Dynamical Systems Analysis of Biophysical Models with Multiple Timescales

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Abstract

Many physiological systems have the property that some processes evolve much faster than others, and mathematical models can be constructed with multiple timescales to reflect this property. A gonadotropin-releasing hormone (GnRH) neuron model developed by Duan et al. [Theoretical Biology 276 (2011), 22-34] provides an example of such a system and has variables that evolve on at least three timescales. Techniques such as geometric singular perturbation theory (GSPT) have previously been developed to analyse systems with two timescales, but methods for analysing models with three or more timescales are still limited.

This thesis aims to advance understanding of systems with three timescales by studying a selection of different types of three timescale models. First we investigate a three-dimensional system with three timescales, specifically the food chain model of Rosenzweig et al. [The American Naturalist 97 (1963), 209-223]. Second we construct a more general three-dimensional three timescale system than the food chain model, to illustrate the required conditions for generating a certain type of oscillation seen in the food chain model. Third, we couple two two-dimensional fast-slow systems in a configuration based on the structure of the GnRH neuron model. In each case, we apply methods from GSPT, extending the techniques where necessary to allow for the presence of three timescales. We investigate a selection of complex oscillations seen in these models, and explain the origin of the various features seen.

We find that the shapes and relative positions of two invariant manifolds of related singular systems, specifically the critical manifold and the superslow manifold, are crucial to an explanation of the complicated patterns of oscillation seen in the three timescale systems. Also, we find that the existing theory for two timescale systems is not appropriate for explaining all the folded singularities observed in three timescale systems.

Finally, we reassess the oscillations in the models of interest, with the aim of identifying which patterns are intrinsically three timescale phenomena and which could also be seen in models with only two timescales. We find examples of both types of oscillation and in particular show that three timescales are needed to generate a time series like the solution of interest in the GnRH neuron model.
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The coupled Morris-Lecar model (equations (5.4), Chapter 5) was formulated in collaboration with J. Rubin and Y. Wang. The analysis of this model as presented in Chapter 5 is almost entirely my own work.

**Nature of contribution by PhD candidate**

Construction of bifurcation diagrams and bifurcation sets. Simulation of system (5.4) over a range of parameter values. Nondimensionalisation of the model, GSPT analysis of the model and development of figures.

**Extent of contribution by PhD candidate (%)** 75%

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The undersigned hereby certify that:

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# Glossary

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<td>ATP</td>
<td>Adenosine triphosphate</td>
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<td>B</td>
<td>Bautin bifurcation</td>
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<tr>
<td>BT</td>
<td>Bogdanov-Takens bifurcation</td>
</tr>
<tr>
<td>ER</td>
<td>Endoplasmic reticulum</td>
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<tr>
<td>FHN</td>
<td>FitzHugh-Nagumo</td>
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<tr>
<td>FS</td>
<td>Folded singularity</td>
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<tr>
<td>GnRH</td>
<td>Gonadotropin-releasing hormone</td>
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<td>GSPT</td>
<td>Geometric singular perturbation theory</td>
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<tr>
<td>HB</td>
<td>Hopf bifurcation</td>
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<td>HC</td>
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<td>HH</td>
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<td>HR</td>
<td>Hindmarsh-Rose</td>
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<tr>
<td>IP₃</td>
<td>Inositol (1, 4, 5)-trisphosphate</td>
</tr>
<tr>
<td>IP₄</td>
<td>Inositol (1, 3, 4, 5)-tetrakisphosphate</td>
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<tr>
<td>M-L</td>
<td>Morris-Lecar</td>
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<td>OS</td>
<td>Ordinary singularity</td>
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<td>S</td>
<td>Critical manifold</td>
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<td>SN</td>
<td>Saddle-node bifurcation</td>
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<td>SNIC</td>
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<td>SNpo</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>SR</td>
<td>Sarcoplasmic reticulum</td>
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<td>SS</td>
<td>Superslow manifold</td>
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Chapter 1

Introduction

Many mathematical models are constructed to be multiple timescale systems, that is, variables in the model evolve on two or more different timescales. This is in order to reflect the reality that in many physiological processes, different components evolve at different speeds. A gonadotropin-releasing hormone (GnRH) neuron model [14, 44] that we are interested in is an example of such a system. As will be discussed later, in this model, the transmembrane voltage oscillates much faster than the cytoplasmic calcium concentration, while the inactivation of the sodium (Na$^+$) current and the activation of the potassium (K$^+$) current evolve on an intermediate timescale.

We are interested in understanding the dynamics of mathematical models of biophysiological systems, because this can help determine the physiological mechanisms that underlie particular physiological processes. The analysis procedure for multiple timescale systems is normally not as simple as for those systems whose variables evolve on comparable timescales. For instance, the stiffness arising from the timescale separation of the system will cause some numerical issues, and generic bifurcation theory may be unhelpful. Techniques such as geometric singular perturbation theory (GSPT) [19, 30] have been developed to analyse systems with multiple timescales. Methods for analysing two timescale systems are already mature, but less is understood for systems with three or more timescales. Krupa et al. have studied some aspects of mixed-mode oscillation dynamics in three timescale systems [29, 37, 38], but those systems have a specific form, i.e., the timescale difference between the fast and slow variables and the slow and superslow variables are all $O(\varepsilon)$. In this thesis, we aim to make progress on understanding the dynamics of mathematical models with three distinct timescales in more general form, i.e., the timescale separation between the fast and slow variables and the slow and superslow variables are independent. More specifically, our goal is to determine typical dynamical phenomena of three timescale systems and then to apply our knowledge to understand the dynamics of the GnRH neuron model.
Before showing the equations of the GnRH neuron model, in sections 1.1-1.2, we will introduce some basic biophysical model structures which are common and which will be useful for what follows. Specifically, we discuss the structure of conductance-based models and calcium models.

1.1 Conductance-Based Neuron Models

One of the most common ways of simulating the activities of excitable cells, such as neurons, is to construct conductance-based models [26, 33, 34]. Biologically, neuron membranes are semi-permeable and are composed of lipid bilayers and different types of proteins. In some types of cell membranes, the ratio of protein to lipid is very low. This fact results in the cell membrane acting as an insulator with very high resistance, or, more appropriately, as a capacitor [32]. Some transmembrane proteins contain aqueous pores which form ion channels on the cell membrane. Through these channels, ions are transported across the cell membrane. Normally, an essential activity of an excitable cell, such as the action potentials, will involve several types of ion channel. The ionic currents ($I$) induced by the movement of ions through the channels give rise to changes of the transmembrane voltage ($V$), which in turn influences the conductances of these channels. The voltage-dependent feature of the conductance of ionic channels is reflected by the use of “gating variables”. Depending on the membrane voltage, the amount of ions that can go through a channel varies; it seems like there is a gate on the ionic channel which controls the flux. A gating variable is the variable utilised to describe the probability that a channel gate is open.

![Equivalent circuit representation](image-url)
or closed. It is dimensionless and takes values between 0 and 1 [26, 65]. Figure 1.1 shows an equivalent circuit representation for a neuron membrane with three ionic channels.

Based on the biological nature of cell membranes, a conductance-based model usually contains several evolution equations for “activation” and “inactivation” gating variables, which could evolve on different timescales, and an equation for $V$, which is obtained by applying Kirchhoff’s law, i.e., the transmembrane current is equal to the sum of the individual ionic currents.

### 1.1.1 The Hodgkin-Huxley Model

The Hodgkin-Huxley (HH) model [18, 26, 33], which simulates the membrane action potential of the space-clamped squid giant axon, is an example of a conductance-based model. The ionic currents in the HH model consist of a fast sodium current ($I_{Na}$), a delayed rectifier potassium current ($I_K$), and a small “leakage current” ($I_L$) which consists mainly of chloride ions. The model is defined by the following four-dimensional system of ordinary differential equations:

\[
\begin{align*}
C \frac{dV}{dt} &= -I_{Na} - I_K - I_L + I_{app} \\
\frac{dm}{dt} &= \phi[\alpha_m(V)(1 - m) - \beta_m(V)m] \\
\frac{dh}{dt} &= \phi[\alpha_h(V)(1 - h) - \beta_h(V)h] \\
\frac{dn}{dt} &= \phi[\alpha_n(V)(1 - n) - \beta_n(V)n],
\end{align*}
\]

where $C$ is the capacitance density in $\mu F/cm^2$, $V$ is the membrane potential in $mV$ and $t$ is the time in $ms$. The ionic currents on the right hand side of the first equation are given by

\[
\begin{align*}
I_{Na} &= g_{Na} m^3 h (V - V_{Na}), \\
I_K &= g_K n^4 (V - V_K) \\
I_L &= g_L (V - V_L),
\end{align*}
\]

and $I_{app}$ is the stimulus current applied to the space-clamped axon. The applied current $I_{app}$ could be an arbitrary constant and will always be treated as the bifurcation parameter when we draw bifurcation diagrams.

The dynamics of the voltage dependent gating variables are described by the remaining three equations in (1.1). Variables $m$ and $h$ denote the activation and inactivation of the sodium ($Na^+$) current, respectively; and $n$ is the activation of the potassium ($K^+$) current. Since the activation and deactivation rates for ionic channels depend sensitively on the temperature, there is a temperature factor in the
model which is given by

\[ \phi = Q_{10}^{(T - T_{\text{base}})/10}. \] (1.3)

\( Q_{10} = 3 \) gives the ratio of the rates as a consequence of increasing the temperature by 10 °C. \( T \) is temperature, and \( T_{\text{base}} = 6.3 \, ^\circ C \) for the squid giant axon [26]. From now on, all the analysis of the HH model will be done with the assumption that \( \phi = 1 \), i.e., the temperature is 6.3 °C, unless otherwise indicated. The specific functions \( \alpha_x \) and \( \beta_x \) \((x = m, h, n)\) in units of \((ms)^{-1}\) are

\[
\begin{align*}
\alpha_m(V) &= \frac{(V + 40)/10}{1 - \exp(-(V + 40)/10)} \\
\beta_m(V) &= 4\exp(-(V + 65)/18) \\
\alpha_h(V) &= 0.07\exp(-(V + 65)/20) \\
\beta_h(V) &= \frac{1}{1 + \exp(-(V + 35)/10)} \\
\alpha_n(V) &= \frac{(V + 55)/100}{1 - \exp(-(V + 55)/10)} \\
\beta_n(V) &= 0.125\exp(-(V + 65)/80),
\end{align*}
\] (1.4)

and the parameters of the model are given in Table 1.1.

<table>
<thead>
<tr>
<th>Parameter values of the HH model</th>
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<tbody>
<tr>
<td>( g_{Na} )</td>
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<tr>
<td>( g_K )</td>
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<td>( g_L )</td>
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<tr>
<td>( V_{Na} )</td>
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<td>( V_K )</td>
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<tr>
<td>( V_L )</td>
</tr>
<tr>
<td>( C )</td>
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</tbody>
</table>

Table 1.1: The values of the parameters in the HH model, equations (1.1) and (1.2).

### 1.1.2 Timescales of the HH Model

An action potential generated by the HH model with \( I_{\text{app}} = 9.6 \mu A/cm^2 \) is shown in Figure 1.2(a). The evolution of the three gating variables during the action potential is plotted in Figure 1.2(b). During the action potential, \( m \) appears to evolve faster than \( h \), in the sense that \( m \) takes less time to reach its maximum than \( h \) takes to reach its minimum. The graphs of \( h \) and \( n \) are approximately symmetric, which indicates they are evolving at similar speeds. The observations are consistent with those from experiments, where the Na⁺ current is seen to turn on much faster than it is turned off, and the outward K⁺ current is activated at about the same time as the Na⁺ current is inactivated [26]. Such a difference in speed of evolution between \( m \) and \( (h, n) \) plays an important role in forming the action potential.
Equation (1.1) is often written in the form:

\[
\begin{align*}
C dV/dt &= -I_{Na} - I_{K} - I_{L} + I_{\text{app}} \\
\frac{dm}{dt} &= (m_\infty(V) - m)/\tau_m(V) \\
\frac{dh}{dt} &= (h_\infty(V) - h)/\tau_h(V) \\
\frac{dn}{dt} &= (n_\infty(V) - n)/\tau_n(V),
\end{align*}
\] (1.5)

using the assumption that \( \phi = 1 \), and with \( x_\infty \) and \( \tau_x \) \( (x = m, h, n) \) defined by

\[
x_\infty(V) = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)} \quad \text{and} \quad \tau_x(V) = \frac{1}{\alpha_x(V) + \beta_x(V)},
\] (1.6)

where \( x_\infty \) is the steady-state function of its corresponding gating variable and \( \tau_x \) is called the \textit{time constant}, which determines the rate at which a solution approaches its final value \( x_\infty \) for any given voltage step. Generally, \( \tau_x \) is a skewed bell-shaped function of \( V \). The three time constants are plotted in Figure 1.3, which indicates that \( \tau_m \) is much smaller than \( \tau_h \) and \( \tau_n \).

In order to reveal the timescales of a system analytically, we need to nondimensionalise the model and compare the typical timescales of each of the variables. The detailed process of nondimensionalisation is introduced in section 2.1, where we will show that the HH model, equations (1.5), can be regarded as a two timescale model, with \( (V, m) \) being fast variables and \( (h, n) \) being slow variables.

![Figure 1.2](image)

(a): An action potential simulated by the HH model, equations (1.1), with \( I_{\text{app}} = 9.6 \mu A/cm^2 \). (b): The evolution of the gating variables during the action potential.
1.2 Calcium Models

The concentration of free cytosolic calcium ([Ca\(^{2+}\)]\(_i\)) oscillates in many cell types, and these oscillations are thought to be crucial to many cellular processes. Under normal conditions, [Ca\(^{2+}\)]\(_i\) is much lower than the calcium concentration outside the cell and in the internal stores such as the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). By using energy from adenosine triphosphate (ATP), the ATPase pumps in the plasma membrane (or ER) can pump calcium out of the cell (or back into the ER) to maintain the concentration gradients. These steep concentration gradients allow the calcium in the cell cytoplasm to increase rapidly once the calcium channels are opened. Without any feedback mechanisms, an increase in [Ca\(^{2+}\)]\(_i\) cannot result in oscillations. The exact feedback mechanisms for certain cell types or oscillatory patterns may be difficult to determine, but there are two main hypotheses [59] about the ways in which intracellular calcium oscillation are controlled.

The initial steps in a calcium oscillation are mainly accepted as being as follows: an agonist such as a hormone or neurotransmitter first binds to a cell membrane receptor (R), resulting in the activation of a G-protein (G), and then leading to the activation of phospholipase C (PLC) [33], as illustrated in Figure 1.4. This series of reactions cause the formation of a second messenger, inositol (1, 4, 5)-trisphosphate (IP\(_3\)). Then IP\(_3\) diffuses within the cell, binding to IP\(_3\) receptors (IPR), which are calcium channels that are located on the membrane of the ER. The IPR open when they bind IP\(_3\), leading to the release of calcium (Ca\(^{2+}\)) from the ER into the cytoplasm.

In a Class I feedback mechanism, Ca\(^{2+}\) can then stimulate the release of additional calcium from the ER by binding to the IPR and increasing its open probability. However, Ca\(^{2+}\) can also bind to a different site of the IPR to inhibit calcium release.
Figure 1.4: A sketch of the main physiological components involved in producing calcium oscillations, showing the influxes and effluxes of cytosolic Ca$^{2+}$. Each dashed arrow has a ‘+’ or ‘−’ showing whether the effect of the feedback is positive or negative. The Class I feedback mechanism of calcium on the IP$_3$ receptors (IPR) is shown in red and the Class II feedback of calcium on the production and degradation of IP$_3$ is shown in blue. Adapted from Keener and Sneyd [33].

The latter process happens on a slower timescale than the former one. After calcium release terminates, the ATPase pumps carry Ca$^{2+}$ back into the ER, leading to a decrease of [Ca$^{2+}$]$_i$ and resetting the oscillation. In a Class II feedback mechanism, on the other hand, Ca$^{2+}$ promotes the production of IP$_3$. As a result, more Ca$^{2+}$ is released from the ER. However, increasing [Ca$^{2+}$]$_i$ enhances the activity of 3-kinase, which phosphorylates IP$_3$ to inositol (1, 3, 4, 5)-tetrakisphosphate (IP$_4$). This process is a negative feedback on [Ca$^{2+}$]$_i$. Figure 1.4 shows the two feedback pathways together with the main physiological mechanisms that produce calcium oscillations. Calcium models then can be constructed depending on which mechanism is thought to drive the oscillations.

1.2.1 General Form of Calcium Models

Using $J_{\text{release}}$ and $J_{\text{serca}}$ to represent the Ca$^{2+}$ released from the ER and pumped back to the ER, respectively, and denoting by $J_{\text{in}}$ and $J_{\text{pm}}$ the influxes and effluxes
of the Ca\(^{2+}\) through the plasma membrane, respectively, then the general form of a mathematical model for calcium oscillations will be

\[
\frac{dc}{dt} = J_{\text{release}} - J_{\text{serca}} + \rho(J_{\text{in}} - J_{\text{pm}}) \\
\frac{dc_e}{dt} = \gamma(J_{\text{serca}} - J_{\text{release}}),
\]

(1.7)

where \(c\) represents \([\text{Ca}^{2+}]_i\) and \(c_e\) is the calcium concentration in the ER (\([\text{Ca}^{2+}]_e\)). The dimensionless scaling factor \(\rho\), which is always a small quantity, relates the total fluxes across the plasma membrane to the ER fluxes. The parameter \(\gamma\) denotes the ratio of the cytoplasmic volume to the ER volume. The particular model used for each of the flux terms can then be determined according to a specific cell type or a specific calcium oscillation pattern. For example, to model \(J_{\text{serca}}\), the flux through the ATPase pumps into the ER, it is common to use a simple Hill function \([33]\) in the form:

\[
J_{\text{serca}} = \frac{V_e c^n}{K_e^n + c^n},
\]

(1.8)

with a justified choice of Hill coefficient \(n\).

Sometimes in a calcium model, rate equation(s) are needed to describe the dynamics of IP\(_3\) or/and IPR. The forms of these evolution equations may vary according to the cell types. For example, the dynamics of IP\(_3\) can be modeled by the following rate equation for \(p\):

\[
\frac{dp}{dt} = \alpha - \beta p,
\]

(1.9)

where \(\alpha\) is a function that describes the rate of IP\(_3\) production and needs to be determined in individual cases; the decay rate of IP\(_3\) is represented by \(\beta\) and is always a constant.

### 1.2.2 General Timescales of Calcium Models

In many cell types, changes of \([\text{Ca}^{2+}]_i\) happens on a much faster timescale than the evolution of the total calcium concentration (\([\text{Ca}^{2+}]_t\)) in the cell. In order to make the timescale separation of a calcium model explicit, the differential equation for \(c_e\) (the calcium concentration in the ER) can be converted into a differential equation for \(c_t\), which denotes \([\text{Ca}^{2+}]_t\) in the cell and satisfies \(c_t = c_e/\gamma + c\). Equations (1.7) then can be transformed into the following system:

\[
\frac{dc}{dt} = J_{\text{release}} - J_{\text{serca}} + \rho(J_{\text{in}} - J_{\text{pm}}) \\
\frac{dc_t}{dt} = \rho(J_{\text{in}} - J_{\text{pm}}),
\]

(1.10)

where the variable \(c_e\) in the model is replaced by \(\gamma(c_t - c)\).
1.3 A GnRH Neuron Model

Normally, the calcium concentration scales for \( c \) and \( c_t \) are the same. Hence, if the scaling factor \( \rho \) is sufficiently small, the evolution of \( c \) will be much faster than the evolution of \( c_t \). System (1.10) therefore is a fast-slow system with a fast variable \( c \) and a slow variable \( c_t \). Other variables included in the calcium model to describe the dynamics of IP\(_3\), IPR or IP\(_4\) could be fast or slow variables depending on the model assumptions.

1.3 A GnRH Neuron Model

Gonadotropin-releasing hormone (GnRH) is important for mammalian maturation and fertility; it stimulates the release of follicle-stimulating hormone (FSH) and luteinising hormone (LH). It is synthesised and released from GnRH neurons within the hypothalamus [14]. Duan et al. attempted to elucidate the mechanisms underlying electrical bursting and synchronous calcium (Ca\(^{2+}\)) transients in GnRH neurons by construction of a mathematical model [44]. The full model can be considered as a coupling of a voltage submodel and a calcium submodel. The voltage submodel is a conductance-based (Hodgkin-Huxley type) model, which contains an equation for the membrane potential \( V \), three equations for gating variables, and two equations for the open states of a slow Ca\(^{2+}\)-activated afterhyperpolarisation current \( sI_{\text{AHP-UCL}} \). The slow Ca\(^{2+}\)-activated \( sI_{\text{AHP-UCL}} \) current is a pacemaker current. It is thought to be crucial for the generation of bursting in the GnRH neurons. The calcium submodel is composed of \( c \), the cytosolic concentration of free intracellular calcium ([Ca\(^{2+}\)]\(_i\)), and \( c_e \), the concentration of calcium in the ER ([Ca\(^{2+}\)]\(_e\)).

1.3.1 The GnRH Neuron Equations

The ionic currents \( I_x \) in the GnRH neuron model of Duan et al. are given by:

\[
\begin{align*}
I_{kdr} &= g_{kdr}N_{kdr}^4(V - V_k) \\
I_{kir} &= g_{kir}N_{kir}\infty(V - V_k) \\
I_{km} &= g_{km}N_{km}(V - V_k) \\
I_{cal} &= g_{cal}M_{cal}\infty(V - V_{ca}) \\
I_{cat} &= g_{cat}M_{cat}\infty H_{cat}\infty(V - V_{ca}) \\
I_{naf} &= g_{naf}M_{naf}\infty H_{naf}\infty(V - V_{na}) \\
I_{nap} &= g_{nap}M_{nap}\infty H_{nap}\infty(V - V_{na}) \\
sI_{\text{AHP-SK}} &= g_{sk}(C_{sk}^{n_{sk}} + K_{sk}^{n_{sk}})(V - V_k) \\
sI_{\text{AHP-UCL}} &= g_{ucl}(O_{ucl} + O_{ucl}^*)(V - V_k) \\
I_{\text{leak}} &= g_{\text{leak}}(V - V_{\text{leak}}),
\end{align*}
\]
where $I_{kdr}$, $I_{kir}$ and $I_{km}$ represent the delayed rectifier, inward rectifier, and M-type potassium currents; $I_{cal}$ and $I_{cat}$ are two different types of calcium currents; $I_{naf}$ and $I_{nap}$ are the fast and persistent sodium currents, respectively. The SK-type Ca$^{2+}$-activated potassium current ($sI_{AHP-SK}$) is a pacemaker current which controls the dynamics of both the firing within bursts and the interburst interval, while the $sI_{AHP-UCL}$ current only controls the interburst dynamics. Note that the $sI_{AHP-SK}$ current and the $sI_{AHP-UCL}$ current are the only mechanism in the full model by which $[\text{Ca}^{2+}]_i$ feeds back to the voltage submodel. The membrane leakage current is denoted by $I_{\text{leak}}$. If we use $I_{\text{ionic}}$ to represent the sum of these ionic currents, i.e.,

$$I_{\text{ionic}} = I_{kdr} + I_{kir} + I_{km} + I_{cal} + I_{cat} + I_{naf} + I_{nap} + sI_{AHP-SK} + sI_{AHP-UCL} + I_{\text{leak}},$$

(1.12)

the equation for $V$ will be given by the following:

$$C_m \frac{dV}{dt} = -I_{\text{ionic}} + I_{\text{app}},$$

(1.13)

where $C_m$ is the membrane capacitance, and $I_{\text{app}}$ is the applied current. The steady-state functions of the ionic currents are as follow:

\[
\begin{align*}
M_{naf\infty} &= (1 + \exp(-(V + 40)/4.3))^{-1} \\
M_{nap\infty} &= (1 + \exp(-(V + 70)/4.1))^{-1} \\
H_{nap\infty} &= (1 + \exp((V + 80)/5))^{-1} \\
N_{kir\infty} &= 0.8(1 + \exp((V + 80)/12))^{-1} + 0.2 \\
M_{cal\infty} &= (1 + \exp(-(V + 30)/2))^{-1} \\
M_{cat\infty} &= (1 + \exp(-(V + 56.1)/10))^{-1} \\
H_{cat\infty} &= (1 + \exp((V + 86.4)/4.7))^{-1},
\end{align*}
\]

(1.14)

and the equations for the three gating variables $N_{kdr}$, $N_{km}$, and $H_{naf}$ are

\[
\begin{align*}
\frac{dN_{kdr}}{dt} &= \frac{1}{\tau_{N_{kdr}}}(N_{kdr\infty} - N_{kdr}) \\
\frac{dN_{km}}{dt} &= \frac{1}{\tau_{N_{km}}}(N_{km\infty} - N_{km}) \\
\frac{dH_{naf}}{dt} &= \frac{1}{\tau_{H_{naf}}}(H_{naf\infty} - H_{naf}),
\end{align*}
\]

(1.15)

with time constants $\tau_x$ (units in ms) as follows:
\[ \tau_{N_{kdr}} = \frac{21}{\exp((V + 30)/15) + \exp(-(V + 30)/15)) + 1.4 \]
\[ \tau_{N_{km}} = \frac{11.5}{\exp((V + 30)/15) + \exp(-(V + 30)/15)) } \]
\[ \tau_{H_{na\text{f}}} = \frac{75}{\exp((V + 80)/19) + 2 \exp(-2(V + 80)/19)), }\]

and steady-state functions:
\[ N_{kdr\infty} = \frac{1}{1 + \exp(-(V + 25)/15))} \]
\[ N_{km\infty} = \frac{1}{1 + \exp(-(V + 37)/4))} \]
\[ H_{na\text{f}\infty} = \frac{1}{1 + \exp((V + 66.1)/10.8))} \] (1.17)

The transitions within the \( sI_{\text{AHP-UCL}} \) subunits are shown in the following reaction scheme:

\[
\begin{align*}
S_{\text{ucl}} & \quad \xrightleftharpoons[k_{11} \cdot c]{k_{-11}} O_{\text{ucl}} \\
 & \quad \xrightarrow[k_{33}]{k_{22}} O^*_{\text{ucl}} \\
& \quad \xrightarrow[O_{\text{ucl}}]{O^*_{\text{ucl}}} \\
\end{align*}
\]

where \( O_{\text{ucl}} \) and \( O^*_{\text{ucl}} \) are two open states and \( S_{\text{ucl}} \) is the closed state, and where \( O_{\text{ucl}} + O^*_{\text{ucl}} + S_{\text{ucl}} = 1 \). The rate constant \( k_{33} \) is a small value which indicates the \( sI_{\text{AHP-UCL}} \) channel will be turned off slowly. The reaction scheme reflects the fact that the channel will shift into the open state when calcium concentration is increased, and will stay in the closed state in the absence of calcium [14]. The differential equations describing the dynamics of the open states \( O_{\text{ucl}} \) and \( O^*_{\text{ucl}} \) are
\[
\begin{align*}
\frac{dO_{\text{ucl}}}{dt} & = k_{11}c(1 - O_{\text{ucl}} - O^*_{\text{ucl}}) - (k_{-11} + k_{22})O_{\text{ucl}} \\
\frac{dO^*_{\text{ucl}}}{dt} & = k_{22}O_{\text{ucl}} - k_{33}O^*_{\text{ucl}}. \\
\end{align*}
\] (1.18)

The system governing \([\text{Ca}^{2+}]_i\) and \([\text{Ca}^{2+}]_e\) has the same general form as equation (1.7). Equations for each term in (1.7) are
\[
\begin{align*}
J_{\text{release}} & = (K_fO_4 + J_{er})(c_e - c) \\
J_{\text{serca}} & = P_{\text{rate}} c - a_1 c_e a_2 + a_3 c + a_4 c_e + a_5 c c_e \\
J_{\text{in}} & = -\alpha(I_{\text{cal}} + I_{\text{cat}}) + \beta \cdot IP_3 \\
J_{\text{pm}} & = V_p c^2 + K_p^2 + V_{\text{naca}} c^3 + K_{\text{naca}}^4, \\
\end{align*}
\] (1.19)
where

\[ O_4 = \frac{q_{12}q_{32}q_{24}}{q_{12}q_{32}q_{24} + q_{42}q_{23}q_{12} + q_{42}q_{32}q_{12} + q_{42}q_{32}q_{21}}, \]  

(1.20)

\[ q_{23} = a_{23} - \left( \frac{V_{23}}{k_{23}^2 + c^2} + b_{23} \right) \left( \frac{V_{-23}c^5}{k_{-23}^5 + c^5} + b_{-23} \right), \]  

(1.21)

and where \( q_{12}, q_{21}, q_{24} \) and \( q_{42} \) are constants; their values can be seen in Table 1.2.

For convenience in timescale analysis, we convert \( c_e \) into \( c_t \), the total calcium concentration in the cell \([\text{Ca}^{2+}]_t\), before we start to analyse the system. As introduced in section 1.2.2, the calcium submodel becomes:

\[
\frac{dc}{dt} = J_{\text{release}} - J_{\text{serca}} + \rho(J_{\text{in}} - J_{\text{pm}}),
\]

\[
\frac{dc_t}{dt} = \rho(J_{\text{in}} - J_{\text{pm}}),
\]

(1.22)

where \( c_e \) is replaced by \( \gamma(c_t - c) \) in the model.

The eight dimensional full GnRH neuron model therefore is as follows:

\[
C_m \frac{dV}{dt} = -I_{\text{ionic}} + I_{\text{app}}
\]

\[
\frac{dN_{kdr}}{dt} = \frac{1}{\tau_{N_{kdr}}} (N_{kdr\infty} - N_{kdr})
\]

\[
\frac{dN_{km}}{dt} = \frac{1}{\tau_{N_{km}}} (N_{km\infty} - N_{km})
\]

\[
\frac{dH_{naf}}{dt} = \frac{1}{\tau_{H_{naf}}} (H_{naf\infty} - H_{naf})
\]

\[
\frac{dO_{ucl}}{dt} = k_{11}c(1 - O_{ucl} - O_{ucl}^*) - (k_{-11} + k_{22})O_{ucl}
\]

\[
\frac{dO_{ucl}^*}{dt} = k_{22}O_{ucl} - k_{33}O_{ucl}^*
\]

\[
\frac{dc}{dt} = J_{\text{release}} - J_{\text{serca}} + \rho(J_{\text{in}} - J_{\text{pm}})
\]

\[
\frac{dc_t}{dt} = \rho(J_{\text{in}} - J_{\text{pm}}),
\]

(1.23)

with all the parameters as specified in Table 1.2 and the currents \( I_x \) and calcium fluxes \( J_x \) as specified in equations (1.11) and (1.19) respectively. Note that the calcium submodel is affected by the voltage submodel via the two calcium currents \( I_{\text{cal}} \) and \( I_{\text{cat}} \), while on the other hand, the voltage submodel is affected by the calcium submodel through currents \( sI_{\text{AHP-SK}} \) and \( sI_{\text{AHP-UCL}} \).
1.3 A GnRH Neuron Model

Parameter values of the GnRH neuron model of Duan et al. [44]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_m$</td>
<td>16 pF</td>
</tr>
<tr>
<td>$g_{hdr}$</td>
<td>2 nS</td>
</tr>
<tr>
<td>$g_{cal}$</td>
<td>0.05 nS</td>
</tr>
<tr>
<td>$g_{naf}$</td>
<td>190 nS</td>
</tr>
<tr>
<td>$g_{nap}$</td>
<td>20 nS</td>
</tr>
<tr>
<td>$g_{kdr}$</td>
<td>2 nS</td>
</tr>
<tr>
<td>$g_{kir}$</td>
<td>0.02 nS</td>
</tr>
<tr>
<td>$g_{km}$</td>
<td>8 nS</td>
</tr>
<tr>
<td>$g_{cal}$</td>
<td>0.05 nS</td>
</tr>
<tr>
<td>$g_{cat}$</td>
<td>2 nS</td>
</tr>
<tr>
<td>$g_{leak}$</td>
<td>100 mV</td>
</tr>
<tr>
<td>$n_{sk}$</td>
<td>2</td>
</tr>
<tr>
<td>$K_{sk}$</td>
<td>1 µM</td>
</tr>
<tr>
<td>$k_{-11}$</td>
<td>1.2 ms$^{-1}$</td>
</tr>
<tr>
<td>$q_{12}$</td>
<td>0.74 ms$^{-1}$</td>
</tr>
<tr>
<td>$a_{23}$</td>
<td>3.6 ms$^{-1}$</td>
</tr>
<tr>
<td>$k_{23}$</td>
<td>100 mV</td>
</tr>
<tr>
<td>$q_{22}$</td>
<td>0.5 ms$^{-1}$</td>
</tr>
<tr>
<td>$a_{23}$</td>
<td>1/1.023 ms$^{-1}$</td>
</tr>
<tr>
<td>$k_{32}$</td>
<td>2 µM</td>
</tr>
<tr>
<td>$b_{23}$</td>
<td>2.2 ms$^{-1}$</td>
</tr>
<tr>
<td>$k_{23}$</td>
<td>0.072 µM</td>
</tr>
<tr>
<td>$b_{-23}$</td>
<td>0.042</td>
</tr>
<tr>
<td>$k_{32}$</td>
<td>0.52 µM</td>
</tr>
<tr>
<td>$b_{32}$</td>
<td>0.005 ms$^{-1}$</td>
</tr>
<tr>
<td>$a_1$</td>
<td>10$^{-4}$</td>
</tr>
<tr>
<td>$a_2$</td>
<td>35 ms</td>
</tr>
<tr>
<td>$a_4$</td>
<td>7 µM$^{-1}$ ms</td>
</tr>
<tr>
<td>$a_5$</td>
<td>35 µM$^{-2}$ ms</td>
</tr>
<tr>
<td>$K_p$</td>
<td>0.425 µM</td>
</tr>
<tr>
<td>$P_{rate}$</td>
<td>1</td>
</tr>
<tr>
<td>$IP_3$</td>
<td>0.3 µM</td>
</tr>
<tr>
<td>$\beta$</td>
<td>2 × 10$^{-5}$ ms$^{-1}$</td>
</tr>
<tr>
<td>$IP_3$</td>
<td>0.3 µM</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>4.8 × 10$^{-3}$ µM ms$^{-1}$ pA$^{-1}$</td>
</tr>
</tbody>
</table>

Table 1.2: The values of the parameters in the GnRH neuron model, equation (1.23).

1.3.2 Bursting Phenomenon

We are interested in the bursting phenomenon exhibited by the GnRH neuron model when $I_{app}$ is close to zero. Bursting activity is a common mode of firing in many excitable cells, and is characterised by a phase of repetitive spikes alternating with a period of near steady-state behaviour or quiescence. These two phases have been called the active and silent phases respectively [1, 18, 51].

A time series of each variable of the GnRH neuron model at $I_{app} = 0$ pA is shown in Figure 1.5. In the V time series, the active phases has three spikes. Corresponding to these spikes, in the c time series, there are three steps to increase $[\text{Ca}^{2+}]$. This phenomenon can be seen more clearly if we plot the spike region of V in the same picture as c (see Figure 1.6). After the active phase of the V time series, the concentration of cytosolic calcium continues increasing to a maximum, then decreases and enters its silent phase. Figure 1.7 shows this typical bursting solution plotted in a three-dimensional phase space ($O_{ucl}; c, V$), in which different phases of the bursting
Figure 1.5: Oscillating solutions of each of the variables in the GnRH neuron model at $I_{app} = 0$ pA. Enlargement of the spike region of $V$ is shown in Figure 1.6.

are indicated by different colours. The active phase of the voltage bursting oscillation is shown in black, and the black segment in the $c$ time series shows the period corresponding to the active phase of $V$. It can be seen in the $c$ time series that the black region is a portion of the spike of the $[\text{Ca}^{2+}]$, oscillation. After that, $V$ enters
1.3 A GnRH Neuron Model

![Image of a GnRH neuron model](image)

1.31 1.32 1.33 1.34 1.35 1.36 1.37 1.38 1.39 1.4

\( x \times 10^4 \)

\( -50 \)

\( 0 \)

\( V \)

Figure 1.6: An enlargement of time series for \( V \) (in black) and \( c \) (in red) from Figure 1.5, in the region around the active phase of voltage bursting.

its silent phase while \([\text{Ca}^{2+}]_i\) keep increasing to its maximum value. The phase in blue shows the region from the end of the active phase of the voltage bursting to the end of the calcium spike. When the colour changes to red, both \( V \) and \( c \) are in the silent phase. Comparing the two panels in Figure 1.7, we can see the solution trajectory spends the least time in the black phase, and the longest time in the red phase. Therefore, three distinct timescales which are indicated by three colours can

![Image of time series plots](image)

Figure 1.7: Left: the time series of \( V \) and \( c \) within one period, where the active phase of the voltage bursting oscillation is shown in black, and the long quiescence for calcium oscillation is in red. The region from the end of the active phase of the voltage bursting to the beginning of the silent phase of calcium oscillation is in blue. Right: the bursting solution shown in the left panel, now plotted in \((O_{ucl}^*, c, V)\)-space, with corresponding colour indication.
be observed in this kind of bursting solution.

In this thesis, we are aiming to understand the mechanisms underlying the bursting solution shown in the $V$ time series and the reason for the appearance of the small wiggles and the long quiescence in the $c$ time series. The ultimate goal is to reveal whether or not this kind of bursting oscillation is an intrinsic three timescale phenomenon.

1.4 Aims and Outline of the Thesis

A specific bursting phenomenon (see section 1.3.2) exhibited by the GnRH neuron model appears to involve at least three different timescales. Methods for the analysis of models with two distinct timescales are now well established, but little is known about the case of three or more timescales. The aim of this thesis is to advance the understanding of systems with three timescales, and specifically, to find examples of intrinsically three timescale dynamics.

In Chapter 2, we introduce the mathematical methods that are useful for analysing dynamical systems with multiple timescales. Specifically, we explain the process of nondimensionalising a physiological model and the application of geometric singular perturbation theory (GSPT) to systems with two different timescales.

A common feature of mathematical models of physiological systems is that they can contain many variables, each used to represent one detailed component involved in a biophysical process. For instance, the GnRH neuron model has eight dimensions. Since it is complex and difficult to analyse a system with many dimensions, we seek an appropriate reduction before we perform any analysis on the model. By ‘appropriate reduction’, we mean that in the reduced system: 1. the structure of the bifurcation diagram remains qualitatively the same as the original system, 2. the behaviour of the voltage and calcium time series remain qualitatively the same as in the original system, and 3. the dimension of the model is as small as possible.

In Chapter 3, we reduce the dimension of the GnRH neuron model by revising the ionic currents. It turns out that the dimension of the model can be reduced by one if we modify the assumption about the transitions within the $sI_{AHP-UCL}$ subunits. When we combine the ionic currents for the same ions into one current, we find the model can be further reduced by one dimension. Then we apply the quasi-steady-state approximation to the six-dimensional reduction and also try to use a linear function of one variable to approximate another variable, but it seems none of these methods works for the model. Therefore, the eight-dimensional GnRH model can be reduced to a six-dimensional system. The nondimensionalistion performed on the six-dimensional GnRH neuron model reveals that the model involves three timescales.
In Chapter 4, we discuss the application of GSPT to general three timescale systems with three dimensions. Then we use a food chain model [53] as an example to show how GSPT can be applied. Based on the food chain model, we construct a more general three-dimensional system with three timescales, and we find a three timescale phenomenon generated by the constructed model.

In Chapter 5, we construct a three timescale model by coupling two fast-slow systems in a way that is reminiscent of the timescale structure of the GnRH neuron model. We identify three types of three timescale oscillations from the coupled model and analyse these oscillations by exploiting GSPT.

In Chapter 6, we classify intrinsic three timescale phenomena from the oscillations seen in Chapter 4 and 5. Then we apply GSPT to the six-dimensional reduced GnRH neuron model and show the typical bursting solution generated by the neuron model is intrinsically three timescale bursting.

In Chapter 7, we summarise the main results obtained in the thesis and discuss some possible directions for future work.
Chapter 2

Mathematical Methods

In this chapter, we introduce some mathematical ideas that are useful for analysing biophysical systems with multiple timescales.

2.1 Timescale Analysis

Systems such as the Hodgkin-Huxley (HH) model, which contain variables that evolve on distinct timescales, are called multiple timescale systems. Models with multiple timescales are very common in mathematical physiology, since many physiological systems have the property that some processes evolve much faster than others. Techniques like geometric singular perturbation theory (GSPT) have been developed to explore the complicated dynamics that may occur in models with multiple timescales. The main idea of standard GSPT is to consider two singular limits of the full system, known as the reduced system and the fast subsystem. Information gained by studying these singular limit systems separately can then be combined to give information about the full system; since the limit systems are lower dimensional than the full model, this can greatly simplify the analysis process. In order to properly separate the fast variables from the slow ones, it is helpful to first nondimensionalise the model.

2.1.1 Nondimensionalisation

Models for physiological processes are usually written down initially in a form where different variables directly represent different physical quantities and therefore have physical units associated with them. By suitable rescaling of variables, these units can be removed and intrinsic properties, such as time constants of a system, can be revealed. The procedure of eliminating the units of variables and showing their intrinsic timescales is known as nondimensionalisation.
The steps in nondimensionalisation of an ordinary differential equation model can be summarised as follows. First, identify all the dependent and independent variables and rewrite each of them in the form of an \( O(1) \) dimensionless variable multiplied by a corresponding unknown characteristic scale. Second, rewrite the differential equations in terms of the dimensionless quantities and determine a characteristic scale for each variable. This step would vary depending on the specific system that the nondimensionalisation is performed on. Finally, determine a typical timescale for each variable and identify fast/slow variables by comparing their typical timescales.

We now nondimensionalise the HH model to illustrate the method [54]. The dependent variables in the HH model are \( V \) (in mV) and dimensionless gating variables \( m, h \) and \( n \). The independent variable is \( t \) (in ms). In order to remove the units of the variables (\( V, t \)), we introduce a typical voltage scale \( R_V \) and a typical timescale \( R_t \), and define new dimensionless variables (\( v, \tau \)) by

\[
V = R_V \cdot v, \quad t = R_t \cdot \tau. \tag{2.1}
\]

Appropriate values for \( R_V \) and \( R_t \) will be identified below.

Substituting (2.1) into system (1.5) and rewriting all the equations in terms of the dimensionless quantities, we obtain the dimensionless version of the HH model:

\[
\begin{align*}
\frac{dv}{d\tau} & = \frac{R_t \cdot g_{\text{max}}}{C}(-\bar{g}_{\text{Na}}m^3h(v - \bar{V}_{\text{Na}}) - \bar{g}_K n^4(v - \bar{V}_K) \\
& \quad - \bar{g}_L(v - \bar{V}_L) + \bar{I}_{\text{app}}) \\
\frac{dm}{d\tau} & = \frac{R_t}{\tau_m(v)}(m_\infty(v) - m) \\
\frac{dh}{d\tau} & = \frac{R_t}{\tau_h(v)}(h_\infty(v) - h) \\
\frac{dn}{d\tau} & = \frac{R_t}{\tau_n(v)}(n_\infty(v) - n),
\end{align*}
\]

where \( \bar{V}_x = V_x / R_V, \bar{g}_x = g_x / g_{\text{max}} \) (for \( x = \text{Na, K, L} \)) and \( \bar{I}_{\text{app}} = I_{\text{app}} / (R_V \cdot g_{\text{max}}) \). We have rescaled the quantities \( g_x \) because we want all terms in the brackets of the right hand side of the first equation in system (2.2) to be bounded (in absolute value) by 1. According to the values given in Table 1.1, \( g_{\text{max}} := g_{\text{Na}} = 120 \text{ mS/cm}^2 \). In the equations of the gating variables in (2.2), all of the terms \( x_\infty(v) - x \) are \( O(1) \). Hence, the timescale of each dependent variable can be obtained by considering the factor outside the brackets of the right hand side of each equation in system (2.2).

Next, we determine characteristic scales \( R_V \) and \( R_t \) for the variables (\( V, t \)). The natural range of the observed action potentials satisfies \( V_K \leq V \leq V_{\text{Na}} \), so in the HH model, the maximum variation of the membrane potential is \( \bar{V}_{\text{Na}} - \bar{V}_K = 127 \text{ mV} \),
2.1 Timescale Analysis

Figure 2.1: The multiplicative inverse of the time constant (in ms$^{-1}$) of each gating variable as a function of the dimensionless voltage $v$.

which is $O(100)$. Therefore, we choose $R_V = 100$ mV as a typical voltage scale. Then $v$, which is $V/R_V$ from (2.1), is in the range $[-0.77, 0.5]$.

In order to get a typical timescale $R_t$, we need to know the typical timescales $R_{t,i}$ (here $i = v, m, h, n$) for the variables. The typical timescale of $v$ in system (2.2) is $R_{t,v} = C/g_{max} = 1/120$ ms $= O(10^{-2}$ ms). Note that the $\tau_x$ are functions of $v$ in the dimensionless system (2.2), and so we cannot simply write $R_{t,x} = \tau_x(v)$ for the gating variables. Define $T_x = \max(1/\tau_x(v))$ over the range $v \in [-0.77, 0.5]$. Then the factors $R_t/\tau_x(v)$ can be written as $(R_t \cdot T_x)/\hat{\tau}_x(v)$ where the $\hat{\tau}_x(v)$ are $O(1)$ dimensionless functions. A typical timescale of each gating variable, therefore, is $R_{t,x} = 1/T_x$. We plot the graph of $1/\tau_x$ for $v \in [-0.77, 0.5]$ in Figure 2.1, from which we see that $T_m$ is approximately $O(100\text{ ms}^{-1})$, and $T_h \approx T_n \approx O(1\text{ ms}^{-1})$. The typical timescales of the gating variables are therefore: $R_{t,m} = 1/T_m = O(10^{-1}$ ms), $R_{t,h} = 1/T_h = O(1\text{ ms})$ and $R_{t,n} = 1/T_n = O(1\text{ ms})$. Now we can choose one of $R_{t,i}$ as a typical timescale for system (2.2). Normally, the choice of $R_t$ depends on whether the fast or the slow dynamics are under consideration.

If, for example, we let $R_t := R_{t,n} = 1/T_n$, and set

$$\varepsilon := \frac{C \cdot T_n}{g_{max}} \ll 1,$$  \hfill (2.3)

then the timescale of $m$ is

$$\frac{T_n}{T_m} = \varepsilon \frac{g_{max}}{C \cdot T_m} \ll 1,$$  \hfill (2.4)

and the timescale for $h$ is

$$\frac{T_n}{T_h} \approx 1.$$ \hfill (2.5)
Note that in (2.4), \( g_{\text{max}}/(C \cdot T_m) \approx 10 \) indicates the evolution of \( m \) is actually slower than \( v \), but in order to easily apply the singular perturbation theory which will be introduced in the following section, \( v \) and \( m \) can be grouped together as fast variables [54]. The nondimensionalised HH model (2.2) from this point of view can be written as follows in the form of a singularly perturbed system:

\[
\begin{align*}
\varepsilon \frac{dv}{d\tau} & = -m^3h(v - \bar{V}_{\text{Na}}) - \bar{g}_K n^4(v - \bar{V}_K) - \bar{g}_L (v - \bar{V}_L) + \bar{I}_{\text{app}} \\
\varepsilon \frac{dm}{d\tau} & = (m_\infty(v) - m) / \hat{\tau}_m(v) \\
\frac{dh}{d\tau} & = (h_\infty(v) - h) / \hat{\tau}_h(v) \\
\frac{dn}{d\tau} & = (n_\infty(v) - n) / \hat{\tau}_n(v),
\end{align*}
\]

(2.6)

where \( \varepsilon \), a small constant, separates the timescales among variables. The right hand side of each equation in (2.6) is \( O(1) \), and so it is now clear that in the HH model, variables \((V, m)\) evolve faster than variables \((h, n)\). This reflects the observation that the activation of the sodium channel is much faster than its inactivation or the activation of the potassium channel.

### 2.2 Geometric Singular Perturbation Theory

Geometric singular perturbation theory (GSPT) [19, 30, 31] is a set of techniques designed to exploit the presence of timescale separation to help explain the dynamics of a system of ordinary differential equations. The ideas introduced in this section can be found in many papers; see [35, 39, 61, 62, 70] and references therein.

GSPT is typically applied to systems that can be written in the form:

\[
\begin{align*}
\frac{dx}{dt} & = f(x, y, \varepsilon) \\
\frac{dy}{dt} & = \varepsilon g(x, y, \varepsilon),
\end{align*}
\]

(2.7)

where \( x \in \mathbb{R}^m, y \in \mathbb{R}^n \). The functions \( f \) and \( g \) are assumed to be sufficiently smooth, typically \( C^\infty \), on a set \( U \times V \), where \( U \subset \mathbb{R}^N \) is open, with \( N = m + n \), and where \( V \) is an open interval in \( \mathbb{R} \) containing the origin [19, 30]. The real positive constant \( \varepsilon \ll 1 \) is used to separate the timescales between the phase space variables \( x \) and \( y \). In this situation, we call \( x \) the fast variables and \( y \) the slow variables. System (2.7) evolves on the fast timescale \( t \), but if \( \varepsilon \neq 0 \), it can be reformulated with a change of
timescale to give the equivalent system
\[
\begin{align*}
\varepsilon \frac{dx}{d\tau} &= f(x, y, \varepsilon) \\
\frac{dy}{d\tau} &= g(x, y, \varepsilon),
\end{align*}
\]
(2.8)
where \( \tau = \varepsilon t \) is the slow timescale. We are interested in the singular limit obtained by taking \( \varepsilon \to 0 \) in each of (2.7) and (2.8).

Letting \( \varepsilon \to 0 \) in (2.7), we obtain the layer problem (also called the fast subsystem)
\[
\begin{align*}
\frac{dx}{dt} &= f(x, y, 0) \\
\frac{dy}{dt} &= 0,
\end{align*}
\]
(2.9)
which is an \( m \)-dimensional system of ordinary differential equations in the fast variables \( x \) with \( n \) additional parameters since the slow variables \( y \) become constants. The layer problem provides information about evolution on the fast timescale.

The critical manifold \( S \), which is defined by \( \{ (x, y) \in \mathbb{R}^m \times \mathbb{R}^n \mid f(x, y, 0) = 0 \} \), is the set of equilibria for the layer problem. \( S \) is, at least locally, an \( n \)-dimensional manifold, as it is formed by solving \( m \) equations in \( \mathbb{R}^{m+n} \). A compact subset \( S_h \) of \( S \) is said to be normally hyperbolic if the Jacobian matrix of \( f \) in (2.9) evaluated at each point in \( S_h \) has no eigenvalues with zero real part. The stability of the normally hyperbolic manifold \( S_h \) is consistent with the stability of the equilibria of the layer problem. That is, \( S_a \subseteq S_h \) is attracting if all eigenvalues of the Jacobian \( D_x f(x, y, 0) \) have negative real part for all \( (x, y) \in S_a \), and \( S_r \subseteq S_h \) is repelling if all eigenvalues of the Jacobian \( D_x f(x, y, 0) \) have positive real part for all \( (x, y) \in S_r \). Otherwise, the subset of \( S_h \) is of saddle-type. The solution trajectories governed by the fast dynamics move away from a repelling manifold \( S_r \) and toward an attracting manifold \( S_a \). The behaviour of solutions that start close to a saddle-type manifold will depend on initial conditions [22], and this situation is not discussed here. Trajectories of the layer problem are called fast fibres if \( m = 1 \).

Alternatively, letting \( \varepsilon \to 0 \) in (2.8), we obtain the reduced system (or the slow subsystem)
\[
\begin{align*}
0 &= f(x, y, 0) \\
\frac{dy}{d\tau} &= g(x, y, 0),
\end{align*}
\]
(2.10)
which is a differential-algebraic system describing the evolution of the slow variables \( y \) constrained to the \( n \)-dimensional critical manifold \( S \).

Equations (2.10) can be written in the following form if we differentiate the first
equation with respect to $\tau$ and combine with the second equation:

$$
-D_x f \cdot \frac{dx}{d\tau} = ((D_y f) \cdot g)(x, y, 0)
$$
$$
\frac{dy}{d\tau} = g(x, y, 0),
$$

(2.11)

for $(x, y) \in S$. The new representation is a projection of the reduced flow onto the critical manifold $S$. System (2.11) is singular if $\det(D_x f) = 0$ at some $(x, y)$ on $S$, and the set of these points generically forms a fold $L$ of $S$. In this case, we can desingularise the system by rescaling the time by $\tau_1 = -\det(D_x f(x, y, 0))\tau$. We then obtain the desingularised reduced system:

$$
\frac{dx}{d\tau_1} = (\text{adj}(D_x f) \cdot (D_y f) \cdot g)(x, y, 0)
$$
$$
\frac{dy}{d\tau_1} = -(\det(D_x f) \cdot g)(x, y, 0).
$$

(2.12)

This desingularised system has the same phase portrait as system (2.11) except the directions of solutions are reversed on sections of $S$ such that $-\det(D_x f)(x, y, 0) < 0$. Therefore, the dynamics of the reduced flow can be determined from the dynamics of (2.12).

In summary, the layer problem (2.9) tells us how solution trajectories evolve away from the critical manifold $S$ when $\varepsilon = 0$, and the reduced system (2.10) or (2.11) tells us how the solutions evolve restricted to $S$ when $\varepsilon = 0$. In order to combine this information to describe the dynamics of the full system (2.7) or (2.8) where $\varepsilon > 0$ but very small, we use Fenichel theorem [19, 30].

**Theorem 2.2.1** (Fenichel’s Theorem). Suppose $S^0_h$ is a compact normally hyperbolic subset (possibly with boundary) of the critical manifold $S$ of (2.7) and $f, g \in C^r$ with $r < \infty$. Then for $\varepsilon > 0$ but sufficiently small, the following holds:

1. There exists a $C^r$-smooth manifold $S^\varepsilon_h$ that lies within $O(\varepsilon)$ of $S^0_h$ and is diffeomorphic to $S^0_h$. Moreover it is locally invariant under the flow of (2.7).

2. The manifold $S^\varepsilon_h$ is normally hyperbolic and has the same stability properties with respect to the fast variables as $S^0_h$ given by the layer problem (2.9).

3. As $\varepsilon \to 0$, the flow on $S^\varepsilon_h$ converges to the flow given by the reduced system (2.10) on $S^0_h$.

Fenichel’s theorem guarantees that the normally hyperbolic parts of the critical manifold $S$ persist and perturb smoothly to nearby invariant manifolds $S^\varepsilon_h$ of the full system (2.7) as we increase $\varepsilon$ from zero. Therefore, once the dynamics of the fast and
slow subsystems are obtained, the evolution of solutions of the full system can be predicted for \( \varepsilon \) sufficiently small, and so long as the solutions stay away from regions in which the critical manifold is not normally hyperbolic.

For regions of \( S \) where normally hyperbolicity is lost, such as at the folds of \( S \), the reduced system (2.11) is singular. Although the desingularised system (2.12) can help to determine the dynamics near such folds, at the folds the system is still singular. Thus, techniques which can remove the singularity have to be used to enable the application of Fenichel’s theorem. The blow-up method [15, 39, 40] is an example of this kind of technique; it introduces a coordinate transformation that desingularizes the degenerate points and allows the application of the standard Fenichel theorem.

The precise way in which solutions of the full system are obtained from knowledge of the dynamics of the layer problem and the reduced system depends somewhat on the number of slow variables, \( n \). More detail for specific cases is given below in sections 2.2.1 and 2.2.2.

In summary, GSPT allows one to split an \((m + n)\)-dimensional full system of the form of (2.7) into an \(m\)-dimensional fast subsystem with \( n \) additional parameters and an \( n\)-dimensional slow subsystem that is constrained to an \( n\)-dimensional critical manifold, i.e., the reduced system. Full system solutions can then be constructed by concatenating orbits of the fast subsystem and the reduced system and perturbing in an appropriate way. Since these systems are lower dimensional, the analysis process can be simplified dramatically. Also, since the variables evolve on comparable timescales within each subsystem, the numerical issues arising from the stiffness of the full system can be avoided, at least within the subsystems.

2.2.1 The FitzHugh-Nagumo (FHN) Equations

In this section, the FitzHugh-Nagumo (FHN) equations [21, 47] will be used to illustrate the application of GSPT to systems with one fast and one slow variable. The FHN equations, which model the electric potential across neural cell membranes, are essentially a two-dimensional version [33] of the Hodgkin-Huxley equations introduced in section 1.1.1. The FHN equations are

\[
\frac{dv}{dt} = I(v) - w + I_{\text{app}} = f(v, w) \\
\frac{dw}{dt} = \varepsilon(v - \gamma w) = \varepsilon g(v, w),
\]

where \( I(v) = v(1-v)(v-\alpha) \) and \( t \) is the fast timescale. The fast variable \( v \) represents the transmembrane potential and the slow variable \( m \) is a gating variable. The applied current \( I_{\text{app}} \) is treated as a bifurcation parameter. We fix \( \alpha = 0.1 \) and \( \gamma = 1 \).
Figure 2.2: Left: relaxation oscillation in the FHN equations (2.13) with $I_{\text{app}} = 0.4$ and $\varepsilon = 0.005$. Right: phase portrait of the solution shown in the left panel.

for the rest of the analysis in this section. With a choice of $I_{\text{app}} = 0.4$, periodic solutions known as relaxation oscillations can be observed; see Figure 2.2.

Taking $\varepsilon \to 0$ in system (2.13) gives the layer problem:

$$\begin{align*}
\frac{dv}{dt} &= f(v, w) \\
\frac{dw}{dt} &= 0.
\end{align*}$$

The critical manifold is defined by $S = \{(v, w) \in \mathbb{R}^2 : f(v, w) = 0\}$, which is a cubic shaped curve. Further calculation of $\partial f/\partial v$ shows that the outer branches of $S$ are attracting while the middle branch of $S$ is repelling. Since the trajectories of the layer problem (2.14) satisfy $dw/dt = 0$, away from $S$ they are horizontal lines (fast fibres) leaving the middle branch and heading to the outer branches. The phase portrait of (2.14) is shown in the left panel of Figure 2.3.

The FHN equations written on the slow timescale $\tau = \varepsilon t$ are

$$\begin{align*}
\varepsilon \frac{dv}{d\tau} &= f(v, w) \\
\frac{dw}{d\tau} &= g(v, w).
\end{align*}$$

Letting $\varepsilon \to 0$, we get the reduced system:

$$\begin{align*}
0 &= f(v, w) \\
\frac{dw}{d\tau} &= g(v, w).
\end{align*}$$
2.2 Geometric Singular Perturbation Theory

Figure 2.3: Left: fast fibres (blue lines with arrows) for the layer problem (2.14) with $I_{app} = 0.4$ and $\varepsilon = 0.005$. The attracting parts of the critical manifold $S$ of the FHN equations are shown by red lines, and the repelling branch is indicated by the black dashed curve. Right: flow on $S$ determined by the reduced problem, equations (2.16). The green dashed line is the $w$-nullcline and shows where $g(v, w) = 0$. The fold points of $S$ are indicated by blue dots and the black dot is the unique unstable equilibrium in the FHN equations (2.13) at these values of $I_{app}$ and $\varepsilon$.

Therefore, the flow restricted to $S$ is given by:

$$\frac{\partial f}{\partial v} \frac{dv}{d\tau} = -\frac{\partial f}{\partial w} g(v, w) = g(v, w),$$

i.e.,

$$\frac{dv}{d\tau} = \frac{g(v, w)}{\partial f/\partial v}. \quad (2.17)$$

Note that $\partial f/\partial w = -1$. Away from the folds of $S$ (where $\partial f/\partial v = 0$), the critical manifold is normally hyperbolic, and the direction of the flow can be deduced from (2.17). In the right panel of Figure 2.3, the dynamics of the reduced system (2.16) is shown.

Denote the folds of $S$ by $p^\pm$. If $g(v, w)|_{p^\pm} \neq 0$, then the fold points are known as jump points [39, 40], since the slow flow at $p^\pm$ becomes unbounded ($\partial f/\partial v = 0$ in equation (2.17)) and consequently the solutions jump away from the folds following the fast fibres. In this case, we can combine the information obtained from the layer problem (2.14) and the reduced system (2.16) to form a singular periodic orbit in the full system (2.13) for $\varepsilon = 0$; see Figure 2.4.

To obtain the dynamics of the full system with $\varepsilon > 0$, Fenichel’s theorem (Theorem 2.2.1) tells us there will be two attracting slow manifolds and one repelling slow manifold lying within $O(\varepsilon)$ of the stable outer branches of the critical manifold $S$ and the unstable middle branch of $S$, respectively. The flow on these slow manifolds converges to the flow on the nearby critical manifold as $\varepsilon \to 0$. Hence, a solution trajectory will follow the attracting slow manifolds until it comes near the folds $p^\pm$.

In general, the distance between the attracting and repelling slow manifolds is
non-zero near the fold point when $\varepsilon > 0$. In the case of jump points, the attracting slow manifold is found to pass outside the repelling slow manifold as shown in Figure 2.5 (a). The solutions following the attracting slow manifold will then follow the fast fibres, forming relaxation oscillations, which lie within $O(\varepsilon)$ of the singular orbit, in the full system [39]. This is the situation seen for most parameter values, including our choice of $I_{\text{app}} = 0.4$. Thus, the relaxation oscillation seen in Figure 2.2 can be thought of as a perturbation of the singular orbit plotted in Figure 2.4.

In the case $g(v, w)|_{p^\pm} = 0$, the equilibrium of the full system (2.13) lies at the fold $p^\pm$, removing the singularity in equation (2.17). The solutions of the reduced problem

Figure 2.5: (a): critical manifold $S$ and slow manifold $S^\varepsilon$ in the case of a jump point. (b): critical manifold $S$ and slow manifold $S^\varepsilon$ in the case of a canard point. Adapted from [40].
may pass through the fold points $p^\pm$ in finite time from $S_a$, the attracting branch of the critical manifold, to $S_r$, the repelling branch of $S$. Solutions that behave like this are called *singular canards*. When $\varepsilon > 0$, the attracting slow manifold in this case may stay close to the repelling slow manifold for a while, as shown in Figure 2.5 (b). The distance between the attracting and repelling slow manifolds can be adjusted by varying parameters. At a unique parameter value, the two slow manifolds will connect. The solution at this particular parameter value will remain near the repelling slow manifold for the longest time and is known as a *maximal canard*. Fold points satisfying $g(v, w)|_{p^\pm} = 0$ are called *canard points*. An associated phenomenon, *canard explosion*, which denotes a very fast transition from small amplitude limit cycles to relaxation oscillations upon variation of a parameter, would be expected; for details refer to [15, 40].

### 2.2.2 Systems with One Fast and Two Slow Variables

In this section, we consider three-dimensional systems with one fast and two slow variables that can be written in the form

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y, z, \varepsilon) \\
\frac{dy}{dt} &= \varepsilon g(x, y, z, \varepsilon) \\
\frac{dz}{dt} &= \varepsilon h(x, y, z, \varepsilon),
\end{align*}
\tag{2.18}
\]

where $\varepsilon$ is a parameter with $0 < \varepsilon \ll 1$ and functions $f$, $g$ and $h$ are sufficiently smooth. The variable $x$ is the fast variable, while $y$ and $z$ are slow variables. The independent variable $t$ represents the fast timescale. Many of the ideas from GSPT discussed above for the case of systems with one fast and one slow variable also apply to systems with one fast and two slow variables, but some new ideas are also needed. Specifically, the ideas about jump points and canard points discussed above need to be extended for systems with two slow variables.

#### Critical Manifold

The critical manifold of the system (2.18) is defined by $S := \{(x, y, z) \in \mathbb{R}^3 : f(x, y, z, 0) = 0\}$. For simplicity, we assume function $f$ satisfies:

\[
\begin{align*}
f(0, 0, 0, 0) &= 0, \\
f_x(0, 0, 0, 0) &= 0, \\
f_y(0, 0, 0, 0) &\neq 0, \\
f_{xx}(0, 0, 0, 0) &\neq 0,
\end{align*}
\tag{2.19}
\]
which are sufficient conditions [61] to ensure that $S$ is a smooth, non-degenerate folded surface, that the origin is located on the fold curve $L := \{(x, y, z) \in S : f_x = 0\}$ of $S$, and so is a non-hyperbolic equilibrium of the layer problem. Furthermore, $S$ can be locally given by $y = F(x, z)$ and the fold curve can be parameterized by $z$, i.e., points on the fold curve are given locally by $(\eta(z), \zeta(z), z), z \in I$ for some interval $I$.

Under conditions (2.19), the critical manifold $S$ contains an attracting branch $S_a$ and a repelling branch $S_r$ near the origin, and these two branches are separated by the fold curve $L$. A schematic diagram is shown in Figure 2.6. When $\varepsilon$ increases from 0, these two branches are perturbed smoothly to slow manifolds $S_a^\varepsilon$ and $S_r^\varepsilon$ lying within $O(\varepsilon)$ of $S_a$ and $S_r$, respectively. The normal hyperbolicity is lost in a neighbourhood of the fold curve $L$.

As discussed in the previous section, Fenichel’s theorem is inapplicable along the fold curve. A point $p$ on the fold curve $L$ could be a jump point or a canard point. Define

$$l(p) := (f_y g + f_z h)|_{p \in L}. \quad (2.20)$$

Then if the condition $l(p) \neq 0$, known as the transversality condition [61, 62], is satisfied, the point $p$ is a jump point. That is because, geometrically, the transversality condition guarantees that the projection of the reduced flow onto the $(y, z)$-plane is not tangent to the fold curve at $p$. Hence, solutions reaching the fold will leave directly following the fast dynamics. If $l(p) = 0$, solution trajectories might be able to pass from $S_a$ to $S_r$, thereby forming canards in the system. Fold points $p \in L$ such that $l(p) = 0$ are called folded singularities. The behaviour of solutions near them can be determined by considering the reduced system of (2.18).
2.2 Geometric Singular Perturbation Theory

Reduced Dynamics

Recall that $S$ can be represented by $y = F(x, z)$. The projection of the reduced system onto the $(x, z)$-plane is therefore

$$
-f_x \frac{dx}{d\tau} = f_y g(x, F, z, 0) + f_z h(x, F, z, 0)
$$

$$
\frac{dz}{d\tau} = h(x, F, z, 0),
$$

where $\tau$ is the slow time and satisfies $\tau = \varepsilon t$. Since $f_x = 0$ on the fold curve $L$, system (2.21) is singular on $L$. We thus rescale time to $\tau_1 := \tau/(-f_x)$ to get the following desingularized system:

$$
\frac{dx}{d\tau_1} = f_y g + f_z h
$$

$$
\frac{dz}{d\tau_1} = -f_x h.
$$

The desingularized system (2.22) has the same phase portrait as (2.21) except that the direction of solutions on the repelling manifold $S_r$ (where $f_x > 0$) is reversed. Therefore, we can determine the dynamics of system (2.22) and then reverse the direction of trajectories on $S_r$ to get the dynamics on the critical manifold $S$.

From system (2.22), we can identify two sorts of equilibrium points. Those obtained when $g = h = 0$ are equilibria of the desingularized system as well as of the full system (2.18) since $f = 0$. We call these the ordinary singularities. The other sort of equilibria of system (2.22) occur when $f_x = 0$ and $f_y g + f_z h = 0$; these points are folded singularities because the first condition states the points are on $L$ and the second condition is $l(p) = 0$. Note that folded singularities are not equilibria of the full system. According to their equilibrium type in the desingularized system (2.22), the folded singularities can be classified as folded nodes, folded saddles, folded saddle-nodes Type I or II, folded foci or degenerate folded nodes. The schematic phase portraits near these kinds of folded singularities are shown in Figure 2.7.

It is been shown [61, 69] that in the case of folded saddles, one special solution (a singular canard) can pass from $S_a$ to $S_r$ and another special solution (a singular faux canard) can pass from $S_r$ to $S_a$. In the case of folded nodes and degenerate folded nodes, there is a whole sector of canard trajectories that pass from $S_a$ to $S_r$. For folded foci, there is no singular canard and the solution trajectories on $S_a$ jump away in the vicinity of the fold curve $L$. Folded saddle-nodes Type I and II will be discussed below, for later comparison with folded singularities seen in systems with three timescales.
Figure 2.7: Schematic phase portraits of the reduced system (2.21) projected onto the $(x, z)$-plane, showing different types of folded singularities. Adapted from [61].

The $z$-axis corresponds to the fold curve $L$, $x < 0$ to the attracting manifold $S_a$ (grey region) and $x > 0$ to the repelling manifold $S_r$. The centre manifold is labelled by $W^c$. The type of the folded singularity in each panel is (a) folded node; (b) folded saddle; (c) folded saddle-node Type I; (d) folded saddle-node Type II; (e) folded focus and (f) degenerate folded node. The bold lines in (b), (c) and (d) are the singular canards that pass from $S_a$ to $S_r$ (or from $S_r$ to $S_a$ in case (b)). The shaded areas in (a) and (f) show sectors of canard trajectories that pass from $S_a$ to $S_r$ through the origin. There is no canard in (e).
Folded Saddle-Node Type I and II

If system (2.18) satisfies conditions (2.19) and \( l(p) = 0 \), then it can be transformed to the following form:

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y, z, \varepsilon) = y + x^2 + O(\varepsilon x, \varepsilon y, \varepsilon z, \varepsilon^2, xy, x^3, xyz) \\
\frac{dy}{dt} &= \varepsilon g(x, y, z, \varepsilon) \\
\frac{dz}{dt} &= \varepsilon h(x, y, z, \varepsilon),
\end{align*}
\]  

(2.23)

after a smooth change of coordinates [42, 61]. Setting \( \varepsilon = 0 \) in (2.23) yields the layer problem. The set of equilibria for the layer problem forms the critical manifold \( S := \{(x, y, z) \in \mathbb{R}^3 : y = -x^2(1 + O(x, z))\} \). At the \( z \)-axis, which corresponds to the fold curve \( L \) on \( S \), the critical manifold \( S \) loses normal hyperbolicity.

The desingularized reduced flow constrained to \( S \) is

\[
\begin{align*}
\frac{dx}{d\tau_1} &= g(x, y, z, 0) \\
\frac{dz}{d\tau_1} &= -2x(1 + O(x, z)) \cdot h(x, y, z, 0),
\end{align*}
\]  

(2.24)

where \( \tau_1 = \varepsilon t/(-2x(1+O(x, z))) \). We assume \( g(0, 0, 0, 0) = 0 \), which means the origin is a folded singularity. Generically, \( g_x(0, 0, 0, 0) \neq 0 \), and so without loss of generality, we follow [42] and assume \( g_x(0, 0, 0, 0) = -1 \). The type of the folded singularity at the origin therefore can be determined by considering the phase portrait of system (2.24) in the neighbourhood of the origin. The Jacobian matrix evaluated at the origin is

\[
\begin{pmatrix}
-1 & a \\
-2b & 0
\end{pmatrix},
\]  

(2.25)

where \( a = g_z(0, 0, 0, 0) \) and \( b = h(0, 0, 0, 0) \). The eigenvalues of the linearization of system (2.24) at the folded singularity are \( \lambda_{1,2} = (-1 \pm \sqrt{1 - 8ab})/2 \). Therefore, it can be shown that the origin can be of the following types, depending on \( a \) and \( b \).

<table>
<thead>
<tr>
<th>Type of folded singularity at origin</th>
<th>( ab ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>folded saddle</td>
<td>( ab &lt; 0 )</td>
</tr>
<tr>
<td>folded saddle-node</td>
<td>( ab = 0 )</td>
</tr>
<tr>
<td>folded node</td>
<td>( 0 &lt; 8ab &lt; 1 )</td>
</tr>
<tr>
<td>degenerate folded node</td>
<td>( 8ab = 1 )</td>
</tr>
<tr>
<td>folded focus</td>
<td>( 1 &lt; 8ab )</td>
</tr>
</tbody>
</table>

There are two cases in which we can get a folded saddle-node at the origin: either \( a = 0, b \neq 0 \) or \( a \neq 0, b = 0 \). Note that the more degenerate case \( a = b = 0 \) will not
be discussed. The folded saddle-nodes obtained from these two different cases have different properties and are classified as Type I and Type II [61, 69].

In the case of folded saddle-node Type I, \( a = 0 \) and \( b \neq 0 \). The centre manifold corresponding to the zero eigenvalue is tangent to the fold curve \( L \), i.e., the \( z \) axis, at the origin. The eigenvector corresponding to the nonzero eigenvalue is transverse to the fold curve, and so there is one singular canard that passes from \( S_a \) to \( S_r \). The dynamics near the origin depends on the higher order terms. A schematic phase portrait is shown in Figure 2.7(c). Since \( b \neq 0 \), i.e., \( h(0,0,0,0) \neq 0 \), in a sufficiently small neighbourhood of the origin there is no ordinary singularity. The folded saddle-node Type I can be thought of as a saddle-node bifurcation of folded saddle and folded node.

In the case of folded saddle-node Type II, \( a \neq 0 \) and \( b = 0 \), which means \( g_z(0,0,0,0) \neq 0 \) and \( h(0,0,0,0) = 0 \). The centre manifold corresponding to the zero eigenvalue is transverse to the fold curve \( L \) and the eigenvector corresponding to the nonzero eigenvalue is orthogonal to \( L \) at the origin, i.e., it is the \( x \) axis. In this case, there exists a singular canard that passes from \( S_a \) to \( S_r \); see Figure 2.7(d). The condition \( h(0,0,0,0) = 0 \) also defines an ordinary singularity in system (2.24) and \( g_z(0,0,0,0) \neq 0 \) guarantees this equilibrium crosses the fold curve transversely. Therefore, the folded saddle-node Type II corresponds to a transcritical bifurcation of a folded singularity and an ordinary singularity.

**Dynamics of the Full System**

To describe the dynamics of the full system (2.18) with \( \varepsilon > 0 \), we need to combine the information about the fast dynamics, the slow evolution along the normally hyperbolic parts of the critical manifold, and the local behaviour near the fold, where the normally hyperbolicity is lost. If the singular orbit reaches a fold point \( p \) at a jump point, i.e., the transversality condition (2.20) is satisfied, then in the perturbed system, the solution will jump along the fast fibres of the layer problem from the fold to another attracting branch of the critical manifold. If the singular orbit reaches \( p \) at a folded singularity, then we need to refer to the following theorem [42, 61, 68, 69] about the persistence of canard solutions in the perturbed system:

**Theorem 2.2.2** (Canards in \( \mathbb{R}^3 \)). For a singularly perturbed system of the form (2.18) with \( \varepsilon > 0 \) but sufficiently small, the following holds:

1. For a folded saddle, the two singular canards perturb to maximal canards.

2. For a folded node, suppose its eigenvalues satisfy \( \lambda_s < \lambda_w < 0 \), then the strong canard corresponding to the stronger eigenvalue \( \lambda_s \) perturbs to a maximal canard
as $\varepsilon$ increases from zero; the weak canard corresponding to the weak eigenvalue $\lambda_w$ perturbs to a maximal canard if $\lambda_s/\lambda_w \notin \mathbb{N}$.

3. For a Type I folded saddle-node, a singular canard corresponding to the nonzero eigenvalue perturbs to two canard solutions which lie close to each other.

4. For a Type II folded saddle-node, a singular canard corresponding to the nonzero eigenvalue always perturbs to a canard solution.

5. For a folded focus, there is no singular or maximal canards.

There is no result about the case of the degenerate folded node, since the transversality condition is violated, the existence of canards in this case is unknown [61].

Theorem 2.2.2 shows the existence of the maximal canards when $\varepsilon > 0$. For detailed behaviour of these maximal canards, one can refer to the literature [5, 9, 10, 11, 12] and the reference therein. The dynamics near folded singularities are more complicated than the case of a jump point; a detailed illustration about analysis of the non-hyperbolic points of the critical manifold can be found in [36].

For the rest of this thesis where GSPT is exploited, we always need to calculate the locus of folded singularities. If a solution under consideration reaches the fold of the critical manifold at a point away from all folded singularities, we know it will jump at the fold. Thus, we can explain its dynamics by comparing it with the geometric shape of the slow manifold which is given by Fenichel’s theorem. If the solution passes the fold at or very near a folded singularity, then we have to use Theorem 2.2.2 to predict the existence of canards and more work is required to determine the full dynamics.

So far, we have discussed the application of GSPT to systems with one fast and one slow variable, and to systems with one fast and two slow variables. Under certain assumptions, the application discussed above can be extended to systems with $m$ fast and $n$ slow variables with $m \geq 2$ and $n \geq 3$ [70]. The main idea is as follows. The number of the fast variables in the full system can be reduced to one by a centre manifold reduction. As a result, we will get an $(n + 1)$-dimensional reduction which describes the local dynamics of the full system near the fold of the critical manifold. The reduced system has an $n$-dimensional critical manifold, an $(n - 1)$-dimensional fold manifold with an $(n - 2)$-dimensional manifold of folded singularities. These folded singularities have generically $(n - 2)$ zero eigenvalues and two eigenvalues with nonzero real part. We can classify these folded singularities based on the nonzero eigenvalues. It has been shown that locally the canonical form near a folded singularity is equivalent to the canonical form for systems with one fast and two slow variables [70]. Hence, the local flow near a folded singularity of
the \( n \)-dimensional critical manifold can be described by a three-dimensional system. Therefore, the results from the case of one fast and two slow variables can be used. For details, see \([9, 70]\) and the references therein.

Unlike the case of two distinct timescales which has well-established analysis methods, GSPT theory for systems with three or more timescales is still limited. The aim of this thesis is to make progress on understanding three timescale problems.
Chapter 3

GnRH Neuron Model Reduction

Mathematical models for physiological processes may contain some terms whose inclusion is motivated by biophysical considerations but which are not significant mathematically. That is, removing these terms would not affect the mathematical mechanisms underlying certain dynamical phenomena, but may reduce the analytical complexities remarkably.

The GnRH neuron model of Duan et al. [14, 44], which has eight variables and at least three different timescales, is one such model. The main aim of this chapter is to find an appropriate reduction of the GnRH neuron model. We would like the reduced model to capture the features of the voltage bursting and $[\text{Ca}^{2+}]_i$ oscillations that were described in section 1.3. There is no mathematically justified reduction method that we can follow directly; hence, we seek a reduction through heuristic methods. In section 3.1, we will revise the ionic currents and remove some terms that are mathematically unimportant. Then we check if any of the gating variables can be approximated by their steady-state functions in section 3.2. Finally, based on observation of the shape of the time series, in section 3.3, we try to replace one variable by a linear function of another variable to see whether the model can be further reduced or not.

One criterion that a reasonable reduction needs to satisfy is that it can capture the features of the voltage and calcium oscillations. In other words, the time series of variables $V$ and $c$ produced by the reduced model must be similar to those for the original model (Figure 1.5-1.7). In addition to this, we also require the bifurcation structure of the reduced system to remain qualitatively the same as the full model, at least in the parameter regimes of interest. For the purpose of comparison, a bifurcation diagram of the full GnRH neuron model is shown in Figure 3.1, where $I_{\text{app}}$ is the bifurcation parameter. Physiologically, the applied current $I_{\text{app}}$ could not be as large as 2000 pA. We plot the diagram over such a large range of $I_{\text{app}}$ in order to include the Hopf bifurcation associated with the bursting solutions that we are
Figure 3.1: Partial bifurcation diagram of the eight-dimensional GnRH model, equations (1.23) with parameters shown in Table 1.2, using $I_{\text{app}}$ as the bifurcation parameter. The black curves correspond to stable equilibrium points and the red dashed lines indicate unstable equilibrium points. The dashed/solid blue curves show the maximum $V$-coordinates of the unstable/stable periodic solutions. The meanings of the labels are SN: saddle-node bifurcation; HB: Hopf bifurcation; HC: homoclinic bifurcation and SNpo: saddle-node bifurcation of periodic orbits.

This chapter and Chapter 4 contain many pictures of time series of attracting solutions. In each case, the time series has been obtained by numerical simulation of the model starting from an arbitrary initial condition and allowing the transient to die away; open sets of initial conditions will converge to the same orbit.

The bursting solutions studied in this thesis only exist in a small range around $I_{\text{app}} = 0 \text{pA}$ and transition to continuous spiking when $I_{\text{app}}$ is relatively large. When $I_{\text{app}}$ decreases, the bursting solutions should vanish via a homoclinic bifurcation which is labeled by HC in Figure 3.1. However, numerical simulation indicates that the bursting solutions are hard to observe once $I_{\text{app}}$ passes the value where a saddle-node bifurcation, labeled by SN in Figure 3.1, occurs. Note that the saddle-node bifurcation happens at a slightly greater $I_{\text{app}}$ value than the homoclinic bifurcation. The branch of stable periodic solutions that originates in the HC changes stability at a saddle-node of periodic orbits bifurcation point (SNpo) and then ends at a Hopf bifurcation labelled by HB in Figure 3.1. For a given reduction to be qualitatively the same, this bifurcation structure must be kept.
3.1 Revision of Ionic Currents

In order to reflect the physiological fact that voltage bursting processes in GnRH neurons involve many different types of ionic currents, the eight-dimensional model of Duan et al. (system (1.23)) features a complicated expression for the total transmembrane ionic current. The first step we make towards a suitable reduction is to revise these ionic currents.

3.1.1 Revision of the $sI_{AHP–UCL}$ Current

One assumption made in construction of the GnRH model is that the subunits of the slow Ca$^{2+}$-activated afterhyperpolarisation current $sI_{AHP–UCL}$ feature two open states and one closed state. Consequently, there are two differential equations governing the evolution of the two open states $O_{ucl}$ and $O^*_{ucl}$ of the $sI_{AHP–UCL}$ current.

Since the original modelling assumption (of two open states and one closed state) was somewhat arbitrary, and made simply to ensure that the channel for $sI_{AHP–UCL}$ opens in response to calcium and closes independently of calcium with a very slow speed [44, 60], we consider whether we can simplify the model assumption such that there is only one open state and one closed state for the $sI_{AHP–UCL}$ current, without destroying the bursting behaviour and the bifurcation structure. If this is the case, then the dimension of the full model can be reduced by one.

The transitions within the $sI_{AHP–UCL}$ subunits were introduced in section 1.3.1. If we omit the open state $O_{ucl}$, and create a transition from the state $S_{ucl}$ to the state $O^*_{ucl}$ directly with a new transition rate $k_{new}$, the reaction scheme of the $sI_{AHP–UCL}$ subunits becomes:

$$
S_{ucl} \xrightarrow{k_{new} \cdot c} O^*_{ucl}
$$

where $k_{33}$ is still the rate constant with the value shown in Table 1.2 and $c$ represents the calcium concentration. We define $k_{new} = k \cdot k_{11}k_{22}$, where $k$ is a constant and $k_{11}$, $k_{22}$ remain the same as in Table 1.2. In order to be able to reproduce qualitatively the same solutions as the original system, numerical simulations indicate $k$ could be any constant in an approximate interval from 0.5 to 0.6. In the rest of our analysis, we pick an essentially arbitrary value of $k$, say $k = 0.58$ ms; therefore, $k_{new} = 0.29 \times 10^{-7} \mu M^{-1}ms^{-1}$. The equation of the current $sI_{AHP–UCL}$ shown in
system (1.11) can then be revised to:

\[ sI_{AHP-UCL} = g_{ucl}O_{ucl}^*(V - V_k), \]  

(3.1)

and the two differential equations (1.18) describing the evolution of the two open states of \( sI_{AHP-UCL} \) current are reduced to one equation as follows:

\[ \frac{dO_{ucl}^*}{dt} = k_{\text{new}} \cdot c(1 - O_{ucl}^*) - k_{33}O_{ucl}^*. \]  

(3.2)

The other equations of the model remain the same as (1.23), with parameters shown in Table 1.2. We refer to the new system obtained by simplifying the assumption about the \( sI_{AHP-UCL} \) current as the \textit{seven-dimensional reduction}. A time series of \( V \) and \( c \) for the reduced system are plotted in Figure 3.2; comparison with Figure 1.5 shows that the behaviour of the bursting oscillations does not change qualitatively after reduction of the model, except that the number of spikes during each burst increases from three to four and the interburst interval shortens. These changes can be adjusted by varying the value of \( I_{\text{app}} \). For instance, in Figure 3.3, when \( I_{\text{app}} = -0.08 \) pA, there are three spikes in each burst and the period becomes longer, just as for the eight-dimensional model with \( I_{\text{app}} = 0 \) pA, as shown in Figure 1.5. There is no qualitative difference between the partial bifurcation diagrams of the seven-dimensional reduced GnRH neuron model (Figure 3.4) and the original model (Figure 3.1) in the \( I_{\text{app}} \) interval plotted. The components of the bifurcation diagram important for the burst solution, such as the homoclinic bifurcation and the stable branch of the period solutions, are unchanged. Therefore, by revising the assumption of the subunits of the \( sI_{AHP-UCL} \) current, and reducing the original GnRH neuron
3.1 Revision of Ionic Currents

Figure 3.3: Bursting solutions of $V$ and $c$ in the reduced seven-dimensional GnRH neuron model at $I_{app} = -0.08\, pA$.

In the following sections, we will use the seven-dimensional model with $I_{app} = 0\, pA$ as the starting point of further attempts to simplify the model.

Figure 3.4: Partial bifurcation diagram of the seven-dimensional reduced GnRH model with bifurcation parameter $I_{app}$. Line styles and labels have the same meaning as for Figure 3.1.
3.1.2 Simplification of the Ionic Currents

In the equation for the membrane voltage of the GnRH neuron model (1.13), $I_{\text{ionic}}$ is the sum of all the ionic currents given by equation (1.11). Hence, we have three potassium currents ($I_{\text{kdr}}$, $I_{\text{kir}}$ and $I_{\text{km}}$), two calcium currents ($I_{\text{cal}}$ and $I_{\text{cat}}$) and two sodium currents ($I_{\text{naf}}$ and $I_{\text{nap}}$). The function of each kind of ionic current is nearly

![Graph showing the evolution of each of the ionic currents of the seven-dimensional GnRH neuron model during the oscillation shown in Figure 3.2 with $I_{\text{app}} = 0$ pA. Note that the scales on y-axes are quite different.](image-url)
the same. For instance, all the potassium currents depolarise the cell membrane. This fact motivates us to consider the possibility of reducing the complexity of the ionic currents such that there is only one equation for each of the ions K\(^+\), Ca\(^{2+}\) and Na\(^+\). Since there is no theoretical reduction method that we can follow directly, in this section we will discuss the attempts that we made based on observation of the magnitude of each ionic current in simulations of the model.

We first revise the potassium currents, then go on to check the calcium currents and then the sodium currents. In each step, we only compare the time series of \(V\) and \(c\). The robustness of the bifurcation diagram is checked after we have simplified all of the ionic currents.

During one bursting oscillation, the amplitudes of different ionic currents vary greatly. Figure 3.5 shows the evolution of the ionic currents during the oscillation shown in Figure 3.2. From Figure 3.5, we notice that among the three K\(^+\)-currents, the order of magnitude of the maximum amplitude of \(I_{km}\) is about 100 (respectively 1000) times larger than the maximum amplitude of \(I_{kdr}\) (respectively \(I_{kir}\)). This suggests that we could approximate the combined K\(^+\)-currents \(I_{kdr} + I_{kir} + I_{km}\) by \(I_{km}\), possibly with an accompanying small change in the parameter \(g_{km}\). Omitting \(I_{kdr}\) and \(I_{kir}\) will result in a decrease of the total amount of K\(^+\)-current; this decrease may be counteracted by increasing the value of \(g_{km}\), since \(g_{km}\) is the maximum conductance of the potassium channel associated with \(I_{km}\). Indeed, we find that by omitting \(I_{kdr}\) and \(I_{kir}\) but increasing \(g_{km}\) from 8.00 to 8.14 nS, the behaviour of the oscillating solutions in the seven-dimensional model for \(V\) and \(c\) are preserved; see Figure 3.6.

Once the ionic current \(I_{kdr}\) is eliminated, the differential equation for \(V\) is no
longer dependent on the variable \(N_{\text{kd}}\). The evolution equation for \(N_{\text{kd}}\) in system (1.15) then becomes decoupled from the model. Thus, removing this differential equation will not affect the dynamics of the variables \(V\) and \(c\). That means the seven-dimensional GnRH neuron model can be further reduced to a six-dimensional system:

\[
\begin{align*}
C_{\text{m}} \frac{dV}{dt} &= -I_{\text{ionic}} + I_{\text{app}} \\
\frac{dN_{\text{km}}}{dt} &= \frac{1}{\tau_{N_{\text{km}}}}(N_{\text{km},\infty} - N_{\text{km}}) \\
\frac{dH_{\text{naf}}}{dt} &= \frac{1}{\tau_{H_{\text{naf}}}}(H_{\text{naf},\infty} - H_{\text{naf}}) \\
\frac{dO_{\text{ucl}}^{*}}{dt} &= k_{\text{new}} \cdot c(1 - O_{\text{ucl}}^{*}) - k_{33}O_{\text{ucl}}^{*} \\
\frac{dc}{dt} &= J_{\text{release}} - J_{\text{serca}} + \rho(J_{\text{in}} - J_{\text{pm}}) \\
\frac{dc_{\text{t}}}{dt} &= \rho(J_{\text{in}} - J_{\text{pm}}),
\end{align*}
\]

(3.3)

when we modify the \(K^{+}\)-currents as above. The time series of \(V\) and \(c\) will remain the same as in Figure 3.6. Now, \(I_{\text{ionic}}\) represents the sum of all the currents shown in (1.11) without \(I_{\text{kd}}\) and \(I_{\text{kr}}\).

Next, we consider the \(Ca^{2+}\)-currents. They are negative during the oscillation and hyperpolarise the cell membrane. Since the magnitude of the minimum amplitude of \(I_{\text{cat}}\) is very small, we decided to treat it as a constant. After some exploratory experiments, we find that if we fix \(I_{\text{cat}} = -0.042\) pA, then the \(V\) and \(c\) oscillations will have similar behaviours to those shown in Figure 3.6. In other words, the ap-

![Graph](image.png)

Figure 3.7: Bursting solutions of \(V\) and \(c\) at \(I_{\text{app}} = 0\) pA in the six-dimensional GnRH neuron model, equation (3.3), with simplified \(K^{+}\) and \(Ca^{2+}\)-currents.
Figure 3.8: Bursting solutions of $V$ and $c$ at $I_{app} = 0$ pA in the six-dimensional GnRH neuron model, equation (3.3), with simplified $K^+$, $Ca^{2+}$ and $Na^+$-currents.

proximation $I_{cal} = g_{cal}M_{cal}^2(V - V_{ca}) - 0.042$ can be used in (1.11) and (1.19) instead of the quantity $I_{cal} + I_{cat}$. The solutions of the model (3.3) in the absence of $I_{cat}$ can be seen in Figure 3.7.

Now we consider the two $Na^+$-currents. The magnitude of the minimum amplitude of $I_{nap}$ is much smaller than that of $I_{naf}$. However, excluding it from the system and increasing $g_{naf}$ (the maximum conductance of sodium channel associated with $I_{naf}$) does not produce qualitatively the same oscillating solutions, since there is no bursting anymore at $I_{app} = 0$ pA. We instead try to treat $I_{nap}$ as a constant to see what will happen. By doing this, qualitatively the same oscillations can be obtained. However, with the range of $I_{nap}$ values that were tested, we found that if we kept the interburst interval as long as in Figure 3.7, the number of spikes during each burst increased; if we fixed the number of spikes to three, the interburst interval became much longer compared with the oscillations in Figure 3.7. We found by additionally increasing the value of $g_{naf}$, the long interburst interval, although unable be as short as in Figure 3.7, could be reduced. In the rest of this thesis, we choose to fix $I_{nap} = 3.0$ pA, and then increase $g_{naf}$ from 190.00 nS to 197.05 nS, i.e., use the equation $I_{naf} = g_{naf}M_{naf}^3H_{naf}(V - V_{na}) - 3$ with $g_{naf} = 197.05$ nS in the model. Note this is only one arbitrary choice of the various options.

Solutions obtained after simplifying the $Na^+$-currents in system (3.3) are shown in Figure 3.8. In Figure 3.9, we plot the bifurcation diagram of system (3.3) with simplified $K^+$, $Ca^{2+}$ and $Na^+$-currents on top of the bifurcation diagram of the original eight-dimensional neuron model (Figure 3.1). From this we can see that after revising the $sI_{AHP−UCL}$ current and simplifying other ionic currents, in spite of the Hopf bifurcation shifting a little bit to the right, the bifurcation structure corresponding
Figure 3.9: Partial bifurcation diagram of the six-dimensional GnRH neuron model (3.3)-(3.4) with the bifurcation diagram of the original eight-dimensional model (Figure 3.1). The green dashed (solid) curve shows the maximum $V$-coordinates of the unstable (stable) periodic solutions of the six-dimensional model. The yellow curves and the dashed dark blue curves show the stable and unstable equilibrium points of the six-dimensional model, respectively. The remaining lines are of the eight-dimensional model and have the same meaning as in Figure 3.1. SN: saddle-node bifurcation; HB: Hopf bifurcation; and HC: homoclinic bifurcation. Enlargements of some regions of the diagram are shown underneath.
3.2 Quasi-Steady-State Reduction

to the bursting solutions does not change in the reduced model. Therefore, in the
rest of our analysis, instead of using the full eight-dimensional GnRH neuron model,
we will use the six-dimensional reduction with revised ionic currents, i.e., equation
(3.3) with \( I_{\text{ionic}} = I_{\text{km}} + I_{\text{cal}} + I_{\text{naf}} + sI_{\text{AHP}} - s^I_{\text{SK}} + sI_{\text{AHP}} - s^I_{\text{UCL}} + I_{\text{leak}} \). The equation of
each ionic current is as follows:

\[
\begin{align*}
I_{\text{km}} &= g_{\text{km}} N_{\text{km}} (V - V_{k}) \\
I_{\text{cal}} &= g_{\text{cal}} M^2_{\text{calc}} (V - V_{ca}) - 0.042 \\
I_{\text{naf}} &= g_{\text{naf}} M^3_{\text{naf}} H_{\text{naf}} (V - V_{na}) - 3 \\
sI_{\text{AHP}} - s^I_{\text{SK}} &= g_{\text{sk}} \left( \frac{e^{n_{sk}}}{e^{n_{sk}} + R_{sk}} \right) (V - V_{k}) \\
sI_{\text{AHP}} - s^I_{\text{UCL}} &= g_{\text{ucl}} O^{*}_{\text{ucl}} (V - V_{k}) \\
I_{\text{leak}} &= g_{\text{leak}} (V - V_{\text{leak}}),
\end{align*}
\]

(3.4)

with new parameter values as in Table 3.1. The rest of the parameters in the six-
dimensional reduced model remain the same as in Table 1.2.

| Parameter values of the six-dimensional GnRH neuron model |
|-----------------|-----------------|-----------------|-----------------|
| \( g_{\text{km}} \) | 8.14 nS         | \( g_{\text{naf}} \) | 197.05 nS       | \( k_{\text{new}} \) | \( 0.29 \times 10^{-7} \mu M^{-1} \text{ms}^{-1} \) |

Table 3.1: The values of the parameters in the six-dimensional reduced GnRH neuron
model, equation (3.3) with ionic currents (3.4). The rest of the parameters in the
model remain the same as in Table 1.2.

3.2 Quasi-Steady-State Reduction

Different ionic currents across the cell membrane typically evolve on different time-
scales. Therefore, in a conductance-based neuron model, the gating variables used
to describe the activation or inactivation of ionic channels will evolve over a range
of timescales. Nondimensionalizing the model can help us to find the fastest gating
variables. A common reduction technique is to assume that the fastest variables
equilibrated instantaneously and remain in near-equilibrium. That is, these variables
can be replaced by their steady-state functions and the dimension of the full system
therefore could be reduced. This reduction method is called the quasi-steady-state
(q-s-s) reduction. Applying q-s-s reduction to a system does not always maintain
the important features of the original system [71]. For instance, a Hopf bifurcation
may be destroyed by q-s-s reduction and thus periodic solutions of interest may
disappear. The reason why it fails to do so is still unclear and is the subject of
current research. However, in cases where q-s-s reduction does work, it can simplify a model substantially.

Since the voltage submodel of the GnRH neuron model is a conductance-based model and has gating variables $N_{km}$ and $H_{naf}$, we will apply the q-s-s reduction to the six-dimensional neuron model, equations (3.3) to see whether the dimension of the model can be further reduced by this method or not.

### 3.2.1 Dimensionless Version of the GnRH Neuron Model

In order to apply q-s-s reduction, we need to find out which of the gating variables is fastest. This can be achieved by nondimensionalising the neuron model and then comparing the typical timescales of the variables. The dependent variables in the model are $V$ (in mV), $c$ and $c_t$ (in $\mu$M), and the dimensionless variables $N_{km}$, $H_{naf}$ and $O_{ucl}^*$. The first step towards nondimensionalisation is to remove the units of the variables ($V$, $c$, $c_t$, $t$) and make the magnitudes of the variables in typical solutions comparable; for instance, ensure they are all roughly $O(1)$. The dimensionless gating variables $N_{km}$ and $H_{naf}$ are about $O(1)$, but the magnitude of $O_{ucl}^*$ is quite small, roughly $O(10^{-4})$ when $I_{app} = 0$; hence, we need to rescale $O_{ucl}^*$ by $R_O$ as follows:

$$O_{ucl}^* = R_O \cdot \bar{O}_{ucl}^*,$$

where $R_O = 10^{-4}$ to ensure $\bar{O}_{ucl}^* = O(1)$. Note that rescaling $O_{ucl}^*$ causes it to lose its interpretation as a probability of a channel being open. We also define a typical voltage scale $Q_V$, a typical calcium concentration scale $Q_c$ and a typical timescale $Q_t$ such that for the new dimensionless variables ($\bar{V}$, $\bar{c}$, $\bar{c}_t$, $\tau$), they satisfy:

$$V = Q_V \cdot \bar{V}, \quad c = Q_c \cdot \bar{c}, \quad c_t = Q_c \cdot \bar{c}_t, \quad t = Q_t \cdot \tau.$$  

Numerical simulations of the six-dimensional GnRH neuron model shows $V$ varies between about $-65$ mV and $20$ mV. Correspondingly, we define $T_x = \max(1/\tau_x(V))$ in ms$^{-1}$ over the range $V \in [-65, 20]$ such that $1/\tau_x(V) = T_x/t_{1x}(V)$. We also define $g$ to be the maximum conductance out of the six that appear in (3.4). Substituting these expressions into system (3.3) and rearranging, we get the dimensionless version...
of the six-dimensional neuron model:

\[
\frac{C_m}{Q_t} \frac{dV}{dt} = -I_{km} + I_{cal} + I_{naf} + sI_{AHP-SK} + sI_{AHP-UCL} + I_{leak} - I_{app}
\]

\[
\frac{1}{Q_t T_{N_{km}}} \frac{dN_{km}}{dt} = \frac{1}{t_{1N_{km}}(V)} (N_{km\infty}(V) - N_{km})
\]

\[
\frac{1}{Q_t T_{H_{naf}}} \frac{dH_{naf}}{dt} = \frac{1}{t_{1H_{naf}}(V)} (H_{naf\infty}(V) - H_{naf})
\]

\[
\frac{R_O}{k_{\text{new}} Q_t Q_c} \frac{d\bar{O}_{\text{ucl}}^*}{dt} = \bar{c}(1 - R_O \cdot \bar{O}_{\text{ucl}}^*) - \frac{k_{33} R_O}{k_{\text{new}} Q_c} \bar{O}_{\text{ucl}}
\]

\[
\frac{Q_c}{Q_t \alpha g_{\text{cal}} Q_V} \frac{d\bar{c}}{dt} = \bar{J}_{\text{release}} - \bar{J}_{\text{serca}} + \rho(\bar{J}_{\text{in}} - \bar{J}_{\text{pm}})
\]

\[
\frac{\rho Q_t \alpha g_{\text{cal}} Q_V}{Q_t} \frac{d\bar{c}_t}{dt} = \bar{J}_{\text{in}} - \bar{J}_{\text{pm}},
\]

with the dimensionless currents \( \bar{I}_x \):

\[
\bar{I}_{km} = \bar{g}_{km} N_{km}(V - \bar{V}_k)
\]

\[
\bar{I}_{cal} = \bar{g}_{cal} M_{cal\infty}^2 (V - \bar{V}_{ca}) - \frac{0.042}{Q_V \cdot g}
\]

\[
\bar{I}_{naf} = \bar{g}_{naf} M_{naf\infty}^3 H_{naf}(V - \bar{V}_{na}) - \frac{3}{Q_V \cdot g}
\]

\[
s\bar{I}_{AHP-SK} = \bar{g}_{sk} \left( \frac{Q_{n\infty}^{sk} \cdot \bar{c}^{\infty}_{sk}}{Q_{c}^{sk} \cdot \bar{c}^{\infty}_{sk} + K_{sk}^{n\infty}} \right) (V - \bar{V}_k)
\]

\[
s\bar{I}_{AHP-UCL} = \bar{g}_{\text{ucl}} R_O \cdot \bar{O}_{\text{ucl}}^* (V - \bar{V}_k)
\]

\[
\bar{I}_{leak} = \bar{g}_{\text{leak}} (V - \bar{V}_{\text{leak}})
\]

\[
\bar{I}_{app} = I_{app}/(Q_V \cdot g),
\]

where \( \bar{V}_x := V_x/Q_V \) and \( \bar{g}_x := g_x/g \) and the dimensionless calcium fluxes:

\[
\bar{J}_{\text{release}} = \frac{K_f \gamma Q_c}{\alpha g_{\text{cal}} Q_V} \left( O_4 + \frac{J_{er}}{K_f} \right) (\bar{c}_t - \bar{c} - \bar{\gamma})
\]

\[
\bar{J}_{\text{serca}} = \frac{P_{\text{rate}}}{\alpha g_{\text{cal}} Q_V a_5 \gamma \frac{a_2}{a_5} \bar{Q}_c - \gamma} + \frac{\bar{c} - a_1 \gamma (\bar{c}_t - \bar{c})}{\alpha a_5 \gamma \bar{c} + a_2 a_5 (\bar{c}_t - \bar{c}) + Q_c \bar{c} (\bar{c}_t - \bar{c})}
\]

\[
\bar{J}_{\text{in}} = -i_{\text{cal}} + \frac{\beta \cdot IP_3}{\alpha g_{\text{cal}} Q_V}
\]

\[
\bar{J}_{\text{pm}} = \frac{V_p}{\alpha g_{\text{cal}} Q_V} \left( 1 + \frac{\kappa_f^2}{Q_V^2 \bar{c}_t^2} \right) + \frac{V_{\text{naca}}}{\alpha g_{\text{cal}} Q_V} \left( 1 + \frac{K_{\text{naca}}^2}{Q_V^2 \bar{c}_t^2} \right)
\]

where \( i_{\text{cal}} = I_{\text{cal}}/(g_{\text{cal}} \cdot Q_V) \).

The Nernst potentials \( V_x \) set a natural range for the membrane potential as \( V_k \leq \)
$V \leq V_{ca}$, and we expect $V \in [-65, 20]$, so a suitable choice for the typical voltage scale is $Q_V = 100 \text{mV}$. For the value of $g$, note that $g_{ucl}$ is rescaled by $R_O$ (see equations (3.8)), so we choose $g = g_{naf}$ instead of $g_{ucl}$. The gating variables and their equilibrium functions $N_{km\infty}$ and $H_{naf\infty}$ in (3.7) are all in the interval $(0, 1)$. From numerical simulations of the six-dimensional GnRH neuron model, we choose $Q_c = 1 \mu M$ as a typical calcium concentration scale. Using these values we see that all terms in the right hand sides of equations (3.7) are bounded (in absolute value) by one.

The coefficients of the derivatives in the left hand sides of equations (3.7) now reveal the relative speeds of evolution of the variables. Comparing the values of these coefficients can let us know how fast the corresponding variables are; the larger the value, the slower the corresponding variable. Figure 3.10 shows that $T_{N_{km}}$ and $T_{H_{naf}}$ are all approximately $2.5 \text{ms}^{-1}$. Thus, we find:

$$
\frac{C_m}{g} \sim O(10^{-1}) \text{ms} , \quad \frac{1}{T_{N_{km}}} \approx \frac{1}{T_{H_{naf}}} \sim O(1) \text{ms} , \\
\frac{R_O}{(k_{new} Q_c)} \sim O(10^4) \text{ms} , \quad \frac{Q_c}{(\alpha g_{cal} Q_V)} \sim O(10^2) \text{ms} , \\
\frac{Q_c}{(\rho \alpha g_{cal} Q_V)} \sim O(10^2) \text{ms} .
$$

(3.10)

Note that this result is based on the fact that in our problem, $\rho = 0.5 = O(1)$ which means that we cannot separate the timescales for $\bar{c}$ and $\bar{c}_t$. From (3.10) we choose to group $(\bar{V}, N_{km}, H_{naf})$ and conclude that $(\bar{V}, N_{km}, H_{naf})$ evolve on a fast timescale, $(\bar{c}, \bar{c}_t)$ evolve on a slow timescale, and $\bar{O}_{ucl}^*$ evolves on a superslow timescale. We

![Figure 3.10: Functions $1/\tau_{N_{km}}(V)$ (black solid) and $1/\tau_{H_{naf}}(V)$ (blue dashes) in ms$^{-1}$; refer to equations (1.16).](image-url)
3.2 Quasi-Steady-State Reduction

choose the slow timescale as our reference time, i.e., pick \( Q_t = Q_c/(\alpha g_{cal} Q_e) \approx 100 \text{ ms} \), and set

\[
\begin{align*}
\varepsilon_1 &:= \frac{\alpha g_{cal} Q V C_m}{g Q_c} \approx 0.002 \ll 1, \\
\frac{\alpha g_{cal} Q V}{Q_c} \frac{1}{T_{N_{km}}} &:= \frac{\varepsilon_1}{T_{N_{km}}} \ll 1, \\
\frac{\alpha g_{cal} Q V}{Q_c} \frac{1}{T_{H_{naf}}} &:= \varepsilon_1 \ll 1, \\
\varepsilon_2 &:= \frac{Q_c^2 k_{new}}{\alpha g_{cal} Q V R_O} \approx \frac{0.012}{1},
\end{align*}
\] (3.11)

where \( T_{x}^* \approx 0.23 \sim O(1) \).

Then the dimensionless system (3.7) has the following singularly perturbed form with small parameters \( \varepsilon_1 \) and \( \varepsilon_2 \):

\[
\begin{align*}
\varepsilon_1 & \frac{d \bar{V}}{d \tau} = -(\bar{I}_{km} + \bar{I}_{cal} + \bar{I}_{naf} + s\bar{I}_{AHP-SK} + s\bar{I}_{AHP-UCL} + \bar{I}_{leak} - \bar{I}_{app}) \\
\varepsilon_1 & \frac{d N_{km}}{d \tau} = \frac{1}{t_{N_{km}}(\bar{V})}(N_{km\infty}(\bar{V}) - N_{km}) \\
\varepsilon_1 & \frac{d H_{naf}}{d \tau} = \frac{1}{t_{H_{naf}}(\bar{V})}(H_{naf\infty}(\bar{V}) - H_{naf}) \\
d \frac{d \bar{c}}{d \tau} &= \bar{J}_{release} - \bar{J}_{serca} + \rho(\bar{J}_{in} - \bar{J}_{pm}) \\
d \frac{d \bar{c}_t}{d \tau} &= \bar{J}_{in} - \bar{J}_{pm} \\
d \frac{d \bar{O}_{ucl}^*}{d \tau} &= \varepsilon_2 \left( \bar{c} (1 - R_O \cdot \bar{O}_{ucl}^*) - \frac{k_{new} R_O}{k_{new} Q_c} \bar{O}_{ucl}^* \right),
\end{align*}
\] (3.12)

where \( t_{x}(\bar{V}) := t_{1x}(\bar{V})/T_{x}^* \).

Since both of the gating variables \( N_{km} \) and \( H_{naf} \) are fast variables, we will apply the q-s-s-s assumption to each of them in turn to see whether or not the dimension of the system can be further reduced.

### 3.2.2 Q-S-S Reduction on \( N_{km} \)

For the purpose of easy comparison with the time series and bifurcation diagram of the six-dimensional model, equations (3.3) and (3.4), in this section and the following sections, the calculations are still performed on the system with dimensions (equations (3.3)). Applying q-s-s reduction to \( N_{km} \), i.e., setting this fast gating variable instantaneously to its steady state function \( N_{km} = N_{km\infty} \), we find that the periodic solutions occurring for \( I_{app} = 0 \text{ pA} \) (or nearby) are no longer as the same as in Figure 3.8.

The time series of \( V \) and \( c \) in the system with \( N_{km} = N_{km\infty} \) at \( I_{app} = 0 \text{ pA} \) is shown in Figure 3.11. Comparison of these time series with those in Figure 3.8 indicates that the dynamical mechanism underlying the bursting oscillations of the six-dimensional
model might change when we apply the q-s-s assumption. The partial bifurcation diagram of the system is plotted in Figure 3.12. Note that the loci of equilibrium points will not change after applying q-s-s reduction. Comparing with the partial bifurcation diagram of the six-dimensional GnRH neuron model, we notice that the Hopf bifurcation shifts to the left and two more folds (saddle-node bifurcations of periodic solutions) appear on the branch of periodic solutions. As a result, the stable periodic solutions that formerly existed around $I_{app} = 0$ pA are now unstable.

In order to check whether the Hopf bifurcation seen in the six-dimensional system is the original bifurcation with changed location or is a new one, we define a parameter $\xi$ which varies in the interval $[0, 1]$, and modify the equation for the gating variable $N_{km}$ as follows:

$$\frac{dN_{km}}{dt} = \frac{1}{\tau_{N_{km}}} (N_{km\infty} - N_{kmnew}),$$  

(3.13)

where $N_{kmnew} = \xi N_{km} + (1 - \xi) N_{km\infty}$. Then $\xi = 1$ corresponds to the original six-dimensional system and $\xi = 0$ makes $N_{km} = N_{km\infty}$, thus giving the system after application of q-s-s reduction.

A bifurcation set in the $(I_{app}, \xi)$-plane showing the loci of the two folds of equilibria (the leftmost fold and the fold labeled by “SN” in Figure 3.12), the Hopf bifurcation and the saddle-node bifurcations of periodic solutions are shown in Figure 3.13. From this we confirm that the Hopf bifurcation shifts to the left when setting $N_{km} = N_{km\infty}$. For small $\xi$ values, more than one saddle-node bifurcations of periodic orbits exist. At $\xi = 0$, i.e., $N_{km} = N_{km\infty}$, beside the one from the six-dimensional model, there are two more saddle-node bifurcations of periodic orbits, resulting in
Figure 3.12: Partial bifurcation diagram of the five-dimensional GnRH neuron model with $N_{km} = N_{km\infty}$ together with the bifurcation diagram of the six-dimensional GnRH neuron model, equations (3.3). The black curves and red dashed curves represent the loci of the stable and unstable equilibria of the six-dimensional model, respectively. The maximum $V$-coordinates of the stable (unstable) periodic solutions of the six-dimensional model are shown by the solid (dashed) blue curves. The loci and the stability of the equilibrium points in the five-dimensional model remain the same as for the six-dimensional model except the Hopf bifurcation shifts significantly to the left; the black curve shows the branch of the stable equilibria on the right of the Hopf for the six-dimensional model and the yellow curve shows the case for the six-dimensional model. The maximum $V$-coordinates of the unstable and stable periodic solutions of the five-dimensional model are indicated by the dashed green curves and solid green curve.

the loss of stability of the branch of periodic solutions around $I_{app} = 0$ pA. Therefore, applying q-s-s reduction to $N_{km}$ fails to give a system with the time series of $V$ and $c$ and the bifurcation structure that we require. It seems there are distinct dynamical regimes between the six-dimensional system (3.3) and the five-dimensional reduction according to the number of the saddle-node bifurcations of periodic orbits. This is an interesting phenomenon and worth a careful study. However, we are interested primarily in the cases when $\xi = 1$ and $\xi = 0$, and so will not discuss this phenomenon further in this thesis.

It seems plausible that there is a stable branch of periodic solutions missing from the bifurcation diagram for the five-dimensional system plotted in Figure 3.12 (e.g., such a branch might exist on an isolated loop of periodic solutions just to the left of
Figure 3.13: A bifurcation set showing the loci of bifurcations for different $\xi$ values. $\xi = 1$ and $\xi = 0$ correspond respectively to the six-dimensional case and the five-dimensional case in Figure 3.12. The two red curves show the saddle node bifurcations, the one close to $I_{app} = 0$ pA is labeled as “SN” in Figure 3.12 and the other one is the leftmost fold on the equilibria branch in Figure 3.12. The black curve is the Hopf bifurcation and the green curves are the saddle-node bifurcations of periodic orbits. However, such a branch was not located in the numerical simulations performed.

3.2.3 Q-S-S Reduction on $H_{naf}$

Now we turn to investigating what happens when we apply q-s-s reduction to the gating variable $H_{naf}$, i.e., setting $H_{naf} = H_{naf,\infty}$ in equations (3.3). The time series of $V$ and $c$ at $I_{app} = 0$ pA can be seen in Figure 3.14. Again, the bursting features change significantly. The bifurcation diagram of the five-dimensional reduction is plotted together with the bifurcation diagram of the six-dimensional GnRH neuron model, equations (3.3) in Figure 3.15. The Hopf bifurcation in the six-dimensional model (labelled by (6D)HB in Figure 3.15) no longer exists after applying q-s-s reduction. However, we find a new Hopf bifurcation occurs at $I_{app} \approx -199.28$ pA, which is far away from the Hopf bifurcation in the six-dimensional system. This new Hopf bifurcation and the saddle-node bifurcation of periodic orbits associated with it are well away from $I_{app} = 0$ pA; as a result, we cannot see the stable periodic solutions that existed at $I_{app} = 0$ pA when the system was six-dimensional.
3.2 Quasi-Steady-State Reduction

![Graph 1](image1.png)

Figure 3.14: Periodic solutions of $V$ and $c$ at $I_{app} = 0 \text{ pA}$ of the system obtained by applying q-s-s reduction to $H_{naf}$ in the six-dimensional GnRH neuron model, equation (3.3), with the same initial conditions as in Figure 3.8.

![Graph 2](image2.png)

Figure 3.15: Partial bifurcation diagram of the five-dimensional GnRH neuron model with $H_{naf} = H_{naf\infty}$ together with the bifurcation diagram of the six-dimensional GnRH neuron model, equations (3.3). The meaning of line styles is the same as for Figure 3.12.
In order to see more clearly how q-s-s reduction affects the bifurcation structure, we define a parameter, $\xi$, as before and rewrite the equation for $H_{naf}$ as:

$$\frac{dH_{naf}}{dt} = \frac{1}{\tau_{H_{naf}}} (H_{naf\infty} - H_{naf_{\text{new}}}) ,$$

with $H_{naf_{\text{new}}} = \xi H_{naf} + (1 - \xi) H_{naf\infty}$. Figure 3.16 shows the bifurcation set in the $(I_{\text{app}}, \xi)$-plane including the loci of the two folds of equilibria, the Hopf bifurcation and the saddle-node bifurcations of periodic orbits. We find the Hopf bifurcation persists from the six-dimensional system and shifts to the left ever further than it was in the case for $N_{\text{km}}$.

Since the Hopf bifurcation shifts to $I_{\text{app}} \approx -199.28 \text{pA}$ (too far away from $I_{\text{app}} = 0 \text{pA}$), and the stable branch of periodic solutions around $I_{\text{app}} = 0 \text{pA}$ no longer appears to exist, we cannot see the bursting solutions shown in Figure 3.8 of the six-dimensional model (3.3). The mechanism for the periodic solutions shown in Figure 3.14 after $H_{naf}$ is reduced by the q-s-s reduction is hard to detect numerically, and so it is not included in the partial bifurcation diagram, Figure 3.15. In summary, the q-s-s reduction on $H_{naf}$ seems to destroy the features of the six-dimensional system that we are interested in.

![Figure 3.16: A bifurcation set showing the loci of bifurcations when setting $H_{naf} = H_{naf\infty}$ in (3.3). $\xi = 1$ and $\xi = 0$ correspond respectively to the six-dimensional case and the five-dimensional case in Figure 3.15. The meanings of line styles are the same as for Figure 3.13.](image-url)
3.3 Linear Relationship Between $c_t$ and $O_{ucl}^*$

The approximate symmetry between the time series of $c_t$ and $O_{ucl}^*$ at $I_{app} = 0$ pA in the six-dimensional neuron model (see Figure 3.17, upper panel) leads to another reduction idea. That is, we may try to use a linear function of $O_{ucl}^*$ to represent $c_t$, or vice versa, and then reduce the dimensions of the model to five. This method has not been justified theoretically, but it does work in some cases, such as in the process of reducing the Hodgkin-Huxley model to two dimensions [33]. In this section, we will check two possibilities: when $O_{ucl}^*$ is replaced by a linear function of $c_t$; and when $c_t$ is replaced by a linear function of $O_{ucl}^*$.

3.3.1 Writing $O_{ucl}^*$ as a Linear Function of $c_t$

We are looking for a function in the form of $O_{ucl}^* = p \cdot c_t + q$ where $p$, $q$ are constants. After some numerical simulations in the six-dimensional GnRH neuron model (3.3),

![Graph showing the time series of $c_t$ and $O_{ucl}^*$](image)

Figure 3.17: Upper panel: time series of $c_t$ and $O_{ucl}^*$ at $I_{app} = 0$ of the six-dimensional GnRH neuron model, equation (3.3) are approximately symmetric. Lower panel: time series of $O_{ucl}^*$ in the six-dimensional system (3.3) and its approximation $L(c_t)$ for $c_t$ also from the six-dimensional system.
we choose to set \( O^*_{ucl} = L(c_t) = -10^{-5}c_t + 6.42 \times 10^{-5} \), since this seems to give an acceptable approximation of \( O^*_{ucl} \); see Figure 3.17. This fit was done empirically (by trial and error). It might be possible to fit the coefficients \( p \) and \( q \) by least squares analysis, but we just choose a simple way that works. Consequently, we obtain a five-dimensional system with \( O^*_{ucl} \) no longer a variable:

\[
\begin{align*}
C_m \frac{dV}{dt} &= -I_{\text{ionic}} + I_{\text{app}} \\
\frac{dN_{km}}{dt} &= \frac{1}{\tau_{N_{km}}}(N_{km\infty} - N_{km}) \\
\frac{dH_{naf}}{dt} &= \frac{1}{\tau_{H_{naf}}}(H_{naf\infty} - H_{naf}) \\
\frac{dc}{dt} &= J_{\text{release}} - J_{\text{serca}} + \rho(J_{\text{in}} - J_{\text{pm}}) \\
\frac{dc_t}{dt} &= \rho(J_{\text{in}} - J_{\text{pm}}). 
\end{align*}
\] (3.15)

A time series of \( V \) and \( c \) in system (3.15) is shown in Figure 3.18, from which we can see the features of the bursting solutions are kept.

Since the main features of the bursting solutions of \( V \) and \( c \) are preserved, we turn to check the bifurcation diagram of system (3.15). The upper panel of Figure 3.19 shows the partial bifurcation diagram of system (3.15). In contrast to the case for the full six-dimensional model, the branch of periodic solutions arising from the Hopf bifurcation does not terminate at a homoclinic bifurcation. Instead, it connects to the other Hopf bifurcation located on the equilibrium branch for \( I_{\text{app}} \) negative (below \(-1500\)). Also, there are now two branches of equilibrium points instead of one in the previous cases (see the equilibrium branch in Figure 3.12 and in Figure

![Figure 3.18: Time series of V and c with O^*_{ucl} is replaced by L(c_t), equations (3.15).](image_url)
3.3 Linear Relationship Between $c_t$ and $O_{ucl}$

Figure 3.19: Upper: partial bifurcation diagram of the five-dimensional GnRH neuron model, equations (3.15). There are two separate branches of equilibrium points shown in black and red respectively. The blue curve shows the maximum $V$-coordinates of the periodic solutions. Stability is not indicated. Lower: an enlargement of a part of the upper diagram, showing two branches of equilibrium points.

and some parts of the two branches are quite close and hard to distinguish. An enlargement of these parts are plotted in the lower panel of Figure 3.19.

Despite those changes, at $I_{app} \approx 0 \text{ pA}$, the bifurcation diagram is still quite similar to the one shown for the six-dimensional reduction in Figure 3.9. In Figure 3.20, we plot these two bifurcation diagrams together for $I_{app} \in [-500, 2000]$. The Hopf bifurcation corresponding to the bursting solutions that we are interested in almost does not change; see the second panel on the bottom of Figure 3.20. Therefore, using this method to reduce the dimension of the GnRH neuron model results in some
Figure 3.20: Part of the upper panel of Figure 3.19, the bifurcation diagram of system (3.15), drawn by thin curves, together with the bifurcation diagram of the six-dimensional reduced GnRH neuron model, drawn by thick curves. The yellow and dark blue curves are two branches of equilibrium points shown in black and red in Figure 3.19; and the green curve still shows the maximum $V$-coordinates of the periodic solutions of the five-dimensional model, equations (3.15). The meaning of the thick lines for the six-dimensional model are the same as for Figure 3.12 and 3.15. The enlargements of regions (1) and (2) are shown at the bottom.

Changes in the bifurcation structure, and may lose some important features, but for the bursting solutions we are studying, the reduced system provides an acceptable approximation to the full six-dimensional system.

When people reduce the Hodgkin-Huxley model to two dimensions [20, 50], they use a similar technique, but the linear approximation is made between two variables that evolve on a similar timescale. In our case, we think $c_t$ and $O_{uc}$ evolve on different timescales globally; refer to the analysis in section 3.2.1, where $O_{uc}$ is shown to be much slower than $c_t$. However, while the parameter $\varepsilon_2$ in equations (3.12) is small,
we noticed that the dynamics of $c_t$ is also quite slow except for when the bursting is happening. It is, therefore, perhaps not surprising to see that most of the dynamical features are kept with the replacement of $O_{ucl}^*$ by a function of $c_t$. One thing that needs to be mentioned is that in the reduced system (3.15), there are essentially two timescales instead of three as for the six-dimensional GnRH neuron model, i.e., $(\bar{V}, N_{km}, H_{naf})$ are fast while $(\bar{c}, \bar{c}_t)$ are slow. We are not able to answer why this two timescale system exhibits what appears to be a three timescale phenomenon, i.e., the bursting solutions. Perhaps the slower evolution of $c_t$ than $c$ becomes crucial now.

3.3.2 Writing $c_t$ as a Linear Function of $O_{ucl}^*$

In this section, we consider whether $c_t$ could be replaced by a linear function of $O_{ucl}^*$, say $\bar{L}(O_{ucl}^*)$. A natural function to consider is the inverse function to that used in the last section, i.e., let $\bar{L}(O_{ucl}^*) = -10^5O_{ucl}^* + 6.42$ in the six-dimensional GnRH neuron model. Figure 3.21 shows the time series of this approximation to $c_t$ along with the actual time series of $c_t$ for the six-dimensional model with $I_{app} = 0 \text{ pA}$. The new five-dimensional system without the variable $c_t$ is as follows:

$$
\begin{align*}
C_m \frac{dV}{dt} &= -I_{\text{ionic}} + I_{\text{app}} \\
\frac{dN_{km}}{dt} &= \frac{1}{\tau_{N_{km}}}(N_{km\infty} - N_{km}) \\
\frac{dH_{naf}}{dt} &= \frac{1}{\tau_{H_{naf}}}(H_{naf\infty} - H_{naf}) \\
d\bar{c} &= J_{\text{release}} - J_{\text{serca}} + \rho(J_{in} - J_{pm}) \\
d\bar{O}_{ucl}^*/dt &= k_{\text{new}} \cdot c(1 - O_{ucl}^*) - k_{33}O_{ucl}^*
\end{align*}
$$

(3.16)

![Figure 3.21](image.png)

Figure 3.21: Time series of $c_t$ in the six-dimensional model (3.3) at $I_{app} = 0 \text{ pA}$ and its approximation $\bar{L}(O_{ucl}^*)$ for $O_{ucl}^*$ from the same model.
which still has three timescales, i.e., \((\bar{V}, N_{km}, H_{naf})\) are fast, \(\bar{c}\) is slow and \(\bar{O}_{ucl}\) is superslow. A time series of \(V\) and \(c\) in this five-dimensional system (3.16) is shown in Figure 3.22, from which we can see the main features of the bursting solutions of the original GnRH model remain. The only difference in Figure 3.22 from the time series of system (3.15) is that there are four spikes in each burst rather than three. Either increasing the constant in the linear function \(\bar{L}(O_{ucl}^*)\) slightly or decreasing the value of \(I_{app}\) in the model a little bit can reduce the number of spikes during each burst. Note that the interburst interval will increase when the number of spikes decreases. Figure 3.23 shows the time series of \(V\) and \(c\) obtained after increasing the constant term from 6.42 to 6.46 in function \(\bar{L}(O_{ucl}^*)\). The number of spikes becomes three again.

Figure 3.23: Time series of \(V\) and \(c\) in system (3.16), with \(c_t = -10^5 O_{ucl}^* + 6.46\).
Figure 3.24: Partial bifurcation diagram of the five-dimensional GnRH neuron model, equations (3.16). The meaning of line styles are the same as for Figure 3.1.

The partial bifurcation diagram of system (3.16) with $I_{\text{app}}$ as the bifurcation parameter is plotted in Figure 3.24. The Hopf bifurcation corresponding to the bursting solutions that we are interested has shifted to the left dramatically. The periodic solutions no longer exist for large $I_{\text{app}}$ values, i.e., $I_{\text{app}} > 100$. In Figure 3.25, the bifurcation diagram is compared with that for the six-dimensional model, Figure 3.9. If we only focus on the regime around $I_{\text{app}} = 0$, the unstable equilibrium point in the six-dimensional system becomes stable in the five-dimensional reduction and an unstable periodic orbit arises.

When we approximate $c_t$ by a linear function of $O_{ucl}^*$, although the time series are still similar to those of the six-dimensional model (3.3), the global bifurcation structures are changed. It seems not very reasonable to reduce the dimension of system (3.3) by replacing $c_t$ using $\bar{L}(O_{ucl}^*)$.

Recall in the six-dimensional system (3.3), $c_t$ and $O_{ucl}^*$ evolve on different timescales and tiny wiggles can be observed in the $c_t$ time series while the time series of $O_{ucl}^*$ seems smooth; refer to Figure 3.17. Thus, when we try to reduce the system by using one of them to approximate another, some change in the bifurcation structure may arise. In section 3.3.1, we use a linear function of $c_t$ to approximate $O_{ucl}^*$. This causes the branch of equilibrium points of the six-dimensional model to become two separate branches. In some regions in the $(I_{\text{app}}, V)$-plane, these two branches are quite close to each other (Figure 3.19). The good aspect is the loci of the equilibrium
branch and the periodic solution branch of the reduced system (3.15) remain nearly the same as for the original six-dimensional model. When we instead use a linear function of $O^*_{ucl}$ to approximate $c_t$, there is still one branch of equilibrium points as for the six-dimensional model, but the positions of the equilibrium branch and the periodic solution branch are different. In addition, the range of $I_{app}$ where the periodic solutions exist shrinks dramatically.

Considering that we want to maintain the global bifurcation structure of the original six-dimensional model, the result obtained after replacing $c_t$ by a function of $O^*_{ucl}$ seems worse than making the linear approximation other way around. The reason why one linear approximation is worse than the other is not clear; it might be because the approximation is made between variables with different timescales, and when we write $c_t$ as a function of $O^*_{ucl}$, the tiny wiggles that originally existed in the time series of $c_t$ no longer exist.

Note that the reduction method of making the linear approximation has no mathematical justification. The reason for trying the method is because we want to check if the dimension of the six-dimensional GnRH neuron model can be further reduced. From the point of view of preserving the mechanism underlying the particular bursting solutions in which we are interested, the second linear approximation in section 3.3.2 is better, since there is only one equilibrium branch and the branch of periodic
solutions is terminated in a homoclinic bifurcation; but from the point of view of the global bifurcation locations, the first linear approximation seems better. Since both of the linear approximations lose some bifurcation features, we use neither, and so we use the six-dimensional reduction, that is, equations (3.3) as the starting point for further study.

3.4 Discussion

In order to reduce the dimension of the eight-dimensional GnRH neuron model, equations (1.23), in this chapter we first revised the model assumptions and simplified the equations for ionic currents. By doing this, the dimension of system (1.23) was reduced by two and we obtained a six-dimensional system (3.3). Comparing the bifurcation diagram of system (3.3) with (1.23) impels us to use the six-dimensional model as a reduction since all important bifurcation structures for the bursting solutions are maintained.

Next we checked whether the two fast gating variables could be removed by quasi-steady-state reduction, but, unfortunately, neither resulted in a system with qualitatively the same time series and bifurcation diagram. The dimension of the system could not be further reduced by this method.

Finally, we made a linear approximation between $c_t$ and $O_{ucl}^*$ to see whether the dimension of the six-dimensional reduction could be further reduced. We found that the main features of the time series were preserved in both five-dimensional reductions, but the bifurcation diagrams were changed. When we approximated $O_{ucl}^*$ by a function of $c_t$, the loci of the equilibria and periodic solutions were kept but the mechanism behind the bursting solutions seemed changed slightly. When we instead approximated $c_t$ by a function of $O_{ucl}^*$, the mechanism behind the bursting solutions remained the same but the locations of the equilibria and the periodic solutions were different.

Therefore, the most satisfactory reduction seems to be the six-dimensional system (3.3). We will investigate the dynamics of the GnRH neuron model (1.23) by analysing this reduced system. We continue discussion of the GnRH neuron model in Chapter 6.
Chapter 4

Three Timescale Systems with Three Dimensions

In the previous chapter, we reduced the GnRH neuron model to a six-dimensional system with three different timescales. Although geometric singular perturbation theory (GSPT) has been developing rapidly in recent years and methods for the analysis of models with two timescales are well-established, a systematic theory for the case of three distinct timescales is still lacking. The fact that many mathematical models for physiological processes, like the GnRH neuron model, involve three or more timescales motivates us to investigate three timescale problems. To simplify matters, we will first consider the problem by using a three-dimensional three timescale system rather than the reduced GnRH neuron model.

The chapter is structured as follows. In section 4.1, we will discuss the application of GSPT to general three-dimensional three timescale systems. Then in section 4.2, we will use a food chain model [53] which has three dimensions and has three distinct timescales as an example to illustrate how GSPT can be applied. It turns out that the food chain model has some unusual features due to the specific details of the model. In section 4.3 we construct a more general three-dimensional system based on the food chain model. By analysing the constructed system, we find a new type of three timescale oscillation; this is also discussed in section 4.3. In the last section, we will discuss folded singularities in three timescale systems in general.
4.1 Geometric Analysis

In this section, we consider a three timescale system with three dimensions, which in general takes the following form:

\[
\begin{align*}
\frac{\delta dx}{dt} &= f(x, y, z, \delta, \varepsilon) \\
\frac{dy}{dt} &= g(x, y, z, \delta, \varepsilon) \\
\frac{dz}{dt} &= \varepsilon h(x, y, z, \delta, \varepsilon),
\end{align*}
\]  

(4.1)

where \(\delta\) and \(\varepsilon\) are two independent small constants that separate the timescales of evolution of the variables. GSPT allows us to predict some features of the dynamics of the full system based on knowledge of the dynamics of its singular limit. In a three timescale system such as (4.1), a singular limit can be obtained either by letting \(\delta \to 0\) or letting \(\varepsilon \to 0\). These two limits may provide information about different aspects of the full system’s dynamics. Since each of these two limits makes the problem essentially become a two timescale problem, we can use standard methods from GSPT to analyse them.

4.1.1 Using \(\delta\) as the Perturbation Parameter

First, we fix \(\varepsilon \neq 0\) in system (4.1). Then the singularly perturbed problem with perturbation parameter \(\delta\) can be written in two forms. One form describes evolution on the slow timescale \(t\), i.e., system (4.1). The other form describes evolution on the fast timescale \(t_f := t/\delta\), as follows:

\[
\begin{align*}
\frac{dx}{dt_f} &= f(x, y, z, \delta, \varepsilon) \\
\frac{dy}{dt_f} &= \delta g(x, y, z, \delta, \varepsilon) \\
\frac{dz}{dt_f} &= \delta \varepsilon h(x, y, z, \delta, \varepsilon).
\end{align*}
\]  

(4.2)

Taking the singular limit \(\delta \to 0\) in system (4.2), we obtain a one-dimensional layer problem:

\[
\begin{align*}
\frac{dx}{dt_f} &= f(x, y, z, 0, \varepsilon) \\
\frac{dy}{dt_f} &= 0 \\
\frac{dz}{dt_f} &= 0.
\end{align*}
\]  

(4.3)
From the analysis in section 2.2, we know the equilibrium points of system (4.3), i.e., 
\{(x, y, z) \in \mathbb{R}^3 : f(x, y, z, 0, \varepsilon) = 0\} compose the critical manifold (or slow manifold) 
$S_{0,\varepsilon}$. The stability of $S_{0,\varepsilon}$ is determined by the sign of $\partial f/\partial x$. If $\partial f/\partial x < 0$, $S_{0,\varepsilon}$ is stable, while if $\partial f/\partial x > 0$, $S_{0,\varepsilon}$ is unstable. The points on $S_{0,\varepsilon}$ are non-hyperbolic if $\partial f/\partial x = 0$.

Taking the singular limit $\delta \to 0$ in system (4.1), we get the reduced problem:

$$0 = f(x, y, z, 0, \varepsilon)$$
$$\frac{dy}{dt} = g(x, y, z, 0, \varepsilon) \quad (4.4)$$
$$\frac{dz}{dt} = \varepsilon h(x, y, z, 0, \varepsilon).$$

According to the analysis in section 2.2, we can write down a projection of the reduced flow onto the $(x, z)$-plane in the form of (2.11). Alternatively, without loss of generality, we assume $f(x, y, z, 0, \varepsilon)$ has continuous partial derivatives and $f_y(x, y, z, 0, \varepsilon) \neq 0$. By the implicit function theorem, the equation $f(x, y, z, 0, \varepsilon) = 0$ can be solved for $y$:

$$y = F(x, z, \varepsilon). \quad (4.5)$$

Then the projection of the reduced flow onto the $(x, z)$-plane can be obtained by differentiating equation (4.5) with respect to $t$ and combining with the last two equations in (4.4). Specifically, it is

$$\frac{\partial F}{\partial x} \frac{dx}{dt} = g(x, F, z, 0, \varepsilon) - \varepsilon \frac{\partial F}{\partial z} h(x, F, z, 0, \varepsilon)$$
$$\frac{dz}{dt} = \varepsilon h(x, F, z, 0, \varepsilon). \quad (4.6)$$

Since $\partial F/\partial x = 0$ along the fold curves of $S_{0,\varepsilon}$, we rescale $t$ to $\bar{t} := t/(\partial F/\partial x)$ to remove the singular term. The desingularised reduced system is as follows:

$$\frac{dx}{dt} = g(x, F, z, 0, \varepsilon) - \varepsilon \frac{\partial F}{\partial z} h(x, F, z, 0, \varepsilon)$$
$$\frac{dz}{dt} = \varepsilon \frac{\partial F}{\partial x} h(x, F, z, 0, \varepsilon). \quad (4.7)$$

The desingularized reduced system has the same phase portrait as system (4.6) if $\partial F/\partial x > 0$. When $\partial F/\partial x < 0$, the direction of time in the phase portrait for (4.7) is opposite to that for system (4.6) due to the time rescaling.
4.1.2 Using $\varepsilon$ as the Perturbation Parameter

Alternatively, we can fix $\delta \neq 0$ and use $\varepsilon$ as a perturbation parameter. Again, system (4.1) can be written in two equivalent forms. In accordance with the analysis in section 4.1.1, we still call $t$ the slow timescale. The other timescale $t_s := \varepsilon t$ is the superslow timescale and the evolution of the system on the superslow timescale is determined by

\[
\begin{align*}
\delta \varepsilon \frac{dx}{dt_s} &= f(x, y, z, \delta, \varepsilon) \\
\varepsilon \frac{dy}{dt_s} &= g(x, y, z, \delta, \varepsilon) \\
\frac{dz}{dt_s} &= h(x, y, z, \delta, \varepsilon). 
\end{align*}
\] (4.8)

Taking the singular limit $\varepsilon \to 0$ in system (4.1), we obtain a two-dimensional layer problem:

\[
\begin{align*}
\delta \frac{dx}{dt} &= f(x, y, z, \delta, 0) \\
\frac{dy}{dt} &= g(x, y, z, \delta, 0) \\
\frac{dz}{dt} &= 0. 
\end{align*}
\] (4.9)

Again, the critical manifold is composed of all the equilibrium points of the layer problem (4.9). In order to distinguish from the critical manifold $S_{0,\varepsilon}$, we call the critical manifold of system (4.9) the superslow manifold, label as $SS_{\delta,0}$, with the definition:

\[
SS_{\delta,0} := \{ (x, y, z) \in \mathbb{R}^3 : f(x, y, z, \delta, 0) = g(x, y, z, \delta, 0) = 0 \}. 
\] (4.10)

Remark. The superslow manifold $SS_{\delta,0}$ is a one-dimensional curve which is normally $O(\delta + \varepsilon)$ close to $S_{0,\varepsilon}$. If functions $f$ and $g$ are not dependent on $\delta$ and $\varepsilon$, then $SS$ is a subset of $S$.

The notation $O(\delta + \varepsilon)$ in the remark describes the order of the maximum distance between $SS_{\delta,0}$ and $S_{0,\varepsilon}$. The reason is $SS_{\delta,0}$ and $S_{0,\varepsilon}$ are $O(\delta)$ and $O(\varepsilon)$ away from $SS_{0,0}$ and $S_{0,0}$ respectively, and $SS_{0,0}$ is on $S_{0,0}$. 
Setting $\varepsilon = 0$ in system (4.8) yields the following reduced problem:

\begin{align*}
0 &= f(x, y, z, \delta, 0) \\
0 &= g(x, y, z, \delta, 0) \\
\frac{dz}{dt_s} &= h(x, y, z, \delta, 0),
\end{align*}

which describes the evolution of solutions on the superslow manifold $SS^{\delta,0}$. As in the previous section, we assume $f(x, y, z, \delta, 0)$ has continuous partial derivatives and $f_y(x, y, z, \delta, 0) \neq 0$. The first equation in (4.11) then can be solved for $y$:

\begin{equation}
y = F^{\delta}(x, z, \delta),
\end{equation}

using the implicit function theorem. Substituting this expression for $y$ into the second equation of (4.11), and further assuming $g(x, F^{\delta}, z, \delta, 0)$ has continuous partial derivatives and $g_z(x, F^{\delta}, z, \delta, 0) \neq 0$ without loss of generality, we eventually find that the superslow manifold $SS^{\delta,0}$ projected onto the $(x, z)$-plane has the form:

\begin{equation}
z = G^{\delta}(x, \delta).
\end{equation}

Differentiating equation (4.13) with respect to $t_s$ and combining with the last equation in (4.11), we can deduce:

\begin{equation}
\frac{\partial G^{\delta}}{\partial x} \frac{dx}{dt_s} = h(x, F^{\delta}, G^{\delta}, \delta, 0),
\end{equation}

which describes the dynamics on $SS^{\delta,0}$ in the singular limit $\varepsilon \rightarrow 0$. Since $\partial G^{\delta}/\partial x = 0$ on the folds of $SS^{\delta,0}$, we need to rescale the superslow time $t_s$ such that $t_s = \partial G^{\delta}/\partial x \cdot \bar{t}_s$. The desingularised equation therefore is:

\begin{equation}
\frac{dx}{dt_s} = h(x, F^{\delta}, G^{\delta}, \delta, 0).
\end{equation}

System (4.15) has the same phase portrait as system (4.14) when $\partial G^{\delta}/\partial x$ is positive. When $\partial G^{\delta}/\partial x$ is negative, the directions of time needs to be inverted to match the dynamics of (4.14). Refer to section 2.2. Therefore, the direction of the superslow flow on $SS^{\delta,0}$ is actually determined by the sign of $(\partial G^{\delta}/\partial x) \cdot h$ rather than $h$.

### 4.1.3 Comparing Results with Different Limit Orders

We could obtain further information about the flow constrained to $S^{0,\varepsilon}$, governed by system (4.6) or (4.7), by considering the limit $\varepsilon \rightarrow 0$ of these equations. Similarly, in
section 4.1.2, we can gain more information about the dynamics of system (4.1) if we continue the analysis by further letting \( \delta \to 0 \). To see whether or not these two different orders of taking limits provide us with different information, in this section we compare the results obtained by letting \( \delta \to 0 \) then \( \varepsilon \to 0 \) with the results we would get by letting \( \varepsilon \to 0 \) then \( \delta \to 0 \).

**Letting \( \delta \to 0 \) then \( \varepsilon \to 0 \) in system (4.1)**

In section 4.1.1, we treat \( \delta \) as the singular perturbation parameter. The layer problem (4.3) defines a critical manifold \( S^{0,\varepsilon} \). With \( \varepsilon \to 0 \), \( S^{0,\varepsilon} \) converges to \( S^{0,0} \), which is defined by \( \{(x, y, z) \in \mathbb{R}^3 : f(x, y, z, 0, 0) = 0 \} \). We assume \( f(x, y, z, 0, 0) = 0 \) can be solved for \( y \) as \( y = F^0(x, z) \). Now we consider the reduced system with the limit \( \varepsilon \to 0 \). Letting \( \varepsilon \to 0 \) in the desingularised reduced system (4.7) yields the following layer problem:

\[
\begin{align*}
\frac{dx}{dt} &= g(x, F^0, z, 0, 0) \\
\frac{dz}{dt} &= 0.
\end{align*}
\]

(4.16)

The equilibrium points of this system compose the superslow manifold \( SS^{0,0} \) and its stability is determined by the sign of \( (\partial f/\partial x) \cdot (\partial g/\partial x) \). As will be shown later, \( SS^{0,0} \) is a singular limit (as \( \delta \to 0 \)) of the superslow manifold \( SS^{0,0} \) given in (4.10).

System (4.7) with perturbation parameter \( \varepsilon \) can be written on the superslow timescale \( t^*_s := \varepsilon \tilde{t} \):

\[
\begin{align*}
\varepsilon \frac{dx}{dt^*_s} &= g(x, F^\varepsilon, z, 0, \varepsilon) - \varepsilon \frac{\partial F^\varepsilon}{\partial z} h(x, F^\varepsilon, z, 0, \varepsilon) \\
\frac{dz}{dt^*_s} &= \frac{\partial F^\varepsilon}{\partial x} h(x, F^\varepsilon, z, 0, \varepsilon).
\end{align*}
\]

(4.17)

When \( \varepsilon \to 0 \), system (4.17) becomes

\[
\begin{align*}
0 &= g(x, F^0, z, 0, 0) \\
\frac{dz}{dt^*_s} &= \frac{\partial F^0}{\partial x} h(x, F^0, z, 0, 0).
\end{align*}
\]

(4.18)

We assume the first equation in system (4.18) can be solved for \( z \): \( z = G^0(x) \). The dynamics on \( SS^{0,0} \) therefore can be deduced from (4.18), as follows:

\[
\frac{dx}{dt^*_s} = \frac{\partial F^0}{\partial x} h(x, F^0, G^0, 0, 0),
\]

(4.19)
where the time is rescaled to $\tilde{t}_s^* := t_s^*/(\partial G^0/\partial x)$ in order to remove the singularity that happens at the fold of $SS^{0,0}$.

In summary, by letting $\delta \to 0$ then $\varepsilon \to 0$, we can find expressions for the critical manifold $S^{0,0}$ and its stability, and can compute the slow flow constrained to $S^{0,0}$. By Fenichel’s theorem (Theorem 2.2.1), $S^{0,0}$ and $SS^{0,0}$ perturb to a slow manifold $S^{0,\varepsilon}$ and a superslow manifold $SS^{0,\varepsilon}$ as $\varepsilon$ increases from zero. Then $S^{0,\varepsilon}$ and $SS^{0,\varepsilon}$ perturb to a slow manifold $S^{\delta,\varepsilon}$ and a superslow manifold $SS^{\delta,\varepsilon}$ when $\delta \neq 0$ but sufficiently small.

**Letting $\varepsilon \to 0$ then $\delta \to 0$ in system (4.1)**

Now we see whether the other order of taking limits will provide us different information about the dynamics of system (4.1). The layer problem (4.9) in section 4.1.2 with perturbation parameter $\delta$ can be written in a form that describes evolution on the fast timescale $t_f$, as follows:

\[
\begin{align*}
\frac{dx}{dt_f} &= f(x, y, z, \delta, 0) \\
\frac{dy}{dt_f} &= \delta g(x, y, z, \delta, 0) \\
\frac{dz}{dt_f} &= 0.
\end{align*}
\] (4.20)

With the limit $\delta \to 0$, system (4.20) is exactly the same as system (4.3) with $\varepsilon = 0$. Therefore, we would get the same information about $S^{0,0}$ as in the previous case. Letting $\delta \to 0$ in system (4.9), we eventually get system (4.16), which means the information about $SS^{0,0}$ is also the same as provided in the previous case and the superslow manifold $SS^{\delta,0}$ in (4.10) converges to $SS^{0,0}$ as $\delta \to 0$.

Taking the limit $\delta \to 0$ in the desingularised equation (4.15), we obtain the following equation:

\[
\frac{dx}{dt_s} = h(x, F^0, G^0, 0, 0),
\] (4.21)

which describes the superslow flow constrained to $SS^{0,0}$. Comparing the timescale $\tilde{t}_s$ used in system (4.21) with the timescale $\tilde{t}_s^*$ used in system (4.19), it is easy to find equation (4.21) has the same phase line as (4.19).

Therefore, by letting $\varepsilon \to 0$ then $\delta \to 0$ in system (4.1), we would get the same result about $S^{0,0}$ and $SS^{0,0}$ as provided by letting $\delta \to 0$ then $\varepsilon \to 0$ in system (4.1). If we want to predict the dynamics with $(\delta, \varepsilon) \neq 0$, then the limits can be taken in either order. Once we have determined the dynamics on $S^{0,0}$ and $SS^{0,0}$, it is usual to proceed by constructing singular orbit made up of appropriate combinations of orbit segments on $S^{0,0}$ and $SS^{0,0}$. If the singular orbit constructed in this way lies
away from any folded singularities, then the orbit in the corresponding full system will be a smooth perturbation of the singular orbit, which means we can explain its dynamics directly by comparing with the geometric structures. Otherwise, we need to consider the folded singularities more carefully, as discussed below.

### 4.2 The Rosenzweig-MacArthur Food Chain Model

The Rosenzweig-MacArthur food chain model [53] is a three-dimensional system. In the articles of Deng et al. [6, 7, 8] which focus on the chaos generated in the model, ideas from GSPT were used to explain the dynamics. The work described below can be seen as complementing their analysis but provides a much more thorough discussion of the application of GSPT to the model and the role of the critical manifold and the superslow manifold in determining the dynamics. The main difference is that they concentrated on the chaos arisen in the food chain model while we are interested in the mechanism underlying an observed bursting solution.

The dimensionless form [6, 7, 8] is as follows:

\[
\begin{align*}
\delta \frac{dx}{dt} &= x \left(1 - x - \frac{y}{\beta_1 + x}\right) := f(x, y) \\
\frac{dy}{dt} &= y \left(\frac{x}{\beta_1 + x} - \alpha_1 - \frac{z}{\beta_2 + y}\right) := g(x, y, z) \\
\frac{dz}{dt} &= \varepsilon z \left(\frac{y}{\beta_2 + y} - \alpha_2\right) := \varepsilon h(y, z),
\end{align*}
\]

where variables \(x, y, z \in [0, 1]\) represent populations of prey, predator and top-predator, respectively. Note that in order to keep \(\delta\) as the timescale parameter in accordance with section 4.1, we changed the notation \(\delta_{1,2}\) and \(\zeta\) in the original model to \(\alpha_{1,2}\) and \(\delta\), respectively. The presence of \(\delta, \varepsilon \ll 1\) indicates this is a three timescale system with fast variable \(x\), slow variable \(y\) and superslow variable \(z\). The values used for other parameters are shown in Table 4.1.

For a certain choice of parameter values in this model, the time series of the slowest variable \(z\) exhibits small wiggles, which are similar to the wiggles shown in the time series of the GnRH neuron model; see Figure 1.6 and Figure 4.1 (\(z\) time series). In order to understand this behaviour and reveal the underlying mechanism

| Parameter values of the dimensionless food chain model |
|-------------------------|------------------|-----------------|------------------|-----------------|
| \(\beta_1\) | \(0.3\) | \(\beta_2\) | \(0.1\) | \(\alpha_1\) | \(0.1\) | \(\alpha_2\) | \(0.4\) |

Table 4.1: Parameter values for the food chain model, equation (4.22).
4.2 The Rosenzweig-MacArthur Food Chain Model

Figure 4.1: Time series of each of the variables in the food chain model, equations (4.22) for parameters in Table 4.1. Small wiggles can be seen in the z time series.

for those wiggles, we use GSPT. Since the functions $f$, $g$ and $h$ in the model do not depend on $\delta$ and $\epsilon$, the superslow manifold always lies on the critical manifold, as discussed in section 4.1.

The analysis procedure is as follows. First, we fix $\epsilon$ and treat $\delta$ as the perturbation parameter. GSPT provides information about the fast dynamics of system (4.22) and part of the slow dynamics. Next, we fix $\delta$ and treat $\epsilon$ as the perturbation parameter; this time, we complete the knowledge of the slow dynamics and learn the superslow dynamics as well. Finally, we combine all the information that we obtained to explain the mechanism of the time series shown in Figure 4.1.

4.2.1 Critical Manifold

First, we fix $\epsilon > 0$ and consider $\delta$ as the perturbation parameter. According to the analysis in section 4.1, the critical manifold $S$ of the food chain model (4.22) is defined as follows:

$$S := \{(x, y, z) \in \mathbb{R}^3 : x(1 - x - y/(\beta_1 + x)) = 0\}, \quad (4.23)$$

which actually contains two parts: the plane defined by

$$S_1 := \{(x, y, z) \in \mathbb{R}^3 : x = 0\}, \quad (4.24)$$
Figure 4.2: Critical manifolds $S_1$ (vertical plane) and $S_2$ (parabolic surface) of the food chain model (4.22). The stable (unstable) branches of them are shown in blue (grey). The dashed blue line indicates where the two manifolds intersect, and the solid blue line shows the fold of $S_2$. The green lines are representative fast fibres in different regions.

and the surface defined by

$$S_2 := \{(x, y, z) \in \mathbb{R}^3 : 1 - x - y/(\beta_1 + x) = 0\}. \quad (4.25)$$

Equation (4.25) defining $S_2$ can be rearranged to make $y$ the subject:

$$y = (1 - x)(\beta_1 + x) := F(x). \quad (4.26)$$

We will use this to compute the projection of the dynamics onto the critical manifold $S_2$. The surfaces $S_1$ and $S_2$ are shown in Figure 4.2.

The stabilities of the components $S_1$ and $S_2$ of $S$ are determined by the sign of $f_x$. Since

$$f_x = 1 - 2x - \frac{\beta_1 y}{(\beta_1 + x)^2}, \quad (4.27)$$

for $S_1$,

$$f_x|_{S_1} = 1 - \frac{y}{\beta_1}. \quad (4.28)$$

Hence, we can conclude:
• when \( y > \beta_1 \), \( S_1 \) is stable (i.e., \( f_x|_{S_1} < 0 \));

• when \( y = \beta_1 \), \( S_1 \) is non-hyperbolic (i.e., \( f_x|_{S_1} = 0 \));

• when \( y < \beta_1 \), \( S_1 \) is unstable (i.e., \( f_x|_{S_1} > 0 \)).

The non-hyperbolic line \( y = \beta_1 \) on \( S_1 \) is the intersection of \( S_1 \) and \( S_2 \) shown by the dashed blue line in Figure 4.2. The stability of \( S_2 \) can be computed from:

\[
f_x|_{S_2} = 1 - 2x - \frac{\beta_1(1 - x)}{\beta_1 + x}. \tag{4.29}
\]

Since both \( \beta_1, x > 0 \), solving \( f_x|_{S_2} > 0 \) is equivalent to solving the inequality

\[
(1 - 2x)(\beta_1 + x) - \beta_1(1 - x) > 0,
- \beta_1 x + x - 2x^2 > 0,
1 - \beta_1 > 2x \quad \text{(since } x > 0),
\text{so } x < \frac{1 - \beta_1}{2}. \tag{4.30}
\]

Therefore, the manifold \( S_2 \) is

• unstable if \( x < (1 - \beta_1)/2 \);

• non-hyperbolic if \( x = (1 - \beta_1)/2 \);

• stable if \( x > (1 - \beta_1)/2 \).

We call the non-hyperbolic curve defined by \( x = (1 - \beta_1)/2 \) on \( S_2 \) the fold curve of \( S_2 \); see Figure 4.2 (the solid blue line). Substituting into \( y = F(x) \), the corresponding \( y \)-coordinate \( \bar{y} \) of the fold curve can be obtained. It is \( \bar{y} = (1 + \beta_1)^2/4 \).

Now, the fast dynamics become clear:

• When \( y < \beta_1 \) and \( x > 0 \), except for solutions with initial conditions on \( S_1 \) (or \( S_2 \)) which will stay on \( S_1 \) (or \( S_2 \)), all the solutions are fast fibres and converge to the stable branch of \( S_2 \).

• When \( y > \bar{y} \) and \( x > 0 \), the solutions away from \( S_1 \) are fast fibres that converge to \( S_1 \) and the solutions on \( S_1 \) will stay on \( S_1 \).

• When \( \beta_1 < y < \bar{y} \) and \( x > 0 \), except for solutions initially on \( S_1 \) (or \( S_2 \)) which will stay on \( S_1 \) (or \( S_2 \)), a solution initially to the left side of the unstable branch of \( S_2 \) (refer to Figure 4.2) will be attracted by \( S_1 \); otherwise, it will converge to the stable branch of \( S_2 \).
Now we investigate the slow motion constrained to the critical manifold. The slow motion on $S_1$ is not very interesting. Consider the evolution equations of system (4.22) with $x = 0$. We know the dynamics on $S_1$ is mainly determined by $dy/dt$ since $\varepsilon$ is so small that the effect of $dz/dt$ can be ignored. On $S_1$, $dy/dt$ is always negative, which indicates that solutions always move downwards (i.e., in the direction that $y$ decreases).

In order to calculate the dynamics on $S_2$, we differentiate $y = F(x)$, the expression for $S_2$, with respect to $t$ and combine with system (4.22) to obtain the projection onto the $(x, z)$-plane of the slow dynamics on $S_2$:

$$
\frac{dF}{dx} \frac{dx}{dt} = g(x, F(x), z) \tag{4.31}
$$

$$
\frac{dz}{dt} = \varepsilon h(F(x), z).
$$

Along the fold curve of $S_2$ ($x = (1 - \beta_1/2)$), $dF/dx = 0$. We desingularize (4.31) by rescaling $t$. Defining $\bar{t} := t/(dF/dx)$, we get the desingularized reduced flow:

$$
\frac{dx}{d\bar{t}} = g(x, F(x), z) \tag{4.32}
$$

$$
\frac{dz}{d\bar{t}} = \varepsilon \frac{dF}{dx} h(F(x), z).
$$

Equations (4.32) describe the dynamics on $S_2$ when $dF/dx$ is positive. If $dF/dx < 0$, we have to reverse the direction of the solutions of (4.32) to obtain the dynamics of system (4.31). In this problem, the sign of $dF/dx$ is as the same as of $\partial f/\partial x$. The dynamics on $S_2$ will be further discussed later in section 4.2.3.

### 4.2.2 Superslow Manifold

The superslow manifold $SS$ can be obtained if we fix $\delta > 0$ and treat $\varepsilon$ as the perturbation parameter in equations (4.22). It is defined as follows:

$$
SS := \{(x, y, z) \in \mathbb{R}^3 : f(x, y) = g(x, y, z) = 0\}. \tag{4.33}
$$

We only consider the region $x, y, z \in [0, 1]$. The specific functions $f$ and $g$ imply the superslow manifold consists of three parts. They are

$$
SS_1 := \{(x, y, z) \in \mathbb{R}^3 : x = 1 \cap y = 0\}, \tag{4.34}
$$

$$
SS_2 := \{(x, y, z) \in \mathbb{R}^3 : y = F(x) \cap z = G(x)\}. \tag{4.35}
$$
where $F$ defined in equation (4.26) and $G$ defined below, and
\[ SS_3 := \{(x, y, z) \in \mathbb{R}^3 : x = y = 0\} . \] (4.36)

In the definition of $SS_2$, the expression $y = F(x)$ ensures $SS_2$ is a subset of $S_2$ and the expression $z = G(x)$ is obtained by solving the following equation:
\[
\frac{x}{\beta_1 + x} - \alpha_1 - \frac{z}{\beta_1 + \beta_2 + (1 - \beta_1)x - x^2} = 0, \]
\[
\text{so } z = G(x) := \left(\beta_1 + \beta_2 + (1 - \beta_1)x - x^2\right)\left(\frac{x}{\beta_1 + x} - \alpha_1\right). \] (4.37)

This equation describes the projection of $SS_2$ onto the $(x, z)$-plane and will be used later for calculating the dynamics constrained to $SS_2$. Figure 4.3 shows the superslow manifold $SS$ (red curves) superimposed on $S$, from which we can see that $SS_1$ and a part of $SS_2$ are located on the stable branch of $S_2$, while $SS_3$ is a straight line which lies on the unstable part of $S_1$.

Since $SS_3$ is unstable, the superslow flow restricted to it is not important to the dynamics of the full system. We only need to find out the dynamics constrained to $SS_1$ and $SS_2$. On $SS_1$, $x = 1$ and $y = 0$; using (4.11) and (4.22) we see the dynamics

![Figure 4.3: Superslow manifold SS of the food chain model (red curves) are superimposed on the critical manifolds. The dynamics on SS1 and SS2 are indicated by the arrows. The red dot is the fold of SS2 and the blue dot is the ordinary singularity of the full system.](image)
Three Timescale Systems with Three Dimensions

on $SS_1$ is determined by

$$\frac{dz}{dt} = -\alpha_2 z,$$

which indicates the solutions are always moving in the negative $z$-direction. To obtain the dynamics on $SS_2$, we need to find the sign of $(dG/dx) \cdot h$ following the discussion in section 4.1.2. Let $x_1$ denote the $x$-coordinate of the fold of $SS_2$ which occurs at $dG/dx = 0$ (the red dot in Figure 4.3) and $x_2$ denote the $x$-coordinate of the ordinary singularity of the model (the blue dot in Figure 4.3). The dynamics on $SS_2$ can then be summarised as follows:

- when $x < x_1$ or $x > x_2$, $dG/dx \cdot h(x) > 0$ and the solutions move along $SS_2$ in the positive $x$-direction; see Figure 4.3;
- when $x_1 < x < x_2$, $dG/dx \cdot h(x) < 0$ and the solutions move along $SS_2$ in the negative $x$-direction.

So far, we have information about the critical manifold $S$ and its stability, and the superslow manifold $SS$ and the dynamics on it. In order to combine these results to get the dynamics of the full system, we need to further investigate the dynamics constrained to $S$ by studying the stability of $SS$. From the analysis in section 4.1.3, we know the stability of the superslow manifold $SS$ is determined by the sign of $(\partial F/\partial x) \cdot (\partial g/\partial x)$.

A calculation shows that for $SS_1$, $\partial g/\partial x > 0$ if $z > z_1 \approx 0.0669$ and $\partial g/\partial x < 0$ if $z < z_1$; for $SS_2$, $\partial g/\partial x > 0$ if $x < x_1$ and $\partial g/\partial x < 0$ if $x > x_1$ where $x_1$ is defined in section 4.2.2. Since $dF/dx$ has the same sign as $\partial f/\partial x$, from section 4.2.1, we know on $S_2$, $dF/dx > 0$ if $x < (1 - \beta_1)/2 = 0.35 := \bar{x}$ and $dF/dx < 0$ if $x > \bar{x}$. Therefore, the stability of $SS_1$ and $SS_2$ can be summarised as follows:

- $SS_1$ is stable if $z > z_1$;
- $SS_1$ is unstable if $z < z_1$.
- when $x < \bar{x}$, $SS_2$ is unstable;
- when $\bar{x} < x < x_1$, $SS_2$ is stable;
- when $x > x_1$, $SS_2$ is unstable.

Combining the flows constrained to $SS_1$ and $SS_2$, we get the dynamics on $S_2$ in the limit case $(\delta, \varepsilon) = (0, 0)$, which is shown in Figure 4.4.
4.2 The Rosenzweig-MacArthur Food Chain Model

4.2.3 Dynamics of the Full System

We can now understand the dynamics of the full system (4.22). By Fenichel’s theorem (Theorem 2.2.1), when $\delta = 0$ and $\varepsilon \neq 0$ but sufficiently small, there exist superslow manifolds that lie within $O(\varepsilon)$ of the normally hyperbolic parts of $SS_1$ and $SS_2$. Furthermore, the superslow flows on them are the same as the reduced flows on $SS_1$ and $SS_2$. Together with the result we learned from section 4.2.1 that the solutions always move in the negative $y$-direction on $S_1$, we have information about the dynamics on both manifolds $S_1$ and $S_2$ at $\delta = 0$ as long as they are normally hyperbolic. Applying the Fenichel’s theorem again, the dynamics of the full system (4.22) close to the hyperbolic regions of the critical manifold with $0 < \delta, \varepsilon \ll 1$ can be predicted. Consequently, we can explain the behaviour of the oscillating solution shown in Figure 4.1.

In Figure 4.5, we plot the oscillating solution together with the critical manifold and the superslow manifold. Note that the solution is far away from the stable part of $SS_2$ and the folded singularity. Therefore, when it moves close to $S_2$, it will not be attracted by $SS_2$; and when it reaches the fold curve of $S_2$, it always meets a jump point [39, 40].

Once the solution jumps away from the fold curve of $S_2$ at the yellow point in
Figure 4.5: The critical manifolds $S_1$ and $S_2$ of the food chain model with the oscillating solution (shown by the black curve) superimposed. The superslow manifold is shown by red curves; dashed curves are unstable and solid curves are stable. The superslow motions restricted to $SS_1$ and $SS_2$ are indicated by the red arrows. The red dot is the fold of $SS_2$. The blue dot is the ordinary singularity of the full system (4.22) and the black dot is the folded singularity. The direction of the solution trajectory is shown by the black arrows. A triple arrow means fast movement and a double arrow means slow motion. The superslow dynamics is denoted by a single arrow.

Figure 4.5, it will be attracted by the stable part of $S_1$. Then it moves along that part slowly following the slow flow on $S_1$, i.e., moves downwards. We use a double arrow to indicate this timescale in order to distinguish from the triple arrow which means the fast jump. When the solution passes the dashed blue line, i.e., $y = \beta_1$ on $S_1$, it comes to the unstable part of $S_1$. Instead of jumping away directly, the solution will follow the unstable part for a while. This short delay is referred to as Pontryagin’s delayed loss of stability [45, 48, 49, 55].

The production of the delay phenomenon can be explained by noticing that in a $\delta$-neighbourhood of the point $(x, y, z) \in \{x = 0, y = \beta_1\}$, $f$ in system (4.22) is order $\delta^2$ so that $dx/dt$ is order $\delta$, which is very small in comparison with the order of $dy/dt$ (about $O(1)$). Hence, the solution of system (4.22) is almost vertical when it passes the line $y = \beta_1$ along $S_1$. Pontryagin’s theory states that the further away from the dashed blue line in Figure 4.5 a solution is when it gets close to $S_1$, the longer it will follow the unstable part of $S_1$ before it can jump away. The Pontryagin delay is similar to the delay caused by a slow passage through a Hopf bifurcation [3, 27].
which has been observed numerically in some neuron models.

In the latter case, a slow variable is treated as a bifurcation parameter and then a bifurcation diagram is plotted for the fast system. When the slow variable passes slowly a Hopf bifurcation, the quiescent state becomes unstable. Counterintuitively, the fast variable does not diverge from the unstable branch of equilibrium immediately, but follows that branch for a while; see Figure 4.6 for an example. If we take a section in Figure 4.5 with fixed $z$, the Pontryagin delay can be seen as the slow variable $y$ passing through a transcritical bifurcation slowly. Thus, both of these delays are caused by a slow passage through a bifurcation value.

After a period of delay, the solution eventually leaves $S_1$ by making a fast jump towards the stable branch of $S_2$. It lands on the left side of the superslow manifold $SS_2$ (i.e., below $SS_2$ in Figure 4.4), and hence (refer to Figure 4.4), it follows the slow flow on $S_2$ towards the fold curve. At the fold curve, the solution jumps away to start the next loop. During the first few loops, the solution always lands on the same side of $SS_2$. Each loop contributes a small increase in $z$ value, which is the reason why small wiggles can be observed in the time series of $z$ in Figure 4.1.

The last time the solution jumps back to $S_2$ from $S_1$, it touches $S_2$ on the other side of $SS_2$ (i.e., above $SS_2$ in Figure 4.4). Following the slow flow, it moves towards the stable part of $SS_1$. Once the solution gets close to $SS_1$, it follows the flow on $SS_1$, and moves even slower. Here is the third timescale, i.e., the superslow timescale exhibited by the solution; we use a single arrow in Figure 4.5 to indicate motion on the

Figure 4.6: Slow passages through a supercritical Hopf bifurcation (upper panel) and a subcritical Hopf bifurcation (lower panel). Adapted from Izhikevich [27].
superslow timescale. The solution moves near $SS_1$ until it passes the intersection of $SS_1$ and $SS_2$. At that point, $SS_1$ becomes unstable. After another Pontryagin delay, the solution leaves $SS_1$ heading towards the fold curve of $S_2$ on the slow timescale. The whole process is completed when the trajectory returns to the yellow point in Figure 4.5 and a new cycle of the periodic orbit start.

In summary, we find that the details of the time series in the food chain model can be explained by comparing with geometric structures from singular limits. The unstable part of $SS_2$, which acts as a separatrix, is crucial to the dynamics. Consequently, the orbit has fast-slow spiking interspersed with quiescent periods when solution evolves on slow and superslow timescales.

We have demonstrated that for this three timescale system at least, GSPT is still a powerful tool for exploring the dynamics. However, different from the case of two timescales where we only calculate the critical manifold, in a three timescale system, we need to also study the superslow manifold since it is also important for the dynamics. Note that the small wiggles shown in the GnRH neuron model (Figure 1.6) are similar to those in the food chain model (Figure 4.1). The mechanism we have learned for the wiggles exhibited in the food chain model suggests a possible mechanism for wiggles in the GnRH neuron model. More about this will be discussed in section 6.4.

4.3 A Constructed System

In this section, we construct a more general system based on the food chain model. This canonical model will be developed to exhibit similar time series to those seen in the food chain model, and will be used to determine sufficient conditions for the existence of the kinds of oscillations seen in the food chain model. A secondary aim is to use the constructed model to help identify more general three timescale phenomena.

The critical manifold in the food chain model was composed of two surfaces which intersected in one line. This geometric structure resulted in a Pontryagin delay in some parts of the orbit. To avoid this phenomenon, we will choose the form of the constructed model so that the critical manifold is one smooth surface and the superslow manifold is one smooth curve.

4.3.1 Sufficient Conditions

The constructed model has the same structure as equations (4.1) with sufficiently smooth functions $f$, $g$ and $h$. As a starting point, we consider the case that those functions are not dependent on the singularly perturbed parameters $\delta$ and $\varepsilon$. To
Figure 4.7: The critical manifold $S$ of the canonical model is a cubic-shaped manifold that satisfies conditions $S1$ and $S2$. That is, $f_x < 0$ and $F_x > 0$ on the outer branches, while $f_x > 0$ and $F_x < 0$ on the middle branch.

To simplify the problem, we choose to have function $f$ independent of $z$. Therefore, the canonical model has the following form:

$$
\begin{align*}
\delta \frac{dx}{dt} &= f(x, y) \\
\frac{dy}{dt} &= g(x, y, z) \\
\frac{dz}{dt} &= \varepsilon h(x, y, z).
\end{align*}
$$

(4.39)

Without loss of generality, we assume $f$ and $g$ have continuous partial derivatives and $f_y \neq 0$, $g_z \neq 0$. By the implicit function theorem, $f(x, y) = 0$ can be solved as $y = F(x)$ and $g(x, F(x), z) = 0$ can be solved as $z = G(x)$. We also assume that the critical manifold $S$, which is defined by $f = 0$, is a cubic-shaped smooth surface, with the properties:

$S1$. The outer branches of $S$ are attracting while the middle branch of $S$ is repelling; see Figure 4.7.

$S2$. The desingularised reduced system has the same phase portrait as the reduced system on the stable branches of $S$.

$S3$. On the left branch of $S$, the slow flow moves up ($y$ increases) towards the upper fold curve of $S$; and on the right branch of $S$, there exists a superslow manifold $SS$ defined by $f = g = 0$. 
Condition $S3$ requires the superslow manifold $SS$ does not intersect the left branch of $S$, but $SS$ could intersect the middle branch of $S$. Since $S$ only depends on $f$, conditions $S1$ and $S2$ are equivalent to the following conditions on $f$:

$f1$. On the outer branches of $S$, $f_x < 0$; on the middle branch of $S$, $f_x > 0$.

$f2$. On the outer branches of $S$, $F_x > 0$; on the middle branch of $S$, $F_x < 0$.

From the general analysis in section 4.1, we know the desingularised reduced system of (4.39) has the following form:

\[
\frac{dx}{d\bar{t}} = g(x, F(x), z) \\
\frac{dz}{d\bar{t}} = \varepsilon \frac{\partial F}{\partial x} h(x, F(x), z),
\]

where $\bar{t} = t/(\partial F/\partial x)$. Hence, condition $S3$ gives the following condition on $g$:

$g1$. On the left branch of $S$, $g > 0$; on the right branch of $S$, $g(x, F(x), z) = 0$, i.e., $z = G(x)$, has a branch of solutions.

Next, we clarify the conditions that $SS$ needs to satisfy. In order to get similar three timescale solutions to those in the food chain model, one option is to construct

Figure 4.8: Schematic of the dynamics restricted to the right branch of $S$ projected onto the $(x, z)$-plane. The black cubic shaped curve is the superslow manifold $SS$. The attracting and repelling branches of $SS$ are shown by solid and dashed curves respectively. The arrows on $SS$ indicate the direction of the superslow flow on $SS$. The slow dynamics on the right branch of $S$ are shown by straight lines with arrows. The blue dashed line corresponds to the right fold curve of $S$ in Figure 4.7. The green line is the intersection of $z$-nullcline and $S$. FS means folded singularity and OS means ordinary singularity.
4.3 A Constructed System

SS as a cubic-shaped curve with the properties as shown in Figure 4.8, i.e., we assume:

SS1. On the outer branches of SS, \( G_x < 0 \); on the middle branch of SS, \( G_x > 0 \).

SS2. The superslow manifold SS intersects the rightmost fold curve of S only once at the left branch of SS.

SS3. The right branch of SS is attracting.

SS4. The flow on the rightmost branch of SS is towards to the right fold of SS.

SS5. Both folds of SS are jump points.

Condition SS2 ensures there exists only one folded singularity in the canonical system and so all the remaining points on the folds of S are jump points. Condition SS3 gives another condition on \( g \):

\[ g < 0 \] on the right branch of SS, \( g_x(x, F(x), z) < 0 \).

Condition SS4 does not specify the flows on other branches of SS, since they are not important for the dynamics of the orbit that we want to construct. These flows could behave as shown in Figure 4.8.

In Figure 4.8, we plot a schematic projection onto the \((x, z)\)-plane of the right branch of S including the superslow manifold SS. To make the flow constrained to SS behave as shown in Figure 4.8, the function \( h \) needs to satisfy:

\[ h < 0 \] for \( F_x = 0 \), \( h = 0 \) for fold curve, \( h > 0 \) for \( g = 0 \).

Figure 4.9: Schematic of the right branch of S projected onto the \((x, z)\)-plane. The shaded region which is bounded by the x-coordinate (red line) of the left fold of SS and the z-nullcline (green line) indicates where the solution have to reach when it returns to the right branch of S. The dashed blue line is the lower fold of S.
h1. The $z$-nullcline of system (4.39) given by $h(x, y, z) = 0$ intersects $S$ on its right branch at a straight line in the form $x = \gamma$.

h2. The $z$-nullcline of system (4.39) intersects $SS$ on its middle branch at one point.

h3. When $x < \gamma$, $h < 0$; when $x > \gamma$, $h > 0$.

The form of the $z$-nullcline assumed in condition $h1$ is one of the simplest ways to get the dynamics as shown in Figure 4.8. Condition $h2$ means there exists an ordinary singularity in the canonical system, as for the food chain model.

The conditions on the functions $f$, $g$ and $h$ derived above ensure that the dynamics restricted to $S$ and $SS$ behave as desired. However, we also need to impose conditions on the global flow to ensure the existence of the periodic solutions that we want.

PO1. When the solution trajectory jumps from the upper fold curve of $S$ to the right branch of $S$, it hits $S$ in the region bounded by the $x$-coordinate of the left fold of $SS$ and the $z$-nullcline, i.e., in the shaded region in Figure 4.9.

![Figure 4.10: Phase portrait of a system that does not satisfy condition PO1. The blue surface is the critical manifold $S$. Two fold curves of $S$ are shown by the yellow lines. The solid and dashed red curves are the attracting and repelling parts of the superslow manifold $SS$. The black curve is a solution trajectory. We use a triple arrow, a double arrow and a single arrow to indicate the fast, slow and superslow timescales on the solution trajectory, respectively. Every time the solution returns to the right branch of $S$, $z$ increases a little bit; thus, no periodic solution which tracks the slow manifold can be formed.](image_url)
Condition PO1 guarantees that every time the solution trajectory of the full system returns to the right branch of $S$, it always hits a point with a lower $z$-coordinate than the last time the trajectory was on the right branch. As a result, the solution eventually lands in region $B$ or $C$ in Figure 4.8, after which it will follow the right branch of $SS$ and climb up to the right fold of $SS$. During this process, $z$ increases, makes it possible to form a periodic orbit in the full system. Figure 4.10 gives an example of the case that condition PO1 is violated. In this example, when a solution trajectory falls off the right fold of $SS$, it follows the slow flow towards to the fold curve of $S$. From there, the solution jumps fast and reaches the left branch of $S$. Along that branch, the solution climbs up slowly until it can jump at the upper fold curve of $S$. Finally, it reaches a point on the right branch of $S$. Since the $z$-coordinate of this point is greater than the $z$-coordinate of the right fold of $SS$, the solution will never be trapped by the superslow manifold, and therefore, it cannot form a periodic solution.

Note that under assumption $SS2$, the system has a folded singularity which happens at the intersection of the lower fold curve of $S$ and the superslow manifold $SS$. If
the $z$-coordinate of the folded singularity is greater than or close to the $z$-coordinate of the right fold of $SS$, then as the solution falls off the right fold of $SS$, it would be attracted by another attracting branch of $SS$. In this case, the solution trajectory that reaches the right branch of $S$ will never leave that branch and will form a slow-superslow relaxation oscillation. An example can be seen in Figure 4.11. Therefore, the canonical model has to satisfy the following condition as well.

PO2. The $z$-coordinate of the folded singularity is smaller by an $O(1)$ amount than the $z$-coordinate of the right fold of $SS$.

### 4.3.2 The Canonical Model

With the conditions discussed in the previous section, the critical manifold $S$ and the superslow manifold $SS$ have the structure shown in Figure 4.12. According to this structure, we can start to construct functions $f$, $g$ and $h$ for the model in the following form:

\[
\begin{align*}
\delta \frac{dx}{dt} &= f(x, y) \\
\frac{dy}{dt} &= g(x, y, z) \\
\frac{dz}{dt} &= \varepsilon h(x).
\end{align*}
\]

(4.41)

In this system, $f(x, y) = 0$ can be solved for $y$: $y = F(x)$ and $g(x, F(x), z) = 0$ can be solved for $z$: $z = G(x)$. Suppose the $x$-coordinates of the fold curves of $S$ and the folds of $SS$ are $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$, respectively with $\alpha_1 < \alpha_2 < \beta_1 < \beta_2$; see Figure 4.12. Since $S$ is a cubic shaped surface with the properties shown in Figure 4.7, we write $F_x = 6a(x - \alpha_1)(x - \alpha_2)$ where $a > 0$ is an arbitrary constant. In this way, $F_x > 0$ on the outer branches of $S$ and $F_x < 0$ on the middle branch of $S$. The function for $F(x)$ can be obtained by integrating $F_x$:

\[
F(x) = \int F_x \, dx = \int [6ax^2 - 6a(\alpha_1 + \alpha_2)x + 6a\alpha_1\alpha_2] \, dx
\]

\[
= 2ax^3 - 3a(\alpha_1 + \alpha_2)x^2 + 6a\alpha_1\alpha_2x + a_0,
\]

where $a_0$ is a constant. Remembering that the sign of $f_x$ is opposite to the sign of $F_x$ on $S$ (i.e., $f_y > 0$), and $f(x, y) = 0$ can be solved as $y = F(x)$, a natural choice of $f$ is $f = y - F(x)$. The function $f$ defined like this provides a critical manifold that does not depend on $z$.

The function for $g$ can be developed in a similar manner. Using the assumptions $g_x, G_x < 0$ on the outer branches of $SS$ and $g_x, G_x > 0$ on the middle branch of
Figure 4.12: Geometric structure of the canonical model. The surface is the critical manifold $S$. The red curve is superslow manifold $SS$. The green line is the intersection of the $z$-nullcline and $S$. The $x$-coordinates of the fold curves of $S$ and the folds of $SS$ are $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$.

SS, we define $G_x := -6b(x - \beta_1)(x - \beta_2)$ with an arbitrary positive constant $b$. The function for $G(x)$ consequently is as follows:

$$
G(x) = \int G_x \, dx = \int [-6bx^2 + 6b(\beta_1 + \beta_2)x - 6b\beta_1\beta_2] \, dx
$$

$$
= -2bx^3 + 3b(\beta_1 + \beta_2)x^2 - 6b\beta_1\beta_2 x + b_0,
$$

with a constant $b_0$ arising from the integration. Since $z = G(x)$ comes from solving $g(x, F(x), z) = 0$, we can simply set $g(x, F(x), z) = G(x) - z$. In order to make the function $g$ depend on $y$, we can add the term $+\sigma y - \sigma F(x)$ to the $g$ function, where $\sigma$ can be any constant. Here we choose $\sigma = -b/a$, which means we can remove the $x^3$ term from the $g$. Thus,

$$
g(x, y, z) = g(x, F(x), z) - \frac{2b}{2a}y + \frac{2b}{2a}F(x)
$$

$$
= 3b((\beta_1 + \beta_2) - (\alpha_1 + \alpha_2))x^2 - 6b(\beta_1\beta_2 - \alpha_1\alpha_2)x
$$

$$
- \frac{b}{a}y - z + \frac{ab_0 + a_0b}{a}.
$$

We use a simple function form for $h$, i.e., $h = x - \gamma$ where $\gamma$ is a constant with $\beta_1 < \gamma < \beta_2$ as we assumed in section 4.3.1. This function produces a $z$-nullcline at $x = \gamma$ and satisfies the requirement $h < 0$ on the left side of the $z$-nullcline.
In summary, the canonical system has the following form:

\[
\begin{align*}
\delta \frac{dx}{dt} &= y - [2ax^3 - 3a(\alpha_1 + \alpha_2)x^2 + 6a\alpha_1\alpha_2x + a_0] \\
\frac{dy}{dt} &= 3b ((\beta_1 + \beta_2) - (\alpha_1 + \alpha_2)) x^2 - 6b(\beta_1\beta_2 - \alpha_1\alpha_2)x \\
&- \frac{b}{a} y - z + \frac{ab_0 + a_0b}{a} \\
\frac{dz}{dt} &= \varepsilon(x - \gamma),
\end{align*}
\]

with \(\alpha_1 < \alpha_2 < \beta_1 < \gamma < \beta_2\). More concisely, we write

\[
\begin{align*}
\delta \frac{dx}{dt} &= y - [a_3x^3 - a_2x^2 + a_1x + a_0] = f(x, y) \\
\frac{dy}{dt} &= b_2x^2 - b_1x - cy - z + c_0 = g(x, y, z) \\
\frac{dz}{dt} &= \varepsilon(x - \gamma) = \varepsilon h(x),
\end{align*}
\]

where \(a_1 = 6a\alpha_1\alpha_2; a_2 = 3a(\alpha_1 + \alpha_2); a_3 = 2a; b_1 = 6b(\beta_1\beta_2 - \alpha_1\alpha_2); b_2 = 3b((\beta_1 + \beta_2) - (\alpha_1 + \alpha_2)); c = b/a\) and \(c_0 = (ab_0 + a_0b)/a\).

Now we need to find the range of each parameter in system (4.46) such that conditions PO1 and PO2 are satisfied. To do so, we write these two conditions symbolically in terms of parameters.

Denote the \(y\)-coordinate of the left fold curve of \(S\) by \(Y_{\alpha_1}\). To satisfy condition PO1, we need to calculate \(\text{Pro}(Y_{\alpha_1})\), the \(x\)-coordinate of the projection of \(Y_{\alpha_1}\) on the right branch of \(S\), and make sure that \(\beta_1 < \text{Pro}(Y_{\alpha_1}) < \gamma\). The value of \(Y_{\alpha_1}\) can be calculated as follows:

\[
Y_{\alpha_1} = F(\alpha_1) = aa_1^2(3\alpha_2 - \alpha_1) + a_0.
\]  

Then we solve for \(\text{Pro}(Y_{\alpha_1})\) by substituting (4.47) into \(f(x, y) = 0\), which is the expression for \(S\). Note that we get three roots; two of them are repeated and are the \(x\)-coordinate of the left fold curve of \(S\), i.e., \(\alpha_1\). The other root is \(\text{Pro}(Y_{\alpha_1})\). More explicitly, \(\text{Pro}(Y_{\alpha_1})\) is one of the roots of

\[
2ax^3 - 3a(\alpha_1 + \alpha_2)x^2 + 6a\alpha_1\alpha_2x + a_0 - [aa_1^2(3\alpha_2 - \alpha_1) + a_0] = 0,
\]  

which is different from \(\alpha_1\) and greater than \(\beta_1\). Since equation (4.48) has a repeated solution \(\alpha_1\), it can be transformed into

\[
(x - \alpha_1)^2[2x + (\alpha_1 - 3\alpha_2)] = 0.
\]
Hence, Pro($Y_{\alpha_1}$) satisfies $2x + (\alpha_1 - 3\alpha_2) = 0$, and so

$$\text{Pro}(Y_{\alpha_1}) = x = \frac{3}{2} \alpha_2 - \frac{1}{2} \alpha_1.$$  \hfill (4.50)

**Remark.** The parameters in the canonical system (4.45) should satisfy

$$\alpha_1 < \alpha_2 < \beta_1 < \frac{3}{2} \alpha_2 - \frac{1}{2} \alpha_1 < \gamma < \beta_2,$$  \hfill (4.51)

which is a condition equivalent to condition PO1.

The folded singularity is the intersection of the right fold curve of $S$ and $SS$. The $z$-coordinate of the folded singularity $Z_{FS}$ is therefore

$$Z_{FS} = G(\alpha_2) = -2b\alpha_2^3 + 3b(\beta_1 + \beta_2)\alpha_2^2 - 6b\beta_1\beta_2\alpha_2 + b_0.$$  \hfill (4.52)

The $z$-coordinate of the right fold of $SS$, denoted by $Z_{\beta_2}$, is

$$Z_{\beta_2} = G(\beta_2) = -2b\beta_2^3 + 3b(\beta_1 + \beta_2)\beta_2^2 - 6b\beta_1\beta_2^2 + b_0.$$  \hfill (4.53)

Condition PO2 states $Z_{FS} < Z_{\beta_2}$, which means:

$$2(\beta_2^2 + \beta_2^2 + \gamma) < 6\beta_1\beta_2 < 3(\beta_1 + \beta_2)(\beta_2 + \alpha_2).$$  \hfill (4.54)

Note that to obtain this result, we use the fact $\beta_2 - \alpha_2 > 0$.

In conclusion, the canonical model should take the form of (4.46) and satisfy conditions (4.51) and (4.54). In the rest of this chapter, we fix the values of the parameters in model (4.45) as shown in Table 4.2. This is equivalent to fixing the values of the parameters in model (4.46) as shown in Table 4.3. Our model then satisfies all conditions. Note that although the coefficients in equations (4.46) are not on the same order, the choice of the values of $\delta$ and $\epsilon$ ensures (4.46) is a three timescale system. The phase portrait of the constructed model is shown in Figure 4.13. The mechanism underlying the periodic solution exhibited in this constructed model is similar to the mechanism for the food chain model. In Figure 4.14, we

<table>
<thead>
<tr>
<th>Parameter values of the canonical model (4.45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$</td>
</tr>
<tr>
<td>$\alpha_1$</td>
</tr>
<tr>
<td>$\gamma$</td>
</tr>
</tbody>
</table>

Table 4.2: The values of the parameters in the canonical model, equations (4.45).
plot the projections of the fold curves of $S$ and the superslow manifold $SS$ onto the $(x, z)$-plane. The $x$-coordinates of these components then can be seen clearly. We also show the time series of the solution in Figure 4.14. Comparing with Figure 4.1, it can be seen that the solution obtained in the canonical model has the same qualitative behaviour as the food chain model except the time has been reversed.

The canonical model (4.45) developed here is a more general three timescale system than the food chain model. It abstracts the structure required for producing the three timescale oscillations seen in the food chain model, and helps us understand the sufficient conditions for this kind of solution to exist. The significance of constructing this model is that we can explore intrinsically three timescale dynamics by varying one or more parameter(s) in the model; from the construction of the model it is then

| Parameter values of the canonical model (4.46) |
|-----|-----|-----|-----|-----|
| $a_3$ | 4.00 | $a_2$ | 5.10 | $a_1$ | 1.56 | $a_0$ | 0.10 |
| $b_2$ | 60.00 | $b_1$ | 80.25 | $c$ | 12.50 | $c_0$ | 27.75 |
| $\gamma$ | 0.92 | $\delta$ | 0.001 | $\varepsilon$ | 0.1 |

Table 4.3: The values of the parameters in the canonical model, equations (4.46).

Figure 4.13: Phase portrait of the constructed model, equations (4.46) with parameter values as in Table 4.3. The perturbation parameters are $\delta = 0.001$ and $\varepsilon = 0.1$. The blue surface is the critical manifold $S$. The green line is the intersection of $z$-nullcline and $S$. The meaning of the remaining line styles are the same as in Figure 4.11.
easy to see what geometric changes we induced by such parameter variation. For instance, when we change the value of $\alpha_1$, we know it is equivalent to changing the $x$-coordinate of the upper fold curve of $S$.

### 4.3.3 Three Timescale Phenomena

As discussed in section 4.3.2, we can study the dynamics of three timescale systems by investigating the canonical model (4.45). To obtain a solution similar to that in
the food chain model, condition PO2 requires the folded singularity in the system to have a much lower $z$-coordinate than the $z$-coordinate of the right fold of SS. We are able to determine what happens when we relax this condition by increasing the $z$-coordinate of the folded singularity.

In system (4.45), increasing the $z$-coordinate of the folded singularity is equivalent to decreasing $\alpha_2$. This is because the yellow line at $x = 0.65$ in the upper panel of Figure 4.14 will shift to the left as $\alpha_2$ decreases, thereby raising the $z$-coordinate of the green dot. Time series for equations (4.45) with $\alpha_2 = 0.59$ are plotted in the upper panel of Figure 4.15. The projection of the solution trajectory onto the $(x, z)$-

![Figure 4.15](attachment:image.png)

Figure 4.15: Upper: the time series of system (4.45) with $\alpha_2 = 0.59$. Other parameter values are as in Table 4.2. Lower: dynamics of system (4.45) with $\alpha_2 = 0.59$ projected on $(x, z)$-plane with the solution trajectory superimposed. The meaning of the line styles are the same as in Figure 4.13.
4.3 A Constructed System

plane together with the fold curves of $S$ and the superslow manifold can be seen in the lower panel.

The evolution of this kind of solution involves three different timescales. Near the folded singularity, the solution trajectory exhibits small oscillations with decreasing amplitudes. Once the trajectory passes the lower fold curve of $S$ (the yellow line at $x = 0.59$ in Figure 4.15), the solution starts moving along the attracting branch of $SS$ on the superslow timescale. Therefore, the evolution of the solution constrained to the right branch of $S$ involves slow and superslow timescales as indicated by the double arrow and single arrow, respectively, in Figure 4.15. As in the case $\alpha_2 = 0.65$, the large spikes present in the time series evolve on fast and slow timescales depending on whether the solution is moving close to the critical manifold or not. The phase portrait for equations (4.45) with $\alpha_2 = 0.59$ is shown in Figure 4.16.

Note that we initially imposed condition PO2 to prevent the occurrence of a slow-superslow oscillation. However, as we see in this example, relaxing condition PO2 has produced an oscillation that is more complex than a slow-superslow oscillation. We believe that the case shown in Figures 4.15 is a transition case between the oscillation in Figure 4.14 and a slow-superslow oscillation; this oscillation is discussed further in section 6.2.

Other three timescale phenomena exhibited by the canonical model (4.45) might

Figure 4.16: Phase portrait of equations (4.45) with $\alpha_2 = 0.59$. The parameters are as in Table 4.2. The blue surface is the critical manifold $S$. The black trajectory is the same solution as in Figure 4.15. The meaning of the remaining line styles are the same as for Figure 4.13.
be discovered and explored in the same manner. Furthermore, we could add $O(\delta)$ and $O(\varepsilon)$ terms to the functions $f$, $g$ and $h$ in the model, and then study three timescale behaviours in this more general context. This sort of study is left for future work.

The method used to construct system (4.45) in section 4.3.2 could be generalised to explore other features of three timescale systems. For instance, in Chapter 5 it will be conjectured that in general, the relative positions of the folds of $S$ and the folds of $SS$ are an important influence on the dynamics of a three timescale system. Although investigating this conjecture is beyond the scope of this thesis, it seems likely that a construction along the lines of that outlined in section 4.3.2 would be useful for testing the conjecture in a specific model.

4.4 Folded Singularities

In section 2.2.2, we discussed folded singularities (FS) in three-dimensional systems with one fast and two slow variables. In a three-dimensional three timescale system, as we mentioned before, the intersections of the superslow manifold $SS$ and $L$, the fold curve of the critical manifold $S$, are the FS. One question that arises is whether there are any differences between these two sorts of FS. In this section, we will try to find the answer.

Suppose a three timescale system has just one folded singularity. As explained in the discussion in section 2.2.2, this folded singularity can be translated to the origin, i.e, the three timescale system takes the general form as follows:

$$
\begin{align*}
\delta \frac{dx}{d\tau} &= y + x^2 + O(\varepsilon x, \varepsilon y, \varepsilon z, \delta x, \delta y, \delta z, \delta^2, \varepsilon^2, x y^2, x^3, x y z) \\
&:= f(x, y, z, \delta, \varepsilon) \\
\frac{dy}{d\tau} &= g(x, y, z, \delta, \varepsilon) \\
\frac{dz}{d\tau} &= \varepsilon h(x, y, z, \delta, \varepsilon),
\end{align*}
$$

(4.55)

with $g(0, 0, 0, 0, 0) = 0$.

In the singular limit $\delta \to 0$ and $\varepsilon \to 0$, the desingularized reduced flow constrained to the critical manifold $S := \{(x, y, z) \in \mathbb{R}^3 : y = -x^2(1 + O(x, z))\}$ is given by

$$
\begin{align*}
\frac{dx}{d\tau_1} &= g(x, y, z, 0, 0) \\
\frac{dz}{d\tau_1} &= 0,
\end{align*}
$$

(4.56)

where $\tau_1 = \tau/(-2x(1 + O(x, z)))$. The reason the second differential equation in (4.56)
4.5 Discussion

The six-dimensional GnRH neuron model with three timescales motivates us to make progress on understanding more general systems with three different timescales. Since a systematic theory for the case of three distinct timescales does not yet exist, instead of using the GnRH model, we started our analysis by investigating a food chain model.
with three dimensions. The application of GSPT to the food chain model helps us understand the mechanism of the small wiggles exhibited in the time series of the model, and this provides a possible mechanism for the wiggles in the GnRH neuron model. We will discuss this part further in Chapter 6.

Based on the food chain model, we constructed a more general three-dimensional, three timescale system. By using the constructed model, we determined sufficient conditions for the existence of the oscillation seen in the food chain model, and identified another three timescale phenomenon.

In order to gain more information about systems with three timescales, in the next chapter, we will continue our analysis by considering a system with similar structure to but fewer dimensions than the GnRH neuron model. Then, we will review the GnRH model in Chapter 6.
Chapter 5

A Coupling of Two Fast-Slow Systems

In the previous chapter, we considered three-dimensional, three timescale systems and investigated the geometric mechanism underlying the small wiggles seen in the time series for the $z$ variable of the food chain model (see Figure 4.1). This provided us with some ideas about the mechanism underlying the wiggles exhibited in the $c$ time series in Figure 3.8 of the six-dimensional reduced GnRH neuron model (3.3). In this chapter, we construct a model based on the structure of the reduced GnRH neuron model and analyse it to see if we can improve understanding about the behaviour of solutions of the neuron model or gain more knowledge about three timescale systems in general.

The work in this chapter is part of a collaboration with J. Rubin and Y. Wang, aimed of understanding the dynamics of the model described below. My contribution to the project has been to apply GSPT techniques to the model, as described in this chapter. Rubin and Wang have been primarily interested in a different approach, trying to understand the dynamics by linking various two-dimensional projections, which are corresponding either to the phase plane of one oscillator or to the second subsystem of the model. We anticipate that our work will be published as a joint paper, presenting both points of view, at some stage in the future.

Recall that the neuron model (3.3) contains two fast-slow subsystems: the voltage submodel and the calcium submodel. These two subsystems are coupled; the evolution equation for membrane potential, $V$, depends on the cytosolic concentration of free intracellular calcium, $c$, and the evolution equation for $c$ depends on $V$. We wish to construct a model with this basic structure. We start with a combination of two fast-slow subsystems, and so the minimum dimension of the model is four. Each subsystem has two variables $(V_i, w_i)$ where $V_i$ is the fast variable and $w_i$ is the slow variable ($i = 1, 2$). To make the model into a three timescale system, we assume the
fast variable in the second subsystem evolves at a comparable rate to $w_1$. Instead of fully coupling the two subsystems as in the GnRH model, at this stage we restrict to a simpler coupling, that is, we let the evolution of $V_1$ depend on $V_2$ but have the evolution of $V_2$ be independent of $V_1$. Thus, the model takes the form:

$$
\begin{align*}
\varepsilon_1 \frac{dV_1}{dt} &= f_1(V_1, V_2, w_1) \\
\frac{dw_1}{dt} &= g_1(V_1, w_1) \\
\frac{dV_2}{dt} &= f_2(V_2, w_2) \\
\frac{dw_2}{dt} &= \varepsilon_2 g_2(V_2, w_2),
\end{align*}
$$

(5.1)

where each variable is dimensionless and of $O(1)$, and $\varepsilon_1, \varepsilon_2$ are two small independent constants.

We choose to use the Morris-Lecar (M-L) equations [17, 46, 52] as the subsystems in model (5.1). The M-L equations were developed as a model to describe the voltage oscillations of barnacle muscle fibres [46]. Our reason for using the M-L model is that it is a two-dimensional neuron model with one fast and one slow variable that can undergo a transition from excitable to oscillatory solutions when the system parameter (applied current) varies. Another possible choice would have been to use the FitzHugh-Nagumo (FHN) equations; however, we prefer M-L oscillators since they have a wider variety of dynamics than the FHN oscillators. Some work on coupled FHN oscillators has appeared in the literature [41] but attention in that paper is mostly in the dynamics of observed mixed-mode oscillations and is not directly relevant to our work described here.

In section 5.1, we study the dynamics of a single M-L oscillator as system parameters are varied. Then, based on the analysis in section 5.1, in section 5.2, we pick values of the parameters for our coupled M-L model and perform analysis on three selected types of oscillations produced by the coupled model. At the end of section 5.2, we discuss the folded saddle-node in the coupled M-L model.

### 5.1 Morris-Lecar Equations Type I and II

The two-dimensional Morris-Lecar (M-L) equations [17, 46, 52] take the following form
5.1 Morris-Lecar Equations Type I and II

\[ C \frac{dV}{dt} = I - g_{Ca} m_\infty(V)(V - V_{Ca}) - g_K w(V - V_K) - g_L(V - V_L) \]

\[ \frac{dw}{dt} = \phi(w_\infty(V) - w)/\tau_w(V), \]

where

\[ m_\infty(V) = 0.5(1 + \tanh((V - K_1)/K_2)) , \]

\[ w_\infty(V) = 0.5(1 + \tanh((V - K_3)/K_4)) , \]

\[ \tau_w(V) = 1/(\cosh((V - V_3)/(2V_4))) . \]

Variable \( V \) represents the membrane potential and \( w \) corresponds to the activation of the delayed rectifier potassium (K\(^+\)) current. The parameter values we use are given in Table 5.1. Note that to avoid confusion we use the notation \( K_i \) instead of \( V_i \) as in the original model. With a suitable choice of system parameter values, the M-L equations can be excitable, with an attracting equilibrium point, or oscillatory, with an attracting limit cycle. The transition from the former state to the latter state can be induced by increasing the parameter \( I \) in the \( V \)-equation. This change of state can occur through either a Type I or a Type II dynamical mechanism [17], according to a classification introduced by Hodgkin [25]. According to Hodgkin’s classification, excitable neurons can be divided into two types depending on the frequency of emerging oscillations:

- Type I neurons begin oscillating with an almost zero frequency. The frequency increases as the applied current increases.

- Type II neurons begin oscillating with a fixed frequency, which cannot be made arbitrarily small. The frequency is relatively insensitive to changes in the applied current.

In the context of codimension one bifurcations in a mathematical model of a neuron, those two different types of excitability are typically identified with the following

<table>
<thead>
<tr>
<th>( C )</th>
<th>20 ( \mu )F/cm(^2)</th>
<th>( V_{Ca} )</th>
<th>120 mV</th>
<th>( K_1 )</th>
<th>-1.2 mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( g_K )</td>
<td>8 mS/cm(^2)</td>
<td>( V_K )</td>
<td>-84 mV</td>
<td>( K_2 )</td>
<td>18 mV</td>
</tr>
<tr>
<td>( g_L )</td>
<td>2 mS/cm(^2)</td>
<td>( V_L )</td>
<td>-60 mV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1: Fixed parameters in the M-L equations (5.2) and (5.3).
System parameters for the Type I and II M-L model [23, 52]

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{Ca}$</td>
<td>4 mS/cm$^2$</td>
</tr>
<tr>
<td>$K_3$</td>
<td>12 mV</td>
</tr>
<tr>
<td>$\phi$</td>
<td>1/15</td>
</tr>
<tr>
<td>$K_4$</td>
<td>17.4 mV</td>
</tr>
</tbody>
</table>

Table 5.2: Parameters for the M-L equations (5.2) and (5.3) for which the model is Type I or a Type II. The rest of the parameter values are fixed as in Table 5.1.

bifurcation mechanisms [27]:

- Type I excitability occurs when the model has a saddle-node on an invariant circle (SNIC) bifurcation.

- Type II excitability occurs when the model has a Hopf bifurcation.

Figure 5.1: Bifurcation diagram of the M-L equations (5.2) and (5.3) with parameter values as in Tables 5.1 and 5.2 for Type I. The bifurcation parameter is $I$, the applied current. Stable and unstable equilibrium solutions are indicated by black curves and red dashed curves, respectively. The dashed green curves show the maximum and minimum $V$-coordinates of the unstable periodic solutions; and the blue curves show the maximum and minimum $V$-coordinates of the stable periodic solutions. The subcritical Hopf bifurcation (HB) is at $I \approx 97.788 \mu A/cm^2$. The saddle-node bifurcation of periodic solutions (SNpo) is at $I \approx 116.11 \mu A/cm^2$. The saddle-node bifurcation (SN) occurs at $I_l \approx -9.949 \mu A/cm^2$ and the saddle-node on an invariant circle bifurcation (SNIC) is at $I_r \approx 39.963 \mu A/cm^2$. As $I$ increases, the corresponding phase portrait will change from that labelled 5 in Figure 5.6 to (in order) those labelled 4, 7, 3 and 8 in Figure 5.6.
Table 5.2 shows some choices of system parameters that will lead to Type I and II M-L models, following the references [23, 52]. A bifurcation diagram for a representative Type I M-L model is shown in Figure 5.1. Using $I$ as the bifurcation parameter, we see there is a subcritical Hopf bifurcation at $I^* \approx 97.788 \mu A/cm^2$; the branch of periodic solutions that arises from this Hopf bifurcation will terminate at a SNIC bifurcation which occurs at the value $I^r \approx 39.963 \mu A/cm^2$. A saddle-node bifurcation occurs at $I^l \approx -9.949 \mu A/cm^2$. Therefore, when $I^l < I < I^r$, the system has three equilibria and one of them is stable. The M-L model is an excitable system in this parameter interval. As $I$ increases through $I^r$, the stable equilibrium coalesces with another equilibrium and both of them disappear. The system now has a stable periodic solution because $I$ passes the SNIC bifurcation, and so the M-L model enters a repetitive firing state.

In Figure 5.2, we plot a bifurcation diagram for a Type II M-L model, using parameter values as for Type II in Table 5.2. In this case, there is no saddle-node bifurcation of equilibrium solutions. The periodic solutions arise from a subcritical Hopf bifurcation, which occurs at $I \approx 212.02 \mu A/cm^2$, and terminate at another subcritical Hopf bifurcation located at $I \approx 93.86 \mu A/cm^2$.

![Figure 5.2: Bifurcation diagram of the M-L equations (5.2) and (5.3) with parameter values as in Tables 5.1 and 5.2 for Type II. The bifurcation parameter is the applied current $I$. Line styles have the same meaning as for Figure 5.1. Subcritical Hopf bifurcations (HB) occur at $I \approx 93.858 \mu A/cm^2$ and $I \approx 212.019 \mu A/cm^2$. The two saddle-node bifurcations of periodic solutions (SNpo) are at $I \approx 88.293 \mu A/cm^2$ and $I \approx 216.9 \mu A/cm^2$. As $I$ increases, the corresponding phase portrait will change from that labelled 5 in Figure 5.6 to (in order) those labelled 6, 7, 3 and 8 in Figure 5.6.](image-url)
As illustrated in Figures 5.1 and 5.2, a Type I M-L model can convert into Type II if values of some system parameters are changed. In the following two subsections, we study in more detail the transition from Type I to Type II as system parameters are changed.

Similar results were also found independently by [64], although they looked at a much more restricted range of parameter values. A thorough understanding of the dynamics of a single M-L oscillator is helpful for choosing model parameters for our coupled M-L system, but the remainder of section 5.1 contains no results about the three timescale systems; a reader interested in three timescale phenomena could safely skip to section 5.2.

5.1.1 Transition Induced by Varying $K_3$

The bifurcation set of the M-L equations in the $(I, K_3)$-plane is shown in the upper panel of Figure 5.3. Other system parameters are fixed to values for the Type I model as shown in Table 5.2. When $K_3$ is large ($K_3 > 44.55$), the system has two saddle-node bifurcations. A bifurcation diagram corresponding to fixing $K_3 = 50$ (as indicated by the line segment marked (i)) and varying $I$ is shown in Figure 5.4(i). As $I$ increases, the system will pass through region 5 then region 1 then region 8 as labelled in Figure 5.3. Schematic phase portraits in the regions labelled by different numbers are shown in Figure 5.6.

At $(I, K_3) \approx (-189.23, 44.55)$, the system exhibits a Bogdanov-Takens (BT) bifurcation [4, 43, 63]. A Hopf bifurcation curve and a homoclinic bifurcation curve are known to emanate from a BT point; therefore, when $K_3$ decreases below the value for the BT bifurcation, besides the two saddle-node bifurcations that already exist, a Hopf bifurcation and a homoclinic bifurcation appear in the bifurcation diagram. A representative bifurcation diagram is shown in Figure 5.4(ii), corresponding to fixing $K_3 = 30$ and varying $I$. As $I$ increases, the system exhibits five qualitatively different phase portraits as it passes from region 5 to 4 to 2 to 1 to 8 in the bifurcation set.

The Hopf bifurcation and the homoclinic bifurcation originating from the BT bifurcation shift to the right in the $(I, K_3)$-plane as $K_3$ decreases. At $(I, K_3) \approx (38.21, 18.34)$, the homoclinic bifurcation curve meets the saddle-node bifurcation curve and vanishes. Numerical calculation indicates a saddle-node bifurcation of periodic solutions originates from the same point. Simultaneously, a saddle-node on an invariant circle bifurcation (SNIC) curve appears. Therefore, as $K_3$ keeps decreasing, the M-L model is a Type I neural model as long as $K_3 \in (18.34, 5.6)$. On the other hand, as $K_3$ decreases, the Hopf bifurcation moves to the right and crosses the saddle-node bifurcation curve. Bifurcation diagrams shown in Figure 5.4(iii) and 5.4(iv) illustrate the cases before and after the Hopf bifurcation curve crosses the
Figure 5.3: Upper: the bifurcation set of the M-L equations (5.2) and (5.3) in the $(I, K_3)$-plane. The other parameters are as in Tables 5.1 and 5.2 for Type I. The black curves show the location of the saddle-node bifurcations (SN). The red curves are the Hopf bifurcations (HB). The blue curves show the saddle-node bifurcations of periodic solutions (SNpo). The green curves are the homoclinic bifurcation (HC). The labels BT and B denote the Bogdanov-Takens bifurcation and the Bautin bifurcation, respectively. Lower: an enlargement of the bifurcation set shown in the upper panel.
Figure 5.4: Bifurcation diagrams of the M-L equations (5.2) and (5.3) at (i) $K_3 = 50$; (ii) $K_3 = 30$; (iii) $K_3 = 17$; (iv) $K_3 = 10$; (v) $K_3 = 4.2$; (vi) $K_3 = 0$. Other parameters are as in Tables 5.1 and 5.2 for Type I. The stable and unstable equilibrium solutions are shown by the black and red curves. The maximum and minimum values of the stable (unstable) periodic solutions are indicated by the blue (green) curves.

saddle-node bifurcation curve. In the former case, the system goes through regions 5 to 4 to 2 to 3 to 8 as $I$ increases, and in the later case, it goes through region 5 to 4 to 7 to 3 to 8 in the bifurcation set.

For $K_3 < 5.6$, there are once again distinct homoclinic and saddle-node bifurcation curves. An enlargement of the region where $K_3 \in (4.1, 5.5)$ provides more detail; see
Figure 5.5: Bifurcation diagrams of the M-L equations (5.2) and (5.3) at (a) $K_3 = 5.3$; (b) $K_3 = 5$; (c) $K_3 = 4.52$; (d) $K_3 = 4.48$; (e) $K_3 = 4.4$. Other parameters are as in Tables 5.1 and 5.2 for Type I. Line styles have the same meaning as for Figure 5.4.

the lower panel of Figure 5.3. The bifurcation diagram shown in Figure 5.5(a) for $K_3 = 5.3$ and varying $I$, i.e., at the $K_3$ value indicated by the line segment (a) in Figure 5.3, is an example showing that the $I$-coordinate of the homoclinic bifurcation is between the $I$-coordinates of the two saddle-node bifurcations.

At $K_3 \approx 5.15$, there is another BT bifurcation. Once $K_3$ is below the value for this second BT bifurcation, a Hopf bifurcation curve appears in the system. This newly arisen Hopf bifurcation is subcritical and the branch of the unstable periodic solutions created in this bifurcation terminates in a homoclinic bifurcation associated
with a saddle-node equilibrium. We call this homoclinic bifurcation curve the right one to distinguish from the previously mentioned homoclinic bifurcation curve, since it is always on the right of the previous one in the \((I, K_3)\)-plane. The one-parameter bifurcation diagrams in the interval \(4.54 < K_3 < 5.15\) are qualitatively the same as the one shown in Figure 5.5(b), i.e., the phase portrait of the system changes

![Figure 5.6: Schematic representative phase portraits of M-L equations (5.2) and (5.3) for each of the regions labelled by numbers in Figure 5.3. The V-nullcline and the \(w\)-nullcline are shown in red and green, respectively.](image-url)
qualitatively as $I$ increases from region 5 to 4 to 9 to 10 to 11 to 7 to 3 to 8 in the bifurcation set.

At $(I, K_3) \approx (46.84, 4.54)$, the originally mentioned homoclinic bifurcation curve touches the saddle-node bifurcation curve. Emanating from this point, as $K_3$ decreases, there is a SNIC bifurcation curve. Note that fixing $K_3 < 4.54$ does not give a Type I M-L model because the system undergoes a saddle-node bifurcation of periodic solutions before the SNIC as $I$ increases, and there exists a stable equilibrium when $I$ passes through the SNIC point; see Figure 5.5(c).

The SNIC bifurcation curve ends at $(I, K_3) \approx (46.96, 4.51)$, where the right homoclinic bifurcation curve reaches the saddle-node bifurcation curve and disappears. Therefore, in the bifurcation diagram shown in Figure 5.5(d), no homoclinic bifurcation exists. Instead, the two Hopf bifurcation are joined together by the branch of periodic solutions.

The Hopf bifurcation curve emerging from the second Bogdanov-Takens bifurcation makes it possible for the M-L model to become a Type II system. As $K_3$ decreases further, this new Hopf bifurcation curve crosses the saddle-node bifurcation curve, resulting in the occurrence of the Hopf bifurcation at a smaller $I$ value than either of the two saddle-node bifurcations. Figure 5.5(e) shows an example. Then the two saddle-node bifurcations coalesce and disappear at a cusp point. As a result, there are no folds on the equilibrium branch in the bifurcation diagram. The M-L model becomes Type II; see Figure 5.4(v), the bifurcation diagram for fixed $K_3 = 4.2$ and varying $I$.

Finally, there is a Bautin bifurcation [43] at $(I, K_3) \approx (221.29, 4.22)$. The Hopf bifurcation curve with larger $I$-coordinate passes through this point, with the Hopf bifurcation changing from subcritical to supercritical as it does so. The curve of the saddle-node bifurcations of periodic solutions terminates at the Bautin bifurcation. A representative bifurcation diagram can be seen in Figure 5.4(vi), corresponding to fixing $K_3 = 0$ and varying $I$.

From the bifurcation set shown in Figure 5.3, we see that the M-L model can change from Type I to Type II as $K_3$ varies. If we require the system to exhibit Type I oscillations, we need to set $K_3 \in (5.6, 18.34)$; and if we require the system to exhibit Type II oscillations, we pick $K_3 < 4.51$. With other $K_3$ values, the system is neither Type I nor Type II. Note that the range of $K_3$ considered in this thesis is $[-20, 60]$.

### 5.1.2 Parameter Intervals for the M-L Equations

Similar analysis can be performed for variation of other system parameters. In this section, we show how transitions from Type I to Type II can occur as $\phi$, $g_{Ca}$ and $K_4$
The bifurcation set in the \((I, \phi)\)-plane is shown in Figure 5.7. Note that \(\phi\), which is a factor in the evolution equation for \(w\), sets the timescale for the recovery process. Thus, we only consider the bifurcation sets for positive value of \(\phi\). When the rest of the parameters in the M-L equations are fixed, decreasing \(\phi\) will increase the timescale separation between the fast variable, \(V\), and the slow variable, \(w\). Figure 5.7 shows that the M-L model never exhibits Type II oscillations in the considered range. The SNIC bifurcation curve exists in the \((I, \phi)\)-plane when \(\phi \in (0.02, 0.19)\), which means the M-L model is Type I if \(\phi\) is in this interval. If \(\phi\) is smaller than 0.02, there is a homoclinic bifurcation curve on the left side of the saddle-node bifurcation curve. Below the BT point, which occurs at \((I, \phi) \approx (39.96, 0.012)\), the system possesses two homoclinic bifurcations at the same value of \(\phi\). Therefore, when the timescale separation between \(V\) and \(w\) is sufficiently large, the M-L model is neither Type I nor Type II.

To determine the range of \(g_{Ca}\) such that the M-L model is Type I (or Type II), we fix the remaining parameters as for Type I in Table 5.2 and plot the bifurcation set in the \((I, g_{Ca})\)-plane. The bifurcation set displayed in Figure 5.8 demonstrates the M-L model is Type I if \(g_{Ca} \in (2.48, 5.62)\). The Hopf bifurcation existing in this interval is subcritical. At the BT bifurcation, where \((I, g_{Ca}) \approx (54.74, 2.46)\), another Hopf
5.1 Morris-Lecar Equations Type I and II

bifurcation is born. This Hopf bifurcation is supercritical and is connected to the subcritical Hopf bifurcation curve at the Bautin bifurcation (B) point. Therefore, for relatively small values of $g_{Ca}$, the system exhibits two Hopf bifurcations with no saddle-node bifurcation. In the sense that the oscillation starts with non-zero frequency, the M-L model is Type II in this case. The transition from Type I to Type II according to the variation of $g_{Ca}$ can be studied by looking at the small region around the BT point and the cusp point of the saddle-node bifurcation curve, just as we did in section 5.1.1. We will not discuss the detailed transition process further here.

If all the system parameters except $K_4$ in the M-L model are fixed as for Type I in Table 5.2, the bifurcation set in the $(I, K_4)$-plane shows that the M-L model remains Type I if $K_4 \in (7.63, 22.13)$. When $K_4 \in (31.55, 47.09)$, the system has two Hopf bifurcations and they are joined by the branch of periodic solutions; there are no homoclinic bifurcation in the system for these $K_4$ values. In this case, the M-L model is Type II. Note that different from the representative bifurcation diagram for Type II M-L equations shown in Figure 5.2, three unstable equilibrium points coexist with the stable periodic orbit. The transition from Type I to Type II is quite similar to the case seen when $K_3$ is varied, and we will not show the details here.

Plotting bifurcation sets is a direct way to find out whether the M-L model with
a particular choice of parameters is Type I or Type II. A disadvantage is that we can only plot bifurcation sets for one parameter varying in addition to \( I \), making it necessary to repeat the whole process if a variation of a third parameter is required. We will use the bifurcation sets found in this section to inform our choice of parameters in the coupled M-L model discussed in the next section.

### 5.2 The Four-Dimensional Coupled System

Coupling two copies of the M-L equations, we get a four-dimensional system with three timescales as follows:

\[
\begin{align*}
C_1 \frac{dV_1}{dt} &= I_1 - g_{Ca}m_{\infty}(V_1)(V_1 - V_{Ca}) - g_Kw_1(V_1 - V_K) \\
&\quad - g_L(V_1 - V_L) - g_{syn}S(V_2)(V_1 - V_{syn}) \\
\frac{dw_1}{dt} &= \phi_1(w_{\infty}(V_1) - w_1)/\tau_w(V_1) \\
C_2 \frac{dV_2}{dt} &= I_2 - g_{Ca}m_{\infty}(V_2)(V_2 - V_{Ca}) - g_Kw_2(V_2 - V_K) \\
&\quad - g_L(V_2 - V_L) \\
\frac{dw_2}{dt} &= \phi_2(w_{\infty}(V_2) - w_2)/\tau_w(V_2),
\end{align*}
\]

Figure 5.9: Bifurcation set of M-L equations (5.2) and (5.3) in \((I, K_4)\)-plane. Other parameters are as in Tables 5.1 and 5.2 for Type I. Line styles have the same meaning as for Figure 5.3.
with

\[ S(V_i) = \alpha(V_i)/(\alpha(V_i) + \beta) \]
\[ \alpha(V_i) = 1/(1 + \exp(-(V_i - \theta_s)/\sigma_s)) \]
\[ m_{\infty}(V_i) = 0.5(1 + \tanh((V_i - K_1)/K_2)) \]
\[ w_{\infty}(V_i) = 0.5(1 + \tanh((V_i - K_3)/K_4)) \]
\[ \tau_w(V_i) = 1/\cosh((V_i - K_3)/2K_4) \]

(5.5)

where \( i = 1, 2 \). We think of \((V_1, w_1)\) as being one M-L oscillator and \((V_2, w_2)\) being the second oscillator. The parameter \( g_{\text{syn}} \), with units of mS/cm², determines the coupling strength between these two oscillators. As a starting stage, in this thesis, we choose that the evolution equation of \( V_1 \) depends on \( V_2 \) but the evolution equation of \( V_2 \) is independent of \( V_1 \), i.e., the dynamics of \((V_2, w_2)\) affects the dynamics of \((V_1, w_1)\) but not vice versa.

The parameters of system (5.4) are fixed at the values shown in Table 5.3. These values are selected so that in the absence of coupling \( (g_{\text{syn}} = 0) \), the \((V_1, w_1)\) system has an attracting equilibrium and is excitable, and the \((V_2, w_2)\) system has an attracting relaxation oscillation, as shown in Figure 5.10. The parameter values are also picked such that there is clear separation of timescales between \( V_i \) (fast) and \( w_i \) (slow) in each oscillator and so that \( w_1 \) and \( V_2 \) evolve at a comparable rate. In a more biologically realistic model for calcium and voltage interactions, \( V_1 \) might represent membrane potential and \( V_2 \) intracellular calcium concentration, in which case equations (5.4) and (5.5) might be interpreted as an intracellular calcium oscillator driving calcium-dependent neural membrane potential oscillations. The physical units of some parameters in Table 5.3 and details of some terms in the model would need to be altered correspondingly. Due to the unidirectional coupling we have in

<table>
<thead>
<tr>
<th>Parameter values in the constructed equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_1 )</td>
</tr>
<tr>
<td>( C_2 )</td>
</tr>
<tr>
<td>( I_1 )</td>
</tr>
<tr>
<td>( I_2 )</td>
</tr>
<tr>
<td>( \phi_1 )</td>
</tr>
<tr>
<td>( \phi_2 )</td>
</tr>
<tr>
<td>( V_{\text{Ca}} )</td>
</tr>
<tr>
<td>( g_{\text{Ca}} )</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>( K_3 )</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>( \beta )</td>
</tr>
<tr>
<td>( \sigma_s )</td>
</tr>
</tbody>
</table>

Table 5.3: The values of the parameters in the coupled M-L model given by equations (5.4) and (5.5).
A Coupling of Two Fast-Slow Systems

Figure 5.10: Set up for the two M-L systems without coupling. In each plot, the $V$-nullcline and the $w$-nullcline are shown in red and green, respectively. The dots in black, blue and yellow denote equilibrium solutions of sink, saddle and source type, respectively. The $(V_1, w_1)$ system lacks a periodic solution, while the attracting periodic orbit for the $(V_2, w_2)$ system is shown in black. Note that the $V_i$ axis direction is reversed in accordance with the rest of the figures in this chapter.

our system, the $(V_2, w_2)$ oscillator does not change its dynamics when $g_{syn}$ varies.

From simulations of system (5.4) over a range of $g_{syn}$ values, we have selected three fundamental solution types on which to focus our analysis. They are obtained by setting $g_{syn}$ to 1.0, 4.1 and 5.1mS/cm$^2$, respectively. Time series for the attracting solutions at these three values of $g_{syn}$ are shown in Figure 5.11. From this figure, we see that the properties of these solutions are indicative of the presence of multiple timescales.

Our methods for analysis of the model will depend heavily on exploiting the presence of different timescales. As a first step in the analysis, therefore, it is helpful to rescale the variables in system (5.4) so that the important timescales can be explicitly identified.

### 5.2.1 Dimensionless Version of the Model

Define new dimensionless variables $(v_1, v_2, \tau)$, voltage scale $Q_v$ and timescale $Q_t$ such that

$$V_1 = Q_v \cdot v_1, \quad V_2 = Q_v \cdot v_2, \quad t = Q_t \cdot \tau.$$  \hfill (5.6)

Values for $Q_v$ and $Q_t$ will be determined below. Note that $w_1$ and $w_2$ are already dimensionless in equations (5.4).

From numerical simulations, we find that the membrane potential for the uncoupled M-L oscillators typically lies between $-70$ mV and $60$ mV. We define $T_w = \max(1/\tau_w(V_i))$ over the range $V_i \in [-70, 60]$ and then define $t_w(V_i)$, a rescaled ver-
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Figure 5.11: Time series of system (5.4) and (5.5) at $g_{\text{syn}} = 1.0$, 4.1 and 5.1mS/cm$^2$ with other parameters as in Table 5.3. The blue curve shows the $V_1$ time series and the red curve is the $V_2$ time series.

sion of $\tau_w(V_i)$, by $t_w(V_i) = T_w \tau_w(V_i)$. We also define $g_{\text{max}}$ to be the maximum of the three conductances $g_{Ca}$, $g_K$, and $g_L$. Substituting these expressions into equations (5.4)-(5.5) and rearranging, we obtain the following dimensionless system:

\[
\begin{align*}
\frac{C_1}{Q_1 \cdot g_{\text{max}}} \frac{dv_1}{d\tau} &= \bar{I}_1 - \bar{g}_{Ca} m_\infty(v_1)(v_1 - \bar{V}_{Ca}) - \bar{g}_K w_1(v_1 - \bar{V}_K) \\
&- \bar{g}_L (v_1 - \bar{V}_L) - \bar{g}_{\text{syn}} S(v_2)(v_1 - \bar{V}_{\text{syn}}) \\
\frac{1}{\phi_1 Q_1 T_w} \frac{dw_1}{d\tau} &= \frac{1}{t_w(v_1)} (w_\infty(v_1) - w_1) \\
\frac{C_2}{Q_2 \cdot g_{\text{max}}} \frac{dv_2}{d\tau} &= \bar{I}_2 - \bar{g}_{Ca} m_\infty(v_2)(v_2 - \bar{V}_{Ca}) - \bar{g}_K w_2(v_2 - \bar{V}_K) \\
&- \bar{g}_L (v_2 - \bar{V}_L) \\
\frac{1}{\phi_2 Q_2 T_w} \frac{dw_2}{d\tau} &= \frac{1}{t_w(v_2)} (w_\infty(v_2) - w_2),
\end{align*}
\]

(5.7)

with dimensionless parameters $\bar{I}_x = I_x/(Q_v \cdot g_{\text{max}})$, $\bar{g}_x = g_x/g_{\text{max}}$ and $\bar{V}_x = V_x/Q_v$.

Since we expect $V_i \in [-70, 60]$, a suitable choice for the voltage scale is $Q_v = 100 \, \text{mV}$. We also see that values of $m_\infty(V_i)$, $S(V_i)$, $w_\infty(V_i)$ and $w_i$ all lie in the range $[0, 1]$. For the choice of parameters specified in Table 5.3, the maximum conductance is $g_K$, so we have $g_{\text{max}} = g_K$. Numerical evaluation of $1/\tau_w(V_i)$ for $V_i \in [-70, 60]$
shows that $T_w \approx 5.5 \text{ms}^{-1} = O(10) \text{ms}^{-1}$. Using these values we see that all terms in the right hand sides of equations (5.7) are bounded (in absolute value) by one.

The coefficients of the derivatives in the left hand sides of equations (5.7) now reveal the relative rates of evolution of the variables. We find that $C_1/g_{\text{max}} \sim O(1) \text{ms}^{-1}$, $1/(\phi_1 T_w) \approx C_2/g_{\text{max}} \sim O(10) \text{ms}^{-1}$ and $1/(\phi_2 T_w) \sim O(100) \text{ms}^{-1}$, from which we conclude that $v_1$ evolves on a fast timescale, $w_1$ and $v_2$ evolve on a slow timescale, and $w_2$ evolves on a superslow timescale. We choose the slow timescale as a reference time, i.e. pick $Q_t = 10 \text{ms}$, and set

$$
\varepsilon_1 := \frac{C_1}{Q_t \cdot g_{\text{max}}} \ll 1,
\varepsilon_2 := \phi_2 Q_t T_w \ll 1,
$$

(5.8)

Then the dimensionless system (5.7) becomes the following singularly perturbed form:

$$
\varepsilon_1 \frac{dv_1}{d\tau} = \tilde{I}_1 - \tilde{g}_{\text{Ca}} m_{\infty}(v_1)(v_1 - \tilde{V}_{\text{Ca}}) - \tilde{g}_{\text{K}} w_1(v_1 - \tilde{V}_{\text{K}})
- \tilde{g}_{L}(v_1 - \tilde{V}_{L}) - \tilde{g}_{\text{syn}} S(v_2)(v_1 - \tilde{V}_{\text{syn}}) := f_1(v_1, v_2, w_1)
$$

$$
\frac{dw_1}{d\tau} = R_{w_1} \frac{1}{t_w(v_1)}(w_{\infty}(v_1) - w_1) := g_1(v_1, w_1)
$$

$$
\frac{dv_2}{d\tau} = R_{v_2}(\tilde{I}_2 - \tilde{g}_{\text{Ca}} m_{\infty}(v_2)(v_2 - \tilde{V}_{\text{Ca}}) - \tilde{g}_{\text{K}} w_2(v_2 - \tilde{V}_{\text{K}})
- \tilde{g}_{L}(v_2 - \tilde{V}_{L})) := f_2(v_2, w_2)
$$

$$
\frac{dw_2}{d\tau} = R_{v_2} \frac{1}{t_w(v_2)}(w_{\infty}(v_2) - w_2) := \varepsilon_2 g_2(v_2, w_2),
$$

(5.9)

with independent small parameters $\varepsilon_1$ and $\varepsilon_2$. Both $R_{w_1}$ and $R_{v_2}$ are dimensionless parameters bounded by one. The values of $\varepsilon_1$ and $\varepsilon_2$ can be varied by changing $C_1$ and $\phi_2$, respectively. The timescale separation remains the same as in (5.9) as long as $g_{\text{syn}} \leq g_K = 8 \text{mS/cm}^2$. When $g_{\text{syn}} > g_K$, $g_{\text{max}} = g_{\text{syn}}$ instead of $g_K$, in which case we might get a different result about the timescale of each variable.

### 5.2.2 GSPT Analysis

To study the underlying mechanism for each time series shown in Figure 5.11, we use the same technique as for the food chain model in Chapter 4 adapted slightly to allow for the higher dimension of the system in this chapter. The singularly perturbed system (5.9) is evolving on the slow time $\tau$. Replacing the time variable $\tau$ by $t_s$, we
5.2 The Four-Dimensional Coupled System

see that system (5.9) has the form

\[
\begin{align*}
\varepsilon_1 \frac{d v_1}{d t_s} &= f_1(v_1, v_2, w_1) \\
\frac{d w_1}{d t_s} &= g_1(v_1, w_1) \\
\frac{d v_2}{d t_s} &= f_2(v_2, w_1) \\
\frac{d w_2}{d t_s} &= \varepsilon_2 g_2(v_2, w_1), \\
\end{align*}
\]

where \( f_1, g_1, f_2 \) and \( g_2 \) are \( O(1) \) functions and \( \varepsilon_1 \) and \( \varepsilon_2 \) are small parameters.

Introducing a superslow time \( t_{ss} = \varepsilon_2 t_s \), which changes slowly relative to \( t_s \), yields the following evolution system on the superslow timescale, \( t_{ss} \):

\[
\begin{align*}
\varepsilon_1 \varepsilon_2 \frac{d v_1}{d t_{ss}} &= f_1(v_1, v_2, w_1) \\
\frac{d w_1}{d t_{ss}} &= g_1(v_1, w_1) \\
\frac{d v_2}{d t_{ss}} &= f_2(v_2, w_1) \\
\frac{d w_2}{d t_{ss}} &= \varepsilon_2 g_2(v_2, w_2), \\
\end{align*}
\]

(5.11)

Alternatively, defining a fast time \( t_f = t_s / \varepsilon_1 \), which changes quickly relative to \( t_s \), gives a system evolving on the fast timescale, \( t_f \):

\[
\begin{align*}
\frac{d v_1}{d t_f} &= f_1(v_1, v_2, w_1) \\
\frac{d w_1}{d t_f} &= \varepsilon_1 g_1(v_1, w_1) \\
\frac{d v_2}{d t_f} &= \varepsilon_1 f_2(v_2, w_2) \\
\frac{d w_2}{d t_f} &= \varepsilon_1 \varepsilon_2 g_2(v_2, w_2), \\
\end{align*}
\]

(5.12)

There are several possible singular limits that can be taken in systems (5.10)-(5.12). Fixing \( \varepsilon_2 > 0 \) and taking \( \varepsilon_1 \to 0 \) in system (5.12) yields a one-dimensional layer problem that describes the dynamics of the fast variable, \( v_1 \), for fixed values of the other variables. We call this limit the fast layer problem, and refer to the corresponding dynamics as the fast flow. We define the critical manifold \( S \) to be the manifold of equilibrium points of the fast layer problem, i.e.,

\[
S := \{(v_1, v_2, w_1, w_2) \in \mathbb{R}^4 : f_1(v_1, v_2, w_1) = 0\}. 
\]

(5.13)
Although $S$ is a three-dimensional manifold in the $(v_1, v_2, w_1, w_2)$ space, it does not depend on $w_2$. We can solve $f_1(v_1, v_2, w_1) = 0$ for $w_1$ as a function of $v_1$ and $v_2$ and can therefore represent $S$ as

$$w_1 = F_1(v_1, v_2)$$

for a function $F_1$. This relation allows us to readily visualize the projection of $S$ onto the $(v_1, v_2, w_1)$-space.

Taking the same limit, i.e., $\varepsilon_1 \to 0$ with $\varepsilon_2 > 0$, in system (5.10) yields a system that describes the dynamics of $w_1, v_2, w_2$ restricted to the surface $S$. We call this system the slow reduced problem. By differentiating (5.14), we can write down the desingularised slow reduced problem as follows:

$$\frac{dv_1}{d\tau_s} = g_1 - \frac{\partial F_1}{\partial v_2} f_2 := h(v_1, v_2, w_2)$$
$$\frac{dv_2}{d\tau_s} = \frac{\partial F_1}{\partial v_1} f_2(v_2, w_2)$$
$$\frac{dw_2}{d\tau_s} = \varepsilon_2 \frac{\partial F_1}{\partial v_1} g_2(v_2, w_2)$$

(5.15)

where $\tau_s = (\partial F_1/\partial v_1) t_s$. According to the analysis in section 2.2.2, the folded singularities on the fold surface of $S$ are defined as

$$FS := \{(v_1, v_2, w_1, w_2) \in \mathbb{R}^4 : \frac{\partial F_1}{\partial v_1} = 0 \text{ and } h(v_1, v_2, w_2) = 0\}.$$  

(5.16)

The slow reduced problem is itself a multiple timescale problem, since the slow and superslow timescales are still both present. It is convenient to further separate timescales by letting $\varepsilon_2 \to 0$ in the slow reduced problem. Doing so yields the slow layer problem which describes the dynamics of the slow variables $w_1$ and $v_2$ for fixed values of $w_2$, with all variables restricted to $S$. We refer to the corresponding dynamics as the slow flow.

Alternatively, fixing $\varepsilon_1 > 0$ and taking $\varepsilon_2 \to 0$ in system (5.10) or (5.12) yields a different layer problem from the one obtained in the preceding limit. We call the set of equilibrium points of this three-dimensional system the superslow manifold $SS$, defined by

$$SS := \{(v_1, v_2, w_1, w_2) \in S : g_1(v_1, w_1) = f_2(v_2, w_2) = 0\}.$$  

(5.17)

Note that $SS$ is a subset of $S$.

Taking the same limit in system (5.11), i.e., $\varepsilon_2 \to 0$ with $\varepsilon_1 > 0$, gives a system that describes the dynamics of $w_2$ restricted to $SS$. We call this system the superslow reduced problem and refer to the corresponding dynamics as the superslow flow.
From the discussion in sections 2.2 and 4.1, we know that the normally hyperbolic parts of $S$ (or $SS$) persist and perturb smoothly to nearby invariant manifolds as we increase $\varepsilon_1$ (or $\varepsilon_2$) from zero (Theorem 2.2.1). Therefore, we can use the information obtained from the singular limit to predict the dynamics of the full system with $\varepsilon_1, \varepsilon_2 \neq 0$. However, for regions where normally hyperbolicity is lost, such as at the folds of $S$ and $SS$, things may be more complicated; the discussion in section 2.2.2 indicates that if a solution reaches the fold of $S$ ($SS$) at a jump point, it will jump away following the fast flow (the slow flow); if the solution meets a FS, then depending on the type of this FS, maximal canards might be seen in the full system and accordingly, more complex phenomena may arise (Theorem 2.2.2).

With different $g_{syn}$ values, the shape of $S$ and $SS$ will be different, and the locations of the FS on $S$ and their types may change. Note that since the evaluations of $g_2$ at the folds of $SS$ are not equal to zero, according to section 2.2, the two folds of $SS$ are jump points. In the following sections, for each particular values of $g_{syn}$ that we have chosen, we will present analysis focused on the roles of $S$ and $SS$ in organising the flow of the full four-dimensional model. We also compute the FS (5.16) to see whether a selected solution will pass through a FS when it reaches the fold. If it is the case, further analysis will be performed to determine the dynamics of the full system.

Figure 5.12: The attracting trajectory (black) for system (5.4) with $g_{syn} = 1.0\,\text{mS/cm}^2$. The purple dot indicates the departure point from where the solution makes a fast excursion to the upper branch of $S$. The blue curves indicate the folds on $S$ and the red curves are the attracting (solid) and unstable (dashed) branches of the superslow manifold $SS$. 
model with $\varepsilon_1, \varepsilon_2 \neq 0$. Note that we did the nondimensionalisation of system (5.4) to reveal the timescale of each variable. However, for convenient comparison with the numerical simulations shown in Figure 5.11, the analysis below will be performed on system (5.4) directly rather than its nondimensionalisation.

**Oscillating Solutions at** $g_{\text{syn}} = 1.0$

When $g_{\text{syn}} = 1.0 \text{ mS/cm}^2$, the critical manifold $S$ has three branches. The outer branches are stable while the middle branch is unstable as shown in Figure 5.12. Recall that $S$ is a three-dimensional manifold in the full phase space and thus its folds should be two-dimensional surfaces. Figure 5.12 does not capture the structure of these two surfaces of folds, but they can be visualised in the $(w_2, V_2, V_1)$-space; see Figure 5.13. Within the two-dimensional fold surfaces, we find one-dimensional curves of folded singularities (FS). Plotting these curves shows that for $g_{\text{syn}} = 1.0 \text{ mS/cm}^2$, the solution trajectory always passes the folds at normal jump points [39, 40] rather than at a FS. Therefore, we can interpret the details of the time series shown in the

![Figure 5.13: Surfaces of folds on $S$ and the fold singularities (FS) located on each surface, at $g_{\text{syn}} = 1.0 \text{ mS/cm}^2$. The orange surface is the upper fold and the blue one is the lower fold. The red curves are the same branches of $SS$ shown in Figure 5.14; note that the solid curve lying within the lower branch of $S$ remains below the blue fold surface (see Figure 5.12). As previously, the solution trajectory is black; it jumps from the folds at normal jump points away from the FS curves. The FS curves are colour coded as follows: yellow, saddle FS; light green, source FS; orange, spiral source FS; pink, spiral sink FS; dark green, sink FS.](image-url)
5.2 The Four-Dimensional Coupled System

first panel of Figure 5.11 by comparing with the geometric structure of $S$ and $SS$.

Starting from the point marked with a purple dot in Figure 5.12, which has a relatively large $V_2$ coordinate and lies above the lower fold of $S$ in the $V_1$ direction, the solution follows the fast flow towards the upper branch of $S$. After this fast excursion, the solution moves with the slow flow along $S$ until it reaches the upper fold of $S$ (blue curve, Figure 5.12), from which it will jump on the fast timescale towards the lower branch of $S$. Within the lower branch of $S$, a branch of the superslow manifold $SS$ is attracting for the slow reduced problem, and thus the trajectory makes a long excursion on the lower branch of $S$ towards and then along $SS$ (solid red, Figure 5.12). Note that there are also two branches of $SS$ on the middle branch of $S$ (dashed red curves, Figure 5.12), but they do not influence the dynamics of interest here.

![Figure 5.14: Superslow manifold $SS$ (red curve) of system (5.4) at $g_{syn} = 1.0 \text{mS/cm}^2$. The solution trajectory (black curve) lands on the lower branch of the critical manifold $S$ at the blue point and is attracted by the stable part of the superslow manifold $SS$. The green point indicates the approximate point at which solution starts following $SS$. The two pictures at the bottom are projections on the $(V_2, V_1)$-plane and $(V_2, w_2)$-plane, respectively.](image-url)
To see how the dynamics is dominated by $SS$ on the lower branch of $S$ more clearly, we plot the trajectory and $SS$ in the $(V_1, V_2, w_2)$-space in Figure 5.14. When the trajectory (black curve) reaches the lower branch of $S$ (blue point in Figure 5.14), it is attracted by $SS$ (red curve). The trajectory moves along $SS$ (e.g., from the green point in Figure 5.14) under the superslow flow, until it reaches the fold of $SS$, from which it jumps on the slow timescale to the right stable branch of $SS$. Following this stable branch, the solution moves in a direction of decreasing $w_2$ (Figure 5.14 bottom right) until it reaches the lower fold of $SS$ and jumps back to large $V_2$ on the slow timescale. During this slow jump, $V_1$ keeps increasing, resulting in the solution crossing the fold of $S$ before it can be attracted by the left branch of $SS$. Then, the solution leaves the fold surface of $S$ and transitions to a fast jump towards the upper stable branch of $S$, and one period of the oscillation is completed.

The above discussion reveals the three timescales that contribute to the solution trajectory. The jumps between branches of $S$ are fast, and the excursions along $S$ are initially slow, but once the trajectory is in a neighbourhood of the attracting branch of $SS$, the third, superslow, timescale emerges. Figure 5.15 illustrates the timescales on which the solution evolves.

![Figure 5.15](image_url)

Figure 5.15: One period of the time series shown in the first panel of Figure 5.11. The evolution on fast, slow and superslow timescales are indicated in black, red and green, respectively. The intervals covered by the green bars are the periods that $V_2$ tracks $SS$.

**Oscillating Solutions at $g_{syn} = 4.1$**

In the discussion above, we saw that when $g_{syn} = 1.0$ mS/cm$^2$, three branches of $SS$ exist within $S$ for all $V_2$ values (Figure 5.12). By contrast, in the case $g_{syn} = 4.1$ mS/cm$^2$, there are just two branches of $SS$. One of them is on the middle surface of $S$ and one crosses from the lower surface of $S$ to the middle surface of $S$ (Figure 5.16). As for the previous case, we need to check the influence of the folded
5.2 The Four-Dimensional Coupled System

Figure 5.16: A three-dimensional projection of a trajectory (black) and the critical manifold $S$ of system (5.4) for $g_{syn} = 4.1 \text{mS/cm}^2$. The blue curves denote the folds on $S$, the red curves are the branches of the superslow manifold $SS$ within $S$.

Figure 5.17: Surfaces of folds on $S$ and the fold singularities (FS) located on each surface at $g_{syn} = 4.1 \text{mS/cm}^2$. The meaning of the surfaces and line styles are the same as in Figure 5.13.
singularities on the solution trajectory. Figure 5.17, which shows the attracting solution in the case $g_{syn} = 4.1 \text{ mS/cm}^2$ together with the FS curves, indicates the solution trajectory is not affected by any FS on $S$. Thus, every time the solution reaches the fold surface of $S$, it always meets a jump point. Consequently, the solution will jump from the fold following the fast flow.

The part of the lower branch of $SS$ which is located on the lower surface of $S$ is attracting. Thus, a trajectory starting on the lower branch of $SS$ on $S$ at the green point in Figure 5.16 will follow this branch up to the fold of $S$, from which it undergoes a jump to the upper surface of $S$ on the fast timescale, representing the onset of spikes in $V_1$. During the first period of $V_1$ spikes, $V_2$ increases slowly until reaching the purple point in Figures 5.16 and 5.18. Then $V_2$ increases rapidly (purple point to yellow point, Figure 5.18), and then decreases slowly (yellow point to blue

![Figure 5.18: An alternative three-dimensional projection of a trajectory (black) and the superslow manifold $SS$ (red curves) of system (5.4) for $g_{syn} = 4.1 \text{ mS/cm}^2$. The $V_2$ coordinate of the trajectory evolves on the superslow timescale from the green point to the purple point and from the yellow point to the blue point; and on the slow timescale from the purple point to the yellow point and from the blue point to the green point. The two pictures at the bottom are projections on the $(V_2,V_1)$-plane and $(V_2,w_2)$-plane, respectively.](image-url)
point) and then rapidly again (blue point to green point) until the spiking ends.

In Figure 5.18, we see that the periods of slow drift in $V_2$ occur when the trajectory tracks $SS$, while the more rapid changes in $V_2$ correspond to excursions away from $SS$. Thus, the former in fact occur on the superslow timescale and the latter on the slow timescale. Numerical calculations show that the branches of $SS$ are stable in the $V_2$ direction for $V_2 < -29.6$ and $V_2 > 10.9$ and unstable between these bounds in the limit $\varepsilon_2 \to 0$, and so the switches between superslow and slow rates of change of $V_2$ for the solution of the full system happen very close to these bounds. Figure 5.16 reminds us that the corresponding branch of $SS$ is not on the attracting surface of $S$; as a result, while $V_2$ is elevated or degrading slowly following $SS$, $V_1$ keeps oscillating until the solution can be attracted by the part of $SS$ which is located on the lower surface of $S$. The reason for this interesting phenomenon is that the $(V_1, w_1)$ subsystem is driven by the $(V_2, w_2)$ oscillator, and the $(V_2, w_2)$ plane is invariant in the coupled system. This forces the solution to track a branch of $SS$ that is stable within the $(V_2, w_2)$ plane but is unstable within the full system.

In summary, the oscillating solution at $g_{syn} = 4.1 \text{mS/cm}^2$ evolves on three different timescales. The spikes contain fast jumps between branches of $S$ and slow excursions along $S$. The slow jumps between branches of $SS$ bring the solution from one side of the critical manifold to another side, resulting in the solution changing from spiking with gradually decreasing amplitude to spiking with approximately constant amplitude, and then to the silent phase. During the silent phases, the solution is attracted by $SS$, and so evolves on the superslow timescale. The gradually decreasing amplitude in the phase of rapid spikes is also evidence of the superslow timescale since it is motion along the superslow manifold that changes the $V_2$ coordinate of the orbit during this phase. An illustration can be seen in Figure 5.19.

![Figure 5.19: One period of the time series shown in the second panel of Figure 5.11. The evolution on fast, slow and superslow timescales are indicated in black, red and green, respectively. The intervals covered by the green bars are the periods that $V_2$ tracks $SS$.](image)
Oscillating Solutions at $g_{\text{syn}} = 5.1$

When $g_{\text{syn}} = 5.1 \text{ mS/cm}^2$, a key new feature arises; a branch of $SS$ originally located on the middle surface of $S$ crosses onto the attracting upper surface of $S$ as $V_2$ increases (see Figure 5.20). Therefore, for large $V_2$ there exists a branch of $SS$ on the upper surface of $S$, and for small $V_2$ there exists a branch of $SS$ on the lower surface of $S$. Figure 5.21 shows the relative positions of the FS curves and the solution trajectory in the $(w_2, V_1, V_2)$-space. Although some of the jump points appear to be close to the curve of FS, closer inspection shows that the solution always jumps at normal jump points on the fold surfaces, and so its behaviour is not affected by folded singularities.

In this case, while the onset of $V_1$ spiking is quite similar to what occurs for $g_{\text{syn}} = 4.1 \text{ mS/cm}^2$, once $V_2$ jumps up to the upper branch of $S$ from the purple point in Figure 5.20 and 5.22 (due to $V_2$ falling off the right branch of $SS$; see Figure 5.22, bottom right), the trajectory converges to a neighbourhood of the stable branch of $SS$ within the upper surface of $S$. This convergence yields the depolarised voltage plateaus evident in the time series in Figure 5.11.

Figure 5.22 shows the solution trajectory with branches of $SS$ in the $(V_1, V_2, w_2)$-space. Once the solution reaches the branch of $SS$ on the upper surface of $S$ (which occurs when the value of $V_2$ reaches its maximum), it tracks along $SS$ (with decreasing $V_2$) until it reaches a fold of $SS$ (the blue point in Figure 5.22), from where it jumps on...
the slow timescale and meets the fold of $S$ (refer to Figure 5.21, the orange surface), then it jumps on the fast timescale to the lower surface of $S$ and is attracted to a branch of $SS$ within that surface, near the green point in Figure 5.22. Then another cycle of the periodic solution begins.

Therefore, the oscillating solution at $g_{\text{syn}} = 5.1 \text{mS/cm}^2$ evolves on three distinct timescales. As indicated in Figure 5.23, the spikes contain fast jumps between branches of $S$ and slow excursions along $S$, but once the solution trajectory is close to the attracting branches of $SS$, it starts evolving on the superslow timescale.

### 5.2.3 Folded Singularities

With the three specified $g_{\text{syn}}$ values chosen here, the dynamics of the attracting solutions of system (5.4) do not appear to be significantly affected by any folded singularities, and so we do not need to consider the details of the FS in order to understand the time series of interest. However, in general, FS are important and worth careful consideration.

In the case of three-dimensional systems, FS are isolated and it was shown in Chapter 4 that these FS are folded saddle-node but neither Type I nor Type II. In the case of four-dimensional systems, there are more possibilities for the types of FS.
Figure 5.22: An alternative three-dimensional projection of a trajectory (black) and branches of the superslow manifold $SS$ (red curves) of system (5.4) for $g_{\text{syn}} = 5.1 \text{mS/cm}^2$. At the bottom are the projections on the $(V_2, V_1)$-plane and $(V_2, w_2)$-plane, respectively. The $V_2$ coordinate of the trajectory evolves on the superslow timescale from the green point to the purple point, while slow excursions begin at the purple and blue points. Note that the trajectory tracks $SS$ while $V_2$ is elevated.

Figure 5.23: Time series shown in the last panel of Figure 5.11. The evolution on fast, slow and superslow timescales are indicated in black, red and green, respectively. The intervals covered by the green bars are the periods that $V_2$ tracks $SS$. 
5.3 Discussion

In systems with one fast, two slow and one superslow variable (like system (5.4)), FS generically are not isolated but occur on one-parameter curves. Folded saddle-node can occur within these one-parameter curves but generically do so at isolated points. Specifically, where a section of folded saddles turns into a section of folded nodes (e.g., at the meeting points between the yellow and the light green curves in Figure 5.13, 5.17, and 5.21). A comprehensive theory of FS in three timescale curves still needs to be developed; here, for comparison with section 4.4, we just consider the folded saddle-node in system 5.4.

As mentioned before (section 5.2.2), the FS of the coupled M-L system (5.4) are defined by (5.16). From system (5.15), in the singular limit \( \varepsilon_2 \rightarrow 0 \), the folded saddle-node points can be identified by considering the Jacobian matrix:

\[
A := \begin{pmatrix}
\frac{\partial h}{\partial v_1} & \frac{\partial h}{\partial v_2} \\
\frac{\partial}{\partial v_1} \left( \frac{\partial F_1}{\partial v_1} f_2 \right) & \frac{\partial}{\partial v_2} \left( \frac{\partial F_1}{\partial v_1} f_2 \right)
\end{pmatrix},
\]

and setting its determinant to zero. Since

\[
\det(A) = f_2 \left( \frac{\partial h}{\partial v_1} \cdot \frac{\partial}{\partial v_2} \left( \frac{\partial F_1}{\partial v_1} f_2 \right) - \frac{\partial h}{\partial v_2} \cdot \frac{\partial}{\partial v_1} \left( \frac{\partial F_1}{\partial v_1} f_2 \right) \right) := f_2 \cdot K,
\]

a folded saddle-node point occurs either at \( f_2 \) or \( K = 0 \). Note that \( K \) represents all the terms in the brackets of the right hand side of equation (5.19). The former case corresponds to an intersection of the superslow manifold \( SS \) and the fold surface of \( S \). Recall that the isolated FS discussed in section 4.4 belongs to this case. The latter case corresponds to folds on the FS curve. For details, refer to [66]. Note that in the perturbed systems with \( \varepsilon_1, \varepsilon_2 > 0 \), the locations of the folded saddle-nodes may shift. Hence, in Figures 5.13, 5.17, and 5.21, the folded saddle-nodes occur close to but neither at the folds on the FS curve nor at the intersection of \( SS \) and the fold surface of \( S \). Different from the case discussed in section 4.4, in the point of view that Type I folded saddle-node is corresponding to the coalescence of a folded saddle and a folded node, the folded saddle-node points obtained from both of these two sorts are Type I.

5.3 Discussion

We have studied the dynamics of system (5.4)-(5.5) with three specified \( g_{\text{syn}} \) values. It was shown that all these oscillations evolve on three distinct timescales and that the geometric structure and the stability of the critical manifold and superslow manifold
are crucial to the solution behaviour. The solutions obtained by using these three $g_{syn}$ values are representative cases for an interval of $g_{syn}$. As $g_{syn}$ varies, the transition of solutions through some bifurcation values from one type to another can be observed. We conjecture that these bifurcations correspond to the change of positions of $SS$ relative to the fold of $S$. Although we will not discuss this in the thesis, the transition induced by varying $g_{syn}$ is definitely worth further study.
Chapter 6

Intrinsic Three Timescale Phenomena

In the previous chapters, we have considered some different types of oscillations seen in several systems with three timescales. From a mathematical point of view, all of these oscillations evolve on three timescales. In this chapter, we would like to identify which types of these observed solutions are intrinsically three timescale phenomena and which could be adequately explained by existing theory for two timescale systems. A discussion of this is contained in sections 6.1-6.3. Then, in section 6.4, we apply GSPT to the six-dimensional GnRH neuron model to investigate the mechanism underlying the small wiggles seen in the time series for variable $c$ in Figure 3.8, and to identify the intrinsic timescales involved in typical bursting solutions of the GnRH neuron model.

6.1 The Food Chain Model

Recall that the food chain model discussed in Chapter 4 is a system with three distinct timescales; the bursting oscillation observed in this model (see Figure 4.1) evolves on three timescales. In section 4.3, we constructed a canonical model to reproduce this kind of oscillation and then obtained a more general solution as shown in the lower panel of Figure 4.14. This bursting solution results from a similar mechanism to that for the food chain model.

The active phases of the bursting solutions shown in Figure 4.1 and Figure 4.14 evolve on the fast and slow timescales, respectively and the silent phases evolve on slow and superslow timescales. However, the timescale differences are not clearly visible in the time series, which casts doubt on whether the bursting solution is an intrinsic three timescale phenomenon. Moreover, similar oscillations are observed in systems with two timescales. For instance, the bursting solutions of the Hindmarsh-
Figure 6.1: Time series of each variable in the Hindmarsh-Rose model, equations (6.1) with parameters as in Table 6.1. The oscillatory behaviour is similar to the oscillation seen in the food chain model, Figure 4.1. Small wiggles can be seen in the \( z \) time series.

The Hindmarsh-Rose model \([24]\), which is a reduction of the Hodgkin-Huxley model, describes the qualitative bursting behaviour of a class of neurons. The equations of the model are as follows:

\[
\begin{align*}
\frac{dx}{dt} &= y - ax^3 + bx^2 - z + I := f_1(x, y, z) \\
\frac{dy}{dt} &= c - dx^2 - y := f_2(x, y) \\
\frac{dz}{dt} &= \varepsilon (s(x - x_0) - z) := \varepsilon g(x, z),
\end{align*}
\]

where the variable \( x \) represents the voltage across the cell membrane, and \( y, z \) are gating variables that describe the activation or inactivation of some current(s). Since the rate of change of variable \( z \) is \( O(\varepsilon) \) with \( \varepsilon \ll 1 \), the HR model is a system with two timescales, i.e., \((x, y)\) are the fast variables while \( z \) is the slow variable. The

<table>
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<th>Parameter values of the HR model</th>
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Table 6.1: Parameter values for the HR model, equations (6.1).
values for other parameters are fixed as in Table 6.1.

In the layer problem of (6.1), $\varepsilon = 0$, and so the slow variable $z$ can be treated as a constant. System (6.1) with a fixed $z$ value is called *frozen*, and as a consequence, we can plot a ‘bifurcation diagram’ with $z$ being the bifurcation parameter; see Figure 6.2. The branch of equilibrium points of the frozen problem is equivalent to the critical manifold defined by $S := \{(x, y, z) \in \mathbb{R}^3 : f_1 = f_2 = 0\}$, and is shown in black and red in Figure 6.2. From the picture, we can see that the equilibrium solutions form a cubic-shaped curve, where the lower branch is stable, the middle branch is of saddle type, and the upper branch surrounded by a family of periodic solutions is unstable. In the region bounded by the left saddle-node bifurcation and the homoclinic bifurcation, a stable periodic orbit and a stable equilibrium coexist. This bistable structure is essential to the bursting solutions shown in Figure 6.1. Thus, we magnify this region in Figure 6.3 and superimpose the solution trajectory for the full problem, equation (6.1) with $\varepsilon \neq 0$.

In the full system, $\varepsilon \neq 0$, so $z$ can vary. During the silent phase of the bursting solution, the solution trajectory stays close to the lower attracting branch of the critical manifold. Since this region is below the $z$-nullcline (shown in green in Figure

![Figure 6.2: Bifurcation diagram of the frozen version of the HR model, equations (6.1) with $\varepsilon = 0$ and constant $z$. Parameters are given by Table 6.1. Variable $z$ is treated as the bifurcation parameter. The stable and unstable equilibrium solutions are indicated by the black curves and red dashed curves, respectively. The blue curves show the maximum and minimum $V$-coordinates of the stable periodic solutions that arise from the supercritical Hopf bifurcation (HB) at $z \approx -10.59$. The other HB, at $z \approx 1.93$, is not important to the bursting solution studied here. The labels HC and SN means homoclinic bifurcation and saddle-node bifurcation, respectively.](image)
Intrinsic Three Timescale Phenomena

Figure 6.3: A magnification of the bifurcation diagram in Figure 6.2 with the solution (in purple) shown in Figure 6.1 superimposed. The green line is the $z$-nullcline of system (6.1) indicates where $dz/dt = 0$. Above the green line, $dz/dt > 0$ and below the green line, $dz/dt < 0$.

6.3), $dz/dt < 0$. The trajectory, therefore, moves leftward until the saddle-node bifurcation point (labeled by SN in Figure 6.3) is reached, and then is attracted by the stable periodic branch, initiating the active phase of the bursting. The periodic branch is above the $z$-nullcline, where $dz/dt > 0$, and so the solution trajectory moves rightward as it oscillates. Once the solution reaches the homoclinic bifurcation which is associated with a saddle point on the middle branch of the critical manifold, the active phase of the bursting solution terminates. The solution is then attracted by the lower branch of the critical manifold and the silent phase of the bursting is restarted. For details refer to [56, 57]. According to the bursting classification [18, 27, 51], the bursting solution of the HR model shown in Figure 6.1 is called square-wave bursting. The small wiggles in the time series of variable $z$ are caused by variation in the speed of increase in $z$ during the oscillations within the burst.

Comparing Figure 6.3 with the upper panel in Figure 4.14, which is a more general case describing bursting in the food chain model, we find there is no major qualitative difference between these two cases. If we rescale one of the fast variables in the HR model, say $x$, such that $x$ evolves much faster than the other fast variable $y$, then the dynamics of the new system will be essentially the same as in the three-dimensional canonical system (4.46) with parameters in Table 4.2. Conversely, if we rescale the fast and slow variables in the three timescale system (4.46) such that they evolve on the same timescale which is much faster than the superslow timescale, then the
three timescale bursting oscillations seen in Figure 4.14 will become square-wave bursting. Experimentally, it is very hard to identify timescale differences during the active phase of a bursting solution and it may not be feasible to distinguish whether the system underlying a particular time series possesses two timescales or three. According to the principle the simpler the better, there is therefore no need to construct a three timescale model in order to capture this phenomenon. Therefore, we will not classify the bursting in the food chain model, shown in Figure 4.1 or 4.14, as an intrinsically three timescale phenomenon.

6.2 Three-Dimensional Canonical Model

Recall that the three-dimensional canonical system (4.46) generates a different type of bursting from the one shown in Figure 4.14 if we change the value of $\alpha_2$ from $0.65$ to $0.59$; see Figure 6.4. The active phases of this bursting contain large amplitude spikes and small amplitude oscillations. The large amplitude spikes evolve on the fast and slow timescales and the small amplitude oscillations occur when the solution trajectory is in the vicinity of the folded singularity. The silent phases of the bursting evolve on slow and superslow timescales. Unlike the bursting discussed in the previous section, the timescale differences within the silent phase can be clearly seen from the time series.

The superslow manifold, which is crucial to the bursting solution, is a cubic-shaped curve with a stable upper branch and a saddle type middle branch as shown in Figure 6.4. If similar bursting can be generated by a two timescale system which has two fast variables $(x, y)$ and one slow variable $z$, then based on the analysis in the previous section, we would expect that the critical manifold of this two timescale system, i.e., the branch of equilibrium points of its corresponding frozen system, is like the superslow manifold shown in Figure 6.4. There might be a point on the lower branch of the critical manifold at which there is a supercritical Hopf bifurcation, such that the unstable part of the lower manifold is surrounded by a branch of stable periodic solutions, as in the case of square-wave bursting. Such a structure is illustrated in Figure 6.5.

For a two timescale system corresponding to Figure 6.5, the solution of the full system would follow the upper branch of the critical manifold and move rightward until the right fold on the critical manifold, i.e., the saddle-node bifurcation, and then fall into the oscillating region enclosed by the stable periodic solutions, thereby starting the active phase. As the solution oscillates, it would move leftward slowly until it met a bifurcation that could terminate the oscillations. This bifurcation cannot be a homoclinic bifurcation as for square-wave bursting, because the stability
Figure 6.4: A bursting solution for system (4.46) with $\alpha_2 = 0.59$ and other parameters as in Table 4.2. Upper: projection onto the $(z, x)$-plane. The red curve is the superslow manifold, whose attracting parts are indicated by thick solid lines and repelling parts are shown by dashed lines. The black curve is the bursting solution. Its active phase contains large amplitude oscillations (LA) and small amplitude oscillations (SA). The green dot is the folded singularity. Lower: time series for the bursting solution.

of the critical manifold must also change. The most likely situation is that there exists a supercritical Hopf bifurcation of the frozen system. Once the solution passes this Hopf bifurcation, the active phase would be terminated and the solution trajectory would then follow the stable lower branch of equilibrium points, moving leftward to the left saddle-node bifurcation as shown in Figure 6.5.

When the two fast variables $(x, y)$ evolve on similar timescales, the supercritical Hopf bifurcation is regular, and so the amplitude of periodic solutions of the fast subsystem will tend to zero gradually as $z$ tends to the bifurcation point. As a result, the spikes in the active phase will disappear with a gradually decreasing amplitude, giving the bursting as shown in the lower panel of Figure 6.5. The clear separation of the large amplitude spike and small amplitude oscillations seen in Figure 6.4, therefore, could not be generated.
Figure 6.5: An example shows bursting solution that enters the active phase via a saddle-node bifurcation and ends the active phase via a supercritical Hopf bifurcation. Upper: the structure of the bifurcation diagram of the fast subsystem, equations for \( x \) and \( y \) only. The slow variable \( z \) is treated as the bifurcation parameter. The blue curves indicate the maximum and minimum \( V \)-coordinates of the stable periodic solutions. The remaining line styles have the same meaning as for Figure 6.4. Lower: the bursting generated by the mechanism shown in the upper panel.

However, in the case that the supercritical Hopf bifurcation is singular, the amplitude of the periodic orbit will decrease rapidly as \( z \) nears the bifurcation value. Then bursting that is similar to that shown in Figure 6.4 can be produced. But the existence of a singular Hopf bifurcation implies a separation of timescales within the fast subsystem. That is, one of the fast variables, say \( x \), would have to evolve much faster than the other fast variable \( y \). Since both \((x, y)\) are faster than \( z \), this would mean that there were in fact three timescales in the system. In other words, to generate the bursting solution shown in Figure 6.4, the canonical system (4.46) has to involve three different timescales. Thus, we classify this type of bursting as an intrinsic three timescale phenomenon.
6.3 Four-Dimensional Coupled Model

With three particular choices of $g_{syn}$, the four-dimensional coupled M-L model (5.4) introduced in section 5.2 exhibits oscillations with three timescales; see Figure 5.11. In this section, we discuss whether these oscillations are intrinsically three timescale or not.

6.3.1 Oscillating Solutions at $g_{syn} = 1.0$

We have already shown in section 5.2.2 that the oscillation generated by system (5.4) with $g_{syn} = 1.0 \text{mS/cm}^2$ evolves on three timescales. In this section, we rescale system (5.4) such that it becomes a system with two distinct timescales, and then we compare the solution (shown in the first panel of Figure 5.11) with the one generated by the two timescale system at the same $g_{syn}$ value. There are many ways to group the timescales in the four-dimensional system (5.4). One of the most natural ways arises from slowing the fast variable $V_1$ to make the system contain three slow variables $(V_1, w_1, V_2)$ and one superslow variable $w_2$. Although in this case, the slow and superslow timescales could be relabelled as fast and slow, to avoid ambiguity, we will not do so. Another natural grouping is to speed up the superslow variable $w_2$ so that we get a system with one fast variable $V_1$ and three slow variables $(w_1, V_2, w_2)$.

We will not group the four-dimensional system such that it has two fast variables and two slow variables. That is because setting $(V_1, V_2)$ as fast variables and $(w_1, w_2)$ as slow variables deviates from our original intention of making system (5.4) a slow oscillator driving fast oscillations. More specifically, comparing with the dimensionless form (5.12), this means the loss of $\varepsilon_1$ in the equation for $v_2$ and the loss of $\varepsilon_2$ in the equation for $w_2$. On the other hand, setting $(V_1, w_1)$ as fast variables and $(V_2, w_2)$ as slow variables leads to the disappearance of the relaxation oscillations in

![Figure 6.6](image_url)

Figure 6.6: Time series of system (5.4) at $g_{syn} = 1.0 \text{mS/cm}^2$ with exaggerated timescale separation. The parameters are as in Table 5.3, except $C_1 = 0.8 \mu\text{F/cm}^2$ and $\phi_2 = 0.0001$. 
both subsystems. Comparing with the dimensionless form (5.12), it means the loss of $\varepsilon_1$ in the equation for $w_1$ and the loss of $\varepsilon_2$ in the equation of $w_2$. Since both settings will destroy the behaviour of the solutions shown in Figure 5.11, it is unnecessary to group (5.4) as a system with two fast and two slow variables.

Recall that the timescales of variables $V_1$ and $w_2$ can be varied by altering $C_1$ and $\phi_2$, respectively. With the purpose of emphasising the features that rely on timescale separation, we make the timescales more distinct by a factor of ten in system (5.4), i.e., let $C_1 = 0.8 \mu F/cm^2$ and $\phi_2 = 0.0001$. These new parameter values will also be used in sections 6.3.2-6.3.3 and be summarised in Table 6.2. We then plot the oscillating solution at $g_{\text{syn}} = 1.0 \text{mS/cm}^2$ in Figure 6.6. The time series for $V_1$ is then characterised by a large spike, followed by a bulge which has a plateau at the top, and a period of near steady-state behaviour. Comparing Figure 6.6 with the first panel in Figure 5.11, we see that when the timescales in the system are more distinct, both the plateau part of the bulge and the near steady-state period become longer. These durations are determined by the superslow timescale.

To see the effect of this change on the solution trajectory, we project the solution onto the $(w_2, V_2, V_1)$-space, as we did in Figure 5.13; see Figure 6.7. Note that the purple point, which denotes the beginning of a fast jump after a slow jump from the fold point of the superslow manifold, has a smaller $V_2$-coordinate compared with that in Figure 5.13. This is because the speed along the $V_1$ direction is increased.

![Figure 6.7: The solution trajectory (black curve) shown in Figure 6.6 projected onto the $(w_2, V_2, V_1)$-space. The meaning of the surfaces and line styles are the same as in Figure 5.13.](image-url)
resulting in the solution reaching the fold of the critical manifold (the blue surface in Figure 5.13 and 6.7) sooner after it leaves the superslow manifold. Conversely, if we slow the speed of $V_1$, then the jump at the fold point of the superslow manifold becomes more gradual and the solution needs longer to reach the fold of the critical manifold. In this case, the solution may be attracted by the other stable branch of the superslow manifold, forming a slow-superslow oscillation rather than a three timescale oscillation. The two timescale system with three slow variables and one superslow variable, which is obtained by slowing the variable $V_1$, belongs to this situation, as explained below.

To get the two timescale system with three slow and one superslow variable, we use $\phi_2 = 0.0001$ as for Figures 6.6 and 6.7 and let $C_1 = 80 \mu F/cm^2$. The solution generated at $g_{syn} = 1.0 \text{mS/cm}^2$ will follow one of the attracting parts of $SS$ to the fold point, from where it jumps to the other attracting part, as shown in Figure 6.8. Now the solution performs relaxation oscillations based on a branch of $SS$ (the red curve underneath the blue surface in Figure 6.8), and the large spike in the time series of $V_1$ for the case of three timescales will disappear, resulting in a time series as shown in Figure 6.9. It appears that to ensure the solution reaches the blue fold surface to initiate the large spike in the time series, $V_1$ must be significantly faster.
Figure 6.9: Time series of system (5.4) with three slow variables and one superslow variable, at $g_{syn} = 1.0\,\text{mS/cm}^2$. The other parameters are as in Table 5.3, except $C_1 = 80\,\mu\text{F/cm}^2$ and $\phi_2 = 0.0001$.

than variables $(w_1, V_2)$. That is, the two timescale system with three slow and one superslow variable does not appear to be able to generate a solution similar to the three timescale oscillations shown in the first panel of Figure 5.11 (or in Figure 6.6).

With the choice of parameters $C_1 = 0.8\,\mu\text{F/cm}^2$ and $\phi_2 = 0.01$, system (5.4) becomes a two timescale system with one fast variable $V_1$ and three slow variables $(w_1, V_2, w_2)$. In Figure 6.10, we plot the time series of this system at $g_{syn} = 1.0\,\text{mS/cm}^2$. From the previous analysis, we expect that the large spikes can be produced in the time series of $V_1$ since $V_1$ is faster than other variables. However, we observe that the plateau at the top of the bulge that follows the large spike no longer exists. The reason is as follows. System (5.4) now only has two timescales. The critical manifold $S$ projected onto the $(w_1, V_2, V_1)$-space is exactly the same as shown in Figure 5.12, and has three branches, divided by two folds; the outer branches are stable and the middle branch is unstable. There is no superslow manifold any more. Hence, when the solution moves along the lower branch of the critical manifold, it

Figure 6.10: Time series of system (5.4) with one fast and three slow variables, at $g_{syn} = 1.0\,\text{mS/cm}^2$. The rest of the parameters are as in Table 5.3, except $C_1 = 0.8\,\mu\text{F/cm}^2$ and $\phi_2 = 0.01$. 


only evolves on a slow timescale.

In order to compare with Figure 6.7 and 6.8, we project the solution onto the \((w_2, V_2, V_1)\)-space, as shown in the upper panel of Figure 6.11. The solution arrives at the lower branch of the critical manifold \(S\) at the blue point, from where it moves slowly following the lower branch to the fold of \(S\) (the blue surface). Since the solution reaches a normal jump point on the fold surface, it then leaves the fold, initiating a fast jump from the purple dot to the upper stable branch of the critical manifold \(S\). The red curves in Figure 6.11 show the positions of the superslow manifold \(SS\) of (5.4) when it is a three timescale system. These curves have no special significance for the two timescale version of the system but are shown in Figure 6.11 to demonstrate

![Figure 6.11: Upper: the projection of the solution trajectory (black curve) generated by system (5.4) with one fast and three slow variables \((C_1 = 0.8 \mu F/cm^2 \text{ and } \phi_2 = 0.01)\) onto the \((w_2, V_2, V_1)\)-space. The meaning of the surfaces and line styles are the same as in Figure 5.13. Lower: projection of the solution shown in the upper panel and the superslow manifold onto the \((V_2, w_2)\)-plane.](image)
that the motion of the solution trajectory is independent of them, unlike the situation where there are three timescales. The independence between the solution and $SS$ can be seen more clearly in the lower panel of Figure 6.11, in which the solution and the manifold $SS$ are projected together onto the $(V_2, w_2)$-plane. Comparing this picture with the third panel of Figure 5.14, we can see that after the blue point, the solution will not be trapped by the superslow manifold, and so it cannot form a plateau in the time series of $V_1$. Therefore, the loss of the plateau at the top of each bulge in the time series of $V_1$ is due to the absence of the superslow timescale.

In summary, neither of these two timescale systems captures the full features of the oscillating solution generated by system (5.4) at $g_{syn} = 1.0 \text{ mS/cm}^2$ with other parameters as in Table 5.3, shown in the first panel of Figure 5.11. Since a two timescale system will either lose the large spikes in the $V_1$ time series or will miss the plateaus at the top of the bulges following the large spikes, it appears that to produce the solution shown in the first panel of Figure 5.11, system (5.4) must have three distinct timescales. We therefore classify the solution shown in Figure 5.11 with $g_{syn} = 1.0 \text{ mS/cm}^2$ as an intrinsically three timescale phenomenon.

### 6.3.2 Oscillating Solutions at $g_{syn} = 4.1$

Figure 6.12 shows a time series for system (5.4) with $g_{syn} = 4.1 \text{ mS/cm}^2$, $C_1 = 0.8 \mu\text{F/cm}^2$, $\phi_2 = 0.0001$ and other parameters as in Table 5.3. This choice of parameter values gives a larger separation of timescales than those used to produce the corresponding time series in Figure 5.11. Comparing the $V_1$ time series in Figure 6.12 with the one shown in the second panel of Figure 5.11, we can see the number of the spikes increases dramatically and the silent phase following each cluster of spikes is longer for the new choice of $C_1$ and $\phi_2$. This is because the duration that $V_2$ tracks the stable superslow manifold becomes much longer when the timescales

| Values of $C_1$ and $\phi_2$ for different systems |
|---------------------------------|-----------------|
| three distinct timescales       | $C_1 = 0.8 \mu\text{F/cm}^2$, $\phi_2 = 0.0001$ |
| three slow                     | $C_1 = 80 \mu\text{F/cm}^2$, $\phi_2 = 0.0001$ |
| one superslow                  | $C_1 = 0.8 \mu\text{F/cm}^2$, $\phi_2 = 0.01$ |
| one fast                       | $C_1 = 0.8 \mu\text{F/cm}^2$ |

Table 6.2: The values of $C_1$ and $\phi_2$ used for system (5.4) with different timescale separations.
Figure 6.12: Time series of system (5.4) at $g_{\text{syn}} = 4.1 \text{mS/cm}^2$ with exaggerated timescale separation. The parameters are as in Table 5.3, except $C_1 = 0.8 \mu\text{F/cm}^2$ and $\phi_2 = 0.0001$.

are more separated. However, the qualitative behaviour of the oscillation does not change. Similarly to the second panel of Figure 5.11, each cluster of spikes in the $V_1$ time series in Figure 6.12 can be divided into two parts; one part contains spikes with gradually decreasing amplitudes and the other part contains spikes with nearly constant amplitudes. As discussed in section 5.2.2, the change of the amplitude of the first group of spikes is due to the geometric shape of the critical manifold $S$. However, when the solution trajectory moves to the other end of $S$ after a jump on

Figure 6.13: The projection onto the $(w_1, V_2, V_1)$-space of the solution trajectory (black curve) shown in Figure 6.12 and the critical manifold of system (5.4) with $g_{\text{syn}} = 4.1 \text{mS/cm}^2$. The meaning of the surfaces and line styles are the same as in Figure 5.12.
the slow timescale, the group of spikes with almost identical amplitude is formed. In Figure 6.13, the solution with more distinct timescales is superimposed on the critical manifold $S$. This figure confirms that the mechanisms underlying the form of the solution do not change.

The discussion in section 5.2.2 shows that solutions shown in Figure 5.11 (second panel) and 6.12 evolve on three timescales. To show this behaviour is intrinsic, we rescale the timescales in system (5.4) such that it becomes a two timescale model, and check whether or not features of the time series are lost, just as we did in the previous section.

With $C_1 = 80 \mu F/cm^2$, $\phi_2 = 0.0001$ and other parameters as in Table 5.3, system (5.4) becomes a two timescale system with three slow variables $(V_1, w_1, V_2)$ and one superslow variable $w_2$. The superslow manifold $SS$ of the three timescale problem is the critical manifold of this system. A time series of the new system is given in Figure 6.14. Comparing Figure 6.14 and Figure 6.12, we see that the original group of spikes with similar amplitude disappears and is replaced by small oscillations that taper off to a plateau. In Figure 6.15, we project the solution onto the $(w_1, V_2, V_1)$-space. Besides $SS$ (the red curves), the critical manifold $S$ for the three timescale problem (the coloured surface) is also shown. It can be seen clearly that the solution of the two timescale system does not follow the coloured manifold; as a result, the amplitude of the large spikes in the time series of the three timescale problem will shrink. Recall that the manifold $SS$ consists of two branches. When system (5.4) is a three timescale model, one of these branches is located on the middle branch of the manifold $S$, and so contributes little to the dynamics of the three timescale oscillation. In the case of two timescales with three slow variables and one superslow variable, this branch becomes important. In the $(w_2, V_2, V_1)$-space, as shown in Figure 6.16, we can see this branch is a cubic-shaped curve with two folds which are indicated.
Figure 6.15: The projection onto the \((w_1, V_2, V_1)\)-space of the solution trajectory (black curve) generated by system (5.4) with three slow variables and one superslow variable \((C_1 = 80 \mu F/cm^2 \text{ and } \phi_2 = 0.0001)\). The red curves are SS. The surface is \(S\) of the three timescale problem.

by green and blue dots. The middle part of this branch is repelling while the outer parts are of saddle-type. Both saddle-type branches are stable within the \((V_2, w_2)\) invariant plane.

Once the solution trajectory falls off the attracting part of the lower branch of SS, it begins to oscillate around a saddle-type part of the upper branch of SS until it gets close to the green fold point; see Figure 6.16. Then the solution jumps to the other saddle-type branch, leading to the onset of the small amplitude oscillations. The amplitudes of the small oscillations converge to zero as the solution tends to the blue fold point of SS. Recall that as long as \(w_2\) is slower than \(V_2\), system (5.4) is constructed so that the \((V_2, w_2)\) subsystem has a relaxation oscillation based on SS; see Figure 5.10. Without the adjustment of \(S\) on the spikes, the effect of SS on forming the solution becomes obvious. That is why the solution appears to track along the upper branch of SS even though it is of saddle-type, forming the plateau following the small oscillations in the time series 6.14. Finally, the solution jumps from the blue fold point to the attracting part of the lower branch of SS (labelled by \(SS_a\) in Figure 6.16), completing a period of the oscillation.

The other possible system with two timescales is obtained by setting \(C_1 = 0.8 \mu F/cm^2\) and \(\phi_2 = 0.01\) in (5.4), with the rest of the parameters as in Table 5.3. A periodic solution generated by this system is shown in Figure 6.17.
6.3 Four-Dimensional Coupled Model

Figure 6.16: The projection of the solution trajectory (black curve) of Figure 6.14 onto the \((w_2, V_2, V_1)\)-space. The red curves are \(SS\). The labels \(SS_a\), \(SS_r\) and \(SS_s\) represent the manifold is attracting, repelling and of saddle-type.

it with the three timescale oscillations shown in Figure 5.11 (the second panel) and 6.12, we can see this time series does not capture any features of the three timescale oscillation. The reason can be explained as follows. With the new choice of parameter values, system (5.4) has one fast variable \(V_1\) and three slow variables \((w_1, V_2, w_2)\).

The critical manifold of the new system is the same as the critical manifold \(S\) of the three timescale system; see the upper panel of Figure 6.18. However, there is no superslow manifold \(SS\). Recall that the coupled M-L model was constructed such that the \((V_2, w_2)\) subsystem is an intrinsic oscillator. Without the timescale

Figure 6.17: Time series of system (5.4) with one fast and three slow variables, at \(g_\text{syn} = 4.1 \text{mS/cm}^2\). The rest of the parameters are as in Table 5.3, except \(C_1 = 0.8 \mu \text{F/cm}^2\) and \(\phi_2 = 0.01\).
difference between $V_2$ and $w_2$, the oscillation generated by $(V_2, w_2)$ subsystem is no longer a relaxation oscillation; see the lower panel of Figure 6.18. During one period, $V_2$ decreases or increases, driving the $(V_1, w_1)$ oscillator. Thus, in the upper panel of Figure 6.18, we can see the solution trajectory moves around the critical manifold $S$ with a decreasing $V_2$-coordinate or an increasing $V_2$-coordinate. Along the upper or lower branch of $S$, the trajectory moves slowly. Away from these attracting branches, the solution makes fast jumps. Therefore, in the time series shown in Figure 6.17, only two distinct timescales are exhibited.

In conclusion, we require $w_2$ to be much slower than other variables so that the $(V_2, w_2)$ subsystem can generate relaxation oscillations. In this case, the time series

![Figure 6.18: Upper: the projection of the solution trajectory (black curve) shown in Figure 6.17 and the critical manifold of system (5.4) with $g_{syn} = 4.1 \text{ mS/cm}^2$ into $(w_1, V_2, V_1)$-space. The blue curves are the fold of the critical manifold. Lower: projection of the solution onto the $(V_2, w_2)$-plane. The red curve is the superslow manifold of three timescale problem.](image)
of $V_1$ for the full system is characterised by a long silent phase before the onset of spikes and by two groups of dense spikes that happen at two different regions of the critical manifold $S$. We also require $V_1$ to be much faster than other variables so that the dynamics of the full system are affected by the geometric shape of $S$. Then, as a result, the spikes that happen at one side of the critical manifold have gradually decreasing amplitude and the spikes at the other side have roughly constant amplitude. We conclude that the oscillation shown in the second panel of Figure 5.11 or in Figure 6.12 is an intrinsic three timescale phenomenon.

### 6.3.3 Oscillating Solutions at $g_{\text{syn}} = 5.1$

When $g_{\text{syn}} = 5.1 \text{mS/cm}^2$ in system (5.4), we see the oscillation shown in the last panel of Figure 5.11. This oscillating solution is characterised by a group of spikes with decreasing amplitude, followed by a depolarised voltage plateau and a slowly growing silent phase before the onset of spiking again. Letting $C_1 = 0.8 \mu\text{F/cm}^2$ and $\phi_2 = 0.0001$ in system (5.4), the timescale separation becomes more distinct. A time series of this case is shown in Figure 6.19, which allows us to see the features depending on the superslow timescale more clearly. When the factor $\phi_2$ decreases from 0.001 to 0.0001, the relaxation oscillation of the $(V_2, w_2)$ subsystem spends a much longer time along the superslow manifold $SS$. Therefore, in the $V_1$ time series, the number of spikes increases, and the silent phase before the onset of the spikes and the plateau following the group of spikes becomes longer.

If we set $C_1 = 80 \mu\text{F/cm}^2$ and $\phi_2 = 0.0001$ in system (5.4), the fastest variable $V_1$ will evolve on a speed analogous to $(w_1, V_2)$, and the timescales of the system reduce to two. A time series of this system is given in Figure 6.20. Although the decrease in amplitude of the large spikes is not very obvious, the new time series is quite

![Figure 6.19: Time series of system (5.4) at $g_{\text{syn}} = 5.1 \text{mS/cm}^2$ with exaggerated timescale separation. The other parameters are as in Table 5.3, except $C_1 = 0.8 \mu\text{F/cm}^2$ and $\phi_2 = 0.0001$.](image-url)
Figure 6.20: Time series of system (5.4) with three slow variables and one superslow variable, at $g_{syn} = 5.1 \text{mS/cm}^2$. The other parameters are as in Table 5.3, except $C_1 = 80 \mu\text{F/cm}^2$ and $\phi_2 = 0.0001$.

similar to the one shown in Figure 6.19. Recall that the decrease of spike amplitude is caused by the particular shape of the critical manifold $S$ in the corresponding three timescale system. In the two timescale system, this manifold is lost, the new critical manifold is $SS$, and so the solution is strongly influenced only by $SS$.

As shown in Figure 6.21, the upper branch of $SS$ is a cubic-shaped curve with two folds which are shown in green and blue. The solution leaves the attracting part of the lower branch of $SS$, and starts to oscillate surrounding the saddle-type outer part of the upper branch of $SS$ until it is close to the green fold point. Since

Figure 6.21: The projection of the solution trajectory (black curve) of Figure 6.20 onto the $(w_2, V_2, V_1)$-space. The red curves are $SS$. The labels $SS_a$, $SS_r$ and $SS_s$ represent the manifold is attracting, repelling and of saddle-type.
there is no manifold $S$ to regulate the amplitudes of the spikes, we cannot see an obvious decrease of the amplitude as in the three timescale problem. However, when this change of amplitudes is imperceptible in the experimental records, it is not an important feature of the time series of $V_1$.

Different from the case when $g_{\text{syn}} = 4.1 \text{mS/cm}^2$ where the upper branch of $SS$ is located on the middle branch of the critical manifold $S$, in this case, the manifold $SS$ crosses the fold of $S$; see Figure 5.20. In Figure 6.21, we use a purple dot to denote this intersection. The purple dot separates the middle branch of $SS$ (the branch bounded by the green and blue dots) into two parts; the right-hand side part is repelling and the left-hand side part is of saddle-type. The leftmost outer branch (connected to the saddle-type part of the middle branch of $SS$) is attracting. In both the three timescale case and the two timescale case, the solution trajectory is attracted by this stable outer branch of $SS$ after the spiking phase. Therefore, the depolarised voltage plateaus of the time series shown in Figure 6.20 remain similar to those in Figure 6.19. It seems the oscillation shown in Figure 6.19, i.e., the time series in the last panel of Figure 5.11, can be effectively generated by a two timescale system with three slow variables and one superslow variable. Thus, we do not classify the oscillation at $g_{\text{syn}} = 5.1 \text{mS/cm}^2$ as an intrinsic three timescale phenomenon.

Letting $C_1 = 0.8 \mu\text{F/cm}^2$ and $\phi_2 = 0.01$ in (5.4), we obtain a system with one fast variable and three slow variables. The time series of $V_1$ and $V_2$ are shown in Figure 6.22. The mechanism underlying this oscillating solution is similar to the one explained in the previous section for $g_{\text{syn}} = 4.1 \text{mS/cm}^2$, and so we do not further discuss it.

Based on the discussion above, it seems that the $V_1$ time series of the solution generated by system (5.4) at $g_{\text{syn}} = 5.1 \text{mS/cm}^2$ could also have been generated by a two timescale system. However, for the other two types of oscillations (observed

Figure 6.22: Time series of system (5.4) with one fast and three slow variables, at $g_{\text{syn}} = 5.1 \text{mS/cm}^2$. The other parameters are as in Table 5.3, except $C_1 = 0.8 \mu\text{F/cm}^2$ and $\phi_2 = 0.01$. 
at $g_{\text{syn}} = 1.0$ and $4.1\, \text{mS/cm}^2$), the underlying system must have at least three timescales, since the variation of either $C_1$ or $\phi_2$ results in a change of the oscillating form. We find in Chapter 5 that as $g_{\text{syn}}$ varies, a part of $SS$ crosses the fold surface of $S$, and we conjecture that the bifurcations associated to this crossing are the reason for the transitions between oscillating types. In this section, it appears that in order to have an appropriate understanding about the transitions, we also need to take into account variation of $C_1$ and $\phi_2$. Although it is beyond the scope of this thesis, studying the transitions induced by variation of $g_{\text{syn}}, C_1$ and $\phi_2$ is a possible future direction for research.

6.4 Six-Dimensional GnRH Neuron Model

Now we come back to the GnRH neuron model. In order to find if the solution of the six-dimensional model (3.3) shown in Figure 3.8 is intrinsically a three timescale phenomenon or requires only two timescales, we consider the influence of the critical manifold and the superslow manifold of (3.3) on this solution.

6.4.1 GSPT Analysis

According to the timescale analysis in section 3.2.1, the six-dimensional GnRH neuron model has the following singularly perturbed form:

$$
\begin{align*}
\varepsilon_1 \frac{dV}{dt} &= f_1(V, N_{\text{km}}, H_{\text{naf}}, c, O_{\text{ucl}}^*) \\
\varepsilon_1 \frac{dN_{\text{km}}}{dt} &= f_2(V, N_{\text{km}}) \\
\varepsilon_1 \frac{dH_{\text{naf}}}{dt} &= f_3(V, H_{\text{naf}}) \\
\frac{dc}{dt} &= g_1(V, c, c_t) \\
\frac{dc_t}{dt} &= g_2(V, c) \\
\frac{dO_{\text{ucl}}^*}{dt} &= \varepsilon_2 g(c, O_{\text{ucl}}^*). 
\end{align*}
$$

(6.2)

From the discussion in Chapter 4, we know the critical manifold of the GnRH neuron model is defined by

$$
S := \{(V, N_{\text{km}}, H_{\text{naf}}, c, c_t, O_{\text{ucl}}^*) \in \mathbb{R}^6 : f_1 = f_2 = f_3 = 0\},
$$

(6.3)

and the superslow manifold is defined by

$$
SS := \{(V, N_{\text{km}}, H_{\text{naf}}, c, c_t, O_{\text{ucl}}^*) \in S : g_1 = g_2 = 0\}.
$$

(6.4)
Although $S$ is a three-dimensional manifold in $(V, N_{\text{km}}, H_{\text{naf}}, c, c_t, O_{\text{ucl}}^*)$-space, it does not depend on $(N_{\text{km}}, H_{\text{naf}}, c_t)$. Thus, we plot the projection of it onto the $(O_{\text{ucl}}^*, c, V)$-space; see Figure 6.23. In this space, the critical manifold is a cubic-shaped manifold with an attracting lower branch. With the solution trajectory superimposed, we can see that except for the large spikes of $V$, the remaining parts of the bursting solution move along the lower branch of $S$.

Figure 6.23: Upper: the projection of the critical manifold $S$ of system (3.3) onto the $(O_{\text{ucl}}^*, c, V)$-space. The solution is in black. Lower: the magnification of the region near the lower fold of $S$. The superslow manifold of system (3.3) (the red curve) is also shown.
Now we check which part of the solution evolves on the superslow timescale by calculating the superslow manifold $SS$. The superslow manifold is plotted in red in the $(O^{*}_{\text{ucl}}, c, V)$-space in the lower panel in Figure 6.23. Comparing the position of the solution trajectory with the critical manifold and the superslow manifold, we find that the active phase of the $V$ time series terminates when the solution begins to move along $S$. The silent phase of the $c$ time series starts when the solution begins to move along $SS$. Although the bursting solution shown in Figure 6.23 is from the six-dimensional reduction of the eight-dimensional GnRH neuron model (1.23), it is qualitatively the same as the solution shown in Figure 1.7. Thus, it seems likely that for the bursting solution of the full GnRH model in Figure 1.7, the section in black is away from the critical manifold, the section in blue is along the critical manifold, and the section in red is along the superslow manifold. Therefore, these three parts involve a fast timescale, a slow timescale and a superslow timescale, respectively. This matches our observation in section 1.3.2.

Next, we need to identify whether the three timescale phenomenon seen in the GnRH neuron model is intrinsically three timescale or not. From the discussion in the previous section, we can infer that without the superslow timescale, we will not see the long quiescence in the $c$ time series; and on the other hand, without the fast timescale, except where it moves along $SS$, the solution will not be on or near $S$. Consequently, the pattern of the bursting solutions of the three timescale GnRH neuron model with $I_{\text{app}} = 0$ may change. We check the validity of these conjectures by numerical simulations.

### 6.4.2 Two Timescale Reductions

As in section 6.3, we can identify the significance of the critical manifold on the dynamics of the solution by rescaling the GnRH model into a two timescale system with five slow variables and one superslow variable. In a similar way, we can rescale the three timescale neuron model to a system with three fast variables and three slow variables to show the importance of the superslow timescale.

The rescaled version of the GnRH model with three fast variables and three slow variables is obtained by multiplying the right hand side of the equation for $O^{*}_{\text{ucl}}$ in system (3.3) by a factor 100. A time series of this two timescale reduced GnRH neuron model is shown in Figure 6.24. Comparing it with the time series in Figure 3.8, we see a periodic doubling phenomenon arises. However, we only interested in the interval following the largest spike in the $c$ time series, and we find this interval shortens dramatically in the absence of the superslow timescale. The critical manifold of this two timescale system is defined as the same as (6.3). In Figure 6.25, we plot the region near the lower fold of the critical manifold with the solution trajectory.
Figure 6.24: Bursting solutions of $V$ and $c$ at $I_{app} = 0$ pA in the six-dimensional GnRH neuron model, equation (3.3), with the variable $O^*_ucl$ is a hundred times faster. Shown in Figure 6.24 superimposed. Although in this case, there is no superslow manifold, we still plot the SS manifold for the original six-dimensional system (3.3) in Figure 6.25, in order to show that the solution moving along the lower branch of $S$ will not be affected by SS. The result verifies our conjecture about the dynamics without the superslow timescale, i.e., the long quiescence in the $c$ time series in Figure 3.8 cannot be observed.

Figure 6.25: The solution shown in Figure 6.24 is superimposed on the critical manifold. The superslow manifold (red curve) is also plotted, in order to show the solution does not move along it in this case.
Similarly, we rescale the times for the fast variables \((V, N_{km}, H_{naf})\) such that they evolve on timescales that are roughly the same as \(c\) and \(c_t\). This was done by multiplying the right hand side of the equations for \(V, N_{km}\) and \(H_{naf}\) in system (3.3) by a factor \(1/100\). Then, the neuron model becomes a two timescale system with five slow variables and one superslow variable. A time series is shown in Figure 6.26. There are no small wiggles in the \(c\) time series and no bursting in the \(V\) time series. However, due to the existence of the superslow timescale, the inter-spike long quiescence in the \(c\) time series is still observed. The critical manifold of this two timescale system is defined as \(SS\) in (6.4). Since there is no fast timescale, the solution trajectory will not be affected by manifold \(S\); refer to the first panel in Figure 6.27. As a result, we cannot obtain a bursting solution similar to the one shown in Figure 3.8. The periodic solution in this system moves slowly following the stable branch of the manifold \(SS\) to the fold of \(SS\); from there, it jumps away and then comes back to the stable branch of \(SS\) due to some global return mechanism which will not be discussed in this thesis; see the lower panel of Figure 6.27.

Recall that the analysis in section 6.1 claimed that, for the time series of the slow variable to exhibit small wiggles, there must be at least two distinct timescales. Therefore, in the neuron model, for the \(c\) time series to have small wiggles, \(c\) must be a slow variable. This means the variables \((V, N_{km}, H_{naf})\) are much faster than \(c\). In addition, we need a superslow variable which is slower than \(c\) to ensure there is a long quiescence in the \(c\) time series. This superslow variable can be \(c_t\) or \(O^*_{ucl}\) or both of them. This might be an explanation of why in section 3.3, when we use one of \(c_t\) and \(O^*_{ucl}\) to approximate another, a bursting solution similar to Figure 3.8 can still be generated. All in all, the existence of the characteristic bursting solution in

![Figure 6.26: Bursting solutions of V and c at I_{app} = 0 pA in the six-dimensional GnRH neuron model, equation (3.3), with all the fast variables a hundred times slower.](image-url)
6.5 Discussion

In summary, we find that all the oscillating solutions generated by three timescale systems and investigated in this thesis are three timescale phenomena from the mathematical point of view. However, when we focus on the time series rather than the

the GnRH neuron model requires the existence of three distinct timescales.

6.5 Discussion

In summary, we find that all the oscillating solutions generated by three timescale systems and investigated in this thesis are three timescale phenomena from the mathematical point of view. However, when we focus on the time series rather than the
phase portraits, not all of them are intrinsic three timescale phenomena. That is, if we wished to determine the timescale structure of a mathematical model based only on observations of time series, it would be possible in some cases to generate oscillations with the same overall features from a two timescale model. For example, the bursting solution in the food chain model and the oscillation of the coupled M-L model at $g_{\text{syn}} = 5.1 \text{ mS/cm}^2$ are of this type.

We find three timescale phenomena come in various forms. A three timescale oscillation may or may not involve an passage though the vicinity of a folded singularity, such as the one discussed in section 4.3.3 versus the rest of the three timescale oscillations we studied. In addition, the influence of the superslow timescale over the dynamics of the solution can be easily identified by noticing an explicit movement of the solution trajectory along the superslow manifold, but this is not always how the superslow timescale is manifested. For example, in the case of the coupled M-L model at $g_{\text{syn}} = 4.1 \text{ mS/cm}^2$, the slow shift of the large spikes on the critical manifold is driven by the superslow timescale.

Another observation is that in order to decide whether an oscillation is intrinsically a three timescale phenomenon, sometimes knowing the time series of one variable may not be enough. More specifically, if an experimental simulation of membrane voltage gives us a time series which either looks like the one shown in Figure 6.4 or the one shown in Figure 6.14 due to an ambiguous boundary between the large amplitude spikes and the small amplitude spikes, then we need to further determine a corresponding time series of another variable, say calcium, to judge whether this behaviour is a three timescale phenomenon or a two timescale phenomenon.
Chapter 7

Conclusions

Many physiological systems have the property that different processes evolve on different timescales, and mathematical models of these systems consequently typically have variables that evolve on different timescales. Systematic theory such as geometric singular perturbation theory (GSPT) for analysing systems with two timescales has been well developed, but much less is known about analysis methods for systems with three or more timescales. The aim of this thesis was to advance understanding of dynamical systems with three distinct timescales via the investigation of a number of different models with this property.

Our work was motivated by a model of GnRH neurons developed by Duan et al. [14, 44] which describes the electrical activity and calcium oscillations in GnRH neurons. Time series for this model seem to indicate that there are at least three different timescales that influence the dynamics of the solution. In Chapter 1, the original eight-dimensional GnRH model was discussed. As shown in Chapter 3, the original GnRH model (1.23) can be reduced to a system with six dimensions, given by (3.3) and (3.4). Examination of a nondimensional version of the reduced model showed that three timescales can be identified in the system.

Even after reduction, the GnRH neuron model is still complicated. Thus, before attempting to apply GSPT to the six-dimensional GnRH model, we first studied two three-dimensional models with three timescales in Chapter 4. The first model investigated was a food chain model [53]. By applying GSPT to this model, we uncovered the mechanism underlying the small wiggles observed in the time series. The analysis of the food chain model suggested that the relative positions of the critical manifold and the superslow manifold are crucial to the solution behaviour. Then we studied a canonical model, which can be seen as an abstract form of the food chain model. By constructing the canonical model, we were able to control the geometric features of this three timescale system, such as the position of the folded singularity.
The three-dimensional systems studied in Chapter 4 were too simple to capture the intricate dynamics of the GnRH neuron model. We therefore constructed a minimal model based on the structure of the GnRH model in Chapter 5. Specifically, we coupled two copies of the Morris-Lecar (M-L) equations in such a way that the full system could be regarded as a slow oscillator driving fast oscillations. From the various time series of the coupled M-L model obtained by varying a system parameter $g_{syn}$, we selected three representative types of oscillations which appeared to involve three timescales. By applying GSPT, the details of the time series of these solutions could be explained.

Mathematically, all the oscillations we considered from the above models can be seen to evolve on three timescales, since these solutions involve movements away from and close to the critical manifold, and movement close to the superslow manifold. However, we wanted to know which time series were intrinsically three timescale phenomena, in the sense that qualitatively similar time series could not also be observed in two timescale systems. From this point of view, we showed in Chapter 6 that the typical solution seen in the food chain model and the time series observed from the coupled M-L model with $g_{syn} = 5.1 \text{mS/cm}^2$ should not be classified as intrinsically three timescale oscillations. Finally, we applied GSPT to the reduced GnRH neuron model and showed that the bursting solution of interest is an intrinsically three timescale phenomenon.

The main contributions of this thesis are as follows. First, we advanced understanding of the dynamics of systems with three timescales. There has been little reported research on the dynamics of systems with three distinct timescales; we have provided more examples of the application of GSPT to systems with three timescales. We found that the critical manifold (which is geometrically important for understanding the dynamics of systems with two timescales) and the superslow manifold (which normally is a subset of the critical manifold) were equally necessary for a complete understanding of the dynamics of a three timescale system, and conjectured that the relative positions of the folds of the critical and the superslow manifolds are important in determining the types of oscillatory behaviour possible in a three timescale system. We suggested a way (via use of a constructed model as described in Chapter 4) that this conjecture could be investigated.

We also found that folded singularities can be important in determining the dynamics of a three timescale system and argued that the types of folded singularities that are generic depend on the timescale structure of the system. In particular, we showed that in three dimensional, three timescale systems, a type of folded singularity not generically seen in two timescale systems was generic.

Second, we identified some intrinsic three timescale phenomena. Not all solu-
tions generated by a three timescale system require the existence of three timescales. When a mathematical model is to be constructed to describe an oscillation seen experimentally, then prior knowledge about whether a specific oscillation pattern is an intrinsically three timescale phenomenon helps us to make decisions about how to group the variables in the model and may help restrict the number of timescales included in the model.

Last, we carefully simplified the GnRH neuron model, reducing it from eight to six dimensions. Our discussion of the process applied to make this reduction, including our consideration of methods that ultimately were unhelpful, may be useful for modelers considering the simplification of other physiological models.

The study carried out and the results obtained in this thesis imply some possible directions for future work.

1. The existing theory for systems with two different timescales sometimes is not generic for three timescale systems. For example, results about Type II folded saddle-nodes, developed for two timescale models, do not hold in the three timescale setting. This indicates that a systematic study of three timescale models is required. Such a study could include further numerical investigations of the folded singularities and the construction of systematic theorems for systems with three timescales analogous to those that exist for systems with two timescales.

2. We showed that the geometric properties of the critical manifold and the superslow manifold are particularly important for understanding the dynamics of three timescale systems. By exploiting the three-dimensional canonical model, it might be possible to extend our understanding about the role played by the critical manifold and the superslow manifold. Any such results could then be applied to systems such as the coupled M-L system, to investigate the observed transitions from one oscillation type to another as a system parameter is varied.

3. In Chapter 3, we showed that it was possible to approximate a variable as a linear function of another variable without significantly altering the system dynamics, even when the two variables concerned evolved on very different timescales. This phenomenon is very puzzling but may have important implications for model reduction techniques, and is worthy of further investigation.
Appendix A

Numerical Methods

The numerical software used in this thesis was AUTO [13], XPPAUT [16] and MATLAB. We used XPPAUT to compute solutions of the four-dimensional coupled M-L system; see Figure 5.11. Also, the bifurcation diagrams of the two-dimensional M-L model, such as Figures 5.1, 5.2 5.4 and 5.5, were computed with XPPAUT. The solve method used in XPPAUT was the stiff integrator which is for stiff equations and uses an adaptive step size method.

The bifurcation diagrams of the GnRH neuron model (the full system and the reduced systems) shown in Chapter 3 were computed by AUTO with standard AUTO-constants.

The time series of the GnRH neuron model, the food chain model and the three-dimensional canonical model were integrated using MATLAB with the integrator ode15s. This method is for solving stiff problems. In each figure, the time series was obtained by numerical simulation of the model starting from an arbitrary initial condition and allowing the transient to die away and the solution to converge to a stable periodic solution. Convergence was confirmed by comparing the corresponding phase portrait visually.

To check the accuracy of a bifurcation diagram, we decreased the tolerance in AUTO by decreasing the values of EPSL, EPSU and EPSS by a factor of 100 and/or increasing the value of NTST by a factor of 10 or 100. Then we computed the diagram again with the new tolerance. An acceptable accurate bifurcation diagram was identified if it was the same under visual inspection as the one obtained using a smaller tolerance. We also picked some isolated values for the bifurcation parameter, and then solved the ODE system with the specified parameter value by MATLAB independently. Comparing the maximum (and minimum) value of an oscillating solution with the bifurcation diagram also confirmed the accuracy of a bifurcation diagram.
Bibliography


