and help explain the significant
increase in this duration as $\beta$ is decreased.

Determining the dependence of the leading-order plateau fractions on the glucose-dependent parameter $\beta$ is a first step in predicting theoretical rates of insulin release from models of bursting electrical activity in pancreatic $\beta$-cells. In [65], Miura and Pernarowski demonstrate how leading-order plateau fractions for the Sherman-Rinzel-Keizer model can be matched with experimental plateau fractions to obtain the relationship between $\beta$ and the external glucose concentration. Knowledge of this relationship and the relationship between the experimental plateau fractions and measurements of rates of insulin release from islets in turn permits the determination of theoretical rates of insulin release from the model. This may help to determine the range of glucose concentrations over which the models are valid.

As a final note, we comment on the general applicability of the analytical methods presented in the first part of this thesis. The study of the Sherman-Rinzel-Keizer model by Pernarowski [67] and Pernarowski et al. [67, 70] identified the damping term of the second-order fast subsystem equation as being numerically small. It was the success of that study that led to a search for similar small terms in the corresponding second-order equations for the other models. The question remains whether the reduction that led to this equation is in fact essential for the application of Melnikov's method or the Fredholm alternative method to approximate $z_{HC}$ in Chapter 3. The answer to this question is important for the extension of these analytical methods to the study of second-generation models of BEA in pancreatic $\beta$-cells, since preliminary investigations of these models indicate that they do not immediately lend themselves to the same reduction.

However, the techniques presented in Chapter 4 do not depend on the fast subsystem being written as a perturbed Hamiltonian system. Therefore, we expect that these analytical techniques can be applied to the second-generation models. Since values of $z_{HC}$ for these more recent models can be approximated numerically with AUTO, the
dependence of the plateau fraction on the glucose-dependent parameter can be elicited in an efficient manner for these models as well.

In the second part of this thesis, consisting of Chapter 5, we studied the bursting phenomenon in a broader context using Pernarowski's polynomial analog model [68] of bursting electrical activity. This model exhibits a wide variety of oscillatory solution behaviour depending on the values of the model parameters, including several types of bursting behaviour similar to those observed in excitable cells other than pancreatic β-cells. Many of the different types of solution behaviour also can be obtained by varying parameter values of biophysical models of bursting, in particular, the Chay-Cook [16] model for bursting electrical activity in pancreatic β-cells [10]. However, the advantage of using Pernarowski's polynomial analog [68] model rather than a biophysical model to study the different bifurcation structures of the fast subsystem underlying the various types of solution behaviour is that results can be obtained analytically.

We created a bifurcation map in \((\eta, \hat{u})\) space, the fast subsystem parameter space, by considering the codimension-2 bifurcations associated with Hopf, homoclinic, and saddle-node of periodics bifurcations. Each codimension-2 bifurcation corresponds to a curve on the bifurcation map. These curves bound regions within which the qualitative structure of the bifurcation diagrams of the fast subsystem is the same. Moving across one of these curves on the bifurcation map corresponds, in general, to making one qualitative change in the bifurcation diagram.

The existence of most curves on the bifurcation map can be inferred from a careful investigation of bifurcation diagrams and phase portraits of the fast subsystem at various values of \(\eta\) and \(\hat{u}\). The numerical software packages AUTO and DSTOOL, created precisely for this purpose, are invaluable in this task. For example, the existence of the NSL and CSL (right) curves, representing codimension-2 neutral homoclinic bifurcations and coalescing right homoclinic bifurcations, respectively, was inferred in this
way. However, we stress the importance of analytical techniques, in particular, the use of Melnikov's method, to infer the existence of the remaining curves. For example, the CSL (large) curve, representing coalescing large homoclinic bifurcations, was found in this way, leading to the investigation of detached branches of large periodic orbits.

One observation made during the development of the bifurcation map is that the NSL (large) and CSL curves exhibit discontinuities. At these discontinuities, the curves disappear from the first quadrant of the bifurcation map and reappear in the fourth quadrant or vice versa. We note that all discontinuities occur as both \( \eta \) and \( \hat{u} \) tend to infinity. An asymptotic analysis should be used to further understand the meaning of the discontinuities in terms of the corresponding bifurcation diagrams. This could lead to interesting future work.

Whereas (one-parameter) bifurcation diagrams are very quantitative in nature, the bifurcation map is very qualitative. In order to recover some quantitative information about the location of the codimension-1 bifurcations, we also examined two-parameter diagrams, consisting of curves of codimension-1 bifurcations, generated with AUTO, and related them to horizontal cuts through the bifurcation map. We found that the polynomial model exhibits three qualitatively different two-parameter bifurcation diagrams, depending on the location of the horizontal cuts relative to the points on the bifurcation map where curves meet in a cusp-like fashion, namely \( (\eta, \hat{u}) = (0, 1) \) and \( (\eta, \hat{u}) = (\frac{7}{5}, \frac{2}{5}) \). A careful analysis of the various bifurcations near these loci should be used to obtain a more detailed understanding of the transitions between the bifurcation diagrams in neighbouring regions.

Surprisingly, we discovered that the two-parameter bifurcation diagram generated with the polynomial analog model for \( \hat{u} = 1.5 \) is essentially identical to the diagram generated with the biophysically based Chay-Cook model in [10]. That is, the polynomial analog model not only mimics the wealth of oscillatory behaviour of models of excitable
cells, but it also possesses the same rich bifurcation structure of such models. This raises the question whether this diagram is generic for models of bursting oscillations. A related question is whether the bifurcation map also is generic. In [10], Bertram et al. suggest that the two-parameter bifurcation diagram occurs often in models of neuronal spiking and that the underlying cause is the existence of a codimension-3 degenerate Takens-Bogdanov bifurcation of focus type [29]. Since these models typically have a large number of parameters, they should have sufficient flexibility to exhibit this type of bifurcation and, hence, at least support the types of bursting implied by these diagrams.

In light of the qualitatively different two-parameter bifurcation diagrams obtained with the polynomial analog model for $\dot{u} = 0.8$ and $\dot{u} = 0$, we suggest that the classification scheme of bursting oscillations of Bertram et al. [10] can be taken a step further by considering bifurcation maps. In particular, these maps provide information about the relationships among the various types of oscillatory behaviour as evident from the bifurcation diagrams in the different regions.

Finally, we showed that the size of the asymptotic parameter $\varepsilon$ can alter the solution behaviour of the full system of equations near boundaries of regions on the bifurcation map. Specifically, we showed that a tapered burster can be made to appear to be a square-wave burster by increasing $\varepsilon$ sufficiently. We believe that this non-generic behaviour is typical near boundaries of regions.

In conclusion, the research presented in this thesis extends the mathematical framework with which to study a large class of bursting oscillators. The analysis adds to the understanding of specific models of bursting electrical activity in pancreatic $\beta$-cells and bursting phenomena in general.
Bibliography


Appendix A

Equations and Parameter Values of the First Generation Pancreatic Beta Cell Models

The following sections contain the equations and parameter values of the first-generation models which are analyzed in this thesis, as well as the details of the nondimensionalization used for each model.

A.1 The Reduced Chay-Keizer Model

The dimensional reduced Chay-Keizer model [19] is as follows:

\[
4\pi r^2 C_m \frac{dV}{dT} = -[I_{Ca}(V) + I_K(V) + I_{K, Ca}(V, Ca_i) + I_L(V)],
\]

\[
\frac{dn}{dT} = \frac{n_\infty(V) - n}{\tau_n(V)},
\]

\[
\frac{dCa_i}{dT} = f \left[ \frac{-3}{4\pi r^3 F} I_{Ca}(V) - k_{Ca} Ca_i \right],
\]

where

\[
I_{Ca}(V) = \bar{g}_{Ca} m_\infty^3(V) h_\infty(V)(V - V_{Ca}),
\]

\[
I_K(V) = \bar{g}_K n^4(V - V_K),
\]

\[
I_{K, Ca}(V, Ca_i) = \bar{g}_{K, Ca} \frac{Ca_i}{K_d + Ca_i}(V - V_K),
\]

\[
I_L(V) = \bar{g}_L (V - V_L),
\]

and

\[
\alpha_m(V) = \frac{B_m(V_m - V)}{\exp \left[ \frac{1}{S_m}(V_m - V) \right] - 1},
\]

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The dimensions of all variables and parameters, as well as the values of the parameters are given in Table A.1. We note that instead of the $\lambda$ used in [19], we use $\tau = \lambda^{-1}$. In [19], the value of $\lambda^{-1}$ is given to be 3. In this case, the bifurcation diagram of the fast subsystem is that of a parabolic-amplitude burster (cf. Chapter 5). For consistency among the first-generation models considered in this thesis, we modify $\lambda^{-1}$ to be 3.25, so that the bifurcation diagram is that of a square-wave burster. The qualitative behaviour of the numerical solution of the full system of equations is not affected significantly.

The nondimensionalization of the model equations is as described in Section 2.3, with $\mathcal{X}$ being equal to the dissociation constant $K_d$. The value of $\tau_n$ is taken to be 18 msec. The resulting nondimensional model, written in standard form, then is

$$\frac{dv}{dt} = i_{Ca}(v) - w^4(v + 1) - g(z)(v + 1) + l(v),$$
$$\frac{dw}{dt} = \frac{\bar{w}_{\infty}(v) - w}{\bar{\tau}_w(v)},$$
\[
\frac{dz}{dt} = \varepsilon [\beta e^{-z} i\text{Ca}(v) - 1],
\]

where

\[
i\text{Ca}(v) = \gamma\text{Ca} \tilde{m}_\infty^3(v) \tilde{h}_\infty(v) (v\text{Ca} - v),
\]

\[
g(z) = \gamma K, \text{Ca} \frac{e^z}{1 + e^z},
\]

\[
l(v) = \gamma L (v_L - v),
\]

and

\[
\tilde{\alpha}_m(v) = \frac{b_m(v_m - v)}{\exp\left[\frac{1}{s_m} (v_m - v)\right] - 1},
\]

\[
\tilde{\beta}_m(v) = 4.0 \exp\left[\frac{1}{s_a} (v_a - v)\right],
\]

\[
\tilde{m}_\infty(v) = \frac{\tilde{\alpha}_m(v)}{\tilde{\alpha}_m(v) + \tilde{\beta}_m(v)},
\]

\[
\tilde{\alpha}_h(v) = 0.07 \exp\left[\frac{1}{s_h} (v_h - v)\right],
\]

\[
\tilde{\beta}_h(v) = \frac{1}{\exp\left[\frac{1}{s_h} (v_h - v)\right] + 1},
\]

\[
\tilde{h}_\infty(v) = \frac{\tilde{\alpha}_h(v)}{\tilde{\alpha}_h(v) + \tilde{\beta}_h(v)},
\]

\[
\tilde{\alpha}_w(v) = \frac{b_n(v_n - v)}{\exp\left[\frac{1}{s_n} (v_n - v)\right] - 1},
\]

\[
\tilde{\beta}_w(v) = 0.125 \exp\left[\frac{1}{s_c} (v_c - v)\right],
\]

\[
\tilde{w}_\infty(v) = \frac{\gamma K \tilde{\alpha}_w(v)}{\tilde{\alpha}_w(v) + \tilde{\beta}_w(v)},
\]

\[
\tilde{\tau}_w(v) = \frac{\lambda}{\tilde{\alpha}_w(v) + \tilde{\beta}_w(v)}.
\]

The values of the parameters are given in Table A.1.
Table A.1: Variables and parameters of the dimensional and nondimensional reduced Chay-Keizer model.
A.2 The Chay (1986) Model

The dimensional Chay (1986) model [13] is as follows:

\[
\frac{4\pi r^2 C_m}{dV} = -\left[ I_{Ca}(V, Ca_i) + I_{K(Ca)}(V, Ca_i) + I_L(V) \right],
\]

\[
\frac{dn}{dT} = \frac{n_\infty(V, Ca_i) - n}{\tau_n(V, Ca_i)},
\]

\[
\frac{dCa_i}{dT} = f \left[ \frac{-3}{4\pi r^3 F} I_{Ca}(V, Ca_i) - k_{Ca} Ca_i \right],
\]

where

\[
I_{Ca}(V, Ca_i) = \tilde{g}_{Ca} m_\infty^2(V) (V - V_{Ca}(Ca_i)),
\]

\[
I_{K(Ca)}(V, Ca_i) = \tilde{g}_{K(Ca)} n^2(V - V_K),
\]

\[
I_L(V) = \tilde{g}_L(V - V_L),
\]

and

\[
V_{Ca}(Ca_i) = \frac{RT}{2F} \ln \frac{Ca_o}{Ca_i},
\]

\[
V_C(Ca_i) = A \ln \left( \frac{Ca_i}{1} \right),
\]

\[
\alpha_m(V) = \frac{B_m(V_m - V)}{\exp \left[ \frac{1}{S_m}(V_m - V) \right] - 1},
\]

\[
\beta_m(V) = 4.0 \exp \left[ \frac{1}{S_a} (V_a - V) \right],
\]

\[
m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)},
\]

\[
\alpha_n(V, Ca_i) = \frac{B_n(V_n + V_C(Ca_i) - V)}{\exp \left[ \frac{1}{S_n} (V_n + V_C(Ca_i) - V) \right] - 1},
\]

\[
\beta_n(V, Ca_i) = 0.125 \exp \left[ \frac{1}{S_b} (V_b + V_C(Ca_i) - V) \right],
\]

\[
n_\infty(V, Ca_i) = \alpha_n(V, Ca_i) \frac{\alpha_n(V, Ca_i)}{\alpha_n(V, Ca_i) + \beta_n(V, Ca_i)},
\]

\[
\tau_n(V, Ca_i) = \frac{\alpha_n(V, Ca_i) + \beta_n(V, Ca_i)}{\tau}.
\]
The dimensions of all variables and parameters, as well as the values of the parameters are given in Table A.2. We note that instead of the $\lambda$ used in [13], we use $\tau = \lambda^{-1}$. In [13], the value of $\lambda^{-1}$ is given to be 1.35. Although this value does give rise to square-wave bursting, the bifurcation diagram of the fast subsystem of this model is that of a tapered burster (cf. Chapter 5). For consistency among the first-generation models considered in this thesis, we modify $\lambda^{-1}$ to be 1.4, so that the bifurcation diagram of the fast subsystem is that of a square-wave burster. The qualitative behaviour of the numerical solution of the full system of equations is not affected.

The nondimensionalization of the model equations is as described in Section 2.3, with $X$ being equal to $Ca_0$, $\gamma_K$ replaced by $\gamma_K(V,C_a)$, and the definition of three additional nondimensional parameters as follows:

\[
\mu = \frac{-A}{V_K} \ln Ca_0,
\]
\[
\nu = \frac{-A}{V_K},
\]
\[
\eta = \frac{RT}{2FV_K}.
\]

The value of $\bar{\tau}_a$ is taken to be 8 msec. The resulting nondimensional model, written in standard form, then is

\[
\frac{dv}{dt} = i_{Ca}(v,z) - w^2(v + 1) + l(v),
\]
\[
\frac{dw}{dt} = \frac{\bar{w}_\infty(v,z) - w}{\bar{\tau}_w(v,z)},
\]
\[
\frac{dz}{dt} = \varepsilon [\beta e^{-z}i_{Ca}(v,z) - 1],
\]

where

\[
i_{Ca}(v,z) = \gamma_C a \bar{m}_\infty^2(v)(\eta z - v),
\]
\[
l(v) = \gamma_L (v_L - v),
\]
Appendix A. Model Equations

The values of the parameters are given in Table A.2.
Table A.2: Variables and parameters of the dimensional and the nondimensional Chay (1986) model.
A.3 The Himmel-Chay Model

The dimensional Himmel-Chay model [44] is as follows:

\[
4\pi r^2 C_m \frac{dV}{dT} = - \left[ I_{Ca}(V, Ca_i) + I_K(V) + I_{K,Ca}(V, Ca_i) + I_L(V) \right],
\]

\[
\frac{dn}{dT} = \frac{n_{\infty}(V) - n}{\tau_n(V)},
\]

\[
\frac{dCa_i}{dT} = \int \left[ \frac{-3}{4\pi r^3 F} I_{Ca}(V, Ca_i) - k_{Ca} Ca_i \right],
\]

where

\[
I_{Ca}(V, Ca_i) = \bar{g}_{Ca} m_{\infty}^3(V) h_{\infty}(V) (V - V_{Ca}(Ca_i)),
\]

\[
I_K(V) = g_K n^3(V - V_K),
\]

\[
I_{K,Ca}(V, Ca_i) = \bar{g}_{K,Ca} \frac{Ca_i}{K_d + Ca_i} (V - V_K),
\]

\[
I_L(V) = \bar{g}_L (V - V_L),
\]

and

\[
V_{Ca}(Ca_i) = \frac{RT}{2F} \ln \frac{Ca_o}{Ca_i},
\]

\[
\alpha_m(V) = \frac{B_m (V_m - V)}{\exp \left[ \frac{1}{S_m} (V_m - V) \right] - 1},
\]

\[
\beta_m(V) = 4.0 \exp \left[ \frac{1}{S_a} (V_a - V) \right],
\]

\[
m_{\infty}(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)},
\]

\[
\alpha_h(V) = 0.07 \exp \left[ \frac{1}{S_h} (V_h - V) \right],
\]

\[
\beta_h(V) = \frac{1}{\exp \left[ \frac{1}{S_h} (V_h - V) \right] + 1},
\]

\[
h_{\infty}(V) = \frac{\alpha_h(V)}{\alpha_h(V) + \beta_h(V)},
\]
\[ \alpha_n(V) = \frac{B_n(V_n - V)}{\exp\left[\frac{1}{S_n}(V_n - V)\right] - 1}, \]
\[ \beta_n(V) = 0.125 \exp\left[\frac{1}{S_c}(V_c - V)\right], \]
\[ n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}, \]
\[ \tau_n(V) = \frac{\tau}{\alpha_n(V) + \beta_n(V)}. \]

The dimensions of all variables and parameters, as well as the values of the parameters are given in Table A.3. We note that in [44], the value of \( V_L \) is misprinted as 40 mV. We use \( V_L = -40 \) mV here. Furthermore, \( k_{C_a} \) is given to be 0.045 msec\(^{-1} \) in the appendix of [44]. However, this value gives rise to continuous bursting. Different values of \( k_{C_a} \), varying between 0.01 and 0.045, are used in the text of [44] and we use \( k_{C_a} = 0.03 \) msec\(^{-1} \) here. Finally, instead of the \( \lambda \) used in [44], we use \( \tau = \lambda^{-1} \). In [44], the value of \( \lambda \) is misprinted as 1/0.003. We use the value of \( \lambda \) given in [19], namely \( \lambda = 1/3 \), giving \( \tau = 3 \).

The nondimensionalization of the model equations is as described in Section 2.3, with \( X \) being equal to the dissociation constant \( K_d \), and the definition of two additional nondimensional parameters as follows:
\[ \mu = \frac{RT}{2FV_K} \ln \frac{K_d}{C_{a_o}}, \]
\[ \nu = \frac{RT}{2FV_K}. \]

The value of \( \tau_n \) is taken to be 18 msec. The resulting nondimensional model, written in standard form, then is
\[ \frac{dv}{dt} = i_{C_a}(v, z) - w^3(v + 1) - g(z)(v + 1) + l(v), \]
\[ \frac{dw}{dt} = \frac{\bar{w}_\infty(v) - w}{\bar{\tau}_w(v)}, \]
\[ \frac{dz}{dt} = \varepsilon [\beta e^{-z}i_{C_a}(v, z) - 1], \]
where

\[ i_{Ca}(v, z) = \gamma_{Ca} m^3_{\infty}(v) \tilde{h}_{\infty}(v)(\mu + \nu z - v), \]

\[ g(z) = \gamma_{K, Ca} \frac{e^z}{1 + e^z}, \]

and

\[ \tilde{\alpha}_m(v) = \frac{b_m(v_m - v)}{\exp \left[ \frac{1}{s_m}(v_m - v) \right] - 1}, \]

\[ \tilde{\beta}_m(v) = 4.0 \exp \left[ \frac{1}{s_a}(v_a - v) \right], \]

\[ \tilde{m}_{\infty}(v) = \frac{\tilde{\alpha}_m(v)}{\tilde{\alpha}_m(v) + \tilde{\beta}_m(v)}, \]

\[ \tilde{\alpha}_h(v) = 0.07 \exp \left[ \frac{1}{s_h}(v_h - v) \right], \]

\[ \tilde{\beta}_h(v) = \frac{1}{\exp \left[ \frac{1}{s_b}(v_b - v) \right] + 1}, \]

\[ \tilde{h}_{\infty}(v) = \frac{\tilde{\alpha}_h(v)}{\tilde{\alpha}_h(v) + \tilde{\beta}_h(v)}, \]

\[ \tilde{\alpha}_w(v) = \frac{b_h(v_n - v)}{\exp \left[ \frac{1}{s_n}(v_n - v) \right] - 1}, \]

\[ \tilde{\beta}_w(v) = 0.125 \exp \left[ \frac{1}{s_c}(v_c - v) \right], \]

\[ \tilde{w}_{\infty}(v) = \gamma_{K, w} \frac{\tilde{\alpha}_w(v)}{\tilde{\alpha}_w(v) + \tilde{\beta}_w(v)}, \]

\[ \bar{\tau}_w(v) = \frac{\lambda}{\tilde{\alpha}_w(v) + \tilde{\beta}_w(v)}. \]

The values of the parameters are given in Table A.3.
### Table A.3: Variables and parameters of the dimensional and the nondimensional Himmel-Chay model.

<table>
<thead>
<tr>
<th>Dimensional Model</th>
<th>Nondimensional Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Dimension</td>
</tr>
<tr>
<td>V</td>
<td>mV</td>
</tr>
<tr>
<td>n</td>
<td>-</td>
</tr>
<tr>
<td>Ca&lt;sub&gt;i&lt;/sub&gt;</td>
<td>μM</td>
</tr>
<tr>
<td>T</td>
<td>msec</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dimension</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>g&lt;sub&gt;Ca&lt;/sub&gt;</td>
<td>pS</td>
<td>7000</td>
<td>γ&lt;sub&gt;Ca&lt;/sub&gt;</td>
<td>27.8521</td>
</tr>
<tr>
<td>g&lt;sub&gt;K&lt;/sub&gt;</td>
<td>pS</td>
<td>2000</td>
<td>γ&lt;sub&gt;K&lt;/sub&gt;</td>
<td>7.9577</td>
</tr>
<tr>
<td>g&lt;sub&gt;K,Ca&lt;/sub&gt;</td>
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<td>60</td>
<td>γ&lt;sub&gt;K,Ca&lt;/sub&gt;</td>
<td>0.2387</td>
</tr>
<tr>
<td>g&lt;sub&gt;L&lt;/sub&gt;</td>
<td>pS</td>
<td>28</td>
<td>γ&lt;sub&gt;L&lt;/sub&gt;</td>
<td>0.1114</td>
</tr>
<tr>
<td>V&lt;sub&gt;K&lt;/sub&gt;</td>
<td>mV</td>
<td>-87</td>
<td>v&lt;sub&gt;K&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;L&lt;/sub&gt;</td>
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<td>v&lt;sub&gt;L&lt;/sub&gt;</td>
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<td>v&lt;sub&gt;a&lt;/sub&gt;</td>
<td>-0.5747</td>
</tr>
<tr>
<td>V&lt;sub&gt;b&lt;/sub&gt;</td>
<td>mV</td>
<td>-20</td>
<td>v&lt;sub&gt;b&lt;/sub&gt;</td>
<td>-0.2299</td>
</tr>
<tr>
<td>V&lt;sub&gt;c&lt;/sub&gt;</td>
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<td>-30</td>
<td>v&lt;sub&gt;c&lt;/sub&gt;</td>
<td>-0.3448</td>
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<tr>
<td>V&lt;sub&gt;h&lt;/sub&gt;</td>
<td>mV</td>
<td>-50</td>
<td>v&lt;sub&gt;h&lt;/sub&gt;</td>
<td>-0.5747</td>
</tr>
<tr>
<td>V&lt;sub&gt;m&lt;/sub&gt;</td>
<td>mV</td>
<td>-25</td>
<td>v&lt;sub&gt;m&lt;/sub&gt;</td>
<td>-0.2874</td>
</tr>
<tr>
<td>V&lt;sub&gt;n&lt;/sub&gt;</td>
<td>mV</td>
<td>-20</td>
<td>v&lt;sub&gt;n&lt;/sub&gt;</td>
<td>-0.2299</td>
</tr>
<tr>
<td>S&lt;sub&gt;a&lt;/sub&gt;</td>
<td>mV</td>
<td>18</td>
<td>s&lt;sub&gt;a&lt;/sub&gt;</td>
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</tr>
<tr>
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<td>mV</td>
<td>10</td>
<td>s&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.1149</td>
</tr>
<tr>
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<td>s&lt;sub&gt;c&lt;/sub&gt;</td>
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<td>mV</td>
<td>20</td>
<td>s&lt;sub&gt;h&lt;/sub&gt;</td>
<td>0.2299</td>
</tr>
<tr>
<td>S&lt;sub&gt;m&lt;/sub&gt;</td>
<td>mV</td>
<td>10</td>
<td>s&lt;sub&gt;m&lt;/sub&gt;</td>
<td>0.1149</td>
</tr>
<tr>
<td>S&lt;sub&gt;n&lt;/sub&gt;</td>
<td>mV</td>
<td>10</td>
<td>s&lt;sub&gt;n&lt;/sub&gt;</td>
<td>0.1149</td>
</tr>
<tr>
<td>B&lt;sub&gt;m&lt;/sub&gt;</td>
<td>1/mV</td>
<td>0.1</td>
<td>b&lt;sub&gt;m&lt;/sub&gt;</td>
<td>8.7</td>
</tr>
<tr>
<td>B&lt;sub&gt;n&lt;/sub&gt;</td>
<td>1/mV</td>
<td>0.01</td>
<td>b&lt;sub&gt;n&lt;/sub&gt;</td>
<td>0.87</td>
</tr>
<tr>
<td>C&lt;sub&gt;m&lt;/sub&gt;</td>
<td>10&lt;sup&gt;-7&lt;/sup&gt;F/cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k&lt;sub&gt;Ca&lt;/sub&gt;</td>
<td>msec&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>0.03</td>
<td>β</td>
<td>4.1744</td>
</tr>
<tr>
<td>K&lt;sub&gt;d&lt;/sub&gt;</td>
<td>μM</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>-</td>
<td>0.002</td>
<td>ε</td>
<td>1.08e&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>r</td>
<td>μm</td>
<td>6</td>
<td>λ</td>
<td>0.1667</td>
</tr>
<tr>
<td>τ</td>
<td>msec</td>
<td>3</td>
<td>v</td>
<td>-0.1535</td>
</tr>
<tr>
<td>Ca&lt;sub&gt;o&lt;/sub&gt;</td>
<td>μM</td>
<td>2000</td>
<td>μ</td>
<td>1.0605</td>
</tr>
<tr>
<td>T</td>
<td>K</td>
<td>310</td>
<td>v</td>
<td>-0.1535</td>
</tr>
</tbody>
</table>
A.4 The Chay-Kang Model

The dimensional Chay-Kang model [17] is as follows:

\[
4\pi r^2 C_m \frac{dV}{dT} = -\left[I_{Ca(V,Ca)}(V,Ca_i) + I_K(V) + I_L(V)\right],
\]

\[
\frac{dn}{dT} = \frac{n_\infty(V) - n}{\tau_n(V)},
\]

\[
\frac{dCa_i}{dT} = \int\left[\frac{-3}{4\pi r^3 F} I_{Ca(V,Ca)}(V,Ca_i) - k_{Ca} Ca_i\right],
\]

where

\[
I_{Ca(V,Ca)}(V,Ca_i) = \tilde{g}_{Ca(V,Ca)} m_\infty(V) h_\infty(V,Ca_i)(V - V_{Ca}),
\]

\[
I_K(V) = \tilde{g}_K n(V - V_K),
\]

\[
I_L(V) = \tilde{g}_L (V - V_L),
\]

and

\[
m_\infty(V) = \frac{1}{1 + \exp\left[\frac{1}{\gamma_m}(V_m - V)\right]},
\]

\[
h_\infty(V,Ca_i) = \frac{1}{1 + \frac{Ca_i}{K_h} \exp\left[\frac{\gamma V}{\beta_h}\right]},
\]

\[
n_\infty(V) = \frac{1}{1 + \exp\left[\frac{\gamma n}{\beta_n}(V_n - V)\right]},
\]

\[
\tau_n(V) = \frac{1}{1 + \exp\left[\frac{\gamma n}{\beta_n}(V_n - V)\right]}.
\]

The dimensions of all variables and parameters, as well as the values of the parameters are given in Table A.4. We note that instead of the \( \lambda \) used in [17], we use \( \tau = \lambda^{-1} \). In [17], the value of \( \lambda \) is misprinted as 0.017 msec\(^{-1}\). The value used in the companion paper [14] is 0.117 msec\(^{-1}\), giving \( \tau \approx 8.547 \) msec.

The nondimensionalization of the model equations is as described in Section 2.3, with \( \lambda \) being equal to \( K_h \). The value of \( \tau_n \) is taken to be 9 msec. The resulting nondimensional
model, written in standard form, then is

\[
\begin{align*}
\frac{dv}{dt} &= i_{Ca}(v, z) - w(v + 1) + l(v), \\
\frac{dw}{dt} &= \frac{w_\infty(v) - w}{\bar{\tau}_w(v)}, \\
\frac{dz}{dt} &= \varepsilon \left[ \beta e^{-z_i} i_{Ca}(v, z) - 1 \right],
\end{align*}
\]

where

\[
\begin{align*}
i_{Ca}(v, z) &= \gamma_{Ca}(v, v, Ca) \bar{m}_\infty(v) \bar{h}_\infty(v, z)(v_{Ca} - v), \\
l(v) &= \gamma_L(v_L - v),
\end{align*}
\]

and

\[
\begin{align*}
\bar{m}_\infty(v) &= \frac{1}{1 + \exp \left[ \frac{v_m - v}{s_m} \right]}, \\
\bar{h}_\infty(v, z) &= \frac{1}{1 + e^z \exp \left[ \frac{-v}{s_h} \right]}, \\
\bar{w}_\infty(v) &= \frac{\gamma_K}{1 + \exp \left[ \frac{v_n - v}{s_n} \right]}, \\
\bar{\tau}_w(v) &= \frac{\lambda}{1 + \exp \left[ \frac{v_n - v}{s_n} \right]}.
\end{align*}
\]

The values of the parameters are given in Table A.4.
### Dimensional Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dimension</th>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$</td>
<td>mV</td>
<td>$v$</td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>-</td>
<td>$w$</td>
<td></td>
</tr>
<tr>
<td>$C_{ai}$</td>
<td>$\mu$M</td>
<td>$z$</td>
<td></td>
</tr>
<tr>
<td>$T$</td>
<td>msec</td>
<td>$t$</td>
<td></td>
</tr>
</tbody>
</table>

### Nondimensional Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dimension</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{Ca(V,Ca)}$</td>
<td>pS</td>
<td>250</td>
<td>$g_{Ca(V,Ca)}$</td>
<td>0.4974</td>
</tr>
<tr>
<td>$g_K$</td>
<td>pS</td>
<td>1300</td>
<td>$g_K$</td>
<td>2.5863</td>
</tr>
<tr>
<td>$g_L$</td>
<td>pS</td>
<td>10</td>
<td>$g_L$</td>
<td>1.9894e-2</td>
</tr>
<tr>
<td>$V_{Ca}$</td>
<td>mV</td>
<td>100</td>
<td>$V_{Ca}$</td>
<td>1.25</td>
</tr>
<tr>
<td>$V_K$</td>
<td>mV</td>
<td>-80</td>
<td>$V_K$</td>
<td></td>
</tr>
<tr>
<td>$V_L$</td>
<td>mV</td>
<td>-40</td>
<td>$V_L$</td>
<td>-0.5</td>
</tr>
<tr>
<td>$V_m$</td>
<td>mV</td>
<td>-22</td>
<td>$V_m$</td>
<td>-0.275</td>
</tr>
<tr>
<td>$V_n$</td>
<td>mV</td>
<td>-9</td>
<td>$V_n$</td>
<td>-0.1125</td>
</tr>
<tr>
<td>$S_h$</td>
<td>mV</td>
<td>10</td>
<td>$S_h$</td>
<td>0.125</td>
</tr>
<tr>
<td>$S_m$</td>
<td>mV</td>
<td>7.5</td>
<td>$S_m$</td>
<td>9.375e-2</td>
</tr>
<tr>
<td>$S_n$</td>
<td>mV</td>
<td>10</td>
<td>$S_n$</td>
<td>0.125</td>
</tr>
<tr>
<td>$C_m$</td>
<td>$10^{-7}$F/cm$^2$</td>
<td>10</td>
<td>$C_m$</td>
<td></td>
</tr>
<tr>
<td>$k_{Ca}$</td>
<td>msec$^{-1}$</td>
<td>0.06</td>
<td>$k_{Ca}$</td>
<td>8.5301e-2</td>
</tr>
<tr>
<td>$K_h$</td>
<td>$\mu$M</td>
<td>90</td>
<td>$K_h$</td>
<td></td>
</tr>
<tr>
<td>$f$</td>
<td>-</td>
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<td>$f$</td>
<td>5.4e-4</td>
</tr>
<tr>
<td>$r$</td>
<td>$\mu$m</td>
<td>6</td>
<td>$r$</td>
<td></td>
</tr>
<tr>
<td>$\tau$</td>
<td>msec</td>
<td>8.547</td>
<td>$\tau$</td>
<td>0.9497</td>
</tr>
</tbody>
</table>

Table A.4: Variables and parameters of the dimensional and the nondimensional Chay-Kang model.
A.5 The Sherman-Rinzel-Keizer Model

The dimensional Sherman-Rinzel-Keizer model [87] is as follows:

\[
\begin{align*}
4\pi r^2 C_m \frac{dV}{dT} &= -[I_{Ca}(V) + I_K(V) + I_{K,Ca}(V, Ca_i)], \\
\frac{dn}{dT} &= \frac{n_\infty(V) - n}{\tau_n(V)}, \\
\frac{dCa_i}{dT} &= f\left[\frac{-3}{4\pi r^3 F} I_{Ca}(V) - k_{Ca} Ca_i\right],
\end{align*}
\]

where

\[
\begin{align*}
I_{Ca}(V) &= g_{Ca} m_\infty(V) h_\infty(V)(V - V_{Ca}), \\
I_K(V) &= g_K n(V - V_K), \\
I_{K,Ca}(V, Ca_i) &= \frac{Ca_i}{K_d + Ca_i}(V - V_K),
\end{align*}
\]

and

\[
\begin{align*}
m_\infty(V) &= \frac{1}{1 + \exp\left[\frac{1}{S_m}(V_m - V)\right]}, \\
h_\infty(V) &= \frac{1}{1 + \exp\left[\frac{1}{S_h}(V_h - V)\right]}, \\
n_\infty(V) &= \frac{1}{1 + \exp\left[\frac{1}{S_n}(V_n - V)\right]}, \\
\tau_n(V) &= \frac{\tau}{\exp\left[\frac{1}{S_a}(V_a - V)\right] + \exp\left[\frac{1}{S_b}(V_b - V)\right]}.
\end{align*}
\]

The dimensions of all variables and parameters, as well as the values of the parameters are given in Table A.5. We note that the parameter \( \tau \) used here is equivalent to the \( c/\lambda \) used in [87]. In [87], \( c \) is given to be 60 msec and \( \lambda \) is either 1.6 or 1.7. We use \( \lambda = 1.6 \), giving \( \tau = \frac{60}{1.6} = 37.5 \) msec.
The nondimensionalization of the model equations is as described in Section 2.3, with \( K_d \) being equal to the dissociation constant \( K_d \). The value of \( \tau_n \) is taken to be 22 msec. The resulting nondimensional model, written in standard form, then is

\[
\begin{align*}
\frac{dv}{dt} &= i_{Ca}(v) - w(v + 1) - g(z)(v + 1), \\
\frac{dw}{dt} &= \bar{w}_\infty(v) - w, \\
\frac{dz}{dt} &= \varepsilon [\beta e^{-z} i_{Ca}(v) - 1],
\end{align*}
\]

where

\[
\begin{align*}
i_{Ca}(v) &= \gamma_{Ca} \bar{m}_\infty(v) \bar{h}_\infty(v)(v_{Ca} - v), \\
g(z) &= \gamma_{K,Ca} \frac{e^z}{1 + e^z},
\end{align*}
\]

and

\[
\begin{align*}
\bar{m}_\infty(v) &= \frac{1}{1 + \exp \left[ \frac{1}{\delta_m}(v_m - v) \right]}, \\
\bar{h}_\infty(v) &= \frac{1}{1 + \exp \left[ \frac{1}{\delta_h}(v_h - v) \right]}, \\
\bar{w}_\infty(v) &= \frac{\gamma_K}{1 + \exp \left[ \frac{1}{\delta_n}(v_n - v) \right]}, \\
\bar{\tau}_w(v) &= \frac{\lambda}{\exp \left[ \frac{1}{\delta_a}(v_b - v) \right] + \exp \left[ \frac{1}{\delta_b}(v_b - v) \right]}. 
\end{align*}
\]

The values of the parameters are given in Table A.5.
<table>
<thead>
<tr>
<th><strong>Dimensional Model</strong></th>
<th><strong>Nondimensional Model</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>Dimension</strong></td>
</tr>
<tr>
<td>( V )</td>
<td>mV</td>
</tr>
<tr>
<td>( n )</td>
<td>-</td>
</tr>
<tr>
<td>( C_{a_i} )</td>
<td>( \mu M )</td>
</tr>
<tr>
<td>( T )</td>
<td>msec</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Parameter</strong></th>
<th><strong>Dimension</strong></th>
<th><strong>Value</strong></th>
<th><strong>Parameter</strong></th>
<th><strong>Value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>( \bar{\gamma}_{Ca} )</td>
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<td>( \gamma_{Ca} )</td>
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<tr>
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<td>( \gamma_K )</td>
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</tr>
<tr>
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<td>( \gamma_{K,Ca} )</td>
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<td>110</td>
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</tr>
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<td>mV</td>
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<td>( v_b )</td>
<td>-1</td>
</tr>
<tr>
<td>( V_h )</td>
<td>mV</td>
<td>-10</td>
<td>( v_h )</td>
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</tr>
<tr>
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<td>mV</td>
<td>4</td>
<td>( v_m )</td>
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</tr>
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</tr>
<tr>
<td>( S_h )</td>
<td>mV</td>
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</tr>
<tr>
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<td>( s_m )</td>
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</tr>
<tr>
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<td>mV</td>
<td>5.6</td>
<td>( s_n )</td>
<td>7.4667e^{-2}</td>
</tr>
<tr>
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<td>( 10^{-7} \text{F/cm}^2 )</td>
<td>10</td>
<td>( C_{m} )</td>
<td>10</td>
</tr>
<tr>
<td>( k_{Ca} )</td>
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<td>( \beta )</td>
<td>2.7179e^{-2}</td>
</tr>
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<td>( \mu M )</td>
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<td>( \varepsilon )</td>
<td>6.6e^{-4}</td>
</tr>
<tr>
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<td>-</td>
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<td>( r )</td>
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</tr>
<tr>
<td>( r )</td>
<td>( \mu m )</td>
<td>37.5</td>
<td>( \tau )</td>
<td>1.7045</td>
</tr>
</tbody>
</table>

Table A.5: Variables and parameters of the dimensional and the nondimensional Sherman-Rinzel-Keizer model.
A.6 The Chay-Cook Model

The dimensional Chay-Cook model [16] is as follows:

\[
4\pi r^2 C_m \frac{dV}{dT} = - \left[ I_{Ca}(V) + I_{Ca(V, Ca)}(V, Ca_i) + I_K(V) + I_L(V) \right],
\]

\[
\frac{dn}{dT} = \frac{n_\infty(V) - n}{\tau_n(V)},
\]

\[
\frac{dCa_i}{dT} = f \left[ \frac{-3}{4\pi r^2 F} \left( I_{Ca}(V) + I_{Ca(V, Ca)}(V, Ca_i) \right) - k_{Ca} Ca_i \right],
\]

where

\[
I_{Ca}(V) = g_{Ca} m_\infty(V)(V - V_{Ca}),
\]

\[
I_{Ca(V, Ca)}(V, Ca_i) = g_{Ca(V, Ca)} s_\infty(V, Ca_i)(V - V_{Ca}),
\]

\[
I_K(V) = g_K n(V - V_K),
\]

\[
I_L(V) = g_L (V - V_L),
\]

and

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

\[
s_\infty(V, Ca_i) = \frac{1}{1 + \frac{Ca_i}{K_s} \exp \left( \frac{1}{5_s}(V_s - V) \right)},
\]

\[
n_\infty(V) = \frac{1}{1 + \exp \left[ \frac{1}{5_n}(V_n - V) \right]},
\]

\[
\tau_n(V) = \frac{1}{1 + \exp \left[ \frac{-1}{\tau_n}(V_n - V) \right]}.
\]

The dimensions of all variables and parameters, as well as the values of the parameters are given in Table A.6.

The nondimensionalization of the model equations is as described in Section 2.3, with \( X \) being equal to \( K_s \). The value of \( \tau_n \) is taken to be 9 msec. The resulting nondimensional
### Table A.6: Variables and parameters of the dimensional and nondimensional Chay-Cook model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dimension</th>
<th>Value</th>
<th>Parameter</th>
<th>Dimension</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$</td>
<td>mV</td>
<td>250</td>
<td>$\gamma_{Ca}$</td>
<td></td>
<td>0.4974</td>
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<tr>
<td>$n$</td>
<td>-</td>
<td>10</td>
<td>$\gamma_{Ca(V, Ca)}$</td>
<td>pS</td>
<td>1.9894e-2</td>
</tr>
<tr>
<td>$Ca_i$</td>
<td>$\mu$M</td>
<td>1300</td>
<td>$\gamma_K$</td>
<td>pS</td>
<td>2.5863</td>
</tr>
<tr>
<td>$T$</td>
<td>msec</td>
<td>50</td>
<td>$\gamma_L$</td>
<td>pS</td>
<td>9.9472e-2</td>
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<tr>
<td>$VCa$</td>
<td>mV</td>
<td>100</td>
<td>$\nu_{Ca}$</td>
<td>mV</td>
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</tr>
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<td>mV</td>
<td>-0.75</td>
</tr>
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<td>-60</td>
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<td>-0.275</td>
</tr>
<tr>
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<td>-22</td>
<td>$\nu_n$</td>
<td>mV</td>
<td>-0.1125</td>
</tr>
<tr>
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<td>mV</td>
<td>-22</td>
<td>$\nu_s$</td>
<td>mV</td>
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</tr>
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<td>$s_m$</td>
<td>mV</td>
<td>9.375e-2</td>
</tr>
<tr>
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<td>mV</td>
<td>10</td>
<td>$s_n$</td>
<td>mV</td>
<td>0.125</td>
</tr>
<tr>
<td>$S_s$</td>
<td>mV</td>
<td>10</td>
<td>$s_s$</td>
<td>mV</td>
<td>0.125</td>
</tr>
<tr>
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<td>$10^{-7}$F/cm$^2$</td>
<td>10</td>
<td>$\beta$</td>
<td></td>
<td>5.7578</td>
</tr>
<tr>
<td>$k_{Ca}$</td>
<td>msec$^{-1}$</td>
<td>0.08</td>
<td>$\varepsilon$</td>
<td></td>
<td>7.2e-4</td>
</tr>
<tr>
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<td>$\mu$M</td>
<td>1</td>
<td>$\lambda$</td>
<td></td>
<td>1.01</td>
</tr>
</tbody>
</table>
Appendix B

Bifurcation Diagrams for the Polynomial Analog Model

Figure B.1: Bifurcation diagram for region A. Parameter values used to generate this diagram are $\eta = 0.2$, $\dot{u} = 0.5$, $a = 0.25$. 

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Figure B.2: Bifurcation diagram for region B1. Parameter values used to generate this diagram are $\eta = 0.93$, $\hat{u} = 0.57$, $a = 0.25$.

Figure B.3: Bifurcation diagram for region B2. Parameter values used to generate this diagram are $\eta = 0.93$, $\hat{u} = 0.97$, $a = 0.25$. 
Appendix B. Bifurcation Diagrams for the Polynomial Analog Model

Figure B.4: Bifurcation diagram for region B3. Parameter values used to generate this diagram are $\eta = 0.9$, $\hat{u} = 1.15$, $a = 0.25$.

Figure B.5: Bifurcation diagram for region B4. Parameter values used to generate this diagram are $\eta = 0.7$, $\hat{u} = 1.6$, $a = 0.25$. 
Figure B.6: Bifurcation diagram for region B5. Parameter values used to generate this diagram are $\eta = 0.47$, $\hat{u} = 1.3$, $a = 0.25$. 
Figure B.7: (a) Bifurcation diagram for region C1. Parameter values used to generate this diagram are $\eta = 1.45$, $\hat{u} = 2.56$, $a = 0.02$. (b) Enlarged view of the region of bistability, showing the upper Hopf bifurcation and corresponding branch of periodic orbits, and that the large periodic orbits are stable near the corresponding homoclinic bifurcation.
Appendix B. Bifurcation Diagrams for the Polynomial Analog Model

Figure B.8: Bifurcation diagram for region C2. Parameter values used to generate this diagram are $\eta = 0.6, \hat{u} = 1.77, a = 0.25$.

Figure B.9: Bifurcation diagram for region C3. Parameter values used to generate this diagram are $\eta = 0.43, \hat{u} = 1.56, a = 0.25$. 
Appendix B. Bifurcation Diagrams for the Polynomial Analog Model

Figure B.10: Bifurcation diagram for region C4. Parameter values used to generate this diagram are $\eta = 0.2$, $\hat{u} = 1.5$, $a = 0.25$.

Figure B.11: Bifurcation diagram for region C5. Parameter values used to generate this diagram are $\eta = 0.7$, $\hat{u} = 2.1$, $a = 0.25$. 
Figure B.12: Bifurcation diagram for region C6. Parameter values used to generate this diagram are $\eta = 0.3$, $\hat{u} = 2.6$, $a = 0.25$. 
Figure B.12: Bifurcation diagram for region C6. Parameter values used to generate this diagram are $\eta = 0.3$, $\hat{u} = 2.6$, $a = 0.25$. 
Figure B.13: Bifurcation diagram for region D1. Parameter values used to generate this diagram are $\eta = 2.3$, $\dot{u} = 0.25$, $a = 0.25$.

Figure B.14: Bifurcation diagram for region D2. Parameter values used to generate this diagram are $\eta = 2.2$, $\dot{u} = 0.46$, $a = 0.25$. 
Figure B.15: Bifurcation diagram for region D3. Parameter values used to generate this diagram are $\eta = 1.87$, $\hat{u} = 0.11$, $a = 0.25$.

Figure B.16: Bifurcation diagram for region D4. Parameter values used to generate this diagram are $\eta = 1.7$, $\hat{u} = 0.1$, $a = 0.25$. 
Figure B.17: Bifurcation diagram for region D5. Parameter values used to generate this diagram are $\eta = 2.0$, $\hat{u} = 0.4$, $a = 0.25$. 
Appendix B. Bifurcation Diagrams for the Polynomial Analog Model

Figure B.18: (a) Bifurcation diagram for region E1. Parameter values used to generate this diagram are $\eta = 2.0$, $\hat{u} = 1.1$, $a = 0.02$. (b) Enlarged view of the region of bistability, showing that the large periodic orbits are unstable near the homoclinic bifurcation.
Figure B.19: Bifurcation diagram for region E2. Parameter values used to generate this diagram are $\eta = 1.45$, $\dot{u} = 0.5$, $a = 0.02$.

Figure B.20: Bifurcation diagram for region E3. Parameter values used to generate this diagram are $\eta = 1.1$, $\dot{u} = 0.85$, $a = 0.02$. 
Appendix B. Bifurcation Diagrams for the Polynomial Analog Model

Figure B.21: Bifurcation diagram for region E4. Parameter values used to generate this diagram are $\eta = 1.2$, $\dot{u} = 1.0$, $a = 0.25$.

Figure B.22: Bifurcation diagram for region E5. Parameter values used to generate this diagram are $\eta = 1.0$, $\dot{u} = 1.45$, $a = 0.02$. 
Figure B.23: Bifurcation diagram for region F1. Parameter values used to generate this diagram are $\eta = 1.4$, $\dot{u} = 0.2$, $a = 0.25$.

Figure B.24: Bifurcation diagram for region F2. Parameter values used to generate this diagram are $\eta = 1.51$, $\dot{u} = 0.0$, $a = 0.02$. 
Figure B.25: Bifurcation diagram for region F3. Parameter values used to generate this diagram are $\eta = 1.447$, $\dot{u} = 0.3$, $a = 0.02$.

Figure B.26: Bifurcation diagram for region F4. Parameter values used to generate this diagram are $\eta = 1.64$, $\dot{u} = 0.0$, $a = 0.02$. 