INFORMATION TO USERS

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

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

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

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

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

UMI
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600
RICE UNIVERSITY

A Phase Sensitivity Based Method for Prediction of Modes of Behavior in Quadrupedal Locomotion

by

Anton A. DeFranceschi

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

Master of Science

Approved, Thesis Committee:

John W. Clark, Chairman
Professor of Electrical & Computer Engineering

Ian D. Walker
Associate Professor of Electrical & Computer Engineering

Ka-Yiu San
Associate Professor of Chemical Engineering

Houston, Texas
April, 1996
A Phase Sensitivity Based Method for Prediction of Modes of Behavior in Quadrupedal Locomotion

Anton A. DeFranceschi

Abstract

The objective of this study is development of prediction methods for characterizing the electrical behavior of ring type central pattern generators (CPGs). A mathematical model of the prototypical bursting neuron R15 from the abdominal ganglion of *Aplysia* is used, along with a simple model of the inhibitory synapse, to form a four neuron ring model of a CPG. The basic mode of a four neuron ring CPG model is able to characterize the walk, trot and bound gaits associated with quadrupedal locomotion. The phase sensitivity of neuron R15 to an external input is investigated, and the results are expressed in terms of cophase curves that are used to formulate prediction algorithms for the behavior of ring type networks. These prediction algorithms are utilized in a Network Emulator that provides an accurate simulation of the behavior of the ring type networks at a considerable savings in computation time compared with numerical solutions of the ordinary differential equations associated with these networks. We further extend this work by examining the conditions for control of the modes of three and four neuron ring CPGs by external stimuli.
Acknowledgments

I would like to express sincere thanks to Dr. John W. Clark for his support and guidance, and John Byrne, Doug Baxter, Rob Butera, and Semahat Demir for fruitful discussions and ideas. This research was supported in part by Office of Naval Research grant N00014 – 92 – 1152.
## Contents

Abstract .......................................................... ii
Acknowledgments .................................................. iii
List of Illustrations ........................................... vii
List of Tables .................................................... x

1 Introduction ....................................................... 1
  1.1 Why study CPGs? ........................................... 3
  1.1.1 What are CPGs? ........................................ 5
  1.2 Types of CPGs .............................................. 5
  1.2.1 Endogenous bursters ................................... 6
  1.2.2 Networks with Excitatory Connections ................ 7
  1.2.3 Networks with Inhibitory Connections ................ 7
  1.2.4 Networks with Mixed Inhibitory and Excitatory Connections 9
  1.3 Studies on CPGs ............................................ 9

2 Model Development ............................................... 12
  2.1 Membrane Model .......................................... 12
  2.2 Fluid compartment model ................................ 14
  2.3 Synaptic Model ............................................ 18
  2.3.1 Transmitter release ................................... 19
  2.3.2 Synaptic cleft ......................................... 19
  2.3.3 Post-synaptic transmitter-sensitive ionic membrane current 21
  2.3.4 The Fundamental Synapse .............................. 23
3 Phase Sensitivity Based Prediction Methods

3.1 Phase Sensitivity Analysis ................................... 29
  3.1.1 Phase Sensitivity of the Fundamental Synapse ............. 30
  3.1.2 Phase response curves (PRCs) ............................. 32
  3.1.3 Cophase Curves (CCs) .................................... 34

3.2 Reciprocal-Inhibition Network ................................ 36
  3.2.1 Identical neurons, different synapses ....................... 37

3.3 Development of Prediction Methods for the Ring Type Networks 43
  3.3.1 Graphical Method for the Reciprocal-Inhibition Circuit ........ 43
  3.3.2 Generalization to a ring of n neurons ....................... 45
  3.3.3 Iterative map methods .................................... 48
  3.3.4 The Network Emulator .................................... 49
  3.3.5 Prediction of Mutual Period Using the Network Emulator .... 55

4 Mode Switching in Simple Central Pattern Generators

(CPGs) .................................................................... 59

4.1 A Three Neuron Ring Network ................................ 59
  4.1.1 Mode switching in a three-neuron ring ....................... 61
  4.1.2 Mechanism of Mode Switching ................................. 64
  4.1.3 Regions of successful mode switching ....................... 64

4.2 A four ring network: Quadrupedal gait locomotion CPG ......... 70
  4.2.1 Gait Patterns ............................................. 73

5 Discussion ................................................................ 76

5.1 Synaptic Model .................................................... 76

5.2 Insights from the Phase Sensitivity Analysis ...................... 77
5.3 Comparison of Prediction Methods ........................................ 78
5.4 Comparison of three and four ring CPGs with previous models .... 80
  5.4.1 Recurrent cyclic inhibition CPG (a three neuron ring) ........ 80
  5.4.2 Quadrupedal locomotion CPG (a four neuron ring) ........... 81

6 Conclusions ................................................................. 83

Bibliography ...................................................................... 87

A Development of the iterative map equations for a three neuron ring network ......................................................... 98

B Model Equations .......................................................... 100
## Illustrations

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Sequences of still photographs of a galloping horse</td>
<td>2</td>
</tr>
<tr>
<td>1.2</td>
<td>Diagram of the main neural components involved in locomotion</td>
<td>3</td>
</tr>
<tr>
<td>1.3</td>
<td>Network configurations</td>
<td>8</td>
</tr>
<tr>
<td>2.1</td>
<td>Components of the R15 model</td>
<td>16</td>
</tr>
<tr>
<td>2.2</td>
<td>Model generated membrane voltage and ionic currents</td>
<td>17</td>
</tr>
<tr>
<td>2.3</td>
<td>Coupling between the $Ca^{2+}$-induced presynaptic release of transmitter and the postsynaptic transmitter-receptor reaction</td>
<td>20</td>
</tr>
<tr>
<td>2.4</td>
<td>Coupling of bursting neuron N1 to voltage clamped neuron N2</td>
<td>24</td>
</tr>
<tr>
<td>2.5</td>
<td>Transmitter release from the presynaptic cell and the resulting postsynaptic conductance and postsynaptic current</td>
<td>26</td>
</tr>
<tr>
<td>2.6</td>
<td>IPSP and IPSC for different values of the rate constant $k_r$ associated with the closing of the synaptic channel</td>
<td>27</td>
</tr>
<tr>
<td>3.1</td>
<td>Phase-sensitivity of a bursting neuron to an inhibitory synaptic input</td>
<td>31</td>
</tr>
<tr>
<td>3.2</td>
<td>Effects of synaptic inputs of different durations (short (S), intermediate (I) and long (L)) on the phase sensitivity of R15</td>
<td>33</td>
</tr>
<tr>
<td>3.3</td>
<td>Reciprocal inhibition network</td>
<td>36</td>
</tr>
</tbody>
</table>
3.4 Comparison of activity of neuron N1 (connected in a reciprocal-inhibition network) and a free-running control neuron \( N_C \) ................................................................. 39

3.5 Phase plane of \( s \) and \([Ca^{2+}]\) for the reciprocal inhibition circuit 40

3.6 Comparison of activity of two neurons connected in a reciprocal-inhibition network with synapses of different durations ......................................................... 41

3.7 Phase plane of \( s \) and \([Ca^{2+}]\) for the reciprocal inhibition circuit with different duration synapses ................. 42

3.8 Ring type network consisting of \( n \) neurons connected with inhibitory type synapses ............................................. 46

3.9 Block diagram of the Network Emulator ......................... 50

3.10 Timing diagram for the neurons X and Y used in the Network Emulator ................................................................. 53

3.11 Prediction of the mutual period of the reciprocal-inhibition circuit comprised of identical R15 neurons with identical synapses ......................................................... 57

3.12 Prediction of the mutual period of the reciprocal-inhibition circuit comprised of identical R15 neurons with different synapses ......................................................... 58

4.1 Three neuron ring network ............................................. 60

4.2 Modes of oscillation exhibited by a three neuron ring network 62

4.3 Configuration of external control imposed on a three neuron CPG ................................................................. 63

4.4 Mode switching in a three neuron ring (Network Emulator) 65

4.5 Mode switching in a three neuron ring (Model) ................. 66
4.6 Regions of successful mode switching for different duration synapses ................................................................. 69
4.7 Quadrupedal gait locomotion Central Pattern Generator ........... 70
4.8 Modes of oscillation exhibited by a four neuron ring network ........ 72
4.9 Quadrupedal gaits exhibited by a four neuron ring network ........ 75

A.1 Relationship between the stimulus times for the cycles k and $k + 1$ utilized in the iterative map for a three neuron ring .......... 99
Tables

4.1 Basic gaits of a horse ........................................ 71

B.1 $I_{Na}$: Fast Sodium Current .......................... 101
B.2 $I_{Ca}$: Fast Calcium Current ......................... 102
B.3 $I_{SI}$: Slow Inward Calcium Current .............. 103
B.4 $I_{NS}$: Non-Specific Cation Current ............... 103
B.5 $I_{K}$: Delayed Rectifier .............................. 104
B.6 $I_{R}$: Anomalous Rectifier .......................... 104
B.7 Leakage Current ........................................ 104
B.8 Pumps and Exchangers .................................. 105
B.9 Internal Calcium Concentration ..................... 105
B.10 Internal cAMP Concentration ....................... 105
B.11 Model Parameters ..................................... 106
B.12 Synaptic Model ......................................... 107
B.13 Synaptic model parameters ....................... 107
Chapter 1

Introduction

A centipede was happy quite,
Until a frog in fun
Said, 'Pray, which leg comes after which?'
This raised her mind to such a pitch,
She lay distracted in a ditch
Considering how to run

Mrs Edmund Craster, Centipede

Mrs. Craster's poem humorously illustrates some problems that might arise in an attempt to coordinate hundreds of legs. Although a centipede has numerous legs to coordinate, it is not the only creature pondering the locomotion problem. Throughout history, people have made careful observations of the movements of the animals surrounding them and of their fellow humans. However, naked-eye observations of rapid movements were inadequate for accurately describing rapid movements such as the wing movements of a hummingbird or horse's leg position during a trot or a gallop. By the nineteenth century there were heated debates about the exact pattern of horse's legs during trotting or galloping. According to legend, the application of modern techniques that could answer such questions originated with a bet on a horse. In the late 1870's Leland Stanford, former governor of the state of California had an argument with Frederick MacCrellish over exact placement of the feet of a galloping horse. Stanford put $25,000 behind his hypothesis that during the gallop, at one instant all four legs of a horse are in the air. To settle this wager, a local photographer by the name of Eadweard Muybridge was hired to photograph the different phases
of the gait of a horse. The photographs taken are shown in Fig. 1.1. Muybridge was eventually commissioned by Stanford to photograph the movements of other animals, as well as humans engaged in different gaits such as walking, running, trotting or galloping. Such observations have led physiologists and neurobiologists to uncover the underlying mechanisms that are responsible for creation of such locomotor patterns. Given the complexity of neuron systems in vertebrates, it is not surprising that the first successes came from the study of invertebrates. In the early 1960's, two observations were made which formed the basis for much of contemporary research on the organization of invertebrate motor systems. In 1964, Wiersma and Ikeda [85] showed that stimulation of single neuron in the nerve cord of the crayfish could elicit coordinated behavioral acts. These cells were termed command neurons, and their role was viewed as signaling to the motor system when or when not to generate a particular motor pattern. This finding resulted in a belief that the generation of an appropriate pattern of motor output resided in the motor network itself, and was referred to as a pattern generator. Perhaps the first proof for the existence of such a network was provided by Wilson et al [87, 88], who showed that the isolated nervous system of a
The locust could produce the motor pattern for flight in the absence of sensory feedback. This observation validated the concept that the complex rhythmic behaviors could be generated via pattern generators contained within the central nervous system and furthermore, that they can be controlled from higher neural centers.

### 1.1 Why study CPGs?

In the design of large-scale complex systems, reliability of operation and adaptability for various purposes and environments have been essential requirements.

![Diagram of the main neural components involved in locomotion](image)

**Figure 1.2:** Diagram of the main neural components involved in locomotion

The decentralized autonomous system has been singled out as the system with most promise in attaining such requirements. A decentralized autonomous system is a system where the functional behavior of the whole system is generated by cooperation of
its subsystems, where each subsystem has the autonomy to control a part of the state of the system. So what better place to borrow the concept of realization but from the nature itself, where it is well known that the systems of such character are actually realized in biological organisms. The biological systems are capable of self-organizing various behavioral functions due to autonomous coordination of many system elements. As stated before, animal locomotion is generated by cooperation of many motor neurons driven by an autonomous pattern generator, which is further controlled from the higher centers. One of the important developments in motor studies in recent years has been the analysis of all major mechanisms involved in generation and control of locomotor activity in terms of a general conceptual framework (Fig. 1.2). The neural mechanisms responsible for the generation of coordinated rhythmic outputs from motoneurons are contained in lower centers of the spinal cord (or the relevant ganglia in invertebrates). A collection of neurons that can exhibit a range of coordinating patterns is commonly referred to as a Central Pattern Generator (CPG), and is shown in the shaded region of Fig. 1.2. The CPG is activated and controlled by descending fibers from the higher motor centers, and modulated through feedback paths which relay the information back from the muscles and from the external environment. Despite the variety of body forms and types of locomotion (swimming, walking, running, flying), these main components are present to some extent in the nervous system of most higher organisms. Although simple in concept, the actual identification of groups of neurons forming control pattern generators has proved to be quite difficult. Even in studies on invertebrates where the relevant neurons are relatively large and can be located and analyzed, it has taken many years to describe in relative detail the neuronal mechanisms controlling the generation of simple behaviors such as escape swimming program in Tritonia [40, 42] or the pyloric system of the lobster stomatogastric ganglion [70, 73]. Even though the CPGs responsible
for pattern generation in these invertebrates contain a relatively small number of neurons, the pattern of synaptic connectivity is far from simple. As a result, several theoretical studies have been proposed for the generation of cyclic activity with a hope that mathematical analysis of nonlinear systems and networks may ultimately aid physiologists and neurobiologists in uncovering the secrets of locomotion control.

1.1.1 What are CPGs?

The generation of repeating oscillatory patterns of muscle activity is one of the main functions of motor systems. In recent years, it has been recognized that this property rests within the neural circuits that form the CPG. We define a CPG as an assembly of neurons (either local or distributed) which, by virtue of its intrinsic neuronal properties and synaptic interactions, is capable of generating and controlling the spatial and temporal activity of motor neurons. The spatial and temporal activity of CPGs are manifested in different rhythmic activities such as locomotion, ventilation, circulation, mastication, digestion and reproduction [46]. Interestingly, the view emerging from recent studies is that despite diversity of body structure and variety of existing locomotion patterns in the animal world, the basic types of neural circuits for generating rhythmic motor output are actually quite limited.

1.2 Types of CPGs

The models proposed thus far to account for the production of rhythmic motor patterns can be classified into four main categories: 1) endogenous bursters, 2) networks consisting of cells connected via excitatory connections, 3) networks consisting of cells connected via inhibitory synapses, and 4) networks with mixed excitation and inhibition [72, 82].
1.2.1 Endogenous bursters

Neurons in various molluscan ganglia can produce repeating bursts of impulses even after all contact with other neurons is abolished [4, 6, 35]. The mechanism of endogenous burst production in all known cases involves changes in membrane conductances that are slow relative to the time course of a single action potential. One of the most heavily studied preparations is the abdominal ganglion of Aplysia. In this ganglion, several types of endogenous bursters have been identified. The neurons in this ganglion have been implicated in the control of numerous functions, including respiration, reproduction, circulation, defensive movement of the mantle, excretion, and neuroendocrine processes (such as egg-laying and water balance) [49]. Neurons of the abdominal ganglion are classified as having one of three modes of electrical behavior: 1) silence, in which the cell remains in a hyper-polarized state; 2) bursting, in which the cell alternates between a state of hyper-polarized silence and a grouped discharge of multiple action potentials; and 3) beating, in which the cell fires action potentials at a steady tonic frequency. One of the most frequently studied preparations in neurobiology is the R15 cell, which is located in the abdominal ganglion of Aplysia. This neuron has been used extensively to gain insights into the biophysical mechanisms underlying endogenous bursting activity in nerve cells. Consequently, specific information is known regarding the size and type of membrane currents that underlie individual action potentials, as well as the currents contributing to the slower oscillation that modulates bursting activity [1, 2, 3, 4, 5, 44, 45]. A number of Hodgkin-Huxley equivalent circuit models of R15 have been developed that simulate different aspects of the activity of R15 [4, 22, 23, 24, 67, 69]. More recent models simulate the actual magnitudes and time courses of the component membrane currents and include features such as the description of the calcium-dependent inactivation of $[Ca^{2+}]$ current, as well as the description for the balance of the intracellular calcium balance $[Ca^{2+}]$.
[16, 19, 20, 24, 69]. In this work, the R15 neuron model developed by Butera et al [16], will be utilized to construct and analyze properties of some simple networks.

1.2.2 Networks with Excitatory Connections

An example of mutual excitation network consisting of three cells where each neuron excites its neighbor and vice versa is shown in Fig. 1.3D. In early efforts to model the activity of large groups of neurons, it was found that excitatory connections among individual neurons could produce cyclic reverberatory activity patterns in the neural ensemble. More recent studies show that the intra-cortical connections are localized and are predominantly inhibitory. Furthermore, a purely excitatory type network does not produce stable oscillatory patterns, so it is an unlikely mechanism for the production of rhythmic movements [82].

1.2.3 Networks with Inhibitory Connections

Groups of neurons with exclusively inhibitory interconnections can produce stable oscillatory activity patterns, provided they have particular connection patterns. The simplest example of such a pattern is the model first proposed by Brown [13] to explain the generation of walking and breathing in mammals. This network consists of two neuronal pools which inhibit one another; it is called a reciprocal-inhibition network (Fig. 1.3A). This reciprocal connection pattern has been used to model: 1) up-and-down movements of locust wings during flight [88]; 2) the chewing movement in lobster stomach [59]; and 3) swimming in the sea slug *Melibe* [79]. A network consisting of three neurons with inhibitory connections is commonly referred to as 'recurrent cyclic inhibition' (Fig. 1.3C). This network has been implicated as a possible mechanism for coordination of multiphasic limb movements in the urodelan [78] and the segmental undulations of leech swimming [36, 83]. A network consisting of
Figure 1.3: Network configurations
A) Reciprocal-inhibition circuit, B) feedback inhibition, C) Recurrent cyclic inhibition (a three neuron ring with inhibitory synapses), D) mutual excitation three neuron ring, E) a four neuron inhibitory ring, and F) parallel excitation-inhibition.
four neurons (Fig. 1.3E) has been proposed as a CPG for control of the limbs in a quadruped locomotion [28], and a six-neuron ring has been used by Collins and Stewart [29] to investigate the hexapodal gaits of insects.

1.2.4 Networks with Mixed Inhibitory and Excitatory Connections

Mixed excitation and inhibition connections give rise to more complex pattern generating networks, and presently there are no known theoretical techniques which could predict the behavior of such a complex system. Simple examples of two such networks are given in Fig. 1.3. A feedback inhibition network (panel B) is a network of two neurons connected such that neuron N1 excites N2 which in turn inhibits N1. A single neuron is both inhibited and excited in a parallel excitation and inhibition network shown in panel E. Several complex networks have been identified thus far in invertebrates. For example, the CPG controlling the generation of the escape swimming motor program in Tritonia has been identified by Getting et al [42]. A respiratory CPG of snail Lymnaea was identified and subsequently reconstructed in culture with three neurons by Bulloch and Syed [14]. Meyrand et al [58] have investigated preparations on the stomatogastric nervous system of the lobster Homarus gammarus consisting of four interconnected ganglia. Above CPG generates motor rhythms of the four regions of the foregut of the lobster. Weimann and Marder have investigated the motor neurons in stomatogastric ganglion of the crab Cancer Borealis, thought to generate rhythmic patterns responsible for pyloric and gastric-mill rhythms [89].

1.3 Studies on CPGs

In the early 1970's, several researchers had suggested that 'simple systems' found in invertebrates would allow a detailed specification of the neurons and their synaptic interactions, indicating their respective roles in a particular behavior. However, even
though the number of neurons in many behavior controlling circuits in invertebrates is relatively small, this task has proven to be more difficult than expected. To quote Getting [41]: 'In my own experience with *Tritonia*, it has taken over 10 years to describe, in relative detail, the neuronal mechanisms controlling the generation of the escape swimming motor program'. As a result, a number of researchers have posed a different question: 'What types of symmetries exist in simple networks, and are there any theoretical methods to predict the behavior of these networks?'

A number of different mathematical models have been developed to study CPGs. Kleinfeld and Sompolinsky [54], have used associative neural networks to represent the CPG controlling escape swimming in the mollusk *Tritonia diomedia*. Schoner *et al* [71] on the other hand, utilized theoretical concepts from the synergetics to model quadrupedal CPG. The most numerous studies to date have been involved in construction of coupled nonlinear oscillators. Relaxation oscillators have been used to represent the control mechanisms of a single insect leg and/or group of insect legs. Yuasa and Ito [92], and Bay and Hemami [11] have utilized systems of four coupled nonlinear oscillators to synthesize the limb movements of quadrupeds and segmented bipeds, respectively. Others have used chains of coupled oscillators to model the swimming CPG in lamprey [27, 86] and dogfish [55]. More recently, Collins and Stewart [30], and Stewart and Golubitsky [77], have used group-theoretic approach to predict modes of behavior of symmetric rings of oscillators. Subsequently, Collins and Stewart used group-theory based predictions to examine the modes of behavior of CPGs consisting of four and six neurons to produce the quadrupedal and hexapodal gaits respectively [28, 29].
In the present study, we approach the problem of predicting the behavior of ring type networks based on the phase sensitivity of the endogenous burster cell R15. For this purpose, a generic synaptic model is described in CHAPTER 2 based on the physiological processes in the real cell. Several simple networks are constructed in CHAPTER 3, and examined for the purpose of better understanding the mechanisms underlying the operation of these networks. Based on the simple input-output relationships derived from a phase sensitivity analysis, prediction methods capable of determining the modes of behavior of ring type CPGs are developed in CHAPTER 3. These prediction methods are subsequently applied in CHAPTER 4 to analyze, predict, and control modes of behavior of a four neuron ring CPG for quadrupedal locomotion.
Chapter 2

Model Development

The model of the parabolic bursting neuron R15 first developed by Canavier et al [19], and modified by Butera et al [15] is an integral part of the present study. We employ the complete model of Butera et al, and modify it to include a transmitter-sensitive synaptic membrane current $I_{SYN}$ for the purposes of combining R15 neurons into simple networks, and examining the effects of synaptic properties on the modes of behavior of these networks. For specific details regarding the fundamental development of the model, the reader is directed to [15, 19]. Below, a brief review of the membrane and fluid compartment models is given, followed by the development of the synaptic model which will be employed later to connect the neurons into networks.

2.1 Membrane Model

The model consists of two major components: a Hodgkin-Huxley (HH) type model of the membrane dynamics, and a fluid compartment model which characterizes the intra- and extra-cellular media associated with the neuron soma. The equivalent circuit for the membrane of the single R15 cell is shown in Fig. 2.1A. The terminology associated with the membrane currents is given in [17]. Under space clamp conditions, the differential equation describing the membrane potential ($V$) is:

$$\frac{dV}{dt} = -\frac{1}{C_m} (I_{Na} + I_{Ca} + I_{SI} + I_{NS} + I_K + I_R + I_L + I_{NaCa} + I_{NaK} + I_{CaP})$$  \hspace{1cm} (2.1)
where $C_m$ is the whole-cell membrane capacitance; $I_{Na}$ is the time- and voltage-dependent $Na^+$ current; $I_{Ca}$ and $I_{SI}$ are the voltage-activated and $Ca^{2+}$-inactivated fast inward and slow inward $Ca^{2+}$ currents respectively; $I_{NS}$ is the time- and voltage-dependent non-specific cation current; $I_K$ is the time- and voltage-dependent delayed rectifier $K^+$ current; $I_R$ is the anomalous-rectifier current; $I_L$ is the leakage current; $I_{NaCa}$ is the electrogenic $Na^+/Ca^+$ exchanger current; $I_{NaK}$ is the electrogenic $Na^+/K^+$ pump current; $I_{CaP}$ is the ATP-dependent calcium pump current; $I_{SYN}$ is the transmitter-sensitive synaptic current; and $I_{stim}$ is the stimulus current.

A brief description of some of the more important currents and their effects on the activity of the R15 follows, to facilitate understanding of the mechanisms of frequency and phasic control described later in this study. For detailed descriptions of all currents and variables associated with the R15 model, consult references [15] and [19].

The model-generated membrane voltage and individual ionic current waveforms for the unmodulated R15 cell are shown in Fig. 2.2. Panel A shows the characteristic period of the transmembrane potential waveform in neuron R15, which consists of the depolarizing burst interval followed by the hyperpolarizing interburst interval. Bursting is governed by two slow processes: activation of $I_{SI}$ (Fig. 2.2D), represented by the voltage-dependent gating variable $s$, and intracellular $Ca^{2+}$ concentration (panel G). The slow inward current $I_{SI}$, is the key current responsible for the bursting activity in this model. In addition, it provides a region of negative slope resistance in its current-voltage relationship, which is the underlying basis of the slow-wave oscillation observed during bursting activity. Within the burst interval, the upstrokes of individual action potentials are initiated by the fast inward $Na^+$ current (panel B), while the repolarization phase occurs by activation of the delayed-rectifier $K^+$ current ($I_K$) (panel C). The fast $Ca^{2+}$ current ($I_{Ca}$) is strong in this model, and is
also responsible for the leading edge and the plateau region of the action potentials (panel C). Non-specific cation inward current $I_{NS}$ is activated by action potentials and summates during the burst. This current is largely responsible for the parabolic nature of the frequency of action potentials during the burst (the frequency of the action potentials first increases, and then decreases within a burst activity). The anomalous $K^+$ rectifier current $I_R$ is the dominant current at very hyperpolarized potentials, and tends to keep the cell from hyperpolarizing below $-70\, mV$.

2.2 Fluid compartment model

The fluid compartment model (Fig. 2.1B) provides material balances for both intracellular $Ca^{2+}$ and cyclic adenosine monophosphate (cAMP). Intracellular concentration of $Ca^{2+}$ is regulated by the presence of a calmodulin-type $Ca^{2+}$ buffer and the $Ca^{2+}$ extrusion that is affected by $I_{NaCa}$ and $I_{Ca,P}$. Production of cAMP from adenosine triphosphate (ATP) is catalyzed by adenyl cyclase (AC), which is in turn modulated via second messenger serotonin $5-HT$. Application of $5-HT$ increases the intracellular concentration of cAMP via activation of AC (see Fig. 2.1B). With the exception of the new synaptic current $I_{SYN}$, the equations and associated parameters necessary for the simulation of the membrane currents are identical to those presented in the model of Butera et al [17]. Refer to Appendix B for the complete set of modeling equations and associated parameters.

The model of neuron R15 is modulated both by serotonin ($5-HT$) and dopamine (DA). $5-HT$ modulates two currents ($I_R$ and $I_{SI}$), while DA affects only $I_{SI}$ current. Progressive increases in $5-HT$ concentration causes the R15 model to transition through three distinct states: bursting, silence, and tonic beating. Low concentrations of $5-HT$ ($0\, \mu M \leq 5-HT \leq 2\, \mu M$) cause an increase in the length and depth
of the interburst hyperpolarization with a minimal change in the burst length by increasing the outward current $I_R$. In the range $10\mu M \leq 5\text{--}HT \leq 20\mu M$ $I_R$ is increased sufficiently to bias the model into a hyperpolarized silent state. Further increases in $5\text{--}HT$ cause a dominant increase in the inward current $I_{SI}$, which causes the model to resume bursting activity, with an attendant increase in burst duration, but minimal changes in the length of the interburst interval. At sufficiently high concentrations ($5\text{--}HT \geq 60\mu M$) the model exhibits tonic beating.

Modulation of R15 model by DA causes two distinct states: bursting and silence. An increase in DA concentration in the range $(0\mu M \leq DA \leq 100\mu M)$ leads to progressive cessation of bursting activity via inhibition of $I_{SI}$ which results in diminished $Ca^{2+}$ influx during the burst and a shortened burst length. Higher concentrations $(DA \geq 100\mu M)$ terminate the burst completely, and force the model to stable hyperpolarized silence. The model also exhibits bistable region of behavior, wherein bursting and beating activity coexist. This bistability occurs in a small transitional region between beating and bursting modes for $5\text{--}HT$ concentrations in the range $(58\mu M \leq 5\text{--}HT \leq 63\mu M)$. Butera et al. [17] have shown that model-generated bursting and beating modes within the bistable region exhibit stable long-term electrical behavior.
Figure 2.1: Components of the R15 model

(A) The electrical equivalent circuit of the mathematical model of a single R15 cell. (B) Intracellular fluid compartment model showing \([Ca^{2+}]_i\) buffering and second-messenger mediated modulation of membrane currents \(I_{SI}\) and \(I_R\). The second messenger cAMP activates protein kinase A (PKA) which in turn phosphorylates the channel to modulate current flow. Serotonin (5-HT) causes an increase in [cAMP] by increasing the activity of membrane-bound adenylyl cyclase (AC). Due to lack of experimental details, the slow inward current \(I_{SI}\) is assumed to be directly modulated by dopamine (DA). \(I_{SYN}\) is the transmitter-sensitive synaptic current.
Figure 2.2: Model generated membrane voltage and ionic currents

(A) Model-generated membrane potential exhibiting parabolic burst interval and interburst interval. (B), (C) currents responsible for generating the action potential within the burst interval. (D) Currents $I_R$ and $I_{SI}$ are responsible for starting and ending the bursting phase of the period. (E), (F) Pumps and exchangers (G) Intracellular calcium concentration
2.3 Synaptic Model

The R15 neuron in *Aplysia* is modified by several synaptic inputs. It receives a large monosynaptic excitatory postsynaptic potential (EPSP) from an axon in the right connective nerve [35], as well as from the identified cholinergic interneuron L10 [50, 51], and it receives a synaptically mediated inhibition of long duration (ILD) from interneuron II [61, 84]. Waziri et al. [84] suggest that the long duration IPSP is not due to a single IPSP of long duration, but rather represents a summation of small IPSP's resulting from a high-frequency burst of an interneuron. Most investigations of receptor dynamics in *Aplysia* have been conducted using ionophoretic injection techniques [21, 37, 51] rather than nerve fiber simulation. Using ionophoretic drug application techniques, Carpenter et al. [21] have described and characterized R15 receptors for a variety of neurotransmitters. The identified receptors are discrete, localized, and neurotransmitter specific. They mediate responses which have different ionic bases, time courses and effects on the endogenous discharge. Both acetylcholine (ACh) and \(\gamma\)-aminobutyric acid (GABA) depolarize the cell, thus functioning as excitatory neurotransmitters [21, 53, 91]. On the other hand, glutamate (Glu) and dopamine (DA) function as inhibitory agents by hyperpolarizing the cell [21]. The responses to ACh and Glu have a rapid peak onset and are relatively brief in duration, while the responses to GABA and DA are considerably longer, lasting from several seconds to several minutes [21, 53, 91].

We first examine the behavior of an idealized synaptic junction consisting of two identical R15 neurons coupled by an inhibitory synapse. In this idealized model, the spike discharge of the presynaptic neuron results in the synaptic release of a generic transmitter into a small synaptic cleft between the pre- and post-synaptic membranes. The details of this model are given in the following section.
2.3.1 Transmitter release

It is generally accepted that exocytosis of membrane-attached synaptic vesicles at the presynaptic nerve terminal ending is related to the influx of $Ca^{2+}$ current [7, 8, 9, 33, 76, 90]. Two major hypotheses describe the dependence of transmitter release upon calcium influx: a) it is proposed that there is a nonlinear relationship between $Ca^{2+}$ influx and transmitter release, which is supported by suggestions that intracellular "calcium domains" surround open $Ca^{2+}$ channels in the immediate neighborhood of active release sites. Furthermore, the overlap of these domains is thought to account for a nonlinear relationship between $Ca^{2+}$ influx and transmitter release [76, 90]; and b) Augustine et al. [7, 8], suggest that over the course of an action potential these $Ca^{2+}$ domains do not overlap, and in experiments on the squid giant synapse, they find a clear linear relationship between transmitter release and calcium entry into the presynaptic terminal. We have adopted the latter view and have modeled the flux of transmitter ($F_R$; moles/msec) into the synaptic cleft as a linear function of the calcium current ($I_{Ca}$), that is:

$$F_R \equiv -k_{FR}I_{Ca}$$  \hspace{1cm} (2.2)

where $k_{FR}$ is a proportionality constant expressed in units of coulombs/mole.

2.3.2 Synaptic cleft

We have modeled the synaptic cleft (width 250Å; [10]) as a well-stirred compartment (see Fig 2.3), wherein transmitter concentration is described by the following balance equation:

$$\frac{d[T]_c}{dt} = F_R(t) - k_{HD}[T]_c$$  \hspace{1cm} (2.3)

Here $[T]_c$ is the concentration of transmitter in nM, and $k_{HD}$ is a lumped rate constant describing total loss of transmitter due to the combined effects of transmitter...
hydrolysis and a passive diffusion of transmitter out of the cleft space. To the best of our knowledge, there is no primary experimental data describing the time course of transmitter release and decay for identified neurons in *Aplysia*. However, it is generally accepted that the transmitter release is rapid and that transmitter decay is not the rate limiting process in the transmitter-receptor reaction [38, 57]. Therefore, we have assumed that the time constant of transmitter decay is 0.5 msec, which is comparable to the experimentally determined value for the decay of acetylcholine of 0.27 msec from frog nerve-muscle preparations [57].

![Diagram](image)

**Figure 2.3:** Coupling between the \( Ca^{2+} \)-induced presynaptic release of transmitter and the postsynaptic transmitter-receptor reaction

The presynaptic release of transmitter is described by the flux \( F_R(t) \) \( \text{(moles/msec)} \), while \( [T]_c \) represents the concentration of transmitter in the synaptic cleft. \( [T]_c \) is continually diminished by hydrolysis and by diffusion of transmitter out of the cleft space. The term \( T \cdot R_{closed} \) represents the bound receptor-transmitter complex, while \( k_1 \) and \( k_{-1} \) are the forward and reverse binding rate constants, respectively. The term \( T \cdot R_{open} \) indicates the transmitter-receptor complex which has undergone a conformational change to the open state. The coefficients \( k_F \) and \( k_R \) are the forward and reverse rate constants for the conformational change.
2.3.3 Post-synaptic transmitter-sensitive ionic membrane current

Many kinetic models have been developed for describing the transmitter-receptor interaction [12, 25, 32, 38, 48, 57, 74, 80]. The two-state model considered below represents a simple model of the binding of transmitter to the receptor and the resulting conformational change of the transmitter-receptor complex which leads to the opening of the synaptic channel [57]. More complex multi-step post-synaptic models have been devised which describe intermediate reaction steps that occur between the initial binding step and the opening of the channel [52]. In addition, even more complex presynaptic models have been developed which describe the cyclic release and uptake of the transmitter vesicles, and which account for the desensitisation of the overall transmitter-receptor complex [80].

In the development below, we have been guided by the model first developed by Magleby and Stevens for the frog sartorius neuromuscular junction [57], which views the interaction of transmitter with its receptor as a simple enzymatic process. Following binding of substrate to enzyme, many enzyme-substrate complexes are thought to undergo a conformational change as the first step in the catalytic sequence. By analogy, transmitter first binds to its receptor; thereafter the transmitter-receptor complex undergoes a conformational change which permits ionic flux through post-synaptic transmitter sensitive membrane channels. The following first order kinetic scheme describes the transmitter-receptor interaction:

\[
[T]_c \xrightleftharpoons[k_{-1}]{k_1} T \cdot R_{\text{closed}} \xrightleftharpoons[k_r]{k_f} T \cdot R_{\text{open}}
\]

(2.4)

Here, \(k_1\) and \(k_{-1}\) are the forward and reverse rates of the binding reaction, while \(k_f\) and \(k_r\) are the forward and reverse rate constants respectively, corresponding to the conformational changes that open \(T \cdot R_{\text{open}}\) and close \(T \cdot R_{\text{closed}}\) the transmitter...
mediated ionic membrane current. Thus, according to the first order kinetic scheme (eq. 2.4), the time rate of change of the number of transmitter-receptor complexes in the closed and open conformation are given by the following differential equations, respectively:

\[
\frac{dT \cdot R_{\text{closed}}}{dt} = k_r T \cdot R_{\text{open}} + k_1 [T]_c (N - T \cdot R_{\text{open}} - T \cdot R_{\text{closed}}) \\
- (k_f + k_{-1}) T \cdot R_{\text{closed}}
\]

(2.5)

and

\[
\frac{dT \cdot R_{\text{open}}}{dt} = -k_r T \cdot R_{\text{open}} + k_f T \cdot R_{\text{closed}}
\]

(2.6)

where \( N \) is the total number of receptors available in the postsynaptic cell.

Thus, equations (2.3, 2.5, and 2.6) constitute a general description of the processes involved in generating synaptic current in the postsynaptic cell. To simplify these equations, the following assumptions were made: a) the binding reaction of transmitter to receptor is assumed to be very rapid, and in equilibrium with a dissociation constant \( K_{M,T} = k_{-1}/k_1 \); b) the binding rate constants \( k_1 \) and \( k_{-1} \) are assumed to be large compared to conformational change rate constants \( k_f \) and \( k_r \); and c) only a small fraction of the total number of channels \( N \) is bound at a given time, and each channel has one receptor associated with it. With the above assumptions the time rate of change of the transmitter-receptor complex in the open conformation becomes:

\[
\frac{dT \cdot R_{\text{open}}}{dt} = -k_r T \cdot R_{\text{open}} + k_f \frac{N [T]_c}{K_{M,T} + [T]_c}
\]

(2.7)

We assume further that the conductance of the synaptic channel is directly proportional to the number of transmitter-receptor complexes in the open conformation, i.e.

\[
g_{\text{syn}} \equiv \gamma T \cdot R_{\text{open}}
\]

(2.8)
where \( \gamma \) is the conductance of the single open channel. Thus, the time rate of change of the postsynaptic conductance can be written as:

\[
\frac{dg_{syn}}{dt} = -k_r g_{syn} + k_f \bar{g}_{syn} \frac{[T]_c}{K_{M,T} + [T]_c}
\]  

(2.9)

where, \( \bar{g}_{syn} = \gamma N \) corresponds to the maximum whole cell conductance, and \( K_{M,T} \) is the half-maximal concentration of the neurotransmitter buildup in the cleft space. We furthermore assume that \( [T]_c \) does not approach a saturating concentration in the cleft. This was assumed by setting \( K_{M,T} \) to 2M, which is a relatively large concentration level. The corresponding transmitter-induced postjunctional membrane current is given by:

\[
I_{syn} = g_{syn} \cdot (V - E_{syn})
\]  

(2.10)

where \( E_{syn} \) is the reversal potential for the synaptic current.

2.3.4 The Fundamental Synapse

The properties of the fundamental synaptic connection were examined by connecting two R15 neurons as shown in Fig. 2.4, where bursting neuron N1 represents the presynaptic neuron that is coupled to post-synaptic neuron N2 via inhibitory synapse. To begin, we assume that neuron N2 is clamped at the relatively hyperpolarized level of \(-70mV\), whereas neuron N1 exhibits normal bursting activity. Transmitter is released as a result of calcium influx during the burst period of the presynaptic neuron N1 (Fig. 2.5 panel A), which causes an increase in transmitter concentration \([T]_c\) within the cleft (panel B), and consequently an increase in the conductance of the transmitter sensitive ion channel in the postsynaptic membrane (panel C). The conductance change results in an increase in the inhibitory post-synaptic current labeled \( I_{SYN} \) (panel D).
Figure 2.4: Coupling of bursting neuron N1 to voltage clamped neuron N2
Bursting neuron N1 is coupled to neuron N2 via inhibitory synapse. Neuron N2 is voltage clamped to \(-70mV\)

As previously stated, several putative neurotransmitters modulate endogenous discharge in neuron R15 [21]. The interaction of each transmitter with its specific receptor produces a synaptic current with a characteristic amplitude and time course. These synaptic currents have different effects on the ongoing activity of the postsynaptic bursting neuron. The model presented here was not calibrated to rigorously fit IPSC data or the time course of the conductance change for any particular neurotransmitter. The nominal set of synaptic parameters utilized in our simple junctional model is given in table B.12. The scaling constant \(k_{FR} \text{ (mM/Coulomb)}^{-1}\) was chosen such that the maximum level of the neurotransmitter released in the cleft is about \(1mM\). This value of concentration is consistent with the physiological range of glutamate gated \(Cl^-\) channels in the medial plural neurons of \textit{Aplysia} [53]. Peak conductance of the ionic channel falls within the range \(0.65\pm0.08\mu S\), which are the values reported by Gardner et al [38] for the inhibitory synapses of the buccal ganglia in \textit{Aplysia}. The peak values of IPSC’s in buccal ganglia fall between \(5nA\) and \(30nA\) when the cell is clamped between \(-19mV\) and \(-59mV\) [37].
The first-order scheme describing transmitter concentration in the cleft (eq. 2.3) suggests several possibilities for the rate-limiting step of the transmitter-receptor reaction: 1) transmitter supply; 2) transmitter loss due to hydrolysis and diffusion; or 3) a slow unbinding or conformational change leading to closing of the open synaptic current channels. Gardner et al [38] have determined that the rate limiting step of inhibitory post-synaptic current decay in the buccal ganglia of *Aplysia* is a slow conformational change that closes the open synaptic current channels. For smaller values of the rate constant for the closing of the synaptic channel $k_r$ (corresponding to longer decay time constant values $k_r^{-1}$), the summation effect on the conductance channel is larger, and thus the resulting IPSC’s and IPSP’s reach higher maximum values (see Fig. 2.6). The effects of varying this rate constant on the phase sensitivity of the cell and on the behavioral patterns of activity of reciprocal inhibition circuit and other simple networks is the focus of studies presented in the following section.
Figure 2.5: Transmitter release from the presynaptic cell and the resulting postsynaptic conductance and postsynaptic current

(A) Membrane voltage of the bursting neuron N1. (B) Transmitter released into the cleft space as a result of calcium influx during the burst period of the activity of neuron N1. (C) Transmitter release causes conductance change of the synaptic channel $g_{syn}$ in the membrane of the postsynaptic cell N2. (D) Resulting inhibitory post-synaptic current $I_{syn}$. Postsynaptic neuron N2 is voltage clamped to $-70mV$ in order to isolate the effects of the inhibitory post-synaptic current $I_{syn}$. 
Figure 2.6: IPSP and IPSC for different values of the rate constant $k_r$, associated with the closing of the synaptic channel

(A) Voltage waveform of the presynaptic neuron. (B) Inhibitory post-synaptic potential (IPSP) of the postsynaptic neuron for different values of the rate constant $k_r$, corresponding to the conformational change of the transmitter-receptor complex associated with the closing of the synaptic channel. Neuron N2 was held in silence by application of a -2.0 nA hyperpolarizing background current. (C) Inhibitory post-synaptic current (IPSC) of the postsynaptic neuron for different values of the rate constant $k_r$, corresponding to the conformational change of the transmitter-receptor complex associated with the closing of the synaptic channel. Neuron N2 was clamped to a value of -70mV.
2.4 Computational Aspects

The complete reciprocal-inhibition circuit consists of 28 coupled, first-order, nonlinear differential equations. Each of the R15 neurons (Fig 2.1) in the circuit is described by a set of 14 first-order differential equations which are given in tables B.1- B.12: nine equations describe the ion fluxes across the cell membrane, two are associated with transmitter release and the synaptic conductance, and the remaining three are associated with: 1) the material balance for Ca$^{2+}$ in the intracellular medium; (2) the Ca$^{2+}$ buffer; and (3) the change of cAMP in the cytosol. A Runge-Kutta-Merson numerical integration algorithm [39] which includes an automatic step-size adjustment that is based on an error estimate was employed in these simulations. All simulations were written in the C programming language and were implemented on a Sun Microsystems IPX.
Chapter 3

Phase Sensitivity Based Prediction Methods

3.1 Phase Sensitivity Analysis

In this section, a phase sensitivity analysis is performed on a single bursting neuron, connected via an inhibitory synapse to an arbitrary input neuron. That is, we propose to study the phase-sensitive properties of the single interactive unit (the single synapse and associated lumped membrane properties of the post-synaptic cell). Stimulation of the input neuron is assumed to produce waveforms of transmitter concentration in the synaptic cleft of arbitrary amplitude and duration, which in turn induce synaptic currents of different amplitudes and durations in the post-synaptic bursting neuron. The phasic effects of synaptic inputs on the period of the bursting neuron is usually described by a phase response curve (PRC), [62]. Previous studies by our group [31], indicate that the amplitude of the transmitter concentration waveform has a much smaller effect on the PRC than the duration. Correspondingly, the duration of the post-synaptic current is very important in controlling the phasic response of the bursting neuron, and the duration of this current is conveniently controlled by adjustment of the rate constant ($k_R$) for closing the transmitter-mediated synaptic channel. By systematically adjusting this parameter to achieve synaptic currents of different durations, and calculating the PRCs at each duration, a family of PRCs (and related cophase plots) characterize the phasic behavior of the basic interactive unit. This type of analysis can be extended and leads to quantitative, testable predictions about the interactions of neurons coupled into more complex networks, based on the
fundamental properties of the basic interaction unit. These results are presented later.

3.1.1 Phase Sensitivity of the Fundamental Synapse

The phase response of biological oscillators can be expressed in two different but related ways: 1) phase response curves (PRCs), and 2) cophase curves (CCs). PRCs are constructed by plotting the relative change in period ($\Delta P/P_0$) versus the normalized phase ($\Phi$) of the stimulus applied at time $t_*$ (here $P_0 = 13.3sec$ is the free-running cycle length of the neuron being stimulated). To construct a PRC and CC, the time of stimulus delivery ($t_s$) of cell N2 by the pre-synaptic cell N1, is gradually increased in small increments from the beginning to the end of the free-running cycle length ($P_0$) of the post-synaptic cell N2. The beginning of the cycle corresponds to the upstroke of the first action potential in the burst and is defined to be phase zero (see Fig. 3.1). Cophase curves are constructed by plotting the recovery time (or 'cophase' $t_r$) versus the stimulus time ($t_s$). Cophase is defined as the time from the beginning of the stimulus to the beginning of the next burst, while the stimulus time is defined as the time of delivery of the stimulus relative to phase zero. The sum of the coordinates of the cophase curves ($t_s + t_r$) gives a new period $P_1$ resulting from a delivery of a single stimulus; i.e. the new period of the stimulated neuron N2 is:

$$P_1 = t_s + t_r. \quad (3.1)$$

Depending on where in the cycle the stimulus is delivered, the cycle of the perturbed cell may be shortened, lengthened or remain unaffected. Panel A of Fig. 3.1 shows the unperturbed activity having a control period $P_0$. Panel B shows the shortening of the period (phase advance) as a result of synaptic input being applied during the burst phase of the cycle, while panel C shows lengthening (phase delay) when the synaptic input is applied later during the interburst interval.
Figure 3.1: Phase-sensitivity of a bursting neuron to an inhibitory synaptic input

(A) A model of the bursting neuron has a free-running period $P_0 = 13.3\text{sec}$. Panels (B) and (C) illustrate the new cycle lengths ($P_1$) due to an inhibitory synaptic input applied at time $t_s$. Panel (B) shows the phase advance resulting from a synaptic input applied during the burst phase of the cycle, while panel (C) shows the phase delay resulting from a synaptic input applied in the interburst interval. Cophase ($t_r$) is defined as the time interval between the beginning of the synaptic input and the occurrence of the next burst activity. Stimulus delivery is indicated with an arrow.
Both PRCs and CCs were utilized by Pinsky et al. in studying the synchronization and entrainment properties of the left upper quadrant neuron L3 in the abdominal ganglion of *Aplysia* [64, 65, 66]. Below, the phasic response of a bursting neuron to synaptic input of different durations are considered, and both PRCs and CCs are shown.

### 3.1.2 Phase response curves (PRCs)

The PRC for the single inhibitory synapse is illustrated in Fig. 3.2, where the normalized cycle length of the membrane potential is included in panel A to facilitate better understanding of the biphasic nature of the PRC. The particular shape of the PRC is directly related to the duration of decay of the synaptic current, which as previously mentioned is controlled by the rate constant $k_r$ for the closing of the synaptic channel (see Section 2.3). Three PRCs are shown in Fig. 3.2B corresponding to short (S), intermediate (I), and long (L) duration synaptic inputs. For short duration inputs (decay is equal or smaller than the burst duration), the phase ($\Phi$) can be divided into three distinct intervals denoted I, II, and III. Interval I ($0 \leq \Phi < 0.2$) corresponds roughly to the duration of the burst. Here, the changes in the resulting period $\Delta P$ are negative with a large slope, signifying a drastic shortening of the burst cycle of up to one half the control period $P_0$. Interval II also exhibits shortening of the burst cycle. However, the region of this portion of the PRC curve is almost flat, signifying an almost constant change in period, regardless of the point of delivery of the stimulus. Values of phase in the range ($\Phi^* \leq \Phi < 1$) lie in interval III, where stimuli delivered during this interval prolong the cycle length. For stimuli delivered during the interval $0 \leq \Phi < \Phi^*$, there is a decrease in cycle length $P_1$ (phase advance), while for the stimulus delivered for $\Phi > \Phi^*$, the cycle length is extended (phase delay). Stimuli applied exactly at the critical phase $\Phi = \Phi^*$ have no effect on the cycle length.
Figure 3.2: Effects of synaptic inputs of different durations (short (S), intermediate (I) and long (L)) on the phase sensitivity of R15. (A) One cycle of the free-running R15 for reference. (B) Phase response curves for synaptic inputs of different durations. R15 neuron is more sensitive to short duration synaptic inputs, exhibiting three distinct intervals of the phase response: strong acceleration (I), weak acceleration (II), and delay (III). Increase in the duration of the synaptic inputs shifts the critical phase to the left, and “straightens” the curve, making it more linear. (C) The cophase information is also plotted for the different duration synaptic inputs.
For synaptic inputs of intermediate duration (Fig. 3.2C), interval I likewise corresponds to the duration of the burst, however the slope is smaller, indicating a weaker acceleration zone than in panel B. With this increase in synaptic current duration, the critical phase $\Phi^*$ shifts to the left, shortening interval II and lengthening the delay phase (interval III). Longer duration inputs (Fig. 3.2D), shifts the critical phase ($\Phi^*$) even further to the left, until it lies well within the burst duration. In this case, the shape of the PRC becomes almost linear, and the acceleration phase is very short. Thus, the particular timing of stimulus delivery from a neuron providing input to a neuronal oscillator is very important. Delivery of the stimulus early in the cycle causes a decrease in the period of the oscillator, whereas arrival of the same input later in the cycle causes an increase in period. Extending this reasoning, the same type of input descending from an interneuron onto a population of identical neurons oscillating out of phase with respect to each other, would tend to synchronize the bursting patterns of the component neurons. That is, the population of identical neuronal oscillators receiving the same synaptic input, would tend to establish fixed phase relationships in the population relative to the stimulus activity by phase advancing those neurons whose bursts start prior to the critical phase, and delaying those whose bursts begin after the critical phase.

3.1.3 Cophase Curves (CCs)

An alternative way of representing the phase sensitivity of a biological oscillator is via cophase curves [62]. Although mentioned in literature, this method has not been utilized extensively. It is our experience however, that CCs often provide a clearer means of understanding and interpreting the behavior of a neuron in a context of a network. The cophase curve allows for the separation of the oscillator cycle into two distinct intervals: 1) the time before an external stimulus is delivered ($t_s$), and
2) the time from stimulus delivery to the beginning of the next cycle or recovery time \( t_r \). As with the PRC, the character of the CC changes with the duration of the applied synaptic input (Fig. 3.2C). For synaptic inputs of short duration, the CC is curvilinear, while for longer duration inputs it is almost constant. Note that for constant cophase, the resulting recovery time \( t_r \) has the same duration regardless of what point in the cycle the stimulus was delivered. Extending the reasoning to the case of an interneuron providing a distributed input to a population of identical neurons oscillating out of phase, it is apparent that if the identical synapses are characterized by constant CCs corresponding to long-duration synaptic currents, perfect synchronization would occur since \( t_r \) is constant for all synapses regardless of the particular phase \( t_{n_i} \) \( i = 1, 2, \ldots n \) with which the stimulus is delivered. Thus, CCs can often provide more intuitive insight into phase sensitive behavior than do PRCs.
3.2 Reciprocal-Inhibition Network

Utilizing the fundamental synapse described in Section 2.3.4 two identical neurons are arranged in the form of a reciprocal inhibition circuit for purposes of analyzing the effects of coupling on the intrinsic behavior of the individual neurons comprising this simple network (Figure 3.3).

![Diagram of Reciprocal-Inhibition Network](image)

**Figure 3.3: Reciprocal inhibition network**

Bursting neurons N1 and N2 characterized by the dynamics of an R15 neuron model are mutually coupled via inhibitory synapses.

When two identical neurons bursting at their free-running rates are reciprocally coupled, a brief transition period will occur after which the neurons lock into a certain phase relationship and oscillate periodically at a frequency that is different from the free-running (uncoupled) rate. This new period is called the mutual period $P_M$. The mechanism of coupling is analogous in terms of Fig. 3.4. As a result of the onset of bursting activity in cell N2 (Fig. 3.4A), a postsynaptic inhibitory current is generated which causes hyperpolarization in neuron N1. This voltage drop causes a decrease in the voltage-dependent activation variable $s$ (panel B), which deactivates the slow
inward calcium current $I_{Si}$ (panel C). Since the influx of calcium is also reduced, $[Ca^{2+}]$, decreases compared to the levels reached in the same neuron under control conditions (uncoupled, free-running conditions labeled $N1,c$ in Fig. 3.4D; dashed lines). Furthermore, as a result of the drop in membrane voltage, the inward rectifier $K^+$ current $I_R$ decreases (panel E), thus preventing the cell from hyperpolarizing further. Fig. 3.5 shows the behavior of the two coupled cells in the $s - [Ca^{2+}]_i$ phase plane. As a result of coupling, the cells produce a trajectory that is different from that of the uncoupled cell. To help analyze these differences, the $s$ and $[Ca^{2+}]$, nullclines are also shown in this figure. As a result of inhibitory coupling, the trajectory of each neuron is diverted from its free-running (uncoupled) trajectory towards a fixed point in the $s - [Ca^{2+}]_i$ plane described by the intersection of the nullclines associated with the new coupled system. Note from Fig. 3.5, that as the synaptic current decays, the system is attracted back towards its original trajectory. When two identical cells with identical synapses are coupled, they lock in perfect anti-synchrony (180° out of phase). The resulting mutual period ($P_M$) of oscillations of each cell depends on the duration of the synaptic connections used. That is, synapses of short duration result in a period $P_M$ that is less than $P_0$ while synapses of longer duration result in a period greater than $P_0$ (the free-running period of the uncoupled R15 cell).

### 3.2.1 Identical neurons, different synapses

When identical synapses are used for the synaptic connections on identical neurons, the neurons lock 180° out of phase. However, if different synapses are used, the neurons can lock into other phasic relationships. The particular phase relationship depends on a difference in a relative duration of the synaptic current of the two synapses used. If the synaptic currents have comparable durations, the resulting phase lock will be near 180°. On the other hand, if one synapse is of short duration
(neuron N1), while the other is of long duration (neuron N2), the two neurons will lock such that the phase of N2 relative to N1 is greater than 180° (Fig. 3.6A). Figures 3.6 and 3.7 show the steady state and phase plane behavior respectively for two coupled neurons, where neuron N1 is innervated by a short duration synapse \( (k_R^{-1} = 0.5 sec) \), and N2 is innervated by a synapse of much longer duration \( (k_R^{-1} = 2.0 sec) \). Fig. 3.7 indicates that under operating conditions, the trajectories of each of the neurons are attracted towards different fixed points in the \( s - [Ca^{2+}]_i \) phase plane, which are determined by the properties of their respective input synapses. Note from Fig. 3.6A that neuron N1, which is driven by a short duration synapse, receives synaptic input later in the cycle, while neuron N2 (connected to N1 via a longer duration synapse) receives its input earlier in the cycle. Since N2 has a longer duration synapse, its trajectory is attracted to a fixed point in the \( s - [Ca^{2+}]_i \) phase plane (Fig. 3.7) that lies further down and to the left relative to the fixed point for N1. Furthermore, N2 is attracted towards its fixed point for a longer time than N1, and consequently \( [Ca^{2+}]_i \) diminishes to a greater extent (Fig. 3.6D). Hence, during N2’s succeeding burst, it takes a longer time for \( [Ca^{2+}]_i \) to build up to a level necessary to inhibit \( I_{SI} \) to the extent necessary to terminate bursting. Consequently, under coupled conditions the number of action potentials and the burst duration associated with the N2 discharge is greater than that for N1. Thus, neurons coupled in a reciprocal-inhibition circuit lock into a specific phase relationship and oscillate at a mutual frequency, which can be either slower or faster than the frequency of the uncoupled cell. The mutual frequency at which the two neurons lock is highly dependent upon the properties of the synapse (i.e. duration of synaptic current).
Figure 3.4: Comparison of activity of neuron N1 (connected in a reciprocal-inhibition network) and a free-running control neuron $N_C$

Membrane potential for neurons N1 and control neuron $N_C$ (A), $s$ gating variable (B), $I_{SI}$ (C), calcium concentration $[Ca^{2+}]_I$ (D) and $I_R$ (E) for N1 and $N1_c$ (dashed line). Currents and concentrations for the control case are indicated with a subscript 'c'.
Figure 3.5: Phase plane of $s$ and $[Ca^{2+}]$ for the reciprocal inhibition circuit

Neurons N1 and N2 (solid line) transcribe identical trajectories in $s-Ca^{2+}$ plane, but are 180° out of phase in time domain. Trajectory for the control neuron is indicated by $N_C$ (broken line). $Ca^{2+}$ and $s$ nullclines were generated in the absence of action potentials. Nullclines for the neuron with a synaptic input $I_{SN}$ were generated by assuming a constant current generated by the maximum conductance of the synaptic channel ($g_{syn} = 0.65 \mu S$).
Figure 3.6: Comparison of activity of two neurons connected in a reciprocal-inhibition network with synapses of different durations

The neurons are connected such that N1 has a short, whereas N2 has a long duration type synapse. Membrane potential for neurons N1 and control neuron NC (A), s gating variable (B), ISI (C), calcium concentration [Ca^{2+}] (D) and IR (E) for N1 and NC. Currents and concentrations for the control case are indicated with a subscript 'c'.
Figure 3.7: Phase plane of $s$ and $[Ca^{2+}]$ for the reciprocal inhibition circuit with different duration synapses

Neurons N1 and N2 (solid line) produce identical periodic trajectories in $s-Ca^{2+}$ plane, but are 180° out of phase in time domain. The uncoupled trajectory for the control neuron is indicated by $N_C$ (broken line). The $Ca^{2+}$ and $s$ nullclines were generated in the absence of action potentials (solid nullclines). Nullclines for the neuron with a synaptic input $I_{SYN}$ (dotted nullclines) were generated by assuming a constant current generated by the maximum conductance of the synaptic channel ($g_{syn} = 0.65\mu S$).
3.3 Development of Prediction Methods for the Ring Type Networks

The symmetry of the ring type networks, and the knowledge of the phase sensitivity of a neuron to a transient synaptic input allows us to devise relatively simple prediction schemes, which can be used to predict the modes of behavior of more complex networks, including some central pattern generators. We first describe a prediction method for the simple reciprocal-inhibition network (Fig. 3.3), and then generalize the analysis to the prediction of the behavior of a ring network containing n synaptically coupled oscillators. A solution method is also described that is analogous to an iterative mapping method used to solve nonlinear differential equations. This method provides not only a steady state solution, but is also capable of predicting transient behavior. The technique is based on knowledge of the cophase plots associated with the component synapses of the particular ring network. This information is utilized to develop a Network Emulator, which is capable of solving an arbitrary network having different synaptic connections. We begin this development with a discussion of the techniques that provide the steady-state solutions for the ring type networks.

3.3.1 Graphical Method for the Reciprocal-Inhibition Circuit

When the two bursting neurons of a reciprocal-inhibition circuit (Fig. 3.3) are connected, the cycle length of the activity of the two neurons settles to a mutual period $P_M$. When two identical neurons with two identical synapses are used, they lock 180° out of phase, and the stimulus time ($t_s$) of one neuron is equal to the recovery time ($t_r$) of the second neuron and vice versa. That is,

\[ t_{s1} = t_{r2} = f(t_{s2}) \]  \hspace{1cm} (3.2)

\[ t_{s2} = t_{r1} = f(t_{s1}). \]  \hspace{1cm} (3.3)
Since the two neurons are phase-locked and oscillate at same mutual period $P_M$, the information about the period and the phase of this circuit can be extracted from the cophas e curve of either neuron. Using eq. 3.2 and 3.3, and the knowledge about the phase lock, it follows that the mutual period can be found at the intersection of the cophas e curve and a line through the origin having a slope $Q = 1$. The period ($P_M$) and phase ($\Phi_M$) at which the two neurons will oscillate are then given by:

\[
P_M = t_{s1} + t_{r1} = 2t_{s1} \quad (3.4)
\]

\[
\Phi_M = \frac{t_{s1}}{P_M} = 0.5 \quad (3.5)
\]

This result can be extended to predict the behavior of a reciprocal-inhibition network that consists of two identical neurons having different synapses that are characterized by different cophas e plots. The relationship between the recovery time ($t_r$) of one neuron and the stimulus time ($t_s$) of the other neuron (equations 3.2 and 3.3) are still valid, however, since non-identical synapses exist at each of the neurons, the associated cophas e functions will be different, and the phase lock will not be 180°.

Therefore, in the case of different synapses (Figs. 3.6 and 3.7):

\[
t_{s1} = t_{r2} = f_1(t_{s2}) \quad (3.6)
\]

\[
t_{s2} = t_{r1} = f_2(t_{s1}) \quad (3.7)
\]

where $f_1$ and $f_2$ are the cophas e functions for the two synapses having different duration. Equation 3.6 can be rewritten as:

\[
f_1^{-1}(t_{s1}) = t_{s2} \quad (3.8)
\]

and substituted into eq. 3.7 to yield the following relationship:

\[
f_2(t_{s1}) = f_1^{-1}(t_{s1}) \quad (3.9)
\]
Since the cophase functions $f_1$ and $f_2$ do not have an inverse, we cannot obtain an 
analytical solution for the mutual period and the phase lock. However, the solution 
for the network can be found graphically at the intersection of the curves $f_1^{-1}$ and $f_2$ 
(the graphical equivalent of eq. 3.9). At the intersection, the property of the cophase 
function as stated in eq. 3.1 holds. Consequently, the solution for the mutual period 
and the phase lock are given as:

$$P_M = t_{s1} + t_{r1} = t_{s2} + t_{r2} \quad (3.10)$$

$$\Phi_M = \frac{t_{s1}}{P_M} \quad (3.11)$$

which is consistent with equations developed in the previous section for the special 
case of identical neurons and identical synapses.

### 3.3.2 Generalization to a ring of n neurons

The analysis presented in the previous section can be extended to a general ring 
of n neurons coupled with unidirectional inhibitory synapses of different durations 
(Figure 3.8). As is the case for the reciprocal-inhibition network (the simplest ring 
network), a relationship exists between the recovery and stimulus times of adjacent 
neurons in the n-neuron ring, however the relationship is much more complex than 
that expressed by eq. 3.6. For the case of a three ring network, the stimulus time of 
one neuron is equal to the sum of the recovery times of the other two neurons. In a 
graphical sense, the solution for this case can be visualized as the intersection of three 
surfaces in a three dimensional space. The complexity and difficulty of visualization 
can be easily appreciated as the number of neurons in the ring is increased. As a result, 
we have devised an alternative method of solving this problem based on the fact that 
at any instant of time, an individual member of the ring network oscillates such that 
its period consists of two parts: 1) the time before stimulus, and 2) the recovery time;
Figure 3.8: Ring type network consisting of n neurons connected with inhibitory type synapses

and furthermore, that these two parts are functionally related in a cophase function $t_r = f(t_s)$. In an n-neuron ring, each neuron satisfies the relationship expressed earlier in eq. 3.1, that is,

\[
\begin{align*}
t_{s1} + f_1(t_{s1}) &= P_M \\
t_{s2} + f_2(t_{s2}) &= P_M \\
& \quad \vdots \\
t_{sn} + f_n(t_{sn}) &= P_M 
\end{align*}
\]  

(3.12)

where the unknowns in this set of equations are the $t_{si}$ (for $i = 1, 2, \ldots n$) and $P_M$. The above set of equations can be rewritten in a more compact form as:

\[
\sum_{i=1}^{n} (t_{si} + f_i(t_{si})) = nP_M 
\]  

(3.13)
Above sum can be separated due to the periodic behavior exhibited by the network. Periodicity condition allows for separation of eq. 3.13 into two parts,

\[
\sum_{i=1}^{n} t_{si} = aP_M
\]  

(3.14)

\[
\sum_{i=1}^{n} f_i(t_{si}) = bP_M
\]  

(3.15)

where, \(a\) and \(b\) are integers which must satisfy:

\[
a + b = n
\]  

(3.16)

and,

\[
a, b \neq n.
\]  

(3.17)

The above set of equations can be used to solve an arbitrary network consisting of \(n\) neurons with \(n\) different synapses, provided that all cophase functions are known. The problem can be further simplified for the special case consisting of identical neurons and identical synapses. In this latter case, eq. 3.14 can be used to derive a relationship between \(t_s\) and \(t_r\), which is then used in conjunction with the cophase relationship \(t_r = f(t_s)\) to reduce this system to two equations and two unknowns. The eq. 3.14 can be rewritten as:

\[
n t_s = a(t_s + t_r)
\]  

(3.18)

Solving for \(t_r\):

\[
t_r = \frac{n-a}{a} t_s
\]  

(3.19)

The solution to the above set of equations can be found graphically as the intersection of the cophase function and a straight line passing through the origin with a slope \(Q\) given by:

\[
Q = \frac{n-a}{a}; \quad a = 1, 2, \ldots (n-1).
\]  

(3.20)
Consequently, a ring type network consisting of \( n \) neurons has at most \((n-1)\) solutions corresponding to the intersections of the cophase function with the lines of slope \( Q_i \) \((i = 1, 2, \ldots, n - 1)\). That is, a three ring network will have two possible solutions, corresponding to intersections of cophase function with lines of slope \( Q = 2 \) and \( Q = 1/2 \), whereas a four ring network will have at most three solutions corresponding to slopes \( Q = 1/3, Q = 1, \) and \( Q = 3 \). The existence of a particular solution depends on whether intersection exists. In some cases, the cophase functions corresponding to intermediate and long duration type synapses may not intersect lines having smaller slopes, and thus will have a more limited set of solutions.

3.3.3 Iterative map methods

The graphical methods described in previous sections are very useful in predicting special cases of ring type networks consisting of identical neurons and identical synapses. However, these methods are limited to providing only the steady-state solutions. It is clear that such perfect symmetries do not exist in nature, however we can utilize the knowledge gained to better understand more complex cases. In this section, techniques are developed that allow consideration of ring type configurations that consist of different bursting neurons and different synapses. Importantly, these methods also provide both transient and steady-state solutions. By considering the relationship of the stimulus time \( (t_s) \) of one neuron and the recovery time \( (t_r) \) of the other neuron for the cycles \( k \) and \( k + 1 \), an algebraic relationship can be developed and subsequently implemented as an iterative map [81]. In the case of the simple reciprocal-inhibition network, the stimulus time of neuron \( N1 \) is equal to the recovery time of neuron \( N2 \); i.e., in the \( k \)th cycle:

\[
t_{s1k} = t_{r2k}, \quad (3.21)
\]
and the recovery time of N1 is equal to the stimulus time of N2:

\[ t_{s_{2k}} = t_{r_{1k}} = f_1(t_{s_{1k}}). \quad (3.22) \]

Since the same relationship holds in cycle \(k+1\), it follows that:

\[ t_{r_{2k+1}} = f_2(t_{s_{2k}}) = f_2[f_1(t_{s_{1k}})]. \quad (3.23) \]

Consequently, the stimulus times for N1 in cycles \(k\) and \(k+1\) are related in the following manner:

\[ t_{s_{1k+1}} = f_2[f_1(t_{s_{1k}})]. \quad (3.24) \]

By iterating this equation from a starting condition on N1, both the transient and steady-state behavior of N1 can be determined. Note that the influence of N2 is implied and contained within the equation via the cophasic function \(f_2\).

Analogous to the above development, an iterative map for the three ring network can be devised. In this case, the stimulus times of two adjacent neurons have to be considered simultaneously. The map for the three neuron ring consists of two simultaneous iterative maps considering cycles \(k\) and \(k+1\) for adjacent neurons N1 and N3 (given here without full development):

\[ t_{s_{3n+1}} = f_1(t_{s_{1n}}) + f_2(f_1(t_{s_{1n}}) + f_3(t_{s_{3n}})) \quad (3.25) \]

\[ t_{s_{1n+1}} = f_2(f_1(t_{s_{1n}}) + f_3(t_{s_{3n}})) + f_3(t_{s_{3n+1}}). \quad (3.26) \]

For details regarding the development of these mapping equations consult Appendix A.

### 3.3.4 The Network Emulator

For networks of higher complexity, it is difficult to write a relationship in terms of a compact iterative map as was done in the previous section for small rings consisting
of two and three neurons. However, utilizing the cophase information for different duration synaptic inputs, a relatively simple algorithm can be devised which can either be implemented numerically on a computer, or via circuit elements in a hardware unit. Implemented as a computer program, the Network Emulator (Figure 3.9) considers an arbitrary ring of neurons with different synaptic connections. The inputs to this circuit are the initial timing events for each neuron \((T_{11}, T_{22}, \ldots, T_{NN})\) and the timing events for any external inputs \((T_{EXT1}, T_{EXT2}, \ldots)\) (e.g. higher-level neuronal control signals to the network).

Figure 3.9: Block diagram of the Network Emulator

The inputs to the Network Emulator are the timing events for the cycle \(k\), representing the time when each neuron will begin firing \((T_{11} through T_{NN})\). The output is the updated time for a neuron which was affected by the current bursting activity. Subscript \(k\) denotes current states of timing events for each neuron, while \(k+1\) denotes the next state of the affected neuron as result of activity in cycle \(k\).
The timing event describes a particular point in the cycle of activity and is set to occur at the beginning of the burst. The beginning of the burst is significant since it also marks the beginning of activation of the synaptic current in the post-synaptic cell. Computation is performed in a manner somewhat analogous to an iterative map. In each computing cycle, the timing of a particular neuron is considered, its effects on other members of the network are computed, and the appropriate timing diagram is updated. The Network Emulator is based on the following evaluation sequence (see Fig. 3.9):

1. Timing events for all neurons and any timing events for external stimuli are compared \((T_{1k}, T_{2k}, \ldots, T_{N_k} \text{ and } T_{EXT_{1k}}, T_{EXT_{2k}}, \ldots T_{EXT_{N_k}}\text{, respectively})\). The minimum value is selected, which marks the 'reference time' for this computational cycle, and identifies a neuron whose activity is about to affect the rest of the circuit. We label this neuron the "effector" neuron for this cycle, and refer to it as neuron X (Figs. 3.9 and 3.10);

2. The topology of network connections is contained in the Network Look-Up Table (Fig. 3.9), and is utilized to determine which neuron(s) are affected by the activity of the "effector" neuron. (NOTE: Although one neuron can have an effect on multiple other neurons, for simplicity and consistency with the ring network structure, only a single affected neuron is considered). This identified neuron whose activity is altered, is referred to as the "affected" neuron (labeled Y in Figs. 3.9 and 3.10). The look-up table (Fig. 3.9) produces two pieces of information: which neuron (labeled Y) is affected by the X neuron, and the value of the timing event \((T_{Y_k})\) associated with that neuron;
3. The timing events of the effector neuron X and the affected neuron Y are subtracted at the summing junction (Fig. 3.9) to obtain a time of stimulus delivery \( t_{SY} \) for the affected neuron Y;

4. The stimulus time \( t_{SY} \) is subsequently fed to a bank of cophase functions, which outputs the recovery time \( t_{RY} \) for the affected neuron;

5. The timing events for the \( k + 1 \) cycle of the effector and the affected neurons \( (T_{X_{k+1}} \text{ and } T_{Y_{k+1}} \) respectively) are computed next.

   (a) Timing for the effector neuron \( (T_{X_{k+1}}) \) is computed by adding a free-running period \( (P_0 = 13.3sec) \) to the previous timing event \( (T_{X_k}) \) for this neuron. In essence, the effector neuron is updated as if it will not receive any signals in the future.

   (b) Timing of the affected neuron \( (T_{Y_{k+1}}) \) is computed by summing its recovery and stimulus times, and adding it to the previous timing event \( (T_{Y_k}) \).

6. The computed timing events for the effector and affected neurons are fed back to update the list of timing events, a new 'reference time' is selected, and the process is repeated.

The above evaluation sequence, considers a single temporal event (beginning of the burst activity of one neuron in the network), and its effect on other members of the network (only one neuron is affected in a ring type network). Repetition of this evaluation sequence computes the effects of burst activity of each of the neurons sequentially. Steady-state results are reached when the periods of each of the neurons cease to change, and the phasic relationship between the neurons becomes fixed. In the event that a signal from an external input is being applied to one or more members of the network, the sequence of events is the same as described before, except
that the information regarding the control configuration is contained in the External Control Configuration (Fig. 3.9). Although a number of control configurations could be implemented, for brevity, the control configuration shown in Fig. 3.9 indicates that a single external control signal can be applied only to neuron N1. The cophase information for the type of synapses used by the control signals are included in the bank of cophase functions.

![Figure 3.10: Timing diagram for the neurons X and Y used in the Network Emulator](image)

Knowledge of the beginning of the burst activity for the effector (X) and affected (Y) neurons is used in conjunction with the cophase information to update the timing of the next burst for the affected neuron, $T_{Y,k+1}$. The time reference for processing is indicated by the vertical dashed line and corresponds to firing time of effector neuron X ($T_{X,k}$).
Similar to iterative maps from previous sections, this algorithm simulates both the transient and the steady state behavior of the network. An added benefit of the Network Emulator is that if the network configuration changes, new equations need not be written, but only the content of the lookup table needs to be changed to reflect the new configuration of the network. Furthermore, the Network Emulator allows addition of external control neurons which would permit investigation of the full range of behavior of a given network, as well as conditions for control of said network. Computationally, the Network Emulator saves several orders of magnitude of computer time compared with the time consumed in running the simulations of the network of model neurons. The benefit of time saving comes at the expense of small errors introduced by the changes in a burst duration encountered as a result of synaptic coupling (this will be further discussed in the following section).

An additional main benefit of the Network Emulator is that it can be implemented in hardware with relatively few components. One possible hardware implementation consists of the following major components:

1. a register to hold the timing events for all neurons and external control signals;

2. a comparator used to select the reference timing event from the register by finding the minimum value of all timing events;

3. a decoder used to represent the look-up table; and

4. a function generator block consisting of combination of op-amps and nonlinear resistive elements used to represent the cophase functions, and a multiplexer used to select the appropriate cophase function from the function generator block.

Each of the identified reference timing events resulting from successive iterations could be saved in a memory, representing the time record of the behavior of the circuit for
a particular simulation. This network implemented in hardware, would allow real
time simulation of the behavior of individual neurons comprising the network. Such
a circuit would serve as a prototype for the construction of control systems that
could mimic the operation of central pattern generators, including the control
mechanisms for switching between different modes of operation via external control
neurons.

3.3.5 Prediction of Mutual Period Using the Network Emulator

The ability of Network Emulator to accurately predict the mutual period and the
phase lock is illustrated in Figs. 3.11 and 3.12, which compare the Network Emulator-
generated results with simulation results obtained with a reciprocal-inhibition model.
Fig. 3.11 shows the results for the reciprocal inhibition network consisting of identical
neurons and identical synapses. Note that the mutual period $P_M$ for the coupled cir-
cuit is less than that for the uncoupled neurons ($P_b$) for time constants in the range
$0.1 \leq k_R^{-1} \leq 0.5 \text{sec}$. For larger values of $k_R^{-1}$, the mutual period increases. Over
the complete range of values for $k_R^{-1}$, the Emulator predictions and the neuron network simulations agree favorably, but increase with increasing $k_R^{-1}$ (Fig. 3.11). The
approximation error, measured as the difference between the values predicted using
the Network Emulator and those from modeled network simulations, is calculated as:

$$E_{APPROX} = \frac{|P_{M, model} - P_{M, predicted}|}{P_{M, model}} \times 100\%,$$

and ranges from 0.1% to 8.0%. The source of this error is due to the fact that burst
duration of a neuron changes as the result of coupling (see Section 3.2). The Network
Emulator assumes that no change in a burst duration occurs. The approximation
error ($E_{APPROX}$) increases with an increase in duration of the synaptic connections
used, since longer duration synaptic currents cause larger changes in the burst dura-
tion. The Network Emulator assumes burst duration is constant and equal to that
value attained under free-running conditions.

Similar results are obtained when the simple reciprocal-inhibition network is coupled via synapses having different durations. Fig. 3.12 shows model-generated and predicted results for the case where one neuron is innervated with a fundamental synapse ($k_{R}^{-1} = 0.5 \text{sec}$), while the synapse for the other neuron is swept through a range $0.1 \text{sec} \leq k_{R}^{-1} \leq 3.0 \text{sec}$. As with identical synapses, the source of error in predictions for the mutual period $P_{M}$ is the change in burst duration occurring as a result of coupling. Predictions for the phasic relationships $\Phi_{M}$ between the two neurons have a much smaller error than those for the mutual period because the changes in burst duration occur at both neurons, and tend to offset each other. When two synapses of similar durations are used, both neurons undergo approximately the same changes in the burst duration, and thus the error is very small. On the other hand, when the difference in duration is greater, there is greater discrepancy in burst duration changes. Consequently, the error in the phase lock prediction is greater (see Fig. 3.12B).
Figure 3.11: Prediction of the mutual period of the reciprocal-inhibition circuit comprised of identical R15 neurons with identical synapses

A) Mutual period $P_M$ of the reciprocal-inhibition network is controlled by synaptic properties, specifically the time constant $k_R^{-1}$ (associated with the closing of the synaptic channel). Open circles indicate data points for the simulated mutual periods of two R15's connected in the reciprocal inhibition circuit, whereas filled triangles indicate the predicted values of the mutual period $P_M$. Dashed line represents the free-running period $P_0$ of the unconnected bursting neuron. B) Approximation error is in the range 0.1% to 8.0%, and it increases with the increase in $k_R^{-1}$.
Figure 3.12: Prediction of the mutual period of the reciprocal-inhibition circuit comprised of identical R15 neurons with different synapses

Identical neurons with different synapses come to a mutual frequency, smaller or greater than the control period \( P_0 \) (A), and lock to an arbitrary phase (B). Circles indicate simulated, whereas squares indicated predicted values for the mutual period \( P_M \) and phase lock \( \Phi_M \), whereas filled triangles indicate the predicted values. Duration of synaptic current for N1 is held constant \( k_R^{-1} N1 = 0.5sec \), whereas the duration of synaptic current for N2 is swept to include a range of durations (corresponding to values \( 0.1sec \leq k_R^{-1} N2 \leq 3.0sec \)). C) Approximation error is in the range 0.5% to 6.0%, and it increases with the increase in \( k_R^{-1} \).
Chapter 4

Mode Switching in Simple Central Pattern Generators (CPGs)

In this section we utilize the techniques and prediction methods developed in section 3.3 to extend our analysis to more complex ring type networks. The utility of the Network Emulator in this context is demonstrated in a number of specific examples. First, it is used to demonstrate the ability of switching from one mode of behavior to another in a three ring network, with a single external stimulus delivered to only one of the ring neurons. Second, the Network Emulator is utilized in investigating the possible modes of behavior of a CPG generating timing for the movement of legs in a quadruped locomotion. These examples demonstrate the utility of the prediction methods and the validity of the Network Emulator.

4.1 A Three Neuron Ring Network

Although no specific motor program is known to be generated by the simple three ring network shown in fig. 4.1, it has been implicated as a possible mechanism in coordinating the multiphasic limb movements in urodelans and the segmental undulations of leech swimming [36, 41]. Friesen and Stent, [36] have used a recurrent cyclic inhibition circuit (such as the one shown in fig. 4.1) as a locomotion rhythm generator for leech swimming, and have shown that the neuron discharges are separated by phase angles of 120°. They have also shown that the firing order of the three cells occurs in a direction opposite to that of the inhibitory connections forming the ring. Using a group-theoretic approach, Collins and Stewart [30] have presented a similar result,
Figure 4.1: Three neuron ring network
Three neurons in a network are connected via inhibitory synapses. There are two possible modes of behavior for this network, corresponding to a clockwise MODE-1 and a counterclockwise MODE-2 rotating waves.

Showing that this type of network has a single rotating wave solution, predicted by a Hopf bifurcation to a unique branch of rotating waves, and that only one sense of rotation will occur at each generic Hopf bifurcation. From the analysis given in section 3.3, we have shown that it is possible for a three neuron ring network to have two distinct modes of behavior corresponding to rotating waves in either direction around the ring. The two modes of behavior are defined by a solution given in eq. 3.20, which is repeated here for convenience:

\[ Q = \frac{n-a}{a} \quad a = 1, 2, \ldots (n-1) \]  

(4.1)

The two modes are defined graphically by the intersection of the cophase curve with straight lines through the origin of slope Q (corresponding to \( n = 3, a = 1 \) and \( a = 2 \) in eq. 4.1). Figure 4.2A shows the intersections of these lines with the cophase curves for the short (S), intermediate (I), and long (L) duration synapses. Intersection of
the cophase curve with both lines exists only for the short type synapse. In contrast, the intermediate and long type synapses have only one intersection (with a line of slope $Q = 2$), indicating only one possible pattern of oscillations. The two different solutions for the short duration synapse, correspond to two different oscillation patterns. An intersection of the cophase curve with the line of slope $Q = 2$ corresponds to neurons oscillating in a clockwise rotating wave (Fig. 4.1) such that N3 fires first, N2 second, and N1 last (the N3·N2·N1 firing order). We label this pattern MODE-1 (see Figs. 4.1, and 4.2B) and note that the phasic relationship between the neurons is such that N1 leads N2 by 240°. The second solution ($Q = 1/2$) corresponds to an oscillation pattern where N1 fires first, N2 second and N3 last. This solution corresponds to a counterclockwise rotating wave (the N1·N2·N3 firing order), and is shown in Fig. 4.2C. For this second pattern of activity, neuron N1 leads N2 by 120°. The two patterns of behavior, produce different mutual periods ($P_M$) since each solution defines different values for stimulus time $t_s$ and recovery time $t_r$ on the cophase curve. Our simulations extend previous observations about the modes of behavior of a three ring network [30, 36], by showing that the rotating wave can be set either in the clockwise or the counterclockwise direction.

4.1.1 Mode switching in a three-neuron ring

The Network Emulator is further employed to examine the possibility of switching between the two distinct modes of patterned activity exhibited by the three neuron ring. Specifically, the Network Emulator is configured such that the three neuron ring considered earlier is controlled via a single external interneuron (IN), which provides a control signal for neuron N1 via an inhibitory synapse (see fig. 4.3). This simulation mimics the effect of an inhibitory interneuron descending from a higher control center to influence the CPG. With this configuration it is quite possible to switch the pattern
Figure 4.2: Modes of oscillation exhibited by a three neuron ring network. Two modes of behavior are defined by intersections of the cophase curve with lines of slope $Q = 2$ (defining MODE-1) and slope $Q = 1/2$ (defining MODE-2), (A). The time record for all three neurons is shown in both cases: MODE-1 (B), and MODE-2 (C).
of the modes of a three-neuron ring, with a supervisory control signal presented to any single member of the network. Fig. 4.4 shows that a single transient supervisory event applied to any one member of the ring, can switch the network between its two patterns of behavior (clockwise or counterclockwise rotary behavior). Mode switching from MODE-2 to MODE-1 and back to MODE-2 is illustrated in fig. 4.4. The time of supervisory signal application is very important in achieving a successful mode switch. Depending on the time of external stimulus application within the cycle of bursting neuron N1, any one of the following events may occur: 1) the network may switch immediately to a new mode; 2) it may switch after a transient period during which the neurons are not phase-locked; or 3) it may be only slightly perturbed, causing the ring to transiently fall out of lock, but still remain in the same mode.

![Diagram](image)

**Figure 4.3:** Configuration of external control imposed on a three neuron CPG
External control neuron (IN) is connected to a three neuron ring CPG via an inhibitory connection to neuron N1.
4.1.2 Mechanism of Mode Switching

When the external supervisory signal is delivered with a phase relative to the ongoing activity of N1 that can produce mode switching, it prolongs the hyperpolarization period of N1 and delays the onset of the following burst (Fig. 4.4). This allows N2 to come out of its hyperpolarization faster (since it doesn’t receive an input from N1 on this cycle). When the activity of N2 is accelerated, the activity of N3 is also accelerated, causing N3 to fire sooner, hence switching the mode. Thus, on transition from MODE-2 to MODE-1 the supervisory signal extends the hyperpolarization period of N1 sufficiently to allow both N2 and N3 to fire before the onset of burst activity in N1. Wave motion around the ring changes from counterclockwise to clockwise. Mode switching was also simulated using the R15 model neurons combined in a ring configuration. Specifically, mode switching from MODE-2 to MODE-1 and back to MODE-2 is illustrated in fig. 4.5, and the results of the neuron model simulation closely correspond to those of the Network Emulator (Fig. 4.4). The particular simulations shown in figs. 4.4 and 4.5 correspond to about 140sec of simulation time (twelve cycles of activity for each neuron). The simulation took approximately seven hours, while the results produced by the Network Emulator (fig. 4.4) were generated in under two minutes.

4.1.3 Regions of successful mode switching

The regions of successful mode transitions were investigated utilizing the Network Emulator. Due to symmetry of the ring structure of this network, its mode of behavior can be switched by applying an external control signal to any neuron. For consistency, we investigated the mode switching by applying the control signal to N1 (see diagram in Fig. 4.3) at different times in the cycle of its activity. This process was repeated for several control signals having different duration synaptic currents
Figure 4.4: Mode switching in a three neuron ring (Network Emulator)
An oscillatory mode in a three neuron ring network can be switched by applying an external inhibitory synaptic input to any of the neurons in the ring. In this example, external input $I_{EXT}$ was delivered to neuron N1. First external input caused a switch from MODE-2 (an $N1 \cdot N2 \cdot N3$ firing pattern with a period $P_M = 15.38\text{sec}$ and a phase $\Phi_M = 120^\circ$) to MODE-1 (an $N3 \cdot N2 \cdot N1$ firing pattern, $P_M = 11.3\text{sec}$ and $\Phi_M = 240^\circ$). A second application of the external input switches the mode again. Identical neurons with identical synaptic connections ($k_R^{-1} = 0.5\text{sec}$) were used.
Figure 4.5: Mode switching in a three neuron ring (Model)
An oscillatory mode in a three neuron ring network can be switched by applying an external inhibitory synaptic input to any of the neurons in the ring. In this example, external input $I_{EXT}$ (5nA for 4.6sec) was delivered to neuron N1. First external input caused a switch from MODE-2 (an $N1 \cdot N2 \cdot N3$ firing pattern with a period $P_M = 15.38\text{sec}$ and a phase $\Phi_M = 120^\circ$) to MODE-1 (an $N3 \cdot N2 \cdot N1$ firing pattern, $P_M = 11.3\text{sec}$ and $\Phi_M = 240^\circ$). A second application of the external input switches the mode again. Identical neurons with identical synaptic connections ($k_{R^{-1}} = 0.5\text{sec}$) were used.
(short (S), intermediate (I) and long (L); Figs. 4.6B, C, and D respectively). As a result of application of an external signal, the network can either remain in its present mode, or it can switch its mode of behavior after a transient period. Fig. 4.6 shows that the mode can be switched if an external signal is delivered just before or just after the onset of bursting activity in controlled neuron N1. This is valid for both the transition from \( N3 \cdot N2 \cdot N1 \) (MODE-1) to \( N1 \cdot N2 \cdot N3 \) (MODE-2) and transitions from MODE-2 to MODE-1. When the control signal is delivered during the interburst interval of N1, the network does not switch modes, but rather returns to the same mode after a transient period resulting from the perturbation. Figure 4.6 shows the regions of effective mode switching via the shaded regions shown in panels B, C, and D. The regions for which the application of external control signal does not result in a successful mode switch are left unshaded. The lighter gray shading indicates regions of successful transition from MODE-2 to MODE-1, whereas the darker gray shading represents regions of successful transition from MODE-1 to MODE-2. The length of the region indicates relative range of stability of the two modes. For each type of control signal (shown in panels B, C, and D) the darker gray region is longer than the lighter gray region signifying that it is easier to switch out of MODE-1. This finding could have been expected from the knowledge of where the particular solutions reside on the cophase curve (CC). Solution for MODE-1 resides on the steeper portion of the CC than MODE-2 (fig. 4.2), which indicates that it is easier to perturb the system out of that mode, than out of MODE-2 which resides on a relatively flat portion of the CC. The mode switch is successful if the external pulse is delivered just prior or just after the onset of the bursting activity of the controlled neuron (e.g. N1 in Fig. 4.3). The region of the successful mode switch right after the onset of the burst is relatively independent of the duration of external control signal (Fig. 4.6B, C, and D), whereas the region just prior to the onset of the burst increases with the increase
in the duration of the control signal. Besides identifying what regions of application of external stimuli result in successful mode transition, from the standpoint of control theory, it is of great interest to identify a mode transition which results in a minimum transient. We have found that the mode switching transient is minimized if: 1) the external signal and network connections are 'matched' (i.e. duration of external signal is identical duration of synaptic currents within the network), and 2) if the external signal is delivered as close as possible, but prior to the onset of the burst of the controlled neuron. Above point is illustrated in Fig. 4.4, where the lock to a new mode is achieved within one cycle from the delivery of the external signal.
Figure 4.6: Regions of successful mode switching for different duration synapses

The most efficient mode transition is achieved when an external input is delivered just before or just after the onset of the burst for a given neuron. Different duration external synapses have different regions in which successful transitions (shaded areas) are possible. Transitions with the shortest transient are achieved when an external input is of the same duration as the synapses interconnecting neurons in the ring network. Regions of successful mode switching for S, I, and L type synapses are shown separately in panels B, C, and D (corresponding time constants are $k_R^{-1} = 0.1\sec, 0.5\sec, \text{ and } 2.0\sec$). Lighter gray shading represents regions of successful MODE-2 to MODE-1 transitions, while darker gray shading represents MODE-1 to MODE-2 transition.
4.2 A four ring network: Quadrupedal gait locomotion CPG

The four ring network configured as in Fig. 4.7, has been utilized as the simplest Central Pattern Generator capable of producing several distinct patterns of activity corresponding to timing events associated with leg locomotion in a four legged animal [30]. The outputs of neurons N1, N2, N3 and N4 in Fig. 4.7 provide the timings for the right-hind (RH), right-front (RF), left-hind (LH) and left-front (LF) limbs, respectively.

![Diagram of a four ring network]

**Figure 4.7: Quadrupedal gait locomotion Central Pattern Generator**
A four ring network is configured such that its modes of behavior correspond to the animal locomotion leg patterns in four legged animals. Note that the above configuration is simply a ring that has been “twisted”.

The three most common gaits exhibited by a horse (a representative four-legged animal) are: the walk, trot and bound. Each gait exhibits a distinct pattern of leg motion and a phasic relationship among the legs is maintained throughout the gait. From standstill, the walk mode is initiated by the movement of one of the hind legs. For consistency, we choose the RH limb to be the initiating leg. The phasic relationships of other limbs are defined relative to the initiating leg. Thus, in a walk, the legs move sequentially in a figure-eight wave, where each limb is lagging the previous one by a quarter turn (90°). In the trot, the diagonal limbs move in phase, and the
two diagonal pairs are 180° out of phase with each other. In the bound gait, the hind and front legs form two synchronous pairs, and the phase difference between the front and hind pairs is 180°. The phasic relationship, the limb order, and the neuron corresponding to the particular leg are summarized in Table 4.1, along with an indication of which solution of the four ring network (Qi, i = 1, 2, 3) applies to each mode.

The theoretical predictions of section 3.3 indicate that at most three different oscillating solutions exist for this four ring network. The three solutions are defined by the intersection of the cophase curve with the lines of slope Qi (i = 1, 2, 3) (Fig. 4.8A). For this network, the solution slopes are Q = 3, Q = 1 and Q = 1/3, which will be referred to as MODE-1, MODE-2 and MODE-3 solutions respectively. Figure 4.8A shows that a network can exhibit all three modes of behavior only if the short type synapse (S) is used for network connections. In contrast, a network connected via intermediate (I) or long (L) type synapse will exhibit only two modes of behavior. The short duration cophase curve corresponds to a synaptic current 0.5sec in duration, whereas the I and L cophase curves correspond to synaptic currents of 3.2sec and 8.0sec in duration, respectively.

<table>
<thead>
<tr>
<th>GAIT</th>
<th>WALK</th>
<th>TROT</th>
<th>BOUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEURON</td>
<td>RH,LF</td>
<td>RH,LF</td>
<td>RH,LH</td>
</tr>
<tr>
<td>LIMB</td>
<td>LF</td>
<td>RF</td>
<td>RF,LF</td>
</tr>
<tr>
<td>PHASE</td>
<td>0.0</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLUTION</td>
<td>Q=1/3</td>
<td>Q=3</td>
<td>Q=1</td>
</tr>
</tbody>
</table>

Table 4.1: Basic gaits of a horse
Figure 4.8: Modes of oscillation exhibited by a four neuron ring network
Three modes of behavior are defined by intersections of the cophase curves with lines of slope $Q = 3$ (defining MODE-1), slope $Q = 1$ (defining MODE-2), and slope $Q = 1/3$ (defining MODE-3) (A). The time records generated by the Network Emulator for all three neurons are shown in panels B, C and D.
4.2.1 Gait Patterns

If we consider the bursting activity of each neuron in the ring to correspond to a particular limb of the quadruped being planted on the ground (whereas, the interburst interval corresponds to the same foot raised in the air), then the three modes exhibited by the four ring network closely correspond to the three gaits: walk, trot and bound (see Table 4.1). For the network consisting of identical neurons and identical synapses, the three solutions correspond to the following patterns of activity:

1. slope $Q = 1/3$, yields a pattern where neurons fire sequentially in the following sequence: $N1 \cdot N2 \cdot N3 \cdot N4$ ($RH \cdot RF \cdot LH \cdot LF$), and each neuron is a quarter period out of phase. This mode of behavior corresponds to a walk gait of the quadruped;

2. slope $Q = 1$ defines a pattern where neurons N1 and N4 (a left diagonal in fig. 4.7) fire synchronously and $180^\circ$ out of phase relative to N1 and N3 (which are in phase with each other). Thus a firing sequence is $N1 \cdot N3$, $N2 \cdot N4$ ($RH \cdot LH, RF \cdot LF$), which corresponds to a bound gait;

3. slope $Q = 3$ defines a pattern where neurons fire sequentially similar to a rotating wave of case 1), but in opposite direction. Thus the firing sequence is $N4 \cdot N3 \cdot N2 \cdot N1$.

The last mode does not correspond to a trot as described in Table 4.1, and thus indicates that a four ring network with identical synapses does not adequately produce all three gaits. However, if the phasic relationship of neuron N4 relative to N1, and that of neuron N3 relative to N2 could be reduced, this pattern would resemble a trot to a higher degree. This requirement identifies a need for adaptive control of synaptic connections within the network. The trot gait can be achieved by adjusting synaptic connections within the network such that front and hind legs have different
duration synapses. Specifically, the phasic relationship appropriate to the trot gait is easily achieved if the front leg neurons are innervated with a shorter type synapse ($k_R^{-1} = 0.5\text{sec}$), whereas the hind leg neurons are innervated with a longer duration synapse ($k_R^{-1} = 1.0\text{sec}$). As a result of this change in synaptic durations for the front and hind limb neurons, the bursting activity of neurons N4 and N2 are moved closer to the bursting activity of N1 and N3 respectively, thus synchronizing the left and right diagonal pairs to a greater degree (Fig. 4.9). The pattern produced is in greater agreement with the trot mode, than that produced with a four ring network with identical synapses (see fig. 4.8).

The adaptive control of synapses could be applied to other gaits as well. For example, specifying different duration synapses for front and hind legs (e.g. S and L type synapses, respectively), brings the action of the front legs closer to the activity of the hind legs. Therefore, the resulting phasic relationship between front and hind legs is less than $180^\circ$. This is actually a better representation of the bound gait than that of the perfect symmetry ($180^\circ$ phasic relationship between the front and hind legs) described in Table 4.1.
Figure 4.9: Quadrupedal gaits exhibited by a four neuron ring network

When different duration synapses are used on the front and back “legs” of the four neuron ring network, MODE-1 corresponds more closely to a trot gait. (A),(C),(E) show the timing when the leg touches the ground (dark areas), while (B),(D),(F) show the corresponding time course of the individual neurons generated by the Network Emulator.
Chapter 5

Discussion

5.1 Synaptic Model

The networks examined in this study were constructed utilizing a model of the prototypical bursting neuron R15, and a synaptic model that was developed for the purpose of connecting bursting neurons into networks that emulate central pattern generators (CPGs). The synaptic model utilized incorporates most of the major components of synaptic transmission, but complexity was kept to a minimum. The resulting two-state synaptic model describes the process of transmitter release into the synaptic cleft as a result of $[Ca^{2+}]$ influx into the pre-synaptic cell, and the subsequent binding of transmitter to a receptor in the post-synaptic membrane, which activates a synaptic current in the post-synaptic cell. Synaptic events in models of neural networks are often formalized as stereotyped, time-varying channel conductance waveforms. The most commonly used waveform is the so-called $\alpha$-function [32, 63, 68, 75] which is usually written in the following form:

$$g_{syn}(t) = \frac{t - t_0}{\tau} \exp\left[\frac{-(t - t_0)}{\tau}\right]; \quad t \geq t_0$$

(5.1)

where $g_{syn}(t)$ is the lumped membrane conductance associated with the synaptic current, and $t_0$ is the time of transmitter release. In this relationship, the synaptic conductance waveform bears only an approximate correspondence to physiological recordings of the post synaptic response, but otherwise lacks correlation with the underlying biophysical processes. In contrast, our kinetic model of the synapse pro-
vides biophysically based estimates of the changes in post-synaptic conductance (and related current) in response to transmitter release.

5.2 Insights from the Phase Sensitivity Analysis

Several investigators have shown that the concepts derived from the oscillator theory can be a useful tool aiding physiologists and neurobiologists who are investigating behaviors of neural circuits [47, 64]. Oscillator theory can provide a precise description of the dynamic behavior of the neuronal oscillators, and furthermore, it can provide empirical testable predictions. Phase sensitivity analysis has been successfully utilized by Pinsker et al [64, 65] in an investigation of synchronization and entrainment of endogenous neural oscillators in the isolated abdominal ganglion of Aplysia californica. Furthermore, Ayers and Selverston [47] have described PRCs for both excitatory and inhibitory synaptic modulation of the slow bursting neurons in the lobster pyloric system, and have also demonstrated the relationship between the PRCs and steady-state entrainment curves.

Our examination of the phase sensitivity of an R15 cell to external synaptic inputs proved to be very fruitful, in that several important insights were derived. First, one might expect that the model R15 neuron would be phase sensitive to changes in both amplitude and duration of the synaptic current. However, sensitivity analysis revealed that the R15 neuron is dependent mostly on the duration of the synaptic current, and changes in magnitude have little or no effect. These points were extensively investigated in previous studies by our group [31], which provided strong evidence that relatively small changes in the duration of the synaptic current have large effects on the phase sensitivity of a given cell. Furthermore, Demir et al [31], have shown that the shape of the signal has a small effect on the character of the phase
response of the model R15 neuron (i.e. different profiles of synaptic current, but of equal duration result in approximately identical phase response). The second insight gained, is that for the purpose of analyzing network behavior, the cophase curve (CC) is better suited than the PRC. Specifically, the CC provides very simple input-output relationship that reduces the intrinsic behavior of the R15 cell and its synaptic drive to the consideration of a simple functional relationship. Thus, the essence of the behavior of a relatively large system (fourteen coupled non-linear differential equations) is captured in the specification of a relatively simple input-output relationship, the cophase curve. Third, the general shape of either the PRC or the CC can provide intuitive insight into the effects of a given synapse on the activity of the neuron. Shorter duration synapses can produce either a phase delay or a phase advance depending on the timing of the input stimulus, whereas longer duration synapses produce only a delaying effect regardless of the timing of the stimulus.

5.3 Comparison of Prediction Methods

As stated in the INTRODUCTION, identifying all of the neurons and possible connections that might be a part of a given CPG has proved to be difficult even in 'simple' nervous systems of invertebrates [41]. Several investigators have constructed model CPGs to aid in experimental investigations of specific functions in invertebrates, such as leech swimming [18, 40, 42, 43], pyloric rhythm in lobster stomatogastric ganglion [56, 70, 89], and lamprey locomotion [26, 34, 86]. There have been two theoretical studies that have considered symmetric ring type oscillator networks. Stewart and Golubitsky [77] and Collins and Stewart [30] have developed a group theoretic approach to the solution of networks consisting of rings of coupled oscillators representing neurons. Their investigation was motivated by the observation that most animal gaits posses a degree of symmetry, and they related the changes in gait pat-
terns to symmetry-breaking activities. Specifically, they explored an analogy between typical gaits and the periodic oscillations in symmetric dynamical systems. A different approach was developed by Glass and Young [43] who used a directed graph called a state transition diagram to analyze and predict the behavior of oscillating networks. Their approach is restricted to network oscillators containing no rhythm determining pacemaker neurons, and no neurons exhibiting self-limiting properties such as post-inhibitory rebound. Compared with the aforementioned symmetric dynamic approach [30, 77], this later approach [43] has the advantage that it can generate the transient as well as the steady-state solution of the system. Both of these theories are limited to highly symmetric rings, and offer no mechanisms for control.

The two prediction methods developed in this study (the iterative mapping technique and the Network Emulator) also focus on the symmetric ring type CPGs. These methods are based on a simple input-output relationship derived from a phase sensitivity analysis of an arbitrary system. The iterative mapping method is very useful in providing transient and steady-state results for the behavior of a single neuron in the network consisting of a small number of neurons. However, with an increase in the number of neurons in the network, the functional inter-relationships of the component iterative maps become increasingly complex and non-intuitive. To further reduce the complexity of the network, a related method has been developed, which is simpler in concept since it considers only the timings associated with the onset of bursting activity for each neuron. The resulting algorithm (the Network Emulator) is simple to implement computationally and is also amenable to hardware implementation. The Network Emulator is also more versatile and flexible, since it allows adaptive changes of the topology of the network (i.e. changes in the character of the synaptic connections), as well as specification of external control to any neurons in the network.
Furthermore, the hardware implementation of the Network Emulator could produce a useful tool to aid experimental research, as well as construction of nonlinear control systems in robotics applications.

5.4 Comparison of three and four ring CPGs with previous models

5.4.1 Recurrent cyclic inhibition CPG (a three neuron ring)

A three neuron ring CPG has been implicated as a single segment within a layer network of concatenated ring networks, responsible for the swimming rhythm of the leech [36, 41, 82]. Friesen and Stent [36], have indicated that such a network can generate a rotating wave such that the phasic activity of the three component cells is separated by 120°, and the wave progresses in a sense opposite to that of the inhibitory connections forming the ring. This pattern corresponds to a clockwise rotating wave, or MODE-1, shown in Fig. 4.1. Similarly, Collins and Stewart [30] in their group theoretic approach to rings of biological oscillators indicate that for a three neuron ring only one sense of rotation will occur, and that adjacent oscillators will be 120° degrees out of phase.

Utilizing phase sensitivity based methods, we have shown that under certain conditions, a three neuron ring can set up oscillation patterns in both the clockwise and the counterclockwise directions around the ring (see Figs. 4.1, and 4.2). In each case the bursting activities of the adjacent neurons have a 120° phase difference, which is consistent with findings by Friesen and Stent [36] and Collins and Stewart [30]. Thus, we have shown that the structure of oscillations of a three neuron ring is richer than previously expected. In addition, we have demonstrated how the two modes of
oscillation can be controlled via an external command neuron providing signals to initiate the mode switching (Fig. 4.3).

5.4.2 Quadrupedal locomotion CPG (a four neuron ring)

Our investigation of a quadrupedal locomotion CPG was motivated by results obtained by Collins and Stewart [28]. They have used three different oscillator models to represent each of the oscillators in a ring, in an attempt to show that the group theoretic results are model independent, and furthermore, that the four ring CPG can produce multiple phase-locked oscillation patterns that correspond to idealized animal gaits (different phasic patterns corresponding to idealized gaits are shown in Table 4.1). In their investigation, each type of oscillator (Stein neuronal model, Van der Pol oscillator, and FitzHugh-Nagumo oscillator) was tonically driven. Of the three different oscillators, the Stein model produced three patterns which corresponded most closely to the three basic idealized quadrupedal gaits (walk, trot and bound). However, in order to achieve the trot gait, a periodic component had to be added to the driving signal. In each case, the production of the respective gaits depended upon the specific values of the system parameters. In addition, not all of the gait transitions could be achieved.

Our investigation of a quadrupedal locomotion CPG employed a more complicated, biologically realistic oscillator model that is capable of yielding a richer array of gait patterns than the simpler oscillators used by Collins and Stewart [28]. Utilizing phase sensitivity based prediction methods developed in this study, we have shown that a four neuron CPG can exhibit three distinct patterns of behavior without the use of a driving periodic signals, or a change in the intrinsic parameters of the model. Furthermore, we have identified conditions on the synaptic connections needed to
achieve patterns which more closely correspond to the natural gaits of a horse. Specifically, the synaptic connections on the front and on the hind legs need to be different in order to "collect" the front and hind legs, such that in the bound gait, they hit the ground with a relatively short delay (small phase difference). The pattern achieved by this adjustment is closer to that of the natural bound gait exhibited by a horse, where the phase difference between the front and hind legs is small (i.e. front legs hit the ground soon after hind legs), and there is a longer period where the horse is suspended with all four legs in the air.
Chapter 6

Conclusions

Prediction methods based on an input-output relationship (the cophase curves) arising from the phase sensitivity analysis of the R15 model to arbitrary synaptic input have been developed. These methods can be classified into two categories: 1) the iterative mapping method, and 2) the Network Emulator. Both methods are capable of simulating transient and steady-state behavior of the network. The most efficient and versatile method (Network Emulator) has been utilized in examining the modes of behavior of both three and four neuron ring CPGs. Furthermore, it has been employed to determine the conditions for control mechanisms capable of switching between the identified modes in these networks. The Network Emulator was also applied in identifying the changes in network interconnections needed to adequately represent all of the basic gaits in quadruped locomotion. The conclusions of this study can be summarized as follows:

1. The response of R15 cell model is more sensitive to variations in duration than variations in amplitude of the synaptic input. Thus, the information content of the synaptic signal is contained mostly within the duration aspect of the synaptic current.

2. From the standpoint of analysis of networks, cophase curve (CC) provides a simpler input-output relationship than the phase response curve (PRC). A cophase curve or a cophase function relates the time associated with the perturbing event (or stimulus time, $t_s$) to the time spent in the recovery period of the cycle...
(or recovery time, $t_r$). These two important events are present in the context of a network, and thus are considered essential in predicting network behavior.

3. Phase sensitivity analysis essentially reduces a complex system consisting of a neuron and its associated synapse to a simple functional relationship. The resulting CC relates the recovery time $t_r$ of a particular neuron to an occurrence of a perturbing signal somewhere in its cycle (stimulus time $t_s$). Thus, a complex dynamical system consisting of many coupled non-linear differential equations can be reduced to a relatively simple input-output relationship represented by the cophase function, where stimulus time ($t_s$) represents an input, and the recovery time ($t_r$) is the output.

4. This simple input-output relationship can be exploited to devise prediction methods capable of generating transient as well as steady-state behavior of ring type networks. The steady-state prediction methods are based on the observation that at steady-state the network settles to a mutual period $P_M$, where the two parts of the cycle for each neuron ($t_s$ and $t_r$) can be related to those same components in other neurons in the network. Iterative mapping methods exploit the fact that as a result of particular network topology, a relationship exists between the stimulus times in the $k$th and the $(k+1)^{st}$ cycles ($t_{s_k}$ and $t_{s_{k+1}}$ respectively) of each neuron. The Network Emulator is more versatile than the iterative mapping technique explored in this study. It is also simpler in a computational sense. It establishes the firing order associated with the onset of the burst activity for each neuron in the network by first choosing a reference time, and then proceeding to sequentially compute the effect of the bursting activity of a given neuron on every other neuron in the network. While an iterative map has to be written for each specific network topology, the Network Emulator
always maintains the same computational principle regardless of network complexity. Specifically, changes in network complexity are simply reflected in the network look-up table, and the cophase function generator (Fig. 3.9).

5. The prediction methods developed in this study allow us to significantly reduce the complexity of the multiple neuron network. This reduction is especially noteworthy in reducing the computational demands. A relatively simple model of a three neuron network consists of 42 non-linear differential equations, and it requires about seven hours of computation time on a Sun Microsystems IPX platform. In contrast, the Network Emulator iteratively evaluates at most three different cophase functions for the same network, and produces similar results within less than two minutes.

6. Although several approaches were taken, we consider the Network Emulator to be the most flexible and versatile prediction method presented in this study. The Network Emulator allows adaptive changes of the network topology, connections, and allows for application of external control signals. Furthermore, the Network Emulator can be implemented in hardware, and used as a 'biological' control system for movement of legged robots.

7. A ring of \( n \) identical neurons connected via identical synapses will have at most \( n-1 \) patterns of behavior defined by the intersections of a cophase curve with lines of different slopes \( Q_i, (i = 1, 2, \ldots, n-1) \) defined by eq. 3.20. The existence of all \( n-1 \) modes for a particular network, is governed by the existence of these intersections. The character of the cophase depends on the duration of the pertinent synaptic current. For three and four neuron rings to exhibit all of the possible modes, the component neurons have to be connected via shorter
duration synapses. If longer duration synapses are used, only a limited subset of all modes will be possible.

8. The utility of the developed prediction methods was demonstrated in both three and four neuron ring CPGs. Contrary to previous studies, it was demonstrated that a three neuron ring can exhibit two distinct modes of behavior, corresponding to rotational waves in both the clockwise and the counterclockwise direction around the ring. Furthermore, utilizing a simple external control mechanism (a single descending neuron forming an inhibitory synapse on one member of the ring) it was demonstrated that the modes can be switched with a single external signal.

9. A four ring network potentially has three different modes of behavior, and thus is a potential candidate as a simplest model CPG capable of generating patterns that correspond to the basic gaits of a quadruped: walk, trot and bound. In order for all three modes to exist, short duration synaptic connections between the neurons have to be used to guarantee the intersection of the cophase curve with the lines of slopes $Q = 3, 1, \text{ and } 1/3$.

10. When identical neurons and identical synapses are used in a four neuron ring, two of the modes correspond perfectly to walk and bound gaits, but the third mode does not adequately represent the trot. An adequate representation of the trot gait can be produced however, by specifying different duration synapses for the front and hind legs. This indicates that adaptive synapses are better suited for representing different gaits, and therefore, that different gaits may require different pattern of interconnections between the four neurons.
Bibliography


Appendix A

Development of the iterative map equations for a three neuron ring network

This appendix contains a full development of the iterative map equations for the three neuron ring network. By considering the relationship of the stimulus time \((t_s)\) of one neuron and the recovery time \((t_r)\) of the other neuron for the cycles \(k\) and \(k+1\), an algebraic relationship can be developed and subsequently implemented as an iterative map [81]. These relationships are illustrated in Fig. A.1, and given below:

\[
\begin{align*}
    s_{1k+1} &= r_{2k+1} + r_{3k+1} \\
    s_{1k+1} &= f_2(s_{2k+1}) + f_3(s_{3k+1}) \\
    s_{2k+1} &= r_{1k} + r_{3k} = f_1(s_{1k}) + f_3(s_{3k}) \\
    s_{3k+1} &= r_{1k} + r_{2k+1} = f_1(s_{1k}) + f_2(s_{2k+1}) \\
    s_{3k+1} &= f_1(s_{1k}) + f_2[f_1(s_{1k}) + f_3(s_{3k})] \\
\end{align*}
\]

By using simple substitutions, and solving for \(s_{1k+1}\) and \(s_{3k+1}\), the relationships for the \((k+1)\)st stimulus times for the neurons N1 and N3 can be written as:

\[
\begin{align*}
    s_{1k+1} &= f_1(s_{1k}) + f_2[f_1(s_{1k}) + f_3(s_{3k})] + f_3(s_{3k+1}) \\
    s_{3k+1} &= f_2[f_1(s_{1k}) + f_3(s_{3k})] + f_3(s_{3k+1}).
\end{align*}
\]
Figure A.1: Relationship between the stimulus times for the cycles $k$ and $k+1$ utilized in the iterative map for a three neuron ring
Appendix B

Model Equations

This appendix contains the equations and values of parameters needed to simulate one R15 neuron. Nine out of the fourteen equations describe the ion fluxes across the cell membrane, 2 are associated with transmitter release and the synaptic conductance, and the remaining three are associated with: 1) the material balance for $Ca^{2+}$ in the intracellular medium; (2) $Ca^{2+}$ buffer; and (3) the change of cAMP in the cytosol. In these equations, time is in msec, current is in nA, potential is in mV, and concentrations are in mM.
Table B.1: $I_{Na}$: Fast Sodium Current

\[
I_{Na} = \bar{g}_{Na}m^3h(V - E_{Na})
\]
\[
\dot{m} = (m_\infty - m)/\tau_m
\]
\[
m_\infty = \frac{1}{1+\exp((-10.23 - V)/10.0)}
\]
\[
\tau_m = 1/(A_m + B_m)
\]
\[
A_m = \frac{0.49(V+6.0)}{1-\exp((-V-6.0)/1.69)}
\]
\[
B_m = 10.75 \exp((-28.0 - V)/4.01)
\]
\[
\dot{h} = (h_\infty - h)/\tau_h
\]
\[
h_\infty = \frac{1}{1+\exp(V+25.0)/3.0}
\]
\[
\tau_h = 1/(A_h + B_h)
\]
\[
A_h = 0.067 \exp((-43.0 - V)/25.0)
\]
\[
B_h = \frac{0.307}{1+\exp((12.65 - V)/23.9)}
\]
Table B.2: \( I_{Ca} \): Fast Calcium Current

\[
I_{Ca} = \bar{g}_{Ca} \frac{1}{1 + \exp \left( \frac{[Ca]_1 - E_{Ca}}{D_{Ca}} \right)} d^2 f(V - E_{Ca})
\]

\[
d = \left( d_{\infty} - d \right) / \tau_d
\]

\[
d_{\infty} = \frac{1}{1 + \exp((10.0-V)/3.8)}
\]

\[
\tau_d = 1/(A_d + B_d)
\]

\[
A_d = \frac{0.0063(V+10.81)}{1 - \exp((-V-10.81)/5.03)}
\]

\[
B_d = 0.01 \exp((25.0 - V)/10.0)
\]

\[
\dot{f} = \left( f_{\infty} - f \right) / \tau_f
\]

\[
f_{\infty} = \frac{1}{1 + \exp((V+20.0)/4.0)}
\]

\[
\tau_f = 1/(A_f + B_f)
\]

\[
A_f = 0.00325 \exp((10.0 - V)/7.57)
\]

\[
B_f = \frac{0.029}{1 + \exp((20.29-V)/5.4)}
\]
Table B.3: $I_{SI}$: Slow Inward Calcium Current

\[ I_{SI} = \bar{g}_{SI} \left( \frac{K_{SI,Ca}}{K_{SI,Ca} + [Ca]_i} \right) sF_{SI,mod}(V - E_{Ca}) \]

\[ \dot{s} = (s_\infty - s)/\tau_s \]

\[ s_\infty = \frac{1}{1 + \exp((-40.0 - V)/11.5)} \]

\[ \tau_s = 1/(A_s + B_s) \]

\[ A_s = \frac{0.0014(V-54.0)}{1 - \exp((-V+54.0)/12.63)} \]

\[ B_s = 0.00013 \exp((-11.32 - V)/16.8) \]

\[ F_{SI,mod} = \left( \frac{K_{DA}}{D_A + K_{DA}} \right) \left( 1 + \frac{K_{SI,mod}}{1 + \exp\left( \frac{-(cAMP) - K_{SI,cAMP}}{D_{SI,cAMP}} \right)} \right) \]

Table B.4: $I_{NS}$: Non-Specific Cation Current

\[ I_{NS} = \bar{g}_{NS} \left( \frac{[Ca]_i}{[Ca]_i + K_{NS,Ca}} \right) b(V - E_{NS}) \]

\[ \dot{b} = (b_\infty - b)/\tau_b \]

\[ b_\infty = \frac{1}{1 + \exp((-15.0 - V)/3.0)} \]

\[ \tau_b = 500 \left( \frac{0.80}{1 + \exp((10.0 + V)/3.0)} + 0.20 \right) \]
Table B.5: $I_K$: Delayed Rectifier

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

\[
\dot{n} = (n_\infty - n)/\tau_n
\]

\[
n_\infty = \frac{1}{1 + \exp((3.65 - V)/14.46)}
\]

\[
\tau_n = 1/(A_n + B_n)
\]

\[
A_n = \frac{0.0035(V + 17.0)}{1 - \exp((-V - 17.0)/3.0)}
\]

\[
B_n = 0.04 \exp((-28.0 - V)/10.0)
\]

\[
i = (l_\infty - l)/\tau_l
\]

\[
l_\infty = \frac{1}{1 + \exp((32.5 + V)/12.7)}
\]

\[
\tau_l = 2000 \left(\frac{0.90}{1 + \exp((28.0 + V)/3.0)} + 0.10\right)
\]

Table B.6: $I_R$: Anomalous Rectifier

\[
I_R = \bar{g}_R F_{R,mod} \frac{(V - E_K + 5.66)}{1 + \exp\left(\frac{(V - E_K - 15.5)E}{RT}\right)}
\]

\[
F_{R,mod} = 1 + \frac{K_{R,mod}}{1 + \exp\left(-\frac{\Delta_{R,AMP}}{\varphi_{R,AMP}}\right)}
\]

Table B.7: Leakage Current

\[
I_L = \bar{g}_L (V - E_L)
\]
Table B.8: Pumps and Exchangers

\[
I_{CaP} = \bar{I}_{CaP} \left( \frac{[Ca]_i}{[Ca]_i + K_{P,Ca}} \right)
\]

\[
I_{NaK} = \bar{I}_{NaK} \left( \frac{[Na]_i}{[Na]_i + K_{P,Na}} \right)^3 \left( \frac{K_C}{K_C + K_{P,Ca}} \right)^2 \left( \frac{1.5}{1.5 + \exp \left( \frac{-V_{th}}{40} \right)} \right)
\]

\[
I_{NaCa} = K_{NaCa} (DF_{in} - DF_{out}) / S
\]

\[
S = 1 + D_{NaCa} ([Ca]_i [Na]_o + [Ca]_o [Na]_i)
\]

\[
DF_{in} = [Na]_i [Ca]_o \exp \left( \frac{(r-2)rF}{HT} \right)
\]

\[
DF_{out} = [Na]_o [Ca]_i \exp \left( \frac{(r-2)(r-1)F}{HT} \right)
\]

Table B.9: Internal Calcium Concentration

\[
[\dot{Ca}]_i = \frac{I_{NaCa} - I_{SI} - I_{Ca} - I_{CaP} - 0.197(I_{PS} V_{th}/E_{Ca})}{2 \Delta \phi F} - n_B [B]_i \dot{O}_C
\]

\[
\dot{O}_C = k_U [Ca]_i (1 - O_C) - k_R O_C
\]

Table B.10: Internal cAMP Concentration

\[
[cAMP] = k_{adc} \left( 1 + K_{mod} \left( \frac{[SHT]}{[SHT] + K_{SHT}} \right) \right) - v_{pde} \left( \frac{[cAMP]}{[cAMP] + K_{pde}} \right)
\]
Table B.11: Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{g}_{Na}$</td>
<td>38 $\mu S$</td>
</tr>
<tr>
<td>$E_{Na}$</td>
<td>54 mV</td>
</tr>
<tr>
<td>$C_M$</td>
<td>17.5 nF</td>
</tr>
<tr>
<td>$[Na]_o$</td>
<td>500 mM</td>
</tr>
<tr>
<td>$\bar{g}_K$</td>
<td>70 $\mu S$</td>
</tr>
<tr>
<td>$E_K$</td>
<td>-77 mV</td>
</tr>
<tr>
<td>$Vol_i$</td>
<td>4.0 nl</td>
</tr>
<tr>
<td>$[Na]_i$</td>
<td>50 mM</td>
</tr>
<tr>
<td>$\bar{g}_{Ca}$</td>
<td>17 $\mu S$</td>
</tr>
<tr>
<td>$E_{Ca}$</td>
<td>65 mV</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.5</td>
</tr>
<tr>
<td>$[Ca]_o$</td>
<td>10 mM</td>
</tr>
<tr>
<td>$\bar{g}_L$</td>
<td>0.075 $\mu S$</td>
</tr>
<tr>
<td>$E_L$</td>
<td>10.3 mV</td>
</tr>
<tr>
<td>$r$</td>
<td>4</td>
</tr>
<tr>
<td>$[K]_o$</td>
<td>10 mM</td>
</tr>
<tr>
<td>$\bar{g}_{NS}$</td>
<td>0.2 $\mu S$</td>
</tr>
<tr>
<td>$E_{NS}$</td>
<td>-22 mV</td>
</tr>
<tr>
<td>$Z$</td>
<td>2</td>
</tr>
<tr>
<td>$[B]_i$</td>
<td>0.1125 mM</td>
</tr>
<tr>
<td>$\bar{g}_R$</td>
<td>0.18 $\mu S$</td>
</tr>
<tr>
<td>$I_{CaP}$</td>
<td>7.0 nA</td>
</tr>
<tr>
<td>$n_R$</td>
<td>4</td>
</tr>
<tr>
<td>$R$</td>
<td>8,314 J/kg mol °K</td>
</tr>
<tr>
<td>$\bar{g}_{SI}$</td>
<td>0.65 $\mu S$</td>
</tr>
<tr>
<td>$I_{NaK}$</td>
<td>7.7 nA</td>
</tr>
<tr>
<td>$T$</td>
<td>295 °K</td>
</tr>
<tr>
<td>$F$</td>
<td>96,500 C/mol</td>
</tr>
<tr>
<td>$K_{Ca}$</td>
<td>0.5 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$K_{NaCa}$</td>
<td>0.01</td>
</tr>
<tr>
<td>$D_{Ca}$</td>
<td>0.15 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$D_{NaCa}$</td>
<td>0.01</td>
</tr>
<tr>
<td>$K_{SI,Ca}$</td>
<td>25 x $10^{-6}$ mM</td>
</tr>
<tr>
<td>$K_{pde}$</td>
<td>3.0 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$K_{P,Ca}$</td>
<td>350 x $10^{-6}$ mM</td>
</tr>
<tr>
<td>$v_{pde}$</td>
<td>2.4 x $10^{-6}$ mM/msec</td>
</tr>
<tr>
<td>$K_{NS,Ca}$</td>
<td>150 x $10^{-6}$ mM</td>
</tr>
<tr>
<td>$K_{SI,mod}$</td>
<td>5.5</td>
</tr>
<tr>
<td>$K_{R,K}$</td>
<td>30 mM</td>
</tr>
<tr>
<td>$K_{R,mod}$</td>
<td>1.5</td>
</tr>
<tr>
<td>$K_{P,K}$</td>
<td>0.621 mM</td>
</tr>
<tr>
<td>$K_{mod}$</td>
<td>1.5</td>
</tr>
<tr>
<td>$K_{P,Na}$</td>
<td>5.46 mM</td>
</tr>
<tr>
<td>$K_{SHT}$</td>
<td>6.0 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$K_{R,AMP}$</td>
<td>1 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$K_{DA}$</td>
<td>0.2 mM</td>
</tr>
<tr>
<td>$D_{R,AMP}$</td>
<td>0.4 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$k_U$</td>
<td>100 mM$^{-1}$ msec$^{-1}$</td>
</tr>
<tr>
<td>$K_{SI,AMP}$</td>
<td>4.2 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$k_{adc}$</td>
<td>0.6 x $10^{-6}$ mM/msec</td>
</tr>
<tr>
<td>$D_{SI,AMP}$</td>
<td>0.35 x $10^{-3}$ mM</td>
</tr>
<tr>
<td>$k_R$</td>
<td>0.238 msec$^{-1}$</td>
</tr>
</tbody>
</table>
Table B.12: Synaptic Model

\[ F_R(t) = -k_{FR}I_{Ca} \]
\[ \dot{T} = F_R(t) - k_{HD}[T] \]
\[ g_{syn} = -k_r g_{syn} + k_f \bar{g}_{syn} \frac{[T]}{[T] + K_{M,T}} \]
\[ I_{YN} = g_{syn} \cdot (V - E_{syn}) \]

Table B.13: Synaptic model parameters

\[ k_{HD}^{-1} = 0.5 \text{ msec} \]
\[ k_{FR} = 0.01 \]
\[ k_f = 12 \text{ mM}^{-1} \text{ msec}^{-1} \]
\[ k_r = 0.002 \text{ msec}^{-1} \]
\[ K_{M,T} = \frac{k_{-1}}{\bar{k}_1} \text{ mM} = 2000 \text{ mM} \]
\[ \bar{g}_{syn} = 6.5 \mu S \]
\[ E_{syn} = -77 \text{ mV} \]