Neural Cartography: Computer Assisted Poincare Return Mappings for Biological Oscillations

Jeremy J. Wojcik
Georgia State University

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NEURAL CARTOGRAPHY: COMPUTER ASSISTED POINCARÉ RETURN MAPPINGS FOR BIOLOGICAL OSCILLATIONS

by

JEREMY WOJCIK

Under the Direction of Dr. Andrey Shilnikov

ABSTRACT

Because of intrinsic cellular properties, previous conditions and network connections, neurons have many distinct oscillatory behaviors. The qualitative theory of differential equations offers tools that can be used to describe solutions for the differential equations that model neurons. Primarily, Poincaré Return Maps are used for investigating global stability. The maps capitalize on the recurrent nature of oscillations and are able to analyze changes in dynamics, even at bifurcation points where most other methods fail.

Elliptic bursting models are found in numerous biological systems, including the external Globus Pallidus (GPe) section of the brain; the focus for studies of epileptic seizures and Parkinsons disease. However, the bifurcation structure for changes in dynamics remains incomplete. This dissertation develops computer-assisted Poincaré maps for mathematical and biologically relevant elliptic bursting neuron models and central pattern generators (CPGs). The first method, used for individual neurons, offers the advantage of an entire family of computationally smooth and complete mappings, which can explain all of the systems dynamical transitions. A complete bifurcation analysis was performed detailing the mecha-
nisms for the transitions from tonic spiking to quiescence in elliptic bursters. A previously unknown, unstable torus bifurcation was found to give rise to small amplitude oscillations.

The focus of the dissertation shifts from individual neuron models to small networks of neuron models, particularly 3-cell CPGs. A CPG is a small network which is able to produce specific phasic relationships between the individual cells. The output rhythms may represent a number of biologically observable actions, such as walking or running gates. A 2-dimensional map is derived from the CPGs phase-lags. The cells are endogenously bursting neuron models mutually coupled with reciprocal inhibitory connections using the fast threshold synaptic paradigm. The mappings generate clear explanations for rhythmic outcomes, as well as basins of attraction for specific rhythms and possible mechanisms for switching between rhythms. This dissertation provides the framework for network bifurcation theory which can be applied to both higher dimensional models and larger networks with various coupling paradigms and strengths.

INDEX WORDS: Central pattern generator, Bifurcation, Return mappings, Polyrhythmic, Bursting, Duty cycle, Elliptic bursting, Motifs, Inhibitory, Multistability, Poincaré map, Interneuron, Phase-lag, Network, Synaptic, Fast threshold modulation, Saddle-node, Multifunctional
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JEREMY WOJCIK

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

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2012
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by

JEREMY WOJCIK

Committee Chair: Dr. Andrey Shilnikov

Committee: Dr. Robert Clewley

Dr. Igor Belykh

Dr. Vladimir Bondarenko

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences
DEDICATION

I would like to dedicate this to my wife and son who have been an inspiration and shown great understanding. I never would have continued this far without the encouragement of my wife, Ellen. Pursuing a P.h.D. while having a family is a daunting task and without the support of my family I never could have finished.
ACKNOWLEDGEMENTS

There are a plethora of individuals who I would like to thank for their help and inspiration along the road to my Ph.D. First off, my family inspired me to return to college and finish my undergraduate degree in physics, and then to pursue a Ph.D., despite the many personal sacrifices it would require, and obstacles along the way. Their support and understanding was crucial to my finishing.

Special thanks must be given to my advisor, Dr. Andrey Shilnikov. To express my full thanks, I must digress into a short story. In 1998, I left college in Michigan to work as an aircraft mechanic in Atlanta. For the next seven years, I used no higher math than fractions. When I decided to return to college, I naively made the choice to continue my math studies where I had left off seven years prior, with a course in ordinary differential equations. Dr. Shilnikov taught the class. Not surprisingly, I failed the first test miserably. But, Dr. Shilnikov did not write me off. He allowed me to redeem myself and mentored me in advanced topics in dynamical systems theory and differential equations. Despite my rough beginning, through Dr. Shilnikov’s tutelage I have managed to develop a thorough understanding of the qualitative theory of differential equations and dynamical systems theory. Without Dr. Shilnikov’s support, I never would have completed a Ph.D. in Mathematics or achieved a detailed level of understanding in dynamical systems theory. I have kept that first, disastrous test for prosperity.

I would also like to thank the other professors with whom I have studied at Georgia State University. Dr. Genady Cymbalyuk started me down the path of mathematic neuroscience. Dr. Robert Clewley provided a different prospective that was both welcome and very helpful in my studies, particularly in my research on 3-cell motifs. Drs. Igor Belykh, Michael Stewart, Vladamir Bondarenko, Brian Thoms, and Changyong Zhong all helped immensely in my studies and research. I owe them all a debt of gratitude, as they have influenced me greatly.

Finally, I would like to thank my fellow students who have helped me, especially with proofreading my writing. Special thanks to Bryce Chung for his particularly helpful com-
ments; Tingli Xing, for stimulating conversations and our work with the Lorenz attractor; and Paul Channell and Matt Brooks for their work on the pilot phases of my research. Thanks also to Sajiya Jalil, Aaron Keley, Justus Schwabedal, Enis Gunay, Joseph Youker, and Dane Allen for helpful comments, advice and discussions.
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LIST OF ABBREVIATIONS

• 1-D - One dimensional
• 2-D - Two dimensional
• 3-D - Three dimensional
• CPG - Central Pattern Generator
• AH - Andronov-Hopf
• FP - Fixed point
• SN - Saddle node
• DC - Duty cycle
• HCO - Half center oscillator
• FNR - Fitzhugh-Nagumo-Rinzel
• HH - Hodgkin-Huxley
• GPe - External segment of the Globus Pallidus
• FTM - Fast threshold modulation
FORWARD

What is Neural cartography? The Webster dictionary defines *cartography* as: the art or business of forming charts or maps. We do not mean that we are charting the physical location of neurons in animals. The diversity of neuron locations in different species is great. Even among different animals of the same species the identification of homologues is sometimes difficult to identify and is a study unto itself. In this dissertation we are concerned with the dynamics of neurons. We wish to explain how neurons change behavior.

Neurons have a multitude of distinct oscillatory behaviors due to previous conditions, sensory feedback, intrinsic cellular properties, and network connections. Neurons have been modeled with systems of ordinary nonlinear differential equations for more than fifty years. The qualitative theory of differential equations offers a wide range of knowledge and tools which can be used to describe solutions for differential equations e.g. local and global stability, bifurcations causing dynamical changes in the system. The primary tool for investigation of global stability is the Poincaré return map. Poincaré maps are organically suited to explain the oscillations and changes in oscillatory behavior in biological systems. The maps capitalize on the recurrent nature of oscillations and are able to analyze changes in dynamics even at bifurcation points where most other methods fail.

This dissertation is written such that each chapter can be read alone without knowledge of preceding chapters. As such, there is some repetition between chapters. Chapter 1 begins with the study of an single neuron, several different models of elliptic bursters, and creates a family of 1-Dimensional mappings for a voltage variable. The voltage is an easily measured quantity in wet experiments and was chosen so future experimental studies could be used to verify the findings. Through the implementation of our algorithm we can identify the slow-motion manifolds and the Poincaré return mappings for an entire parameter range of a given model. The parameter family of mappings allows us to completely explain all dynamic changes in the model. We point out that we utilize a model of differential equations, however a phase-space may often be reconstructed directly from data (provided there is sufficient data sampling) [1, 2]. The creation of a phase-space from experimental data would allow the application of the methods presented here to experimental data with little modification.
Chapter 2 introduces a 3 interneuron networks arranged as a central pattern generator (CPG). A CPG is a neural microcircuit comprised of cells whose synergetic interactions, without a sensory input, can produce rhythmic bursting patterns that determine motor behaviors of an animal, such as heart beat, respiration, and locomotion [3, 4]. We introduce phase relations between the 3-cells and create 2-dimension Poincaré return mappings to explore changes in rhythmic outcomes of the CPG. The 2-dimensional mappings make analysis of phase-locked states particularly clear. Also, we are able to study how different perturbations effect the rhythmic patterns seen in experimental voltage traces. The neurons are model with differential equation, however the analysis does not require any knowledge of the equations. We do not need explicit phase equations to completely analyze the rhythmic outcomes of the 3-cell motifs. This method offers tools that could be used by experimentalists to investigate network behavior.

Finally, in Chapter 3 we provide a more detailed description of the 3-cell motifs and develop a bifurcation theory for networks. We identify bifurcation parameters and there effect on rhythmic outcomes. We identify the fixed points of saddle type which are the global organizing centers in any system. We are able to show how we can control saddles individually and hence CPG rhythms. The study also provides a possible explanation for network plasticity, and how identical cells can have a variety of rhythmic outcomes.

But back to the main question: What is Neural cartography? We define neural cartography as the study neural dynamics through the use of Poincaré return mappings and bifurcation theory for both individual neurons and the creation of an associated bifurcation theory for networks. Mappings of neural dynamics will allow for an increased understanding of biological systems. The mappings will let experimentalist tell where they are, dynamically speaking, in an animal. As the saying goes; a picture is worth a thousand words. We have 42 figures in the 3 chapters [5] which we feel is adequate to explain the concepts presented in this dissertation. A myriad [6] of mappings are provided in the Appendices to allow the curious reader to explore all intermediate stages of dynamics which are not specifically addressed in the text but we had to stop sometime for more details see [7, 8, 9, 10] and subsequent works.
CHAPTER 1

ONE DIMENSIONAL RETURN MAPPINGS FOR A VOLTAGE INTERVAL IN ELLIPTIC BURSTING NEURONS

1.1 Introduction to Poincaré mappings and elliptic bursting models

Activity types of isolated neurons and their models may be generically classified as hyper- and de-polarizing quiescence, sub-threshold and mixed mode oscillations, endogenous tonic spiking and bursting. Bursting is as an example of composite, recurrent dynamics comprised of alternating periods of tonic spiking oscillations and quiescence. The type of bursting in which tonic spiking oscillations alternate with sub-threshold oscillations is often referred to as Mixed Mode Oscillations (MMO). Various endogenous bursting patterns are the natural rhythms generated by central pattern generators (CPG) [11]. A CPG is a neural network, or a mini circuit, controlling various vital repetitive locomotive functions of animals and humans [3]. We contend that understanding all plausible transitions of the activity patterns of individual neuron models would allow for better understanding of networked models. In this study we elaborate on the transition mechanisms by revealing the underlying bifurcations between neuronal activities on the elliptic bursting models of (inter) neurons which are the building blocks in the CPG circuitry.

Bursting represents direct evidence of multiple time scale dynamics of a neuron. Deterministic modeling of bursting neurons was originally proposed and done within a framework of three-dimensional, slow-fast dynamical systems. Geometric configurations of models of bursting neurons were pioneered by Rinzel [12, 13] and enhanced in [14, 15, 16, 17]. The proposed configurations are all based on the geometrically comprehensive dissection approach, or the time scale separation which have become the primary tools in mathematical neuroscience. The topology of the slow motion manifolds is essential to the geometric understanding of neurodynamics. Through the use of geometric methods of the slow-fast dissection, where the slowest variable of the model is treated as a control parameter, it is possible to detect
and follow the manifolds made of branches of equilibria and limit cycles in the fast subsystem. Dynamics of a slow-fast system are determined by, and centered around, the attracting sections of the slow motion manifolds [18, 19, 20, 21, 22, 23, 24, 25].

![Figure 1.1: A point-wise mapping (black +) for the local v-maximums of the bursting solutions starting from randomized initial conditions in the phase space of the FitzHugh-Nagumo-Rinzel model at $c = -0.7$ and overlaid with the “continuous” mapping graph obtained using the proposed technique.](image)

The slow-fast dissection approach works exceptionally well for a multiple time scale model, provided the model is far from a bifurcation in the singular limit. On the other hand, a bifurcation describing a transition between neuron activities may occur from reciprocal interactions involving the slow and fast dynamics of the model. Such slow-fast interactions may lead to the emergence of distinct dynamical phenomena and bifurcations that can occur only in the full model, not in a subsystem of the model. Hence slow-fast dissection fails at the transition where the solution is no longer constrained to stay near the slow motion manifold, or when the time scale of the dynamics of the fast subsystem slows to that of the slow system, near the homoclinic or saddle node bifurcations for example.

Activity transitions pose a challenge as the dynamics of a model may become complex and in many instances exhibit deterministic chaos [26, 27, 28, 29, 30, 31, 32, 33]. The spectrum of bifurcations and dynamical phenomena that initiate bursting in the models of mathematical neuroscience is rich and includes, but not limited to; period-doubling cascades, the blue sky catastrophe, multistability, and formation and subsequent breakdown of
a canard-torus in elliptic bursters. Transformative bifurcations of repetitive oscillations, such as bursting, are most adequately described by Poincaré mappings [34], which allow for global bifurcation analysis. Time series based Poincaré mappings have been heavily employed for examinations of oscillatory voltage activities in mathematical neuroscience, as well as other applied sciences [35, 36, 37, 38], despite limitations due to sparseness. Often a feasible mapping of the slowest variable can be achieved through the aforementioned dissection tool in the singular limit [39, 40, 41, 42, 43, 34]. However, this method often fails for elliptic bursters since no single valued mapping for the slow variable can be derived for the particular slow motion manifold.

![Figure 1.2](image)

Figure 1.2: (A) Transient solution in the FitzHugh-Nagumo-Rinzel model for \( c = -0.6192979 \) representing the transition from chaotic tonic spiking (blue) to bursting (green), and (B) the corresponding pointwise return mapping for the local v-maximums. Inset (C) gives the magnification of the mapping section revealing the period doubling cascade preceding the transition from tonic spiking to bursting (for comparison with the mappings in Figs. 1.11 and 1.12 obtained using the technique proposed in this paper.)

Elliptic bursters have been a focus of extensive studies, including deterministic and stochastic modeling: see recent [44, 45, 46, 47, 48] and referenced therein. Elliptic bursting models are not restricted to the realm of neuroscience however. A feature of elliptic bursters is the occurrence of canard-based MMO [35, 36, 37] shown in Insets B of Fig. 1.3. MMOs are typical for excitable systems describing various (electro)chemical reactions, including the famous Belousov-Zhabotinsky reaction [38, 49]. One way of examining the complex MMO
dynamics in such systems, experimentally and numerically, is to reduce the model to the
dynamics of a single, significant variable, such as voltage in neuroscience. Figure 1.1 demonstra-
tes the pointwise mapping (black +) generated by the local maximums of voltage time
series initiated from random initial conditions in the phase space of the FitzHugh-Nagumo-
Rinzel model, overlaid with a “continuous” mapping (blue) for contrast. The approach,
solely available in experimental studies may typically reveal some select fragments of the
return mappings, very similar to the mappings identified in the (electro)chemical reactions
[36, 49, 37], but not the mapping graph as a whole.

MMOs happen to be a typical phenomenon found in neurophysiology and have been
found in elliptic bursters, and are tied to the emergence of the Hopf-initiated canards [50,
51, 52, 53, 54]. The properties of MMOs, or broadly the current description of transitions
between bursting, tonic spiking and subthreshold oscillations in elliptic bursters is incomplete
and presents a challenging problem for mathematical neuroscience and the dynamical systems
theory in general.

In this paper we refine and expound on the technique of creating a family of one-
dimensional mappings, proposed in [27, 55, 56] for the leech heart interneuron, into the class
of elliptic models of endogenously bursting neurons. We will show a wealth of information,
both qualitative and quantitative that can be derived from the mappings to thoroughly
describe the bifurcations as a model undergoes transformations. We also demonstrate the
power of deriving not only individual mappings, but the additional benefits of having the
entire family of mappings created from an elliptic bursting model. We will also discuss the
limitations of our method and show the similarity of our mappings to higher dimensional
and biologically plausible models of the elliptic bursters, namely: a bursting adaption of
the classical Hodgkin-Huxley model and the realistic Rubin-Terman model for the external
segment of the Globus Pallidus.
1.2 FitzHugh-Nagumo-Rinzel Model

The mathematical FitzHugh-Nagumo-Rinzel model of the elliptic burster is given by the following system of equations with a single cubic nonlinearity:

\[
\begin{align*}
    v' &= v - v^3/3 - w + y + I, \\
    w' &= \delta(0.7 + v - 0.8w), \\
    y' &= \mu(c - y - v);
\end{align*}
\]  \hspace{1cm} (1.1)

Here we fix \( \delta = 0.08, \ I = 0.3125 \) an applied external current, and \( \mu = 0.002 \) is a small parameter determining the pace of the slow \( y \)-variable. The slow variable, \( y \), becomes frozen in the singular limit, \( \mu = 0 \). We employ \( c \) as the primary bifurcation parameter of the model: variations of which elevate/lower the slow nullcline given by \( y' = 0 \). The last equation is geometrically in the plane given by \( v = y - c \) in the three-dimensional phase space of the model, see Fig. 1.3. The two fast equations in (1.1) describe a relaxation oscillator in a plane, provided \( \delta \) is small. The fast subsystem exhibits either tonic spiking oscillations or quiescence for different values of \( y \) corresponding to a stable limit cycle and a stable equilibrium state, respectively. The periodic oscillations in the fast subsystem are caused by a hysteresis induced by the cubic nonlinearity in the first “voltage” equation of the model.
Figure 1.3: (A) Topology of the tonic spiking, $M_{lc}$, and quiescent, $M_{eq}$ manifolds. Solid and dashed branches of $M_{eq}$ (blue) are made of stable and unstable equilibria of the model, resp. The space curve, $V_{\text{max}}^*$ (in green) corresponds to the v-maximal coordinates of the periodic orbits composing $M_{lc}$. An intersection point of $y' = 0$ with $M_{eq}$ is an equilibrium state of (1.1). Shown is grey is the bursting trajectory traced by the phase point: the number of spikes per burst is the same as the number of turns the phase point makes around $M_{lc}$. Spikes are interrupted by the periods of quiescence when the phase point follows $M_{eq}$ after it falls from $M_{lc}$ near the fold. (B1) A voltage trace for $c = -0.67$, displaying the voltage evolution in time as the phase point travels around the slow motion manifolds. Green dots at the voltage maximums correspond to the green spheres on $V_{\text{max}}^*$ in (A). (B2) While the maximal voltages in inset (B1) appear to be constant, enlarging the maximums reveals significant variations in the v-maximal values. (B3) Enlargement for the subthreshold voltage oscillations.

Stability loss of the equilibrium state in the fast subsystem is known to be caused by a sub-critical Andronov-Hopf bifurcation which occurs when an unstable limit cycle collapses onto the equilibrium state. Both stable and unstable limit cycles emerge in the fast subsystem through a saddle-node bifurcation. Using a traditional slow-fast dissection, one can locate and continue the corresponding branches, labeled by $M_{lc}$ and $M_{eq}$ in Fig. 1.3 that compose
limit cycles and equilibrium states (resp.), of the fast subsystem by varying the frozen $y$-variable in the extended $(v, w; y)$-phase space of the model $(1.1)$.

Fig. 1.3 (A) presents a 3D view of the slow motion manifold in the phase space of the FitzHugh-Nagumo-Rinzel model. The tonic spiking manifold $M_{lc}$ is composed of the limit cycles for the model $(1.1)$, both stable (outer) and unstable (inner) sections. The fold on $M_{lc}$ corresponds to a saddle-node bifurcation, where the stable and unstable branches merge. The vertex, where the unstable branch of $M_{lc}$ collapses at $M_{eq}$, corresponds to a subcritical Andronov-Hopf bifurcation. The manifold $M_{eq}$ is the space curve made from equilibria of the model. The intersection of the plane, $y' = 0$ with the manifold, determines the location of the existing equilibrium state for a given value of the bifurcation parameter $c$: stable (saddle-focus) if located before (after) the Andronov-Hopf bifurcation on the solid (dashed) segment of $M_{eq}$. The plane, $y' = 0$ (slow nullcline), above (below) which the $y$-component of a solution of the model increases (decreases). The plane moves in the 3D phase space as the control parameter $c$ is varied. When the slow nullcline cuts through the solid segment of $M_{eq}$, the model enters a quiescent phase corresponding to a stable equilibrium state. Raising the plane to intersect the unstable (inner) cone-shaped portion of $M_{lc}$ makes the equilibrium state unstable through the Andronov-Hopf bifurcation. Notice that the Andronov-Hopf bifurcation which is subcritical in the singular limit becomes supercritical at a given value of the parameter $\varepsilon = 0.002$, see Fig. 1.5(A). Continuing to raise the slow nullcline by increasing $c$ gives rise to bursting represented by solutions following and repeatedly switching between $M_{eq}$ and $M_{lc}$. Bursting occurs in the model $(1.1)$ whenever the quiescent $M_{eq}$ and spiking $M_{lc}$ manifolds contain no attractors, i.e. neither a stable equilibrium state nor a stable periodic orbit exist. The number of complete revolutions of the phase point around $M_{lc}$ corresponds to the number of spikes per burst. The larger the number of revolutions the longer the active phase of the neuron lasts. Spike trains are interrupted by periods of quiescence when the phase point falls from $M_{lc}$ near the fold and follows the branch $M_{eq}$, see Fig. 1.3. The length of the quiescent period, as well as the delay loss of stability (determined mainly, but not entirely, by the small parameter $\mu$), begins after the phase point passes through the subcritical Andronov-Hopf bifurcation onto the unstable section of $M_{eq}$. Further increase of the bifurcation parameter, $c$, moves the slow nullcline up so that it cuts through the stable
cylinder-shaped section of the manifold $M_{lc}$ far from the fold. This gives rise to a stable periodic orbit corresponding to tonic spiking oscillations in the model.

We are interested in the scenarios or the sequence of bifurcations which the solutions of the model has near the transitions between tonic spiking, bursting and quiescence. MMOs occur at the transition between bursting and quiescence. Prior to the onset of MMO, the model demonstrates a plethora \[57\] of small amplitude, subthreshold oscillations due to the emergence and breakdown of an invariant torus, followed by a period doubling cascade involving unstable periodic orbits, see Figs. 1.4B and 1.19.

Figure 1.4: (A) Period doubling cascades showing the large tonic spiking orbits of period-1 at $c = -0.6$, period-2 at $-0.6192$ and of period-16 at $-0.61926$. (B) Unstable subthreshold oscillations of period-1 at $c = 0.894$, period-4 at $-0.89335$ and chaotic at $-0.89307$.

The transition from tonic spiking to bursting is accompanied with another sequence of period doubling bifurcations. The bifurcation starts when the stable periodic orbit reaches a fold of $M_{lc}$ and becomes unstable, Fig. 1.4(A), depicts the first three stages of the cascade. Geometrically, this transition takes place while the slow-nullcline is lowered through the fold at $\varepsilon = 0.002$ on the space curve $\langle v \rangle$ for the averaged values of the $v$-coordinate of the periodic orbits composing the slow-motion manifold, $M_{lc}$. The bifurcation diagram in Fig. 1.5 elucidates there are at least two saddle-node bifurcations involved in addition to the period-doubling cascade. This is confirmed by the fragmentary pointwise mapping in Fig. 1.2 taken at the transition between tonic spiking and bursting.
1.2.1 Averaging method: pros and cons

The averaging method was introduced for slow-fast systems by Pontryagin and Rodygin [22]. The averaging method employs the detection of bifurcations for periodic orbits by reducing the problem to stability analysis of corresponding equilibrium states to a single average equation for the slow variable, $y$ in the model (1.1). In essence, averaging reduces the periodic orbit to a point which is the center of gravity of the orbit [58]. The average equation is obtained by making a parameter sweep for periodic orbits along the two-dimensional manifold $M_{lc}$ in the phase space of the entire model. Suppose that the model, at $\mu = 0$, has a $T(y)$-periodic orbit given by $v = \varphi(y, v_0)$. Since the model is continuous, the evolution of the $y$-coordinate of the phase point for $|\mu| \ll 1$ near the normally hyperbolic (ie. far from bifurcations) portion of $M_{lc}$ can be evaluated in first order approximation by the following average equation:

$$
\langle y'(t) \rangle = \frac{\mu}{T(y)} \int_0^{T(y)} (c - y - \varphi(y, v_0)) \, dt \simeq \mu (c - \langle y \rangle - \langle v(y) \rangle) \leq \langle F(y, c) \rangle,
$$

(1.2)

where $\langle v(y) \rangle$ is the $v$-coordinate of the periodic orbit averaged over the period. Note that equation (1.2) preserves the linear relation of the arguments. The graph of the function $\langle F \rangle$ in the right-hand side of (1.2) is shown in Fig. 1.5(B). A simple zero of $\langle F(y, c) \rangle$ is an equilibrium state, stable or not, of the average equation that corresponds to a periodic orbit on $M_{lc}$ of the FNR model. This periodic orbit could be stable, repelling (totally unstable), or of the saddle type. The stability depends on: (1) location on the stable/unstable, in the $(v, w)$-plane, section of $M_{lc}$ and (2) whether the graph of $\langle F(y, c) \rangle$ increases or decreases at the given zero. Variations of the bifurcation parameter $c$ translate the graph of $\langle F \rangle$ vertically. The graph of the bi-folded average function in the righthand side of (1.2) is interpreted as follows: the low section of graph corresponds to $\langle F \rangle$ evaluated on the stable, cylinder-shaped portion of $M_{lc}$. The upper section of the graph corresponds to $\langle F \rangle$ evaluated on the repelling, cone-shaped portion which terminates at the Andronov-Hopf bifurcation. The averaging technique elucidates whether there exists a periodic orbit on either section of $M_{lc}$. The interpretation of the average equation is ambiguous near the fold, when $c = -0.61$. 
The bi-valued graph of \( F \) shows the separation into the sections of \( M_{lc} \) is no longer obvious: the magnification of \( F \) in Fig. 1.5(C) indicates that there should be two saddle-node bifurcations corresponding to double zeros of \( F \). One zero is from a sharp cusp, whereas the other saddle-node, for smaller value of \( c \), would yield a proper quadratic tangency typical for such a bifurcation (this assertion is supported by examination of the mappings in Fig. 1.6.) Inset (C) of Fig. 1.5 shows that the bifurcation sequence at this transition is more complex than a trivial stability loss or disappearance of the tonic spiking orbit at the fold. Consequently, we need more advanced tools than the slow-fast dissection or average differential equation (1.2) for the global examination of the dynamics of the model. Examination of the global dynamics can be accomplished through a reduction to Poincaré return mappings. Poincaré return mappings allow for an accurate description of complex oscillatory behaviors and bifurcations, such as period doubling, for solutions of the model.
Figure 1.5: (upper) (V, c)-bifurcation diagram for the FNR model showing the intervals of tonic spiking, bursting and quiescence in the model. All three branches; maximal $V_{max}$, averaged $\langle V \rangle$, and minimal $V_{min}$ of the voltage variable of the periodic orbits emerge from the subcritical Andronov-Hopf bifurcation (AH). Note two folds corresponding to two saddle-node bifurcations occurring en route from bursting to tonic spiking. Fig. 1.3 gives the corresponding 3D view of the tonic-spiking and quiescent manifolds found parametrically, i.e. as the parameter $c$ is varied, in the phase space of the FitzHugh-Nagumo-Rinzel model. (A) Maximal $V_{max}$, averaged $\langle V \rangle$, and minimal $V_{min}$ branches plotted against the averaged $\langle y \rangle$-variable of the periodic orbits moving along the tonic spiking manifold $M_{lc}$ as the bifurcation parameter $c$ is varied. The slow nullcline $\langle y' \rangle = 0$ at $c = -0.79$ passes through the unstable segment of $\langle V \rangle$ between the AH point and the fold for bursting to occur in the model. (B) A zero, around 0.00105, of the averaged function $\langle F \rangle$ defined in (1.2) plotted against $\langle y \rangle$, corresponds to a hyperbolic equilibrium states of the average equation, and respectively to a stable periodic orbit on $M_{lc}$. Inset (C) shows an enlarged section of the graph of $\langle F \rangle$ near the fold in question, where the latter becomes a multi-valued function indicating the failure of the averaging approach near the transition at $c = -0.61$. 
1.3 Voltage interval mappings

Methods of the global bifurcation theory are organically suited for examinations of recurrent dynamics such as tonic spiking, bursting and subthreshold oscillations [50, 59, 60], as well as their transformations. The core of the method is a reduction to and derivation of a low dimensional Poincaré return mapping with an accompanying analysis of the limit solutions; fixed, periodic and homoclinic orbits each representing various oscillations in the original model. Mappings have been actively employed in computational neuroscience, see [61, 39, 40, 53, 54] and referenced therein. It is customary that such a mapping is sampled from voltage traces, for example by identifying successive voltage maxima, minima, or interspike intervals [62], Fig. 1.3(B). Notice that the v-maximums in the voltage trace, Fig. 1.3(B1), appear constant. However, the enlargements in Insets (B2) and (B3) show considerable variation in the v-maximus of the voltage traces. A drawback of a mapping generated by time series is sparseness, see Fig. 1.1, as the construction algorithm reveals only a single periodic attractor of a model, unless the latter demonstrates chaotic or mixing dynamics producing a large variety of densely wandering points. Chaos may also be evoked by small noise whenever the dynamics of the model are sensitively vulnerable to small perturbations that do not substantially re-shape intrinsic properties of the autonomous model [56, 48]. Small noise, however, can make the solutions of the model wander thus revealing the mapping graph.

A computer assisted method for constructing a complete family of Poincaré mappings for an interval of membrane potentials for slow-fast Hodgkin-Huxley models of neurons was proposed in [55] following [63]. Having a family of such mappings we are able to elaborate on various bifurcations of periodic orbits, examine bistability of coexisting tonic spiking and bursting, and detect the separating unstable sets that are the organizing centers of complex dynamics in any model. We enhance this technique to understand the bifurcations underlying the transitions between various activity types in the models of the elliptic bursters. Examination of the mappings will help us make qualitative predictions about transitions before the transitions occur in models.
By construction, the mapping $T$ takes the space curve $V_{\text{max}}^*$ into itself after a single revolution around the manifold $M_c$, Fig. 1.6, i.e. $T : V_n \rightarrow V_{n+1}$. This technique allows for the creation of a Poincaré return mapping; taking an interval of the voltage values onto itself. The found set of matching pairs $(V_n, V_{n+1})$ constitutes the graph of the Poincaré mapping for a selected parameter value $c$. Provided the number of paired coordinates is sufficiently large and applying a standard spline interpolation we are able to iterate trajectories of the mapping, compute Lyapunov exponents, evaluate the Schwarzian derivative, extract kneading invariants for the topological entropy, and many other quantities.

Varying the parameter, $c$, we obtain a dense family that covers all behaviors, bifurcations and transitions of the model (1.1). A family of the mappings for the parameter, $c$, varied within the range $[-1, -0.55]$ is shown in Fig. 1.6(left). Indeed, for the sake of visibility, Fig. 1.6(right) depicts a sampling of mappings that indicate evolutionary tendencies of the model. A thorough examination of the family allows us to foresee changes in model dynamics. A family of mappings allows us to analyze all the bifurcations whether stable or unstable fixed and periodic orbits including homoclinic and heteroclinic orbits and bifurcations. By following the mapping graph we can predict a value of the parameter at which the corresponding periodic orbit will lose stability or vanish, for example giving rise to bursting from tonic spiking.

A fixed point, $v^*$, is discerned from the mapping as an intersection of the graph with the bisectrix, $45^\circ$ line. Visually we determine the stability of the fixed point by the slope of the graph at the fixed point. If the slope of the graph is less than 1 in absolute value the point is stable. When the slope of the graph at the fixed point is greater than 1 in absolute value the fixed point is unstable. Alternatively stability may be determined from forward iterates of an initial point in the neighborhood of the fixed point which either diverges or converges to the fixed point. Two generic bifurcations through which a stable fixed point becomes unstable or disappears in a plane are: (1) a period doubling bifurcation, and (2) saddle-node, respectively. The latter occurs when the mapping graph becomes tangent to a bisectrix. Prior to the saddle-node bifurcation there are two fixed points, stable and unstable, on the bisectrix. After the bifurcation, both fixed points have merged and been annihilated through the tangency. The flip bifurcation, as a super-critical flip for example, gives rise to
the emergence of a period-two orbit after the fixed point loses stability, where the multiplier becomes less than -1. Flip bifurcations often initiate a period doubling cascade bifurcation. In our case, such a cascade will be shown to cause chaotic subthreshold oscillations and once mixed with large amplitude bursting, will give rise to MMO.
Figure 1.6: (upper) Three sample orbits demonstrating the construction of the return mapping $T: M_n \to M_{n+1}$ defined for the points of the cross-section $V_{\text{max}}$ on the manifold $M_{lc}$. Singling out the $v$-coordinates of the points gives pairs $(V_n, V_{n+1})$ constituting the voltage interval mapping at a given parameter, $c$. (left) A complete family of the $c$-parameter Poincaré return mappings $T: V_n \to V_{n+1}$ for the FitzHugh-Nagumo-Rinzel model at $\mu = 0.002$. (right) Coarse sampling of the $c$-parameter family of the Poincaré return mappings $T: V_n \to V_{n+1}$ for the FitzHugh-Nagumo-Rinzel model at $\mu = 0.002$ as $c$ decreases from $c = -0.55$ through $c = -1$. The grey mappings correspond to the dominating tonic spiking activity in the model. The green mappings show the model transitioning from tonic spiking to bursting. The blue mappings correspond to the bursting behavior in the model. The red mappings show the transition from bursting into quiescence. The orange mappings correspond to the quiescence in the model. An intersection point of a mapping graph with the bisectrix, $45^\circ$ line, is a fixed point, $v^*$, of the mapping. The stability of the fixed point is determined by the slope of the mapping graph, i.e. it is stable if $|T'(v^*)| < 1$. Nearly vertical slopes of graph sections are due to an exponentially fast rate of instability of solutions (limit cycles) of the fast subsystem compared to the slow component of the dynamics of the model.
1.4 Qualitative analysis of mappings

The family of mappings, given in Fig. 1.6, allows for global evolutionary tendencies of the model (1.1) to be qualitatively analyzed. The flat mappings in gray have a single fixed point corresponding to the tonic spiking state. We can further deduce the saddle-node bifurcation, that gives birth to the two unstable fixed points, at the mapping and bisectrix crossing. The fixed points diverge from each other and one fixed point moves towards the stable fixed point in the upper corner. We can now predict that bursting will be born through another saddle-node bifurcation. The green mappings show the actual transition and saddle-node bifurcation after which we have regular bursting patterns, blue mappings. We also see the other unstable fixed point clearly moving to the lower corner. The red mappings indicate the transition from bursting to quiescence, as the fixed point changes stability.

A major benefit of using the voltage interval mapping is that we are able to understand transitions between the activity states of the model by analyzing and comparing the bifurcations between the states. Activity transitions commonly occur in a slow-fast model near the bifurcations of the fast subsystem where the description of dynamics in the singular limit is no longer accurate because of the failure of the slow-fast dissection paradigm. This happens, for example, when the two-dimensional fast subsystem of the model (1.1) is close to a saddle-node bifurcation (near the fold on the tonic spiking manifold \( M_{lc} \)) where the fast dynamics become of the time scale of the slow subsystem. Such an interaction may cause new peculiar phenomena, such as torus formation and subsequent breakdown near the fold on the spiking manifold [64, 53]. We return to the torus bifurcation in the Discussion section below. We now turn our attention to a more thorough analysis of the individual mappings.

1.4.1 Transition from tonic spiking to bursting

Figures 1.7-1.11 elucidate the transformative stages of the voltage mappings for \( c \in [-0.594, -0.620625] \) as the dynamics transform from periodic tonic spiking to complex bursting while the FNR model is being “hyperpolarized.” Recall that the model 1.1 is a purely phenomenological model with variables and parameters without any biophysical cor-
Figure 1.7: (A) Poincaré return mapping for the FitzHugh-Nagumo-Rinzel model at $c = -0.59$ has a single stable fixed point, TS, at the upper corner which corresponds to a single $v$-maximum of the tonic spiking periodic orbit on the manifold $M_{lc}$. Iterates (grey) of an initial point starting near Q show a rapid convergence to the tonic spiking point. (B) Maximal voltage trace shows a rapid establishment of tonic spiking activity. (C) Return mapping at $c = -0.594255$. The convex section from (A) has turned into a cusp and illustrate an imminent saddle node bifurcation. (D) Voltage trace shows that the tonic spiking attractor still dominates the dynamics of the model without any indication of the emergence of the new fixed points.

relation to exact models of neurons. However, the FNR model produces dynamics with vivid similarities typical for the many models within the elliptic bursting class and real neurons.

We begin where the model is firmly in the tonic spiking regime at $c = -0.59$. Tonic spiking is caused by the presence of a stable periodic orbit located far from the fold on the manifold $M_{lc}$ (Fig. 1.3). The only $v$-maximum of this orbit corresponds to a stable fixed point, labeled TS in Fig. 1.7(A). The flat section of the mapping graph adjoining the stable fixed point clearly indicates a rapid convergence to the point in the $v$-direction, as shown by the trace in inset (B). The point, Q, of the mapping located at the quiescent level, $V = -1$, corresponds to the terminal vertex where the tonic spiking manifold, $M_{lc}$, merges with quiescent manifold, $M_{eq}$, through the subcritical Andronov-Hopf bifurcation,
Fig. 1.3. Here the slope of the mapping reflects the exponential instability (stability) of the quiescent (tonic spiking) branch, made of unstable equilibria and stable limit cycles of the fast subsystem of the model.

Figure 1.8: (A) Poincaré mapping at $c = -0.595$ depicts the formation of 2 unstable fixed points immediately after a saddle node bifurcation. (C) Poincaré mapping at $c = -0.615$ depicts the beginning of a hidden transformation aimed to terminate the tonic spiking stable fixed point TS through the secondary saddle-node bifurcation. (B and D) The corresponding traces of maximal voltage values.

We next examine the mapping in Fig. 1.7(C, D), taken for the parameter $c = -0.594255$. Compared to the upper mapping branches in the family represented in Fig. 1.6, one can clearly spot a definite trend resulting in a change of the mapping shape where the convex portion has begun turning into a cusp around $V_0 \approx 1.1$, Fig. 1.7(C, D). The formation of the cusp is an indication of a change in dynamics for the mapping. Thus the mapping insinuates a transition in dynamics of the model (1.1) prior to occupancy. Note that the maximal voltage trace provides no indication of any eminent transition in the model’s behavior.

The mapping in Fig. 1.8(A, B), taken for the parameter $c = -0.595$, clearly illustrates that after the cusp has dropped below the bisectrix, then two additional fixed points, UP1 and UP2, are created. UP1 and UP2 have emerged through a preceding saddle-node bifurcation taking place at some intermediate parameter value between $c = -0.594255$ and $c = -0.595$. 
We draw the reader’s attention to the \((v, c)\)-bifurcation diagram in Fig. 1.5. The diagram reveals two turning points labeled SN\(_1\) and SN\(_2\), corresponding to saddle-node bifurcations that occur near the geometric fold on the tonic spiking manifold \(M_{lc}\). The saddle-node bifurcation in the mapping here corresponds to the turning point SN\(_1\) occurring on route from tonic spiking to bursting. Again, let us stress that the singular limit of the model at \(\mu = 0\) gives a single saddle-node bifurcation through which the tonic spiking periodic orbit looses stability after it reaches the fold on the tonic spiking manifold. We point out that for an instant the model becomes bistable right after the saddle-node bifurcation in Fig. 1.7, leading to the emergence of another stable fixed point with an extremely narrow basin of attraction. Here, as before the hyperbolic tonic spiking fixed point, TS, dominates the dynamics of the model.

![Figure 1.9](image)

Figure 1.9: (A) Poincaré mapping at \(c = -0.6193\) and the voltage trace in (B) both demonstrate chaotic bursting transients. (C) Enlargement of the right top corner of the mapping shows that the tonic spiking fixed point has lost the stability through a supercritical period-doubling bifurcation. The new born period-2 orbit is a new attractor of the mapping, as confirmed by the zigzagging voltage trace represented in (D).

Figure 1.8(C) demonstrates that as the parameter is decreased further to \(c = -0.615\), the gap between the new fixed points widens as the point UP\(_2\) moves toward the stable tonic spiking point, TS. In the resultant this saddle-node bifurcation, these fixed points merge
and annihilate each other; thereby terminate the tonic spiking activity in the FNR model. Before that happens, several bifurcations involving the fixed point, TS, drastically reshape the dynamics of the model. First, the multiplier becomes negative around $c = -0.619$, that is the first indication of an impending period doubling cascade. This is confirmed by the mapping at $c = -0.6193$ in Fig. 1.9(C, D) showing that the fixed point has become unstable through the supercritical period-doubling bifurcation. This period-doubling bifurcation gives rise to a stable period-2 tonic spiking orbit in the mapping and to a stable orbit of the doubled period compared to that of the pre-bifurcating tonic spiking orbit in the phase space of the model (1.1). The location of the period doubling bifurcation may be identified by simple geometric means in the bifurcation diagram in Fig. 1.5. Indeed, let us observe that once the fixed point becomes unstable, the multiplier becomes less than -1. Geometrically this implies that the fixed point slides from the concave up to the concave down section of the mapping graph. Therefore the inflection point between the folds in the bifurcation diagram, Fig. 1.5, corresponds to the given period doubling bifurcation. Another inflection point, labeled PD, on the unstable branch in the diagram corresponds to a period-doubling bifurcation of a subthreshold periodic orbit discussed below.

The new born period-2 orbit becomes the new tonic spiking attractor of the mapping. Observe from the voltage trace in Fig. 1.9(B, C) the transient bursting behavior thus indicating that boundaries of the attraction basin of the period-two orbit become fractal. Next, the model approaches bursting onset, chaotic at first as represented in Fig. 1.10. This figure depicts the behavior of the mapping at $c = -0.62$ and shows the rapid bifurcation sequence that eliminates the period-2 attractor causing the mapping to initiate chaotic dynamics at the transition from tonic spiking to bursting. Correspondingly, the FNR model starts generating chaotic trains of bursts with randomly alternating numbers of spikes per burst. The number of spikes depends on how close the trajectory of the mapping comes to the unstable (spiraling out) fixed point, TS. Each spike train is interrupted by a single quiescent period. The fixed point UP$_1$ sets a threshold between the quiescent (left) and tonic spiking (right) sections of the mapping graph. This unstable point corresponds to a saddle periodic orbit of the model, that is located on the unstable, cone-shaped section of the tonic spiking manifold.
Figure 1.10: (A) Chaotic bursting in the mapping at $c = -0.62$. Fixed point TS has become unstable thus initiated a cascade of period-doubling bifurcations, as the local segment of the mapping graph near TS changes concavity. The shape of the mapping elucidates the effects of small perturbations on the model, which could result in iterates at drastically different locations caused by the chaotic behavior. Each spike train is followed by a quiescent period to the left from the threshold $\text{UP}_1$, separating it from the spiking zone (on the right). (B) Chaos is clearly evident in the voltage trace as bursts vary in length (number of spikes) and amplitude. (C) The magnification of the right upper corner of the mapping reveals that chaotic bursting is due to a cascade of periodic doubling bifurcations that locally increases the instability of the mapping. (D) Upper portion of chaotic burst trains.

$M_{lc}$ in Fig. 1.3. Recall that this saddle periodic orbit is repelling in the fast variables and stable in the slow variable.

By comparing Figs. 1.7-1.8 one could not foresee that the secondary saddle-node bifurcation eliminating the tonic spiking fixed point TS. Additionally, the elimination of the stable periodic orbit on the manifold $M_{lc}$ would preceded by a dramatic concavity change in the mapping shape causing a forward and inverse cascade of period doubling bifurcations would not be apparent. Observe that regular or periodic bursting emerges before the disappearance of the tonic spiking orbit through the saddle-node bifurcation, see Fig. 1.11. The corresponding fixed point, TS, becomes stable again through a reverse sequence of period doubling bifurcations before annihilating through the secondary saddle-node bifurcation. However, the basin of attraction becomes so thin that bursting begins to dominate the bi-
Figure 1.11: (A) Return mapping at $c = -0.620625$ demonstrates regular bursting with six spikes per a burst followed by a single quiescent point located to the left from the threshold $UP_1$. This period-6 bursting orbit co-exists with a stable fixed point $TS$, that has a narrow attraction basin. (B) The corresponding bursting trace. (C) The magnification of the right upper corner of the mapping $c = -0.620625$ shows the coexistence of stable tonic spiking fixed point ($TS$) and period-6 bursting orbit. Both points, $TS$ and $UP_2$ are about to annihilate through a saddle-node bifurcation. (D) Voltage trace shows that the magnitude of spikes does decrease through of the burst. The number of the spikes per burst equates to the number of iterates the phase point makes near the section of the mapping tangent to the bisectrix.

stable dynamics of the model. Note that the bursting behavior becomes regular as the phase points passes through the upper section of the mapping tangent to the bisectrix. The number of the iterates that the orbit makes here determines the duration of the tonic spiking phase of bursting and is followed by a quiescence period initially comprised of a single iterate of the phase point to the right of the threshold $UP_1$. The evolution of bursting into MMO and on to subthreshold oscillations will be discussed in the next section.

1.4.2 From bursting to mixed-mode oscillations and quiescence

The disappearance of the tonic spiking orbit, $TS$, accords with the onset of regular bursting in the mapping and in the FNR model (1.1). In the mapping a bursting orbit is comprised of iterates on the tonic spiking and quiescent sections separated by the unstable
threshold fixed point, UP\(_1\), of the mapping, Fig. 1.12. The shape of the graph had a significant change reflecting the change in dynamics. The fixed points in the upper right section of the mapping disappears through a saddle-node bifurcation. One of the features of the saddle-node is the bifurcation memory such that the phase point continues to linger near a phantom of the disappeared saddle-node. The mapping near the bisectrix can generate a large number of iterates before the phase points diverges toward the quiescent phase. The larger the number of iterates near the bisectrix corresponds to a longer tonic spiking phase of bursting. Figure 1.12 demonstrates how the durations of the phases change along with a change in the mapping shape: from a single quiescent iterate to the left of the threshold, UP\(_1\), to a single tonic-spiking iterate corresponding to a bursting orbit with a single large spike in the model. Notice as the phase point is taken closer to the unstable section Q near \(V = -1\), the quiescent phase of bursting becomes longer. The number of tonic spiking iterates decreases as the threshold fixed point moves to the left and the number of subthreshold oscillations increases. These “winding” numbers during the tonic spiking and quiescent phase define the ordinal type of bursting, for example 5-1 and 1-9 shown respectively in Fig. 1.12 Insets (A, B) and (C, D).

The transition from bursting to quiescence in the model is not monotone because the regular dynamics may be sparked by episodes of chaos. Such subthreshold chaos in the corresponding mapping at \(c = -0.9041\) is demonstrated in Fig. 1.13(A). This phenomena is labeled MMO because the small amplitude subthreshold oscillations are sporadically interrupted by larger spikes (Inset B). Use of the mapping makes the explanation of the phenomena in elliptic bursters particularly clear. In Fig. 1.13(A), after the mapping (or the model) fires a spike, the phase point is reinjected close to the threshold point, UP\(_1\), from where it spirals away to make another cycle of bursting. Note that the number of iterates of the phase point around UP\(_1\) may vary after each spiking episode. This gives rise to solutions that are called bi-asymptotic or homoclinic orbits to the unstable fixed point UP\(_1\) (Inset C). The occupancy of such a homoclinic orbit to a repelling fixed point is the generic property of one-dimensional non-invertible mapping [65], since the point of a homoclinic orbit might have two pre-images. Note that the number of forward iterates of a homoclinic point may be finite in a non-invertible mapping, because the phase point might not converge but merely
Figure 1.12: (A) Periodic bursting with five spikes in the Poincaré interval mapping for the FNR model at $c = -0.625$. The single unstable fixed point $UP_1$ separates the tonic spiking section of the mapping from the quiescent or subthreshold section (left). The number of iterates of the phase point adequately defines the ordinal type of bursting (B). Note a presence of a small hump around ($V_0 = 1.6, V_1 = -0.5$) which is an echo of the saddle-node bifurcation. (C) Poincaré return mapping at $c = -0.89$. The model is further “hyperpolarized” as the threshold, $UP_1$ moves further leftward so that the phase point makes more subthreshold oscillations, here nine, after a single spike per a burst. (D) The voltage trace of 1-9 bursting: a single high amplitude spike is followed by nine subthreshold oscillations.

Jump onto the unstable fixed point after being reinjected. However, the number of backward iterates of the homoclinic point is infinite, because the repelling fixed point becomes an attractor for an inverse mapping in restriction to the local section of the unimodal mapping, see Fig. 1.13(C, D). The presence of a single homoclinic orbit leads to the abundance of other emergent homoclinics [66] via a homoclinic explosion [34].

A small decrease of the bifurcation parameter causes a rapid change in the shape of the mapping, as depicted in Fig. 1.13(A, C); the sharp peak near the threshold becomes lower such that the mapping can no longer generate large amplitude spikes. Instead of MMO dynamics, the mapping exhibits small-amplitude chaotic subthreshold oscillations, which are still caused by homoclinic orbits of the fixed point, $UP_1$. Loosely speaking, this means that the iterates of the mapping come close to the fixed point, that would be isolated in a lacuna otherwise. This fixed point corresponds to a single v-maximum of the saddle
Figure 1.13: (A) Chaotic MMO and bursting in the mapping at $c = -0.9041$ caused by the complex recurrent behavior around the unstable fixed point $UP_1$. (B) Subthreshold oscillations are disrupted sporadically by large and intermediate magnitude spikes thereby destroying the rhythmic bursting in the model. (C) Poincaré return mapping for the FitzHugh-Nagumo-Rinzel model shows no bursting but complex subthreshold oscillations at $c = -0.90476$. (D), after the peak in the mapping decreases in amplitude transforming into a cusp, thus making the occupancy of high amplitude spikes impossible. Here, chaos is caused by homoclinic orbits to the unstable fixed point $UP_1$.

periodic orbit of the FNR model. The orbit is located on the inner, cone-shaped section of the tonic-spiking manifold $M_{lc}$.

As the parameter is decreased further, the unstable fixed point, $UP_1$, becomes stable through a reverse period-doubling cascade. The last two stages of the cascade are depicted in Fig. 1.14(A) and Fig. 1.15. Insets (A) and (C) of the former figure show stable period-4 and period-2 orbits, and their traces in Insets (B) and (D), as the parameter $c$ is decreased from $-0.906$ to $-0.9075$. Here we demonstrate another ability of the interval mappings derived directly from the flow. In addition to the original mapping, $T$, in Fig. 1.14 we see two superimposed mappings, $T^2$ and $T^4$, (shown in light blue) of degree two and four respectively. The four points of periodic orbit in Inset (A) corresponds to the four fixed points of the fourth degree mapping $T^4$ at $c = -0.906$, whereas the period-two orbit in (C)
correspond to two new fixed points of the mapping $T^2$ in (C) at $c = -0.9075$. We see clearly that both periodic orbits are indeed stable because of the slopes of the mappings at the fixed points on the bisectrix. Using the mappings of higher degrees we can evaluate the critical moments at which the period-two and period-four orbits are about to bifurcate. We point out that a period-doubling cascade, beginning with a limit cycle near the Hopf-initiated canard toward subthreshold chaos has been recently reported in slow-fast systems [33, 67].

Figure 1.14: (A) and (C) Stable period-4 and period-2 orbits (green) of the interval mapping at $c = -0.906$ and $c = -0.9075$. Shown in light-blue are the corresponding mappings $T^3$ and $T^2$ of degree four and two with four and two stable fixed points correspondingly. The traces of the orbits are shown in Insets (B) and (D).

Decreasing $c$ further, the period-two orbit collapses into the fixed point, UP$_1$, which becomes stable, Fig. 1.15 inset (A). The multiplier, first negative becomes positive but is still less than one in the absolute value. When the fixed point lowers to the left bottom corner of the mapping near $V=-1$ the corresponding periodic orbit reaches the vertex of the tonic spiking manifold. In terms of the model, this means that the periodic orbit collapses into a saddle-focus through the subcritical Andronov-Hopf bifurcation. After that, the equilibrium state, located at the intersection of the manifold $M_{eq}$ with the slow-nullcline (plane) in Fig. 1.3, becomes stable and the model goes into quiescence for parameter values smaller
then \( c = -0.97 \), see Fig. 1.15(C). The stable equilibrium state corresponds to the fixed point, \( Q \), which is the global attractor in the mapping.

Figure 1.15: (A) Full scale Poincaré return map at \( c = -0.91 \) has a single stable fixed point corresponding to a stable periodic orbit of the FitzHugh-Nagumo-Rinzel model exhibiting regular, periodic subthreshold oscillations. The oscillations are extinguished after the orbit collapses onto the equilibrium state. Inset (C) shows the corresponding mapping with a stable fixed point near \( V = -1 \). (B) and (D) The voltage traces illustrating the transients converging to the periodic subthreshold orbit and the quiescent fixed point.

A complete set of Poincaré return mappings for the FNR model can be found in the appendix A.3. The additional mappings show all intermediate steps in the transitions between tonic spiking, bursting, MMO and quiescence.

1.5 Quantitative features of mappings: kneadings

In this section we discuss quantitative properties of the interval mappings for the dynamics of the model (1.1). In particular, we carry out the examination of complex dynamics with use of calculus-based and calculus-free tools such as Lyapunov exponents and kneading invariants for the symbolic description of MMOs.
Chaos may be quantitatively measured by a Lyapunov exponent. The Lyapunov exponent is evaluated for one-dimensional mappings as follows:

\[
\lambda = \lim_{N \to +\infty} \frac{1}{N} \sum_{i=1}^{N} \log |T'(v_i)|, \tag{1.3}
\]

where \(T'(v_i)\) is the slope (derivative) of the mapping at the current iterate \(v_i\) corresponding to the \(i\)-th step for \(i = 0, \ldots, N\). Note that by construction the mapping graph is polygonal and to accurately evaluate the derivatives in (1.5) we used a cubic spline. The Lyapunov exponent, \(\lambda\), yields a lower bound for the topological entropy \(h(T)\) [68]; serving as a measure of chaos in a model. The Lyapunov exponent values \(\lambda \simeq 0.24\) and \(\lambda \simeq 0.58\), found for the interval mappings at \(c = -0.9041\) and \(c = -0.90476\) (resp.), show that chaos is developed more in the case of subthreshold oscillations than for MMOs.

The topological entropy may also be evaluated though a symbolic description of the dynamics of the mapping that require no calculus-based tools. The curious reader is referred to [69, 70] for the in-depth and practical overviews of the kneading invariants, while below we will merely touch the relevant aspects of the theory. For unimodal mappings of an interval into itself with a single critical point \(v_c\), like for the case \(c = -0.90476\) (Fig. 1.16 inset B), we need only to follow the forward iterates of the critical point to generate the \underline{unsigned kneading sequence} \(\kappa(v_c) = \{\kappa_n(v_c)\}\) defined on \{-1, +1\} by the following rule:

\[
\kappa_n(v_q) = \begin{cases} 
+1, & \text{if } T^n(v_c) < v_c \\
-1, & \text{if } T^n(v_c) > v_c.
\end{cases} \tag{1.4}
\]

here \(T^n(v_c)\) is the \(n\)-th iterate of the critical point \(v_c\).

The kneading invariant of the unimodal mapping is a series of the \underline{signed kneadings} \(\tilde{\kappa}_n\) of the critical point, which are defined through the unsigned kneadings, \(\kappa_i\), as follows:

\[
\tilde{\kappa}_n = \prod_{i=1}^{n} \kappa_i, \tag{1.5}
\]

or, recursively:

\[
\tilde{\kappa}_n = \kappa_n \tilde{\kappa}_{n-1}, \quad i = 2, 3, \ldots \tag{1.6}
\]
Next we construct a formal power series;

$$P(t) = \sum_{i=0}^{\infty} \tilde{\kappa}_i t^i.$$  \hspace{1cm} (1.7)

The smallest zero, $t^*$ (if any), of the series within an interval $t \in (0, 1)$ defines the topological entropy, $h(T) = \ln(1/t^*)$. The sequence of the signed kneadings, truncated to the first ten terms, $\{- + + - + + - + + - + -\}$ for the mapping in Fig. 1.16 inset B, generates the polynomial $P_{10}(t) = -1 + t + t^2 + t^3 - t^4 + t^5 + t^6 + t^7 - t^8 + t^9$. The single zero of $P_{10}(t)$ at $t^* \approx 0.544779$ yields a close estimate for the topological entropy $h(T) \approx 0.6073745$, see Fig. 1.16(A). The advantage of an approach based on the kneading invariant to quantify chaos is that evaluation of the topological entropy does not involve numerical calculus for such equationless interval mappings, but relies on the mixing properties of the dynamics instead. Moreover, it requires relatively few forward iterates of the critical point to accurately compute the entropy, as
the polynomial graphs in Fig. 1.16 suggests. Besides yielding the quantitative information such as the topological entropy, the symbolic description based on the kneading invariants provide qualitative information for identifying the corresponding Farey sequences describing the MMOs in terms of the numbers of subthreshold and tonic spiking oscillations.
1.6 Poincaré mappings for the bursting Hodgkin-Huxley model and the GPe Rubin-Terman model

The interval mappings capture the key features common for the models belonging to the same elliptic class. Here we present for comparison the families of the return mappings and the slow-motion tonic spiking manifolds for two other, exemplary models of elliptic bursters: the four-dimensional “bursting” adaptation of the classical Hodgkin-Huxley model [45] and the five-dimensional Rubin-Terman model for the external segment of the Globus Pallidus [71]. The similarities of the manifolds are evident as are the similarities of the mappings for all three models, see Figs. 1.17 and 1.18. Note the “instability” of vertical sections in the mappings; this instability is due to exponentially fast transitions between the slow-motion manifolds, tonic spiking $M_{lc}$ and quiescent $M_{eq}$, compared to the change rate of the slowest variable in each given model. Also worth mentioning is the instability of the middle, unstable section of $M_{lc}$, comprised of the saddle or canard-like periodic orbits. As the result of this instability, the mapping may take the space curve $V_{\text{max}}$ not exactly into itself, as meant by construction, but to a curve close to $V_{\text{max}}^{**}$, depicted in Fig. 1.17 for bursting Hodgkin-Huxley model.

\begin{align}
C \dot{V} & = I - g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_l (V - E_L), \\
\dot{n} & = 0.01 \frac{10 - V}{\exp(\frac{10 - V}{8}) - 1} (1 - n) - 0.125 \exp(\frac{V}{80}) n, \\
\dot{m} & = 0.1 \frac{25 - V}{\exp(\frac{25 - V}{10} - 1)} (1 - m) - 4 \exp(\frac{V}{18}) m, \\
\dot{h} & = 0.07 \exp(\frac{V}{20}) (1 - h) - \frac{1}{\exp(\frac{20 - V}{10}) - 1} h + I_h, \tag{1.8}
\end{align}

In the model, $I_h \in [-0.19, -0.05]$ is the sweeping parameter used to scan the slow motion manifold $M_{lc}$, as well as generate the corresponding mapping family sampled in Fig. 1.17. Note that $I_h$ only moves the slow nullcline given $h' = 0$ in the phase space of the model.

The third model of the elliptic burster considered in this study was proposed and studied in [71]. The model is meant to describe the voltage dynamics in the external segment of the Globus Pallidus in connection with complex oscillatory activity observed in neurons of the basal ganglia.
The equations for the model are read as follows:

$$C_m \dot{V} = -I_L - I_K - I_{Na} - I_T - I_{Ca} - I_{syn} - I_{Ge} + I_{app},$$  \hspace{1cm} (1.9)

For the complete model refer to Appendix A.1.3.

The reader is referred to the original work that discusses the subjects of the model, and examines in detail the dynamics and bifurcations in it. The Rubin-Terman model is employed here to test the algorithm for mapping derivations and verify that intrinsically the mappings for the model are shaped uniformly similar across a diverse set of the class of elliptic bursters. The tonic spiking and quiescent manifolds, as well as the family of Poincaré return mappings for an interval of the maximal voltage values are shown in Fig. 1.18. The tonic spiking manifold has the characteristic cone-like shape indicating a subthreshold Andronov-Hopf bifurcation, and the fold corresponding to a saddle-node bifurcation. The family of mappings for an interval of the voltage, “accumulating” the dynamics of all other currents, including calcium, reveals the close similarity to the return mappings for all three elliptic bursters discussed.
Figure 1.18: Tonic spiking $M_{lc}$ and quiescent $M_{eq}$ manifolds in the $(n, Ca, V)$-projection of the phase space of the Rubin-Terman model. Shown in light color are bursting oscillations. (B) The GPe mapping family displays the typical shape for the Poincaré return mappings of the maximal voltage values in all three models of the elliptic buster.
1.7 Chapter Summary

We present a case study for a thorough examination of the bifurcations that take place at activity transitions between tonic spiking, bursting and Mixed Mode Oscillations in the FNR model. The analysis is accomplished through the reduction to a single-parameter family of equationless Poincaré return mappings for an interval of the “voltage” variable. We stress that these mappings are models themselves for evaluating the complex dynamics of the full three-dimensional model. Nevertheless the dynamics of the single accumulative variable, $v$, reflects the cooperative dynamics of other variables in the model. The reduction is feasible since the model is a slow-fast system and, hence, possesses a two-dimensional, slow-motion tonic-spiking manifold around which the oscillatory solutions of the models linger. While a reduction to a slow variable though the averaging equation such as (1.2) might seem more mathematically sound [40, 39, 34, 42, 43], averaging sometimes fails as in the elliptic bursting case. We have specifically concentrate on the dynamics of the voltage [27, 56], as it is typically the only measurable variable in experimental studies in neuroscience and physical chemistry.

Figure 1.19: (A) Pointwise mapping for $c = -0.945$ obtained from voltage traces using random initial conditions clearly illustrating a torus formation in the subthreshold voltage oscillations. (B) A repelling torus leaving two circles on the cross-section, which bounds the attraction basin of the subthreshold stable periodic orbit emerging through a supercritical Andronov-Hopf bifurcation.
The algorithm for interval mapping construction has two stages. First, one needs to identify the tonic spiking manifold in the phase space of the slow-fast neuron model in question. This is accomplished by either using the geometric dissection method, or the parameter continuation technique. The more accurately and completely the first stage is performed the more natural and smooth these numerically derived mappings will be. The second stage is to build the mappings for a range of parameter values. The analysis of such mappings lets one identify not only attractors, but more importantly, the unstable sets including fixed, periodic and homoclinic orbits, which are known to be the globally organizing centers governing the dynamics of any model. In addition, having computationally smooth mappings allows one to create symbolic descriptions for dynamics, compute kneading invariants, evaluate Schwarzian derivatives etc. As well as estimate other quantities measuring the degree of complexity for the trajectory behavior like Lyapunov exponents and topological entropy.

Our computational method allows us to thoroughly describe the bifurcations that the model (1.1) undergoes while transitioning between states: from tonic spiking to bursting, bursting to MMO and to quiescence. Taken individually, each mapping offers a glimpse into the system behavior. However, with an entire family of mappings we obtain insight into the evolution of the model’s dynamics though the interplay and bifurcations of the fixed points and periodic orbits of the mappings. This allows for not only the description of bifurcations post factum, but to predict the changes in the dynamics of the model under consideration before they actually occur. The predicting ability of our technique helps to classify all bifurcations in the models of elliptically bursting neurons. We accomplished this through a comparison of the family of mappings derived for the FNR model with the family of mappings of the other models without explicitly finding the bifurcations occurring in other models.

We mention the cons of the approach. First there is a price to pay for the scrutiny as such simulations are time expensive. Another minor drawback of the approach is a small detuning offset in parameter values at which the model and the mapping have nearly identical dynamics, matching orbits, or undergo the same bifurcations. This is caused by the fact that a one-dimensional mapping for a single voltage variable does not fully encompass the dynamics of other, major and minor, variables of the corresponding model. In general, most
features of a dissipative model with a negative divergence of the vector field, that results in a strong contraction of the phase volumes, are adequately modeled by a 1D Poincaré mapping. However, this is not true when such a contraction is no longer in place. For example, when the divergence becomes sign-alternating. There are two such places near the manifold $M_{lc}$ in the model (1.1): one is near the fold, second is close to the cone-shaped tip where the model has an equilibrium state of the saddle-focus type with a pair of complex conjugate eigenvalues with small positive real part and a real negative eigenvalue due to the Andronov-Hopf bifurcation and the smallness of $\varepsilon$.

Under the above conditions a (small) torus can possibly occur locally in the phase space. A small canard torus at $c = -0.945$ is shown in Fig. 1.19(B). The torus is unstable: it bounds a basin of attraction of a stable periodic orbit that emerged through the supercritical Andronov-Hopf bifurcation. As $c$ increases, the torus collapses onto the periodic orbit (see the bifurcation diagram in Fig. 1.5) and makes the orbit unstable. The unstable orbit then initiates the period doubling cascade for the subthreshold oscillations depicted in Fig. 1.4(B) and captured in the mappings in Figs. 1.13 and 1.14. The stability of the torus near the single equilibrium state of the model, a saddle-focus, can be evaluated through the examination of the Lyapunov exponents, as their sum yields the divergence. Making the middle equation of the model (1.1) faster by setting $\delta = 0.5$ changes the type of the torus bifurcation from sub- to supercritical. The stages of the torus’s formation and vanishing are depicted in Fig. 1.21. The stable torus emerges from a periodic orbit with complex Floquet multipliers (Fig. 1.21(A),(B)). Then it comes close to the fold of the manifold $M_{lc}$ (Fig. 1.20), where it shrinks back to the periodic orbit that corresponds to the tonic spiking activity in the model.

It should be noted that since for smaller values of $\delta$ the divergence of the vector field of this 3D model is negative near the fold, the stability loss of the nearby periodic orbit initiates a period doubling cascade instead of the torus bifurcation, see also [28].

It is evident that no 1D return mapping of the interval is intended to detect a torus in the phase plane, whereas the pointwise mappings generated by a forward time series of the voltage can identify the torus formation in the phase space, Fig. 1.19. Note that the torus has a canard-like nature, that is the torus exists within a narrow parameter window. A torus formation in a 3D model with two slow variables near the fold was reported also
Figure 1.20: (A) a 2D torus near the fold of the tonic spiking manifold $M_{lc}$ at $\delta = 0.5$ and $c = -0.38$. (B) Voltage trace revealing slow ($\sim \mu$) characteristic modulation of oscillations.

in [72]. Another parallel of the FNR model with electrochemical systems, including the Belousov-Zhabotinsky reaction, is that the latter also demonstrates a quasiperiodic regime [73]. The emergence of the torus near the fold of the tonic spiking manifold first described in [53, 28] has turned out to be a generic phenomenon observed recently in several plausible models [74, 75], including a model for the Purkinje cells [64, 76], and in a 12D hair cell model [77]
Figure 1.21: 2D cross-section $w = -0.09$ revealing the stages of the torus’s formation and vanishing in the model at $\delta = 0.5$: (A) stable periodic orbit (two spiraling-onto points) at $c = -0.55$ loses stability to a 2D torus (B) (two circles) at $c = -0.5478$ that having approached the fold on the tonic spiking manifold $M_{lc}$ at $c = -0.53$ (C) and (D) at $c = -0.45$ (dark blue), shrinks back to the tonic spiking periodic orbit at $c = 0.363$ (green) and 0.3 (black). Shown in red is the saddle-focus equilibrium state of the model.)
CHAPTER 2

TWO-DIMENSIONAL POINCARÉ RETURN MAPPINGS FOR A 3 INTERNEURON NETWORK MODEL

2.1 Introduction

In this Chapter, we introduce central pattern generators and 2-dimensional Poincaré return mappings for phase-lags. We show the elucidating power of phase-lag mappings for rhythmic outcomes of a small 3-cell network. Detailed analysis of phase-lag mappings can be found in Chapter 3.

A central pattern generator (CPG) is a neural microcircuit comprised of cells whose synergetic interactions, without a sensory input, can produce rhythmic bursting patterns that determine motor behaviors of an animal, such as heart beat, respiration, and locomotion [3, 4]. A dedicated CPG is responsible for robustly generating a single bursting pattern, whereas a multifunctional CPG can exhibit distinct rhythmic behaviors depending on input conditions: for example, switching between trot and gallop gaits in many mammals [78] or between swimming and crawling in leeches [79, 80]. Although such circuits are mostly hypothetical in the central nervous system of mammals, they have been located in many fish and invertebrates and in the spinal cord or peripheral nervous systems of mammals.

Switching between motor rhythms in a multifunctional CPG is attributed to switching between corresponding oscillatory attractors [80]. A key scientific issue is how modulation and control can switch the system between states, and how the CPG achieves robustness to noise and heterogeneity. Even simple biophysical models of CPGs typically involve many coupled differential equations with strong nonlinearities, multiple time scales, and many parameters. Theoretically, the problem is therefore how to obtain parsimonious answers to the scientific questions through mathematical analysis and simulation of these models. What are the potential organizing principles that the nervous system could use to control a multifunctional CPG? A common approach has been to first reduce each neuron’s activity
to a one- or two-dimensional return map using, for example, phase resetting techniques, and then to compose these maps to form an approximate representation of the cycle-to-cycle network activity [81, 82]. Instead, we directly analyze a single return map induced by the full dynamics of a biophysical network CPG model. This map will be defined qualitatively through numerical simulations and does not require knowledge of explicit phase equations for the underlying network model. This makes our technique applicable to a wide range of detailed (high-dimensional) models of rhythmic activity in biological networks, especially those that are not easily reduced to low-dimensional systems of equations by explicit means.

Elemental circuit configurations for CPG models are often reduced to 3 oscillators but their components are typically anatomically and physiologically diverse [83, 84, 85, 86]. For instance, the *Tritonia* swim circuit involves a 3 cell network [87]; the spiny lobster pyloric network can be viewed as a PD-AB pacemaker connected to the PY and LP neurons in a 3 oscillator ensemble [88]; the respiratory CPG of *lymnaea* also comprises 3 cells [89]. We show that even a simple 3-cell motif of identical oscillators possesses essential qualities that could be adapted for use as a universal building block for larger, realistic multifunctional CPGs. In particular, the motif can sustain multiple and robust rhythmic outputs. We consider a model of endogenously bursting neurons coupled in a ring [90] using fast reciprocal synaptic inhibition modeled by fast threshold modulation [91]. The neurons are 3-dimensional reduced models of leech heart interneurons, as defined in ref. [92], consisting of a voltage variable $V$, a slow K$^+$ current activation variable $n$ and a Na$^+$ inactivation variable $h$. (Na$^+$ activation is assumed to be instantaneous.) We study the effect of changing intrinsic timing properties of a burst on the polyrhythmic outcomes of the CPG, and demonstrate that the duty cycle of bursting, the fraction of the burst period in which the cell bursts, is a physiologically relevant order parameter that can be used to control switching between outcomes. We also consider the functional effect of varying coupling asymmetry in the ring-shaped motif. A detailed description of the model and motif can be found in Appendix B.1.
Figure 2.1: (A) Inhibitory 3-cell motif with weak counter-clockwise and strong clockwise coupling asymmetry. (B) Voltage traces: the phase (mod 1) of reference cell 1 (blue) is reset when $V_1$ reaches $\Theta_{\text{th}} = -40$ mV. The time between burst onsets in cell 2 (green) and 3 (red) determine a sequence of phase lags $\{\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)}\}$ normalized to the varying recurrence times of cell 1.
Figure 2.2: Five types of robust bursting rhythms in the medium-length bursting motif, using $g_{\text{syn}} = 5 \cdot 10^{-3}$ (increased from its nominal value to illustrate stable states without long transients). Appropriately-timed inhibitory pulses (horizontal bars) temporarily suppress the targeted cells and switch between the rhythms. Episode (i) shows the $(1 \perp \{2 \parallel 3\})$ rhythm, interrupted by a pulse to cell 2. On release of cell 2 from suppression, the clockwise $(1 \prec 2 \prec 3)$ rhythm is observed, which is a traveling wave (episode (ii)) where one cell is active at a time. After cell 1 is temporarily suppressed, the counter-clockwise $(1 \prec 3 \prec 2)$ rhythm is observed in episode (iii). A pulse releasing cell 3 from inhibition then makes cell 2 lead in the $(2 \perp \{1 \parallel 3\})$ rhythm of episode (iv). After cells 1 and 2 have been simultaneously hyperpolarized, cell 3 leads the motif in the $(3 \perp \{1 \parallel 2\})$ in the last episode (v) of the voltage trace.

2.2 Qualitative analysis of phase-lag maps

We examine polyrhythmic outcomes of the motif for short ($\sim20\%$), medium ($\sim50\%$), and long ($\sim80\%$) bursting DCs. For this we computationally derive return maps for phase lags $\Delta \phi_{21}$ and $\Delta \phi_{31}$ between burst onsets in cell 2 (green) and cell 3 (red) relative to the reference cell 1 (blue) (Fig. 2.1). As the period of network oscillation changes through time, we define the phase between cells to be relative to the time interval between which the voltage $V_1$ of cell 1 increases through a threshold of $-40 \text{ mV}$. We define $\Delta \phi^{(n)}_{1i} \in [0, 1)$ as the phase lag between the $n^{th}$ consecutive burst onsets in cells 1 and $i$. As the network evolves from an initial state, the relative phases of each oscillator on each subsequent cycle $n$ generate a
sequence \( \{\Delta \phi_{31}^{(n)}, \Delta \phi_{21}^{(n)}\} \), which we plot within the unit square; for convenience the iterates are joined with lines to preserve cycle ordering in the phase lag maps (Figs. 2.3–2.5).

Thus, the original, continuous-time 9D system is reduced to a 2D stroboscopic return map for the phase lags defined on a torus \([0, 1) \times [0, 1)\), with \(\Delta \phi_{31} \mod 1\). The maps are not derived as explicit equations, but instead are tabulated on a \(40 \times 40\) (or more) grid of initial points whose iterates comprehensively reveal the underlying vector field (details can be found in Appendix C.2). We then study the geometric properties of the maps when displayed in the phase plane, in which the opposite edges are identified (iterates can wrap around due to the toroidal topology of the space). In particular, we can locate equilibrium points of the maps, which we refer to as fixed points (FPs), and also periodic and heteroclinic orbits of the map (the latter connect saddle points together). We evaluate the stability of these objects and characterize bifurcations by using the methods of the qualitative theory of dynamical systems.

Fig. 2.3A shows the \((\Delta \phi_{31}, \Delta \phi_{21})\) phase-lag map for the homogeneous, medium bursting motif when \(V_{k2}^{\text{shift}} = -21.0 \text{ mV}\). The map possesses five stable FPs (color-coded dots) corresponding to the coexisting phase-locked bursting patterns: red at \((\Delta \phi_{21} \approx 0, \Delta \phi_{31} \approx \frac{1}{2})\), green \((\frac{1}{2}, 0)\), blue \((\frac{2}{3}, \frac{1}{3})\), black \((\frac{1}{3}, \frac{2}{3})\) and gray \((\frac{1}{3}, \frac{2}{3})\). The attraction basins of these points are divided by separatrices (incoming and outgoing sets) of six saddle points (brown dots).
Figure 2.3: (left) Phase-lag map for the homogeneous, medium bursting motif at $V_{\text{shift}}^{k2} = -21.0 \text{ mV}$, showing five phase-locked (fixed point) attractors: red at $\sim (0, \frac{1}{2})$, green $(\frac{1}{2}, 0)$, blue $(\frac{1}{2}, \frac{1}{2})$, black $(\frac{2}{3}, \frac{1}{3})$ and gray $(\frac{1}{3}, \frac{2}{3})$, whose basins are separated by six saddles (brown dots). (right) The map for the asymmetric motif ($g_{as} = 0.151$) is near saddle-node bifurcations that would annihilate three fixed points corresponding to anti-phase bursting rhythms.

Symbolically, we denote the rhythmic patterns as follows: $(1 \prec 3 \prec 2)$ and $(1 \prec 2 \prec 3)$ for counter-clockwise and clockwise bursting (resp.) around the ring (episodes (ii) and (iii) of Fig. 2.2). The corresponding FPs are located near $(\frac{2}{3}, \frac{1}{3})$ and $(\frac{1}{3}, \frac{2}{3})$, respectively. Also, there are three stable FPs corresponding to rhythms where one designated cell fires in anti-phase ($\Delta \phi = \frac{1}{2}$, or symbolically $\perp$) against two cells bursting simultaneously in-phase ($\Delta \phi = 0$, or symbolically $\parallel$). These are: the $(1 \perp \{2 \parallel 3\})$ pattern corresponding to $(\frac{1}{2}, \frac{1}{2})$ (episode (i) of Fig. 2.2); the $(2 \perp \{1 \parallel 3\})$ pattern corresponding to $(\frac{1}{2}, 0)$ (episode (iv)); and the $(3 \perp \{1 \parallel 2\})$ pattern corresponding to $(0, \frac{1}{2})$ (episode (v)). These anti-phase patterns are typically recorded in the leech CPG that controls blood circulation, and in the Tritonia CPG during escape swimming [78, 80].

The outcome of the homogeneous motif depends on the initial phase distributions of the cells. When the cells are about to burst together (e.g., after being suppressed by a
common inhibitory pulse [90, 93]), their initial phases are near the origin in the phase plane. In this case, any of the five rhythmic pattern outcomes has a chance of occurring (Fig. 2.3A). Each rhythm is robust, so well chosen perturbations are needed to switch the motif between rhythms. An efficient and easy way to perturb an inhibitory motif is to apply an appropriately-timed hyperpolarizing pulse to the targeted cell. Fig. 2.2 demonstrates the approach for the homogeneous motif with \( g_{\text{syn}} = 5 \cdot 10^{-3} \text{nS} \), which is used for illustration to ensure fast convergence to steady rhythms in the voltage traces. The phase-lag maps create a guide for where and how long a hyperpolarizing pulse needs to switch between rhythms. For example, if we begin at the FP \( (\frac{1}{2}, \frac{1}{2}) \), the \( (1 \perp \{2 \parallel 3\}) \) rhythm and perturb cell 2 (green) \( \Delta \phi_{21} \). This changes the position on the phase lag diagram and moves the phase point into the basin of attraction of another rhythm, say rhythm \( (1 \prec 2 \prec 3) \) as in Fig. 2.1.

### 2.2.1 Duty cycle is an order parameter of the network

The duty cycle (DC) of bursting oscillations is the fraction of the burst period in which the cell is spiking (Fig. 2.1), and is a property known to affect the synchronization properties of coupled bursters [93]. DC can be measured experimentally from voltage traces in neural dynamics. Many physiological parameters, including intrinsic and external currents, can affect DC. In this study, we control DC through the intrinsic parameter \( V_{\text{shift}}^{K2} \), which measures the deviation from the experimentally identified voltage value at which the slow \( K^+ \) current is half-activated [92]. DC depends monotonically on \( V_{\text{shift}}^{K2} \). As the activation kinetics of this current are shifted to depolarized voltages, the cells produce first short, then medium, and then long burst trains before transitioning to continuous spiking. We consider weak inhibitory coupling determined by the maximal conductance \( g_{\text{syn}} \), which is set at \( 5 \cdot 10^{-4} \) nS in the homogeneous case. Asymmetry in the motif is controlled by the second bifurcation parameter \( g_{\text{as}} \), which weakens (enforces) counter-clockwise (resp., clockwise) coupling strengths \( g_{\bigcirc} = g_{\text{syn}}(1 \pm g_{\text{as}}) \).

Comparison of the maps for the homogeneous motifs in cases of medium (Fig. 2.3), short (Fig. 2.4) and long (Fig. 2.5) bursting demonstrates that the DC is an order parameter for such configurations. As such, short bursting (DC \( \sim 20\% \)) makes both \( (1 \prec 2 \prec 3) \) and
(1≺3≺2) impossible because the corresponding FPs exist but are unstable. In contrast, for long bursting (DC~80%), these patterns equally dominate the dynamics by narrowing the attractor basin of the other FPs—shrinking the range of phases that can lead to alternative patterns.

Figure 2.4: (left) Phase-lag map for the homogeneous, short bursting motif at $V_{K2}^{\text{shift}} = -18.95$ mV, showing three attractors (blue, red, and green dots). Each corresponds to an anti-phase rhythm where one cell bursts solo followed by synchronized bursts in the other two cells. The fixed points for counter-clockwise and clockwise traveling waves (black dots) are unstable. (right) Map for the asymmetric motif ($g_{as} = 0.2$), depicting a stable invariant curve around the fixed point ($\frac{2}{3}, \frac{1}{3}$).

2.2.2 Varying the coupling asymmetry as a bifurcation parameter

Next we consider how the FPs of the phase-lag map bifurcate as the motif becomes asymmetrically connected by increasing $g_{as}$, such that $g_{\circ} = g_{\text{syn}}(1 \pm g_{as})$. In the limit as $g_{as} \to 1$, the system will be coupled in only one direction, so that the (1≺2≺3) rhythm and the corresponding FP may not exist or be unstable, while the (1≺3≺2) rhythm and the FP at ($\frac{2}{3}, \frac{1}{3}$) would dominate by expanding its attraction basin over the entire phase
range in all three cases. Stages of structural transformation in the medium bursting motif are documented in Figs. 2.3 and 2.5B. In Fig. 2.3, as $g_{as}$ increases to 0.151, the three saddles move away from the FP at $(\frac{2}{3}, \frac{1}{3})$, opening its basin, and come close to the stable FPs corresponding to the anti-phase bursting rhythms. Meanwhile, the other three saddles move towards the FP at $(\frac{1}{3}, \frac{2}{3})$ corresponding to the $(1 < 2 < 3)$ rhythm, thus narrowing its basin. As $g_{as}$ is increased further, the attractors and saddles in the bottom right of the unit square merge and vanish simultaneously through saddle-node (SN) bifurcations. Fig. 2.5B shows the phase-lag map for the motif at $g_{as} = 0.3$ where the FP corresponding to the clockwise bursting pattern is about to become the global attractor. Further increasing $g_{as}$ collapses the three saddles onto the FP around $(\frac{1}{3}, \frac{2}{3})$, to make it unstable (specifically, the FP becomes a degenerate saddle with 6 separatrices).

Transformations of rhythms in the long (DC~80%) bursting motif are qualitatively similar (see Fig. 2.5(A)), but as coupling asymmetry is increased from zero the SN bifurcations occur at smaller $g_{as}$ values. In contrast, the SN bifurcations in the short bursting motif (DC~20%) occur much later at $g_{as} \approx 0.48$. In addition, there is another bifurcation preceding the SN that makes the clockwise traveling pattern the global attractor. As one can see from Fig. 2.4A, in this homogeneous motif (DC~20%) the corresponding FP is unstable. To become stable, it underwent a secondary supercritical Andronov-Hopf or torus bifurcation for $g_{as} \approx 0.32$. Fig. 2.4B depicts the map at $g_{as} = 0.2$, which possesses a stable invariant curve near the heteroclinic connections between the three saddles surrounding the unstable FP at $(\frac{2}{3}, \frac{1}{3})$. The invariant curve corresponds to a 2D stable invariant torus in the original 9D system, and implies the appearance of small-magnitude phase modulations in the $(1 < 3 < 2)$ rhythm. In voltage-time traces, these periodic modulations are seen as small cycle-to-cycle variations in the exact timing of bursts, despite the overall order of burst onsets being maintained.
Figure 2.5: (A) Phase-lag map for the homogeneous, long bursting motif at $V_{\text{shift}}^{k_2} = -22.5$ mV, revealing two equally dominant rhythmic attractors: $(1 < 2 < 3)$ at $(\frac{1}{3}, \frac{2}{3})$ and $(1 < 3 < 2)$ at $(\frac{2}{3}, \frac{1}{3})$. (B) Map for the asymmetric ($g_{\text{as}} = 0.3$) medium bursting motif depicting two persistent attractors: $(1 < 3 < 2)$ prevails over $(1 < 2 < 3)$. Further increase in asymmetry leads to a globally stable $(1 < 2 < 3)$ rhythm, because the fixed point $(\frac{1}{3}, \frac{2}{3})$ becomes unstable after it merges with the nearby saddles.

2.3 Chapter Summary

In this work we presented a simple network motif of 3 bursting cells reciprocally coupled by fast inhibitory synapses in a ring. We showed that the model can generate multiple, coexisting rhythms, selected by the initial conditions of the cells. We characterized the essential temporal properties of the coupled system by measuring just two differences (“lags”) in the phase between the three oscillators along simulated orbits. By systematic variation of the initial conditions, the computational exploration of the possible rhythmic outcomes led to a reduction of the original 9D system of differential equations to a graphical and equationless representation of the 2D mapping of cycle-to-cycle phase lags. Crucially, a feature of this reduction is that explicit equations were replaced by a qualitative portrait of the maps. Nonetheless, the geometric properties of the maps, and how they change as
model parameters are varied, can be understood through standard qualitative techniques of dynamical systems theory. In particular, the rhythmic patterns of the motif correspond to fixed and periodic attractors of the maps. The basins of attraction for the rhythms are separated by phase thresholds known as saddles. As parameters are varied, bifurcations of the fixed point attractors determine changes in the rhythmic pattern outcomes. In particular, we varied the asymmetry in the clockwise versus counter-clockwise coupling around the ring, and the duty cycle of the bursts via a property of one of the intrinsic ionic currents in the cells.

We are not aware of previous work that investigates 2D maps induced directly from orbits computed for a fully coupled system of three bursting oscillators. Although our approach does not require explicit equations for the maps in order to study their properties, standard function-fitting techniques could possibly be used to derive equations that accurately describe the maps, such that the equations would also exhibit the same transformations and bifurcations we observed here. However, the power of our technique is that it avoids the need for equations, and as such makes few assumptions about the nature of the models of the coupled oscillators making up the motif or their detailed form of coupling. For instance, the models may be high-dimensional and possess multiple time scales. In order to define the phase lags, we only assume that the cells burst regularly, both endogenously and when bi- and uni-directionally coupled in the ring configuration. In principle, our technique can be generalized to a larger number of cells. Problems of human visualization of higher-dimensional phase-lag maps notwithstanding, the concepts of fixed points and periodic orbits carry through to higher dimensions. The drawbacks are (a) that the objects separating these attractors, and the possible ways that they can change, will have more complex geometry; and (b) that the enumeration of the necessary number of initial conditions to cover a higher-dimensional grid is more computationally challenging.

The attractors in the phase-lag maps and the objects separating them provide the organizing structure for the understanding of all the possible rhythmic interactions in this 3-cell motif. Thus, the properties of the organizing structures provide insight into the robust control of CPG output, as well as a possible source of synergies in motor control [94]. Any given 3-cell bursting model of a specific animal’s CPG is likely to involve greater asymmetry
between cell types and coupling (e.g., see refs. [87, 88]). However, it may be possible to understand the functional possibilities and mechanisms of such a model by viewing it as a structural variation of our generic motif of identical oscillators.

Besides the asymmetry parameter, we discovered that the primary “order parameter” determining the pattern outcomes is the duty cycle of bursting: short bursting promotes anti-phase rhythms, while long bursts will self-arrange into one of two traveling wave patterns typical of unidirectionally-coupled inhibitory rings. The dynamics of the motif with medium-length duty cycle is richer due to the existence of five competing rhythmic outcomes. We therefore hypothesize a possible biophysical control mechanism for switching between CPG patterns: common inhibition or excitation to the circuit, which varies the duty cycle of all cells simultaneously. We predict that future experimental investigations will show duty cycle to play an important role in controlling CPG dynamics in real systems.

Future investigations will explore stronger coupling regimes, changes to individual connections and will consider the addition of simple contextual circuits to the CPG such as proprioceptive feedback from motor control systems [95]. The roles of feedback and modulation from external circuitry may then be understood in many possible ways, including: the selection or masking of stable states of the central CPG, the strengthening or weakening of attractor basins, and other forms of distortion in the phase plane geometry. Our approach also naturally generalizes to other regulatory networks involving reciprocal inhibition, which is a form of feedback found in a diversity of physical networks. Thus, we believe our approach is applicable to improved understanding of various phenomena featuring multistability such as memory formation, decision making, as well as to enhancing synthetic approaches for generating motor behavior from artificial circuits. Additional mappings for various $V_{K2}^{\text{shift}}$ values and $g_{as}$ can be found in Appendix B.2 are provided for the curious reader.
CHAPTER 3

A BIFURCATION STUDY FOR 3 INTERNEURON NETWORK MODEL

3.1 Introduction

A central pattern generator (CPG) is a neural microcircuit of cells whose synergetic interactions, without sensory input, rhythmically produce patterns of bursting that determine motor behaviors such as heartbeat, respiration, and locomotion in animals and humans [78, 3, 4]. While a dedicated CPG generates a single pattern robustly, a multifunctional CPG can flexibly produce distinct rhythms, such as swimming versus crawling, and alternation of blood circulation patterns, in leeches [79, 80, 88]. Switching between such rhythms is attributed to input-dependent switching between attractors of the CPG.

Here we analyze multistability and transformations of several coexisting rhythmic patterns in a 9-D model of a CPG motif (Fig. 3.1) comprised of 3 endogenously bursting leech heart interneurons (details in [92] and supplement) coupled reciprocally by fast inhibitory chemical synapses [90]. Many anatomically and physiologically diverse CPG circuits involve a 3-cell motif [83, 84, 86]. We show how coexisting rhythms of the multistable motif are selected by changing the relative timing of bursts by physiologically plausible perturbations. We also demonstrate how the set of possible rhythmic outcomes can be controlled by varying the duty cycle of bursts, and by varying the coupling around the ring.

We propose a novel computational tool for detailed examination of polyrhythmic bursting in biophysical CPG models with coupling asymmetries and arbitrary coupling strength. The tool reduces the problem of stability and existence of bursting rhythms in large networks to the bifurcation analysis of fixed points (FP) of Poincaré return mappings for phase-lags. Our approach is based on delayed release of cells from a suppressed state, and complements the phase resetting techniques allowing for thorough exploration of network dynamics with spiking cells [81, 82]. It demonstrates that generally inhibitory networks possess stable
bursting patterns that do not occur in similar 3-oscillator motifs with gap-junction coupling, which is bi-directionally symmetric [96, 97, 98].

The duty cycle (DC) of bursting, being the fraction of the burst period in which cells spike, is a key regulator of motif synchronization properties [93, 90]. The DC is sensitive to fluctuations of most cell’s intrinsic parameters, and is affected by applied and synaptic currents [92, 90]. We treat DC implicitly as a bifurcation parameter that defines short (DC~20%), medium (DC~50%), and long (DC~80%) bursting motifs. DC is control by an intrinsic parameter that shifts the activation of the potassium current in the leech heart interneuron. In this study, we only examine weak inhibitory coupling using a maximal conductance \( g_{syn} = 5 \times 10^{-4} \) nS in the symmetric case. This permits us to visualize “smooth” trajectories that expose the qualitative structure of phase-lag return maps, and prepares the basis for understanding more complex patterns in strongly coupled, nonhomogeneous motifs with the same technique. In Chapter 2 we introduced the phase-lag mappings for symmetric and rotational asymmetries, \( g_{ij} = g_{syn}(1 \pm g_{as}) \), \( 0 \geq g_{as} \leq 1 \), from the nominal value \( g_{syn} \). We now expand and discuss this case in greater detail. We also add new asymmetries to the motif by changing individual connections, \( g_{ij} \neq g_{syn} \), as well as changes to multiple connections. We include the details in this chapter and do not make the reader search for information in the Appendix. The Appendix C does contain the numerical methods, and the model for quick reference. Additional mappings for the wide variety of connection changes are given in Appendix C.3 to allow for a complete bifurcation analysis for the interested reader.
3.2 Model

The CPG motif in question is comprised of three cells wired reciprocally by non-delayed fast inhibitory synapses with arbitrarily weak coupling strengths. Time evolution of the membrane potential, \( V \), of each cell is modeled within a framework of the Hodgkin-Huxley formalism:

\[
CV' = -I_{Na} - I_{K2} - I_{L} - I_{app} - I_{syn},
\]

\[
\tau_{Na} h'_{Na} = h_{Na}^\infty(V) - h,
\]

\[
\tau_{K2} m'_{K2} = m_{K2}^\infty(V) - m_{K2}.
\]

The dynamics of the above reduced leech heart interneuron model are based on the fast sodium current, \( I_{Na} \) with the activation described by the voltage dependent gating variables, \( m_{Na} \) and \( h_{Na} \); The slow potassium current \( I_{K2} \) with the inactivation from \( m_{K2} \); and the ohmic leak current, \( I_{leak} \). The equations governing these currents are given by:

\[
I_{Na} = \bar{g}_{Na} m_{Na}^3 h_{Na} (V - E_{Na}),
\]

\[
I_{K2} = \bar{g}_{K2} m_{K2}^2(V - E_K),
\]

\[
I_{L} = \bar{g}_{L} (V - E_L).
\]

In the model, \( C = 0.5 \text{nF} \) is the membrane capacitance and \( I_{app} = 0.006 \text{nA} \) is an applied current. The values of maximal conductances are set as \( \bar{g}_{K2} = 30 \text{nS} \), \( \bar{g}_{Na} = 160 \text{nS} \) and \( g_{L} = 8 \text{nS} \). The reversal potentials are \( E_{Na} = 0.045 \text{V} \), \( E_{K} = -0.07 \text{V} \) and \( E_{L} = -0.046 \text{V} \). The time constants of gating variables are \( \tau_{K2} = 0.9 \text{sec} \) and \( \tau_{Na} = 0.0405 \text{sec} \).

The steady state values, \( h_{Na}^\infty(V) \), \( m_{Na}^\infty(V) \), \( m_{K2}^\infty(V) \), of the of gating variables are given by the following Boltzmann equations:

\[
h_{Na}^\infty(V) = \left[ 1 + \exp(500(V + 0.325)) \right]^{-1}
\]

\[
m_{Na}^\infty(V) = \left[ 1 + \exp(-150(V + 0.0305)) \right]^{-1}
\]

\[
m_{K2}^\infty(V) = \left[ 1 + \exp(-83(V + 0.018 + V_{K2}^{\text{shift}})) \right]^{-1}.
\]

The reduced leech heart interneuron has turned out to be dynamically rich. It can demonstrates a myriad [6] of regular and irregular activity types including; hyper and depolarized quiescent; tonic spiking and bursting oscillations of the membrane potential. Fig-
Figure 3.1 shows a periodic bursting orbit (dark gray) in the 3D phase space of the model due to the dynamic variables, $V$, $h_{Na}$ and $m_{K2}$. The helical coils of the orbit correspond to the active tonic spiking period of bursting due to fast sodium current. The flat section corresponds to the hyperpolarized quiescent period of bursting in voltage traces due to slow recovery of the potassium current. The two snapshots (at $t = 0$ and $t = 10$) in Fig. 3.1 depict the blue, green and red spheres representing the current states of all three cells. The cells are weakly coupled so network interactions can only affect the relative phases of the cells on the intact bursting orbit, i.e. without deforming the bursting orbit.

Figure 3.1: Bursting orbit (grey) in the 3D phase space of the interneuron model. The gap between the slow nullcline, $m'_{K2}$, and the low knee on the slow quiescent manifold, $M_{eq}$, determines the amount of inhibition needed by the active presynaptic cell above the synaptic threshold, $\Theta_{syn}$, to slow or shut down the postsynaptic cell(s). The positions of the red, green and blue spheres on the bursting orbit depict the phases of the weakly-connected cells of the CPG: the active red cell inhibits, in anti-phase, the temporarily inactive blue and green ones.

We employ $V_{K2}^{shift}$, a deviation from the voltage value, $V_{1/2} = -0.018V$, corresponding to the half-activated potassium channel, $m_{K2}^{\infty} = 1/2$, as a bifurcation parameter to control the DC of the bursting cells. The DC is the fraction of the burst period in which the cell is spiking, and is a property known to affect the synchronization properties of coupled bursters.
[93]. An cell bursts within the interval \( V_{K2} \) ∈ [−0.024235, −0.01862]V. At greater values of \( V_{K2} \), it begins oscillating tonically about the depolarized steady state, while becomes hyperpolarizedly quiescent at more negative values of \( V_{K2} \). Therefore, the closer the cell is to either boundary, the DC of bursting becomes longer or shorter respective: DC is about 80% at \( V_{K2} = −0.0225 \)V and 25% at \( V_{K2} = −0.01895 \)V. For DC 50% we set \( V_{K2} = −0.021 \)V, in the middle of the bursting interval, see Fig. 3.2.

Figure 3.2: Burst duration increases or decreases the closer the cell approaches the boundary: tonic spiking (TS) or hyperpolarized quiescence (Q), respectively. The post-synaptic cell on the network can temporarily cross either boundary when excited/inhibited by the synaptic current(s) from the pre-synaptic neuron(s).

When an isolated bursting cell is set close to a transition the network dynamics become sensitive to external perturbations due to excitatory and inhibitory currents from other pre-synaptic cells. So, for example, depending on how close the post-synaptic cell is to the tonic-spiking boundary and the coupling strength, excitation produced by the pre-synaptic cell can cause the post-synaptic cell to burst longer or temporarily move it into the tonic spiking (TS) region. In contrast, inhibition from an pre-synaptic cell decreases the DC of the postsynaptic cell, or may even shut it down completely.

Fast, non-delayed synaptic currents in this study are modeled using the Fast Threshold Modulation (FTM) paradigm as follows [91]:

\[
I_{\text{syn}} = g_{\text{syn}}(E_{\text{syn}} - V_{\text{post}})\Gamma(V_{\text{pre}} - \Theta_{\text{syn}}), \\
\Gamma(V_j) = 1/[1 + \exp\{-1000(V_{\text{pre}} - \Theta_{\text{syn}})\}] ;
\]  

\text{(3.4)}
here $V_{\text{post}}$ and $V_{\text{pre}}$ are voltages of the post- and the pre-synaptic cells; the synaptic threshold $\Theta_{\text{syn}} = -0.03\text{V}$ is chosen so that every spike within a burst in the presynaptic cell crosses $\Theta_{\text{syn}}$, see Fig. 3.1. This implies that the synaptic current, $I_{\text{syn}}$, is initiated as soon as $V_{\text{pre}}$ exceeds the synaptic threshold. The type, inhibitory or excitatory, of the FTM synapse is determined by the level of the reversal potential, $E_{\text{syn}}$. In the inhibitory case, we set $E_{\text{syn}} = -0.0625\text{V}$ so that $V_{\text{post}}(t) > E_{\text{syn}}$. The level of $E_{\text{syn}}$ is raised to zero in the excitatory case to guarantee that $(V_{\text{post}}(t))$ remains below the reversal potential on average over the period of the bursting cell [10]. For excitatory case see Appendix C.

3.3 Numerical Methods and Materials

![Figure 3.3: (A) Homogeneous 3-cell motif configuration with mutually inhibitory connections.](image)

We propose a novel computational tool for detailed examination of polyrhythmic bursting in biophysical CPG models. The tool reduces the problem of stability and existence of bursting rhythms in such networks to the bifurcation analysis of FP’s and invariant curves of Poincaré return mappings for phase-lags between oscillatory cells.
We defined the phase of a cell through the voltage of the given cell. We intentionally chose the phase in relation to the voltage trace since often the voltage is the only experimentally measurable variable. We recorded the event time when the voltage variable increased through a threshold, $\Theta_{th}$, which created an ordered sequence of event times for each cell, $\{\tau_i^{(n)} : i = 1, 2, 3\}$, see Fig. 3.3. Topologically our phase resides on the surface of a torus, Fig. 3.4. We note that our definition for the phase is not unique, but is well defined. We set the threshold to $\Theta_{th} = -0.04V$, to ensure a burst onset with no interburst spike interactions.

We defined the set of phase-lags to be the difference in phases between the reference cell and the other 2 cells, normalized over the current network period:

$$\Delta \phi_{21}^{(n)} = \frac{\tau_1^{(n)} - \tau_1^{(n+1)}}{\tau_1^{(n+1)} - \tau_1^{(n)}} \quad (3.5)$$

We combine the sets of phase-lags into a set of ordered pairs that define a phase-lag trajectory, $\{(\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)})\}$. The initial recurrence time was unknown, since the exact cell interactions are unknown a priori. Hence we estimate (in first order) the first phase-lag, $(\Delta \phi_{21}^{(0)}, \Delta \phi_{31}^{(0)})$, as a fraction of the synchronous period, $T_{synch}$, as $(\Delta \phi_{21}^*, \Delta \phi_{31}^*)$. Note if we take the synchronous solution, $\Delta \phi_{21} = \Delta \phi_{31} = 0$, and let $t = 0$ when $V_1 = \Theta_{th}$ we can parameterize the solution by; time $(0 \leq t \leq T_{synch})$; or by phase-lag $(0 \leq \Delta \phi_{j1} \leq 1)$. We emphasize for “weak” coupling the recurrence time is close to $T_{synch}$ which implies $(\Delta \phi_{21}^*, \Delta \phi_{31}^*) \approx (\Delta \phi_{21}^{(0)}, \Delta \phi_{31}^{(0)})$ and in first approximation was a reasonable estimation.

The phase-lag mappings were created using the following algorithm. The phase-lag trajectories were initialized for uniformly distributed phase-lags covering an $k \times k$ ($k = 40$ typically) grid over the $[0, 1] \times [0, 1]$ torus. All cells were initiated from the same initial condition, $(v_0, n_0, h_0)$, corresponding to the onset of bursting. We created the initial phase-lags by initializing the reference cell at $t = 0$ and suppressed cells 2 and 3 for a duration $t = \Delta \phi_{21}^{(0)} T_{synch}$ and $t = \Delta \phi_{31}^{(0)} T_{synch}$, where $\Delta \phi_{j1}^{(0)}$ was the true (desired) initial phase-lags for the $j^{th}$ cell. The cell interaction may create a non-linear jump from the true initial phase as the cells began to interact and the network period deviated from $T_{synch}$, as such
we began recording the trajectory from the second cycle. We point out that the phase-lag trajectories are discrete sets of ordered pairs and are “weakly” coupled, in order to show transient behavior. However, the algorithm and accompanying analysis is not restricted to the “weak” coupling regime. We connected the points to preserve the ordering and unfolded the torus to ease visualization.

The comprehensive way of interpreting multistability properties of the 3-cell motif capitalizes on the idea of Poincaré return mapping for the phase-lags:

\[
T : \left( \Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)} \right) \to \left( \Delta \phi_{21}^{(n+1)}, \Delta \phi_{31}^{(n+1)} \right)
\]  

(3.6)

The mapping is defined on a 2D torus \([0, 1) \times [0, 1)\) with phases defined on mod 1.

The numerical simulations and phase analysis were accomplished utilizing the freely available PyDSTool (version 0.88) dynamical systems environment [99]. Additional files and instructions are available upon request.

Figure 3.4: Poincaré return mapping for the phase-lags \(\{\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)}\}\) between the bursting cells on a 2D torus \([0, 1) \times [0, 1)\).
3.4 Results

We employed several protocols for varying synaptic coupling in the 3-cell motif. We found FPs, that corresponded to phase locked states. We also found, provided the cells burst, the motif was multistable. The homogeneous case allowed us to characterize the role of DC as an order parameter. The DC, controlled by the intrinsic parameter $V_{\text{shift}}^{K2}$, determined the size, location and stability of the phase locked states in the motif [8]. We introduced heterogeneity into the motif with changes to synaptic coupling strength for inhibitory connections. Complete details can be found below.

3.4.1 Multistability and DC in heterogenous motifs

Figure 3.5(A) represents the superimposed evolutions of the phase-lags, $\Delta\phi_{21}$ and $\Delta\phi_{31}$ over the burst cycle number, $n$, in the motif composed of the medium, 25%DC bursting cells at at $V_{K2}^{\text{shift}} = -0.01895V$. After transient behaviors, the phase-lags show clear exponential convergence to several stable phase-locked states of the network.
Figure 3.5: (upper left) Evolutions of the phase-lags, $\Delta \phi_{31}$ (brown) and $\Delta \phi_{21}$ (orange), exponentially converging to several stable phase locked states after 50 burst cycles at $V_{K2}^{\text{shift}} = -0.01895$. (upper right) The Poincaré phase-lag mapping for the symmetric, short bursting motif at $V_{K2}^{\text{shift}} = -0.01895$ revealing three attracting FPs (blue, red and green) $(\phi_{21}, \phi_{31}) \approx \{(\frac{1}{2}, \frac{1}{2}), (0, \frac{1}{2}), (\frac{1}{2}, 0)\}$, and their attraction basins, for three distinct rhythmic patterns where one cell bursts followed by synchronized bursts in the other two cells, and illustrating the the basins of attraction separated by stable and unstable sets (separatrices) of six saddle FPs. Unstable FPs at $\approx (\frac{2}{3}, \frac{1}{3})$ and $(\approx \frac{1}{3}, \frac{2}{3})$ exclude the clockwise $(1 \prec 2 \prec 3)$ and counter-clockwise $(1 \prec 3 \prec 2)$ traveling waves from the repertoire of the short bursting motif and thus undetectable in Inset (upper left). (bottom) Three coexisting rhythms in the motif with 25%DC at $V_{K2}^{\text{shift}} = -0.01895$ with $\pm 5\%$ random perturbation applied to all inhibitory connections, where one cell bursts in anti-phase with two other sync ones. Switching between rhythms is achieved by application of external hyperpolarized pulses that releases the targeted cells at proper timings.
Since the phase traces in Fig. 3.5(A) are not orderly indexed, one can only evaluate the number of stable phase-locked states \textit{a priori}. Furthermore we cannot state anything about unstable and saddle FPs in the motif. The proposed 2Dimensional Poincaré return mapping for the phase-lags, Eq. 3.3, does not suffer from this drawback. The 2D return map has the advantage of elucidating unstable and saddle FPs in addition to stable FPs and all bifurcations of FPs stable or not, Fig. 3.5(B).

Iterates or forward trajectories of the mapping are connected to preserve order in Fig. 3.5(B). The mapping shows three attracting, two repelling (foci) and six saddle FPs. The attractors correspond to the coexisting stable phase-locked rhythms of the short bursting motif: the red FP at \((\Delta\phi_{2,1} \approx 0, \Delta\phi_{3,1} \approx \frac{1}{2})\), the green FP at \((\frac{1}{2},0)\), and the blue FP at \((\frac{3}{2}, \frac{1}{2})\). Two repelling FPs are located at approximately \((\frac{2}{3}, \frac{1}{3})\) and \((\frac{1}{3}, \frac{2}{3})\), respectively. The attraction basins of the stable FPs are divided by separatrices (incoming and outgoing sets) of six saddles shown by small brown dots in the phase-lag maps. The neighborhood of \((0,0)\) has a complex structure at high magnification (see Fig. C.3), but acts effectively as a global repellor.

In order to distinguish between rhythms, we introduce symbolic descriptions for each of the phase locked states. The bursting rhythms of the motif are denoted symbolically as: one cell fires in anti-phase \((\Delta\phi \sim \frac{1}{2}, \text{ or } \perp)\) against two cells bursting simultaneously in-phase \((\Delta\phi = 0, \text{ or } \parallel)\). The stable FP (blue) at \((\frac{1}{2}, \frac{1}{2})\) corresponds to the \((1 \perp \{2 \parallel 3\})\)-pattern shown in the first episode of Fig. 3.5, the stable (red) fixed \((\frac{1}{2}, 0)\) corresponds to \((3 \perp \{1 \parallel 2\})\)-pattern (second episode), while the stable (green) FP \((0, \frac{1}{2})\) corresponds to \((2 \perp \{1 \parallel 3\})\)-pattern (third episode).

The motif posses 2 additional unstable rhythms: \((1 \prec 2 \prec 3)\) near \((\frac{1}{3}, \frac{2}{3})\) and \((1 \prec 3 \prec 2)\) near \((\frac{2}{3}, 1)\) for clockwise and counter-clockwise traveling waves of bursting (resp.). The phase-lag maps are \textit{de facto} proof of the observability of the matching rhythmic outcomes generated by a motif, symmetric or not. While the existence of some rhythms, like the generic \((1 \prec 2 \prec 3)\) and \((1 \prec 3 \prec 2)\), in a 3-cell motif can hypothetically be deduced using symmetry arguments. The robustness and observability of the rhythms must be justified by accurate computational verification, as their stability strongly correlates with the temporal properties of the bursting cells.
As the DC of the cells is increased the traveling waves, \((1 ≺ 2 ≺ 3)\) and \((1 ≺ 3 ≺ 2)\), become stable in the motif. Fig. 3.6(A) shows the symmetric case when the DC is increased to 50\% at \(V_{\text{shift}}^{K2} = -0.021V\). The FPs near \((\frac{1}{3}, \frac{2}{3})\) (grey) and \((\frac{2}{3}, \frac{1}{3})\) (black) are clearly stable. There exist 5 stable FPs for the 50\% DC motif. The basins of attraction for the 5 FPs are separated by the separatrices of six saddles, or more precisely unstable sets of incoming and outgoing directions of the saddles. Hence, the selection of a particular rhythmic outcome in a multifunctional motif depends on the initial phases of the cells on the bursting orbit.

![Figure 3.6: (left) Phase-lag map for the symmetric, medium bursting motif at \(V_{\text{shift}}^{K2} = -0.021V\), showing five stable FPs: green at \(\sim (\frac{1}{3}, 0)\), red at \((0, \frac{1}{3})\), blue at \((\frac{1}{3}, \frac{1}{3})\), black at \((\frac{2}{3}, \frac{1}{3})\) and gray at \((\frac{1}{3}, \frac{2}{3})\), corresponding to the anti-phase \((3 \perp \{1 \parallel 2\})\), \((2 \perp \{1 \parallel 3\})\), \((1 \perp \{2 \parallel 3\})\) bursts, and traveling clockwise \((1 ≺ 2 ≺ 3)\) and counter-clockwise \((1 ≺ 3 ≺ 2)\) waves, resp. The attraction basins are divided by “separatrices” (stable sets) of six saddles (small brown dots). (right) Phase-lag mapping for the long bursting motif at \(V_{\text{shift}}^{K2} = -0.0225\) possessing two stable FPs \((\frac{2}{3}, \frac{1}{3})\) and \((\frac{1}{3}, \frac{2}{3})\), that equally dominate over the dynamics with two counter-clockwise \((1 ≺ 3 ≺ 2)\) and clockwise \((1 ≺ 2 ≺ 3)\) traveling bursting patterns. The other three FPs have extremely narrow basins.

Phase-lag return mappings offer a particular transparent interpretation for existence of FPs, either stable or unstable, as well as better understanding of the CPG behavior. The
geometry of the phase-lag mapping suggests a methodology for the switching of rhythms to a designated bursting pattern by perturbing the motif in a certain phase direction, i.e. advancing or delaying the constituting cells. A plausible way to control switching is by temporarily suppressing targeted cell(s) for appropriately-timed hyperpolarizing pulses, as demonstrated in Fig. 3.7 for the symmetric, medium bursting motif. In terms of the phase-lag maps, this moves the phase point out of the basin of attraction of a particular rhythm and into the basin of attraction of another rhythm.

Figure 3.7: Voltage trace exploring the five possible rhythmic outcomes for medium DC with $g_{\text{syn}} = 5 \times 10^{-3}$ (increased to secure short transients for the purpose of illustration), and switching between rhythms. Inhibitory pulses (horizontal bars) release the targeted cells, thus causing switching between co-existing rhythms: $(1 \perp \{2 \parallel 3\})$ in episode (i), traveling waves $(1 \prec 2 \prec 3)$ in (ii) and $(1 \prec 3 \prec 2)$ in (iii), followed by $(2 \perp \{1 \parallel 3\})$ led by cell 2 in (iv). Having released cells 1 and 2 simultaneously, cell 3 leads the motif in the $(3 \perp \{1 \parallel 2\})$ rhythm in the last episode (v).

Decreasing the intrinsic bifurcation parameter, $V_{K2}^{\text{shift}}$, increases the DC. This results in an increase in the attraction basins of the FPs, $(\frac{2}{3}, \frac{4}{3})$ and $(\frac{1}{3}, \frac{2}{3})$, while those of the other FPs shrink such that the two counter-clockwise $(1 \prec 3 \prec 2)$ and clockwise $(1 \prec 2 \prec 3)$ traveling bursting patterns become dominant over the dynamics of the long bursting 3-cell motif with 80%DC, see Fig. 3.6(B). Switching between the rhythms in this essentially bi-stable motif is still possible and can be achieved by shutting down the targeted cell and releasing it from inhibition, Fig. 3.7.

We have shown that DC effects the multistability for weak coupled motifs. The question remains as to what, if any other, factors effect the multistability. To answer that question we return to Figs. 3.1 and 3.2. $V_{K2}^{\text{shift}}$ effectively controls the DC of bursting by shifting the
bursting cell toward the boundary of either tonic spiking – 100% DC or hyperpolarized quiescence – 0% DC. At $V_{K2}^{\text{shift}} = -0.01895\text{V}$, weak inhibition from the pre-synaptic cell(s) shut down the post-synaptic cell(s) thereby resulting in three possible rhythms with one cell bursting in anti-phase and the other two cells synchronized. In order to sustain such rhythms at $V_{K2}^{\text{shift}} = -0.0225\text{V}$, the nominal coupling strength, $g_{\text{syn}} = 5 \times 10^{-4}$, must be increased; otherwise the postsynaptic cell remains bursting even while being weakly inhibited. In the aftermath, the motif is able to produce two symmetric traveling patterns. Placing the cells in the middle of the bursting interval at $V_{K2}^{\text{shift}} = -0.021\text{V}$ results in the persistence of all five possible patterns: the anti-phase $(3 \perp \{1 \parallel 2\})$, $(2 \perp \{1 \parallel 3\})$, $(1 \perp \{2 \parallel 3\})$ rhythms, and traveling $(1 \prec 2 \prec 3)$ and $(1 \prec 3 \prec 2)$ waves. Thus, the types of multistability in the 3-cell motif of the bursting cells is determined by a balance involving the intrinsic parameter of the cells and external coupling parameter of the network.

![Figure 3.8: Switching between two counter-clockwise (1 \prec 3 \prec 2) and clockwise (1 \prec 2 \prec 3) traveling waves by an external hyperpolarizing pulse in the long bursting motif with 80%DC.](image)

3.4.2 From multistability to (1 \prec 3 \prec 2) pattern

In this section we briefly examine bifurcations en a route from the homogeneous to heterogenous 3-cell motif by simultaneously increasing clockwise-directed and decreasing counter-clockwise directed synapses. The bifurcation parameter $g_{\text{as}}$ is introduced to deviate the nominal coupling strengths, $g_{\text{syn}} = 5 \times 10^{-4}$, such that $g_{\text{syn}}(1 \pm g_{\text{as}})$, $0 \leq g_{\text{as}} \leq 1$. The limit $g_{\text{as}} \to 1$ makes the motif unidirectionally coupled with only the counter-clockwise $(1 \prec 3 \prec 2)$ traveling wave observable for the short 20%DC motif. Hence, $(1 \prec 3 \prec 2)$ is the only stable fixed rhythm at $(\frac{2}{3}, \frac{1}{3})$ whose attraction basin is the entire torus. Recall that at
$g_{as} = 0$, symmetrically coupled, both traveling patterns are unstable in the short bursting motif (Fig. 3.5(right)).

Figure 3.9: (left) Enlargement of the phase-lag mapping at $V_{K2}^{\text{shift}} = -0.01895$ and $g_{as} = 0.185$ depicts a stable invariant circle near a heteroclinic connection between the surrounding saddles that produces a small amplitude phase jitter in the voltage traces. (right) Enlargement of the phase-lag mapping at $g_{as} = 0.32$ clearly illustrating the change in stability for the FP at $(\frac{2}{3}, \frac{1}{3})$.

Intermediate stages of the structural transformation of the $(1 \prec 3 \prec 2)$ FP are demonstrated in Fig. 3.9. First, as $g_{as}$ increases to 0.185, the three saddles around the unstable FP, $(\frac{2}{3}, \frac{1}{3})$, form a heteroclinic connection. Increasing $g_{as}$ further, breaks the heteroclinic connection and leads to the onset of a stable invariant curve. The invariant curve is associated with the appearance of small cycle to cycle oscillations around the $(1 \prec 2 \prec 3)$ rhythm in voltage traces, i.e. phase jitter. Increases in $g_{as}$ causes the curve to collapse onto the FP at $(\frac{2}{3}, \frac{1}{3})$ through a secondary supercritical Andronov-Hopf or torus bifurcation. The asymmetric motif gains a new robust $(1 \prec 2 \prec 3)$ rhythm, making four possible bursting outcomes. As $g_{as}$ is increased further, the three saddles and the three initially stable FPs (blue, green and red), corresponding to the anti-phase $(3 \perp \{1 \parallel 2\})$, $(2 \perp \{1 \parallel 3\})$, $(1 \perp \{2 \parallel 3\})$ bursting patterns, move toward each other in pairs. The FPs for the anti-phase rhythms merge and
vanish through simultaneous saddle-node bifurcations. Afterwards, the FP \((\frac{2}{3}, \frac{1}{3})\) becomes the global attractor of the network producing a robust counter-clockwise \(1 \prec 3 \prec 2\) traveling bursting rhythm. Notice the simultaneous saddle-node bifurcations are caused by directional symmetry of the coupling strengths in the motif.

![Phase-lag mapping](image)

Figure 3.10: (left) Phase-lag mapping for \(V_{shift}^{K2} = -0.01895\) and \(g_{as} \approx 0.41\): the three saddles surrounding the FP \((\frac{2}{3}, \frac{1}{3})\), are about to merge and vanish simultaneously with the three initially stable FPs through saddle-node bifurcations. Notice the FP at \((\frac{1}{3}, \frac{2}{3})\) remains unstable. (right) For \(g_{as} > 0.42\) the only attractor, \((\frac{2}{3}, \frac{1}{3})\), corresponding to the robust \(1 \prec 3 \prec 2\) traveling wave generated by the heterogeneous 3-cell motif.

3.5 Motifs with asymmetric inhibition

So far we have shown a completely symmetric and a rotational asymmetric case. The rotational asymmetric case did have directional symmetry however. We now break both rotational and directional symmetry by treating individual coupling strengths as the bifurcation parameter(s). We use the 50%DC as the base case, since it is in the middle of the bursting range. The 50%DC case gives the most stable FPs as well as flexibility in reaching either boundary, TS or Q in Fig. 3.2. We begin with all connection at the nominal \(g_{syn}\), and change individual and multiple connection strengths such that \(g_{ij}\) is a percentage of the \(g_{syn}\)
(increased or decreased) connection strength from cell $i$ to cell $j$. We introduce a term, *flux of inhibition*, to explain the dominance of particular attractors. The *flux of inhibition* is defined by the amount of inhibition a cell projects onto another versus the amount of inhibition a cell receives. This will prove invaluable to the qualitative description of rhythmic activities of the CPG. A thorough set of mappings are provided in Appendix C.3, which shows many intermediate maps and mappings for short and long DC.
3.5.1 Single connection asymmetry

Figure 3.11: (left) Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$ and $g_{31} = 1.1g_{\text{syn}}$ lacks the FP $(\frac{1}{3}, \frac{2}{3})$ corresponding the clockwise (1 $\prec$ 2 $\prec$ 3) traveling wave and a saddle after a saddle-node bifurcation. The attraction basin of the vanished traveling wave is absorbed into the attraction basin of the $(3 \perp \{1 \parallel 2\})$ rhythm led by the (red) cell 3. (right) While counterclockwise biased motif with $g_{32} = 1.1g_{\text{syn}}$, $g_{\text{syn}} = 5 \times 10^{-4}$ cannot generate counterclockwise (1 $\prec$ 3 $\prec$ 2) traveling wave as the corresponding FP at $(\frac{2}{3}, \frac{1}{3})$ has annihilated through a saddle-node bifurcation, it produces all other remaining rhythms with the dominating $(3 \perp \{1 \parallel 2\})$ pattern.

We consider a case with a change in coupling to a single synapse, $g_{31}$. The $g_{31}$ synapse projects from the pre-synaptic cell 3 onto the post-synaptic cell 1 and is increased in relative units from the nominal value $5 \times 10^{-4}$. An increase or decrease to a single connection breaks
the rotational symmetry which is the underlying property of the traveling waves, either clockwise \((1 ≺ 2 ≺ 3)\) or counter-clockwise \((1 ≺ 3 ≺ 2)\). Notice the clockwise wave travels across the synapses oriented clock-wise, and \textit{vice versa}. Then variations of the clockwise coupling \(g_{31}\) effect the \((1 ≺ 2 ≺ 3)\) wave corresponding to the FP at \((\frac{2}{3}, \frac{1}{3})\) in the upper-left corner of the phase diagram, Fig. 3.11.

We found each of the 6 connections in the motif controls one specific saddle FP. An increase to an individual coupling strength causes a specific saddle FP to merge and annihilate with the FP corresponding to of the one of the two traveling wave rhythms, \((1 ≺ 2 ≺ 3)\) or \((1 ≺ 3 ≺ 2)\). Figure 3.11 (left) depicts the resulting phase-lag mapping for the motif with the enforced connection from the cell 3 toward the cell 1 by 10\%, \(g_{31} = 1.1 g_{\text{syn}}\). While \(g_{31}\) is gradually increased, the saddle associated with the \(g_{31}\)-connection and the FP for the clockwise \((1 ≺ 2 ≺ 3)\)-traveling wave merge and annihilate through a saddle-node bifurcation at some critical value \(g_{\text{syn}} < g_{31} < 1.1 g_{\text{syn}}\). Notice, the increase of \(g_{31}\) implies an increase in the \textit{flux of inhibition} for cell 3, which causes the red (cell 3) FP to inherit the basin of attraction of the annihilated FP for the \((1 ≺ 2 ≺ 3)\) rhythm.

In contrast, an increase to a single counter-clockwise connection, \(g_{32} = 1.1 g_{\text{syn}}\) is shown in Fig. 3.11 (right), shows the disappearance of the FP at \((\frac{2}{3}, \frac{1}{3})\) corresponding to the \((1 ≺ 3 ≺ 2)\) rhythm. Notice that in either case the \((3 \perp \{1 \parallel 2\})\) FP inherits the basin of attraction of the traveling wave FP since in both cases cell 3 projects more inhibition onto the other cell.
Figure 3.12: (left) Counterclockwise biased motif with $g_{13} = 1.1g_{\text{syn}}$ for $V_{K2}^{\text{shift}} = -0.021$ predictably lacks the counterclockwise $(1 \prec 3 \prec 2)$ traveling wave, but can produce a more robust $(1 \perp \{2 \parallel 3\})$ rhythm in the mapping after the attraction basin of the central FP has increased due to the disappearance of the stable FP $(\frac{2}{3}, \frac{1}{3})$ and the separating saddle. (right) Two connections with enforced $g_{12} = g_{21} = 1.25g_{\text{syn}}$ synapses singling out a dedicated HCO breaking the rotation symmetry of the 3-cell motif. The corresponding phase-lag mapping at $V_{K2}^{\text{shift}} = -0.021V$ has accordingly lost both stable FPs for clockwise $(1 \prec 2 \prec 3)$ and counter-clockwise $(1 \prec 3 \prec 2)$ traveling waves through merges with two saddles via the saddle-node bifurcations. The phase diagram is inherently broken between two large basins of the $(1 \perp \{2 \parallel 3\})$-rhythm – the stable (blue) FP in the middle, and the $(2 \perp \{1 \parallel 3\})$-rhythm – the stable (green) FP at $(\frac{1}{2}, 0)$ which co-exist with a weaker attracting $(3 \perp \{1 \parallel 2\})$-rhythm – the (red) FP at $(0, \frac{1}{2})$ bounded by threshold - saddle FPs nearby at $g_{12} = g_{21} = 1.25g_{\text{syn}}$. 
Let us consider another motif with \( g_{13} = 1.1 g_{\text{syn}} \) without examining the corresponding phase-lag map. We can make a prediction about its structure and therefore about the possible bursting patterns. Generically, as one of the synapses connecting the pre-inhibitory cell with the cell is strengthened, the correspondingly oriented traveling wave is eliminated from the repertoire of the motif. The FP \( \left( \frac{2}{3}, \frac{1}{3} \right) \) or \( \left( \frac{4}{3}, \frac{2}{3} \right) \) disappears through a saddle-node bifurcation after merging with the particular saddle controlled by the pre-synaptic cell. In the case of \( g_{13} = 1.1 g_{\text{syn}} \) the pre- and post-synaptic cells are the (blue) cell 1 and the (red) cell 3 (resp.), and the counterclockwise \( (1 \prec 3 \prec 2) \) traveling wave is excluded after the stable FP \( \left( \frac{2}{3}, \frac{1}{3} \right) \) vanishes through a saddle-node bifurcation, which widens the attraction basin the (blue) FP. The \( (1 \perp \{2 \parallel 3\}) \) rhythm coexists with anti-phase \( (2 \perp \{1 \parallel 3\}) \), \( (3 \perp \{1 \parallel 2\}) \), and clockwise \( (1 \prec 2 \prec 3) \) rhythms, see Fig. 3.12 (right).

Another feature of the coupling is the relative weighting of the synaptic strengths, or more precisely their ratios. Namely, the 10% increase of a single connection is effectively equivalent to a proportional decrease in the two other connections of the same orientation. Corresponding phase-lag maps to support the assertion may be found in Appendix C.3 and are qualitatively identical. For example, the mapping for \( g_{12} = g_{23} = 0.9 g_{\text{syn}} \), is qualitatively identical to that shown in Fig. 3.12 (right); the case of the motif with a single enforced synapse \( g_{31} = 1.1 g_{\text{syn}} \). This property/observation offers a glimpse at several possible mechanisms of network plasticity that the CPG can employ to restore a lost rhythm.

### 3.5.2 Motifs with 2 connection asymmetries

A 3-cell motif with cells coupled reciprocally by inhibitory synapses can be treated alternatively as a group of three half-center oscillators (HCO). Each HCO represents a pair of cells that typically burst in anti-phase in isolation. In this section, we will continue examining transformations of possible rhythmic outcomes as the motif gains a dedicated HCO.
Figure 3.13: (left) Motif with the dedicated HCO inhabiting asymmetrically the targeted cell 3. The \((\Delta \phi_{21}, \Delta \phi_{31})\) phase-lag mapping for the medium (50\%DC) bursting motif at \(V_{K2}^{\text{shift}} = -0.021V\) with \(g_{12} = g_{21} = g_{23} = 1.5g_{\text{syn}}\) with two phase locked states: the dominating anti-phase \((2 \perp \{1 \parallel 3\})\) rhythm corresponding to the (green) FP at \((\frac{1}{2}, 0)\) and the \((3 \perp \{1 \parallel 2\})\) corresponding to the (red) attractor at \((0, \frac{1}{2})\) with a smaller basin. (right) Compare this motif configuration with (left). (right) In contrast to (left) this phase-lag mapping for \(V_{K2}^{\text{shift}} = -0.021V\) and \(g_{12} = g_{21} = g_{13} = 1.5g_{\text{syn}}\) has gained back the FP at \((\frac{1}{2}, \frac{1}{2})\) with the largest attraction basin still coexisting with the (red) FP for the cell 3 as a pacemaker.

We create a single HCO on the motif by strengthening the reciprocally inhibitory connections between the cells 1 and 2 \((g_{12} = g_{21} = 1.25g_{\text{syn}})\), Fig. 3.12(right). Studies have shown that for a strong HCO unidirectionally and symmetrically driven by another cell can be forcefully synchronized even by weak inhibition [93]. Here, the reciprocal coupling remains weak between the HCO and the cell 3. As a result, while still possessing the per-
sistent \((3 \perp \{1 \parallel 2\})\)-rhythm, the motif with an HCO is unable to generate both clockwise \((1 \prec 2 \prec 3)\) and counterclockwise \((1 \prec 3 \prec 2)\) traveling wave because of the broken rotational symmetries. Indeed, as coupling is strengthened between \(g_{12}\) and \(g_{21}\) from the nominal value, the corresponding stable FPs, \((\frac{1}{2}, \frac{3}{2})\) and \((\frac{1}{2}, \frac{3}{2})\) come closer to the saddles. After reaching a threshold, the FPs vanish through saddle-node bifurcations. As a result, the anti-phase \((1 \perp \{2 \parallel 3\})\) and \((2 \perp \{1 \parallel 3\})\) rhythms corresponding to the stable FPs around \((\frac{1}{2}, \frac{1}{2})\) and \((\frac{1}{2}, 0)\) widen their basin of attractions. Note that the choice of the FP inheriting the basin is determined by the outgoing separatrix (set) of the bifurcating saddle-node. Observe from Fig. 3.12(right) that at the chosen value of \(g_{12} = g_{21} = 1.25g_{\text{syn}}\), the stable FPs corresponding to \((1 \perp \{2 \parallel 3\})\) and \((2 \perp \{1 \parallel 3\})\) pacemaking rhythms are located close to saddles. This indicates the possible occurrence of subsequence saddle-node bifurcations, should either connection of this motif is perturbed further. Indeed as both \(g_{12} = g_{21}\) are increased over \(1.5g_{\text{syn}}\), both stable FPs will vanish simultaneously, see Appendix C.3. As the result of these ”heteroclinic” saddle-node bifurcations, the mapping will gain a stable invariant circle that wraps around the torus. This curve gives rise to a phase-slipping phenomena that co-exists with the only intact phase-locked state – the (red) fixed point at \((0, \frac{1}{2})\) for the \((3 \perp \{1 \parallel 2\})\) rhythm. We define the “phase slipping” phenomena as a rhythm with no fixed phase-locked state but time-varying phases of some larger period. The period of the invariant circle depends on how far the mapping is from the ghost of the saddle-nodes, i.e. the mapping has a bifurcation memory. Figure 3.14 demonstrates the phase slipping in the bursting traces. It begins with the \((2 \perp \{1 \parallel 3\})\) rhythm continuously changing into the clockwise \((1 \prec 2 \prec 3)\) traveling wave, followed by the \((1 \perp \{2 \parallel 3\})\)-rhythm, and being continued by the counterclockwise \((1 \prec 3 \prec 2)\) traveling wave and finally returning to the initial \((2 \perp \{1 \parallel 3\})\)-rhythm in 10 bursting cycles, which is the period of the phase slipping. The period, as well as the length of each episode in the phase slipping can be arbitrarily large near the corresponding saddle node bifurcation(s) and controlled by the coupling strength of the specific motif connections.
**Figure 3.14:** Voltage trace in the “phase-slipping” regime (the stable invariant circle wrapping around the torus in Fig. 3.15) beginning with the $\{2 \perp \{1 \parallel 3\}\}$ rhythm and continuously changing into the clockwise $(1 \prec 2 \prec 3)$ traveling wave, followed by the $(1 \perp \{2 \parallel 3\})$-rhythm, and being continued by the counterclockwise $(1 \prec 3 \prec 2)$ traveling wave and coming finally back to the initial $(2 \perp \{1 \parallel 3\})$-rhythm in 10 bursting cycles.

**Figure 3.15:** (left) Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021$ V and $g_{12} = g_{21} = 1.5g_{\text{syn}}$ and $g_{13} = g_{31} = 1.5g_{\text{syn}}$. The addition of the inhibitory connection from the cell 3 (red) to the cell 3 leads to the elimination of the red stable FP at $(0, \frac{1}{2})$ and hence the $(3 \perp \{1 \parallel 2\})$-rhythm, makes the (blue) FP $(\frac{1}{2}, \frac{1}{2})$ the only attractor determining the only feasible $(1 \perp \{2 \parallel 3\})$-rhythm for all initial phase differences. (right) Phase-lag mapping with $g_{12} = g_{21} = 1.5g_{\text{syn}}$ and symmetrically weakening $g_{31} = g_{32} = 0.8g_{\text{syn}}$ making the FPs at $(\frac{1}{2}, \frac{1}{2})$ and $(\frac{1}{2}, 0)$ vanish through heteroclinic saddle-node bifurcations giving rise to the onset of a stable invariant curve wrapping about the 2D torus. The varying bursting pattern is shown in Fig. 3.14.
3.5.3 Motifs with 3 or more connection asymmetries

The next example is the motif with the dedicated HCO inhibiting asymmetrically the targeted cell 3, Fig. 3.13(left). The configuration of the motif allows us to make a feasible prediction about the structure of the corresponding phase-lag mapping. Namely, the (green) cell 2 produces the greatest flux of inhibition, the corresponding the FP \((\frac{1}{2}, 0)\) should possess the largest attraction basin because of the asymmetry \(g_{23} = 1.5g_{13}\). The saddle moves away from the stable FP at \((0, \frac{1}{2})\), while the attractor at \((\frac{1}{2}, \frac{1}{2})\) (as well as the \((2 \perp \{1 \parallel 3\})\)-rhythm) disappear expectedly after a single saddle-node bifurcation. Note that due to symmetric inhibition generated by the cell 3 toward the HCO, the \((3 \perp \{1 \parallel 2\})\)-rhythm still exist.

One could predict that reinstating the value of \(g_{23}\) back to nominal while increasing \(g_{13} = 1.5g_{\text{syn}}\) will make the attractor at \((\frac{1}{2}, 0)\) vanish and bring back the FP at \((\frac{1}{2}, \frac{1}{2})\) to the phase plane, see Fig. 3.12(right). As above, the bio-physical explanation is that the (blue) cell 1 produces the largest flux of outgoing inhibition which makes it the dominating pacemaker in the anti-phase bursting \((1 \perp \{2 \parallel 3\})\) rhythm, coexisting with a less robust \((3 \perp \{1 \parallel 2\})\) rhythm.

An enhancement of the asymmetric motif in Fig. 3.13(right) is a configuration with two HCOs (shown in Fig. 3.15(left)) created by increased coupling for the paired cells 1 and 2, and the paired cells 1 and 3. In this motif the cell 1 reciprocally produces and receives stronger inhibition from cells 2 and 3, then between themselves. Enforcing these coupling connections over a threshold by 50%, leads to two dynamical consequences: (1) changing the inhibition, \(g_{31} = 1.5g_{32}\), from the cell 3 and hence the mapping loses the (red) stable FP around \((0, \frac{1}{2})\) for the \((3 \perp \{1 \parallel 2\})\)-rhythm; and (2) because of \(g_{13} = 1.5g_{23}\), the (green) stable FP at \((\frac{1}{2}, 0)\). For the motif with a single HCO as in Fig. 3.12(right), the \((2 \perp \{1 \parallel 3\})\)-rhythm disappears through another saddle-node bifurcation. As such this motif exhibits the \((1 \perp \{2 \parallel 3\})\)-pattern corresponding to the single (blue) stable FP, \((\frac{1}{2}, \frac{1}{2})\). Note two saddles persist, and recall that in general FPs emerge and vanish in pairs on a torus. Therefore, the mapping must possess another, “missing” hyperbolic FP which appears to reside near the repelling origin corresponding to all three cells bursting synchronously. Synchrony is typically unstable in most reciprocally inhibitory cases [93].
Figure 3.15(right) presents another unfolding for the mapping for the motif with the dedicated HCO due to $g_{12} = g_{12} = 1.25g_{\text{syn}}$ in Fig. 3.12(right). Asymmetric perturbations from reciprocally enforcing $g_{12} = g_{21} = 1.5g_{\text{syn}}$, or alternatively by reciprocally weakening $g_{31} = g_{32} = 0.8g_{\text{syn}}$ lead to two saddle-node bifurcations involving the FPs $(1/2, 1/2)$ and $(1/2, 0)$ simultaneously. Because the saddle-node FPs are on the 2D torus, and their attraction basins are bounded by stable sets of the saddles. These saddle-node bifurcations involve connected *heteroclinic orbits* which are generic and therefore do not increase the codimension of the bifurcations. This implies that as soon as the saddle-nodes disappear, the heteroclinic connections become a stable invariant circle that transversally wraps the torus. The attraction basin of the circle is large compared to that of the (red) FP at $(0, \frac{1}{2})$. For the motif, the presence of the stable invariant circle corresponds to the occurrence of the “phase slipping” phenomena. We would like to point out that phase slipping could be an explanation for alternations of the blood circulation in the leech heart controlled by a CPG composed of several bursting HCOs [3].

Last but not least in the purely inhibitory cases is the motif without the persistent the $(3 \perp \{1 \parallel 2\})$-rhythm. By this time, the reader has figured that to get rid of the stable (red) FP at $(0, \frac{1}{2})$, both reciprocal connections between the cell 3 and the cell 1 or 2 should be enforced or weakened over some critical value corresponding to some saddle-node bifurcation. Such a phase-lag map, with $g_{12} = g_{21} = 1.5g_{\text{syn}}$ and $g_{13} = g_{31} = 0.8g_{\text{syn}}$, is depicted in Fig. 3.16. Here, the wrapping invariant circle is the only attractor on the resonant 2D torus. To logically conclude the bifurcation sequence, one needs to determine the configuration that would correspond to the mapping on the 2D torus without invariant curves and FPs. This can potentially be done by having two repelling FPs and the last saddle merge and vanish through a *homoclinic* saddle-node bifurcation that would make the closed homoclinic orbit become an unstable invariant curve, also wrapping around the torus. The torus becomes ergodic after the stable and unstable invariant curves merge and vanish through a final saddle-node bifurcation in the 3-cell motif system.
Figure 3.16: (left). The 50\%DC CPG motif with increased, $g_{12} = g_{21} = 1.5g_{\text{syn}}$, mutual inhibition between the cells 1 and 2, and the decreased, $g_{13} = g_{31} = 0.8g_{\text{syn}}$. (right) The phase-lag mapping possessing the only attractor - the invariant curve corresponding to the phase-slipping regime (Fig. 3.14). The asymmetry in inhibition flux produced by the cell 3 ceases the $3 \perp \{1\|2\}$-rhythm after the stable FP at $(0, \frac{1}{2})$ is annihilated via a saddle-node bifurcation.
3.6 Chapter Summary

We have created a practical method for the analysis of 3-cell network phase relationships, that is readily understandable without equations. The methods derived here can be easily investigated in wet laboratory experiments. Using the proposed technique for the reduction of dynamics of the 9D 3-cell motif to 2D mappings for the phase-lags between the bursting cells the method is scalable in both with complex high dimensional models and to larger networks, i.e. each “cell” in our 3-cell network can be considered as a network itself.

Here we have described the most typical configurations obtained via minimal transformations from the original symmetric motifs with reciprocally inhibitory fast synapses that features five stable bursting outcomes. We found that a reciprocally inhibitory (non)homogeneous network can be multistable, i.e. can generate several distinct polyrhythmic bursting patterns. We would like to point out that there are multiple ways of creating the motif with pre-set characteristics. This observation indicates that such motifs possess flexibly dynamical properties. We deduce that inhibition enhances the plasticity of the neuronal networks comprised of oscillatory cells and regulates the activity patterns.

It is shown that the observable rhythms of the 3-cell motif are determined not only by (a)symmetry, but the DC serving the role of the order parameter for bursting networks. The DC determines the basins of attraction and stability of rhythmic activities in the network. Furthermore, the DC characterizes the amount of inhibition/excitation needed in a network to push post-synaptic cells over the boundaries into tonic spiking or quiescence. This implies that bursting rhythms can be included, excluded or made more robust by changes to only the DC of constituting cells. This will allow for the explanation of networks in terms of traditional dynamical systems theory with manifolds and nullclines. In networks the coupling may be treated as a nullcline, the position of which on the bursting manifold will determine whether cells can pass a “knee-point” and burst in specific rhythms.

The most practical and profound discovery we made was the control of saddle FPs by specific connections. Saddle FPs are the salt of life in any dynamical system. Without saddles there would be no multistability, only monotonic convergence to equilibrium states, i.e. boring. Saddles add the dynamics to systems and it is the bifurcations of saddles that give
dynamical systems its richness. The discovery that each synaptic connection in the network controls a specific saddle makes the creation (and control) of specific rhythms simple. The knowledge of the existence, stability and possible bifurcations of polyrhythms in this 9D motif composed of the interneuron models is vital for derivations of reduced, phenomenologically accurate phase-models for nonhomogeneous biological CPGs with inhibitory synapses.

We have laid the foundations for a network bifurcation theory. At present bifurcation theory is applied to networks with a patchwork mentality, to our knowledge there is no comprehensive or solid foundation offered for network bifurcation study. We provide a systematic and thorough explanation for rhythmic outcomes in terms of FPs in a phase-lag mapping and the subsequent bifurcations of the FPs. We do not claim to have solved network bifurcation theory, merely given a solid footing for future studies. In the words of Leonardo da Vinci, “art is never finished, only abandoned”. We do not completely abandon the project, however this dissertation must have an ending.

Additional studies are planned to investigate the effects of excitation, see Appendix C.4 as well as mixed inhibitory and excitatory connections. We also plan to use different synaptic coupling regimes (electrical, post-inhibitory rebound, ect.), expand into larger networks and explore small but highly biophysically relevant CPGs. The reader may expect additional published works to follow.
References


A.1 Voltage Interval 1-dimensional Mappings Models

A.1.1 FitzHugh-Nagumo-Rinzel Model

The mathematical FitzHugh-Nagumo-Rinzel model of the elliptic burster is given by the following system of equations with a single cubic nonlinear term:

\[
\begin{align*}
v' &= v - v^3/3 - w + y + I, \\
w' &= \delta(0.7 + v - 0.8w), \\
y' &= \mu(c - y - v);
\end{align*}
\]

(A.1)

here we fix \( \delta = 0.08, I = 0.3125 \) an applied external current, and \( \mu = 0.002 \) is a small parameter determining the pace of the slow \( y \)-variable. The slow variable, \( y \), becomes frozen in the singular limit, \( \mu = 0 \). We employ \( c \) as the primary bifurcation parameter of the model.

A.1.2 Hodgkin-Huxley Model

The 4-dimensional bursting adaptation of the Hodgkin-Huxley model is given by the following system of ODEs:

\[
\begin{align*}
C\dot{V} &= I - \bar{g}_K n^4(V - E_K) - \bar{g}_N a m^3 h(V - E_Na) - \bar{g}_l(V - E_L), \\
\dot{n} &= 0.01 \left( \frac{10-V}{10} \right) (1 - n) - 0.125 \exp(\frac{-V}{80}) n, \\
\dot{m} &= 0.1 \left( \frac{25-V}{25} \right) (1 - m) - 4 \exp(\frac{-V}{18}) m, \\
\dot{h} &= 0.07 \exp(\frac{-V}{20})(1 - h) - \frac{1}{\exp(\frac{-V}{10}) - 1} h + I_h,
\end{align*}
\]

(A.2)

In the model, \( I_h \in [-0.19, -0.05] \) is the sweeping parameter used to scan the slow motion.
manifold \( M_{lc} \), as well as generate the corresponding mapping family sampled in Fig. 1.17. Note that \( I_h \) only moves the slow nullcline given \( h' = 0 \) in the phase space of the model.

For sake of compatibility, the equations of the bursting version of the models used are also given “as is” so the reader can cut-&-paste directly from this pdf document.

\[
\begin{align*}
V' &= 2 + 36 \cdot \text{pow}(n, 4) \cdot (-12 - V) + 60 \cdot \text{pow}(m, 3) \cdot h \cdot (115 - V) + 0.3 \cdot (10.613 - V); \\
n' &= 0.005 \cdot (-V + 10) / (\exp(-0.1 \cdot V + 1) - 1) \cdot (1 - n) - 0.125 \cdot \exp(-V/11) \cdot n; \\
m' &= 0.1 \cdot (-V + 25) / (\exp(-0.1 \cdot V + 2.5) - 1) \cdot (1 - m) - 4 \cdot \exp(-V/18) \cdot m; \\
h' &= 0.002 \cdot (0.2 \cdot \exp(-V/20) \cdot (1 - h) - 1 / (\exp(-0.1 \cdot V + 3) + 1) \cdot h + c).
\end{align*}
\]

**A.1.3 The external segment of the Globus Pallidus, Rubin-Terman model**

The Rubin-Terman model for the external segment of the Globus Pallidus is given by the following equation:

\[
C_m \dot{V} = -I_L - I_K - I_{Na} - I_T - I_{Ca} - I_{syn} - I_{Ge} + I_{app}, \tag{A.3}
\]

For sake of compatibility, the equations of the bursting version of the models used are also given “as is” so the reader can cut-&-paste directly from this pdf document.

\[
\begin{align*}
V' &= -0.1 \cdot (-V + 55) - 30 \cdot \text{pow}(n, 4) \cdot (-V + 80) - 120 \cdot \text{pow}(1 / (1 + \exp((-V + 37) / 10)), 3) \cdot h \cdot (-V + 55) \\
&\quad - 0.5 / (1 + \exp((-V + 57) / 2)) \cdot \text{pow}(1 / (1 + \exp((-V + 57) / 2)), 2) \cdot r \cdot (-V + 120) \\
&\quad - 0.15 \cdot \text{pow}(1 / (1 + \exp((-V + 35) / 2)), 2) \cdot (-V + 120) - 30 \cdot (-V + 80) \cdot (Ca / (Ca + 30)); \\
n' &= 0.05 \cdot ((1 / (1 + \exp((-V + 50) / 14)) - n) / (0.05 + 0.27 / (1 + \exp((V + 40) / 12)))) ; \\
h' &= 0.05 \cdot ((1 / (1 + \exp((V + 58) / 12)) - h) / (0.05 + 0.27 / (1 + \exp((V + 40) / 12)))) ; \\
r' &= (1 / (1 + \exp((V + 70) / 2)) - r) / 30; \\
Ca' &= \epsilon \cdot (-0.15 \cdot \text{pow}(1 / (1 + \exp((-V + 35) / 2)), 2) \cdot (-V + 120) \\
&\quad - 0.5 \cdot \text{pow}(1 / (1 + \exp((-V + 57) / 2)), 3) \cdot r \cdot (-V + 120) - 20 \cdot Ca + c);
\end{align*}
\]

with \( \epsilon = 0.0001 \); here \( c \) is a sweeping parameter in the slow equation used to detect the tonic spiking, \( M_{lc} \), and quiescent manifolds in the phase space of the model, see Fig. 1.18.
A.2 Voltage interval 1-dimensional Mappings Numerical Methods

Paramount to the process of creating the voltage interval return mapping is the generation of the slow motion manifolds for the model. We have developed a practical approach for the localization of manifolds in the phase space of a slow-fast neuronal model using the parameter continuation technique [100]. The core of the parameter continuation technique is a scan of the static manifold in question by translating the slow nullcline in the phase space as the bifurcation parameter is varied. This is possible since a feature of a slow-fast model is that the solutions are constrained to stay near the slow-motion manifolds that are composed of equilibria and periodic orbits of the fast subsystem. Let there be a stable, periodic orbit of the model (A.1.1) for some $c$ on the outer section of the tonic spiking manifold $M_{lc}$. Variations of $c$ move the slow nullcline in the $v$-direction which makes the periodic orbit slide along $M_{lc}$ thereby revealing the manifold. Hence without slow-fast dissection, but rather by parametrically continuing the periodic orbit, we detect the sought manifold $M_{lc}$, see Fig. ?? This parameter continuation approach yields the slow manifolds themselves for a given $\varepsilon$. We stress that our approach has been proven to work exceptionally well for several high-dimensional (12D and 14D) models of neurons [55], (including the 5D Terman-Rubin model A.1.3), in which application of the standard slow-fast dissection for accurately singling out several subsystems becomes problematic due to the presence of multiple time scales of the state variables.

The slow motion manifold, $M_{lc}$, is found by following the branch of the periodic orbits of the model starting from a subcritical Andronov-Hopf bifurcation using the parameter continuation software package CONTENT 1.55 [100]. Each of 5840 orbits are sought with a mesh of 401 points. To determine the exact location corresponding to a local maximum $v' = 0$, we use a point from the mesh data to integrate a solution of the model in MATLAB. We use the ode15s solver with events set as follows: absolute tolerance $10^{-11}$, relative tolerance $10^{-11}$, BDF ‘on’. We repeat this process for each limit cycle of the manifold, hence creating the smooth curve $V_{max}^*$ (green in Fig 1.3). We then utilize the set $\{V_{max}^*\}$ as initial conditions and integrate the model (1.1) again; stopping integration when the next maxima is reached for each member of $\{V_{max}^*\}$. Thus we created a new set of pairs $(V_n, V_{n+1})$,
where $V_n \in \{V_{max}^*\}$ and $V_{n+1}$ is found from integration of the model (A.1.1), see Fig. ??.

We then graph the pairs, $(V_n, V_{n+1})$ and used a cubic spline to computationally smooth the data. This allows us to compute trajectories of the mappings. Hence we create “continuous” (computationally smooth) mappings that can be fully analyzed.

### A.3 Fitzhugh-Nagumo-Rinzel Model voltage interval mappings

A complete set of mappings for the FNR model are provided here, for thorough analysis. Each figure has the graph of the mapping (blue), with iterations (transients (gray) and stable (green)) and FPs (red), in the upper frame and the maximum voltage trace determined by iterations of the mapping, directly below each mapping.

![Figure A.1: Poincaré return mapping for FNR model 1.1 with $c = -0.585$ (left) and $c = -0.591$ (right)](image-url)

Figure A.1: Poincaré return mapping for FNR model 1.1 with $c = -0.585$ (left) and $c = -0.591$ (right)
Figure A.2: Poincaré return mapping for FNR model 1.1 with $c = -0.593$ (left) and $c = -0.59411$ (right)

Figure A.3: Poincaré return mapping for FNR model 1.1 with $c = -0.59412$ (left) and $c = -0.59414$ (right)
Figure A.4: Poincaré return mapping for FNR model 1.1 with $c = -0.59417$ (left) and $c = -0.59424$ (right)

Figure A.5: Poincaré return mapping for FNR model 1.1 with $c = -0.594253$ (left) and $c = -0.5942556$ (right)
Figure A.6: Poincaré return mapping for FNR model 1.1 with $c = -0.5942559$ (left) and $c = -0.594257$ (right)

Figure A.7: Poincaré return mapping for FNR model 1.1 with $c = -0.59426$ (left) and $c = -0.59428$ (right)
Figure A.8: Poincaré return mapping for FNR model 1.1 with $c = -0.59429$ (left) and $c = -0.5943$ (right)

Figure A.9: Poincaré return mapping for FNR model 1.1 with $c = -0.5944$ (left) and $c = -0.5946$ (right)
Figure A.10: Poincaré return mapping for FNR model 1.1 with $c = -0.5947$ (left) and $c = -0.5948$ (right)

Figure A.11: Poincaré return mapping for FNR model 1.1 with $c = -0.595$ (left) and $c = -0.597$ (right)
Figure A.12: Poincaré return mapping for FNR model 1.1 with $c = -0.599$ (left) and $c = -0.6$ (right)

Figure A.13: Poincaré return mapping for FNR model 1.1 with $c = -0.605$ (left) and $c = -0.615$ (right)
Figure A.14: Poincaré return mapping for FNR model 1.1 with \( c = -0.616 \) (left) and \( c = -0.617 \) (right)

Figure A.15: Poincaré return mapping for FNR model 1.1 with \( c = -0.618 \) (left) and \( c = -0.6191 \) (right)
Figure A.16: Poincaré return mapping for FNR model 1.1 with $c = -0.61915$ (left) and $c = -0.61916$ (right)

Figure A.17: Poincaré return mapping for FNR model 1.1 with $c = -0.619162$ (left) and $c = -0.619163$ (right)
Figure A.18: Poincaré return mapping for FNR model 1.1 with $c = -0.619165$ (left) and $c = -0.61917$ (right)

Figure A.19: Poincaré return mapping for FNR model 1.1 with $c = -0.61918$ (left) and $c = -0.6192$ (right)
Figure A.20: Poincaré return mapping for FNR model 1.1 with $c = -0.61927$ (left) and $c = -0.6196$ (right)

Figure A.21: Poincaré return mapping for FNR model 1.1 with $c = -0.6199$ (left) and $c = -0.6201$ (right)
Figure A.22: Poincaré return mapping for FNR model 1.1 with $c = -0.6203$ (left) and $c = -0.620624$ (right)

Figure A.23: Poincaré return mapping for FNR model 1.1 with $c = -0.620625$ (left) and $c = -0.620628$ (right)
Figure A.24: Poincaré return mapping for FNR model 1.1 with $c = -0.62063$ (left) and $c = -0.620635$ (right)

Figure A.25: Poincaré return mapping for FNR model 1.1 with $c = -0.62065$ (left) and $c = -0.6207$ (right)
Figure A.26: Poincaré return mapping for FNR model 1.1 with \( c = -0.6208 \) (left) and \( c = -0.621 \) (right).

Figure A.27: Poincaré return mapping for FNR model 1.1 with \( c = -0.6215 \) (left) and \( c = -0.622 \) (right).
Figure A.28: Poincaré return mapping for FNR model 1.1 with $c = -0.6225$ (left) and $c = -0.623$ (right)

Figure A.29: Poincaré return mapping for FNR model 1.1 with $c = -0.6235$ (left) and $c = -0.625$ (right)
Figure A.30: Poincaré return mapping for FNR model 1.1 with $c = -0.63$ (left) and $c = -0.635$ (right)

Figure A.31: Poincaré return mapping for FNR model 1.1 with $c = -0.64$ (left) and $c = -0.65$ (right)
Figure A.32: Poincaré return mapping for FNR model 1.1 with \( c = -0.66 \) (left) and \( c = -0.67 \) (right)

Figure A.33: Poincaré return mapping for FNR model 1.1 with \( c = -0.68 \) (left) and \( c = -0.69 \) (right)
Figure A.34: Poincaré return mapping for FNR model 1.1 with $c = -0.69$ (left) and $c = -0.7$ (right).

Figure A.35: Poincaré return mapping for FNR model 1.1 with $c = -0.71$ (left) and $c = -0.72$ (right).
Figure A.36: Poincaré return mapping for FNR model 1.1 with $c = -0.73$ (left) and $c = -0.74$ (right)

Figure A.37: Poincaré return mapping for FNR model 1.1 with $c = -0.75$ (left) and $c = -0.76$ (right)
Figure A.38: Poincaré return mapping for FNR model 1.1 with $c = -0.77$ (left) and $c = -0.78$ (right)

Figure A.39: Poincaré return mapping for FNR model 1.1 with $c = -0.8$ (left) and $c = -0.81$ (right)
Figure A.40: Poincaré return mapping for FNR model 1.1 with $c = -0.82$ (left) and $c = -0.83$ (right)

Figure A.41: Poincaré return mapping for FNR model 1.1 with $c = -0.84$ (left) and $c = -0.85$ (right)
Figure A.42: Poincaré return mapping for FNR model 1.1 with $c = -0.86$ (left) and $c = -0.87$ (right)

Figure A.43: Poincaré return mapping for FNR model 1.1 with $c = -0.88$ (left) and $c = -0.89$ (right)
Figure A.44: Poincaré return mapping for FNR model 1.1 with $c = -0.8$ (left) and $c = -0.81$ (right)

Figure A.45: Poincaré return mapping for FNR model 1.1 with $c = -0.895$ (left) and $c = -0.9$ (right)
Figure A.46: Poincaré return mapping for FNR model 1.1 with $c = -0.902$ (left) and $c = -0.903$ (right)

Figure A.47: Poincaré return mapping for FNR model 1.1 with $c = -0.9041$ (left) and $c = -0.9042$ (right)
Figure A.48: Poincaré return mapping for FNR model 1.1 with $c = -0.9044$ (left) and $c = -0.90472$ (right).

Figure A.49: Poincaré return mapping for FNR model 1.1 with $c = -0.90474$ (left) and $c = -0.90478$ (right).
Figure A.50: Poincaré return mapping for FNR model 1.1 with $c = -0.9048$ (left) and $c = -0.905$ (right)

Figure A.51: Poincaré return mapping for FNR model 1.1 with $c = -0.906$ (left) and $c = -0.9075$ (right)
Figure A.52: Poincaré return mapping for FNR model 1.1 with $c = -0.908$ (left) and $c = -0.97$ (right)
Appendix B

TWO-DIMENSIONAL Poincaré Return Mappings for a 3 Interneuron Network Model

B.1 Reduced leech heart interneuron model

A reduced model of the leech heart interneuron is given by the following set of three nonlinear coupled differential equations [92]:

\[
C \frac{dV}{dt} = -I_{Na} - I_{K2} - I_L + I_{app} + I_{syn},
\]

\[
I_L = \bar{g}_L (V - E_L), \quad I_{K2} = \bar{g}_{K2} m_{K2}^2 (V - E_K), \quad I_{Na} = \bar{g}_{Na} m_{Na}^3 h_{Na} (V - E_{Na}),
\]

\[
\tau_{Na} \frac{dh_{Na}}{dt} = h_{Na}^\infty(V) - h, \quad m_{Na} = m_{Na}^\infty(V), \quad \tau_{K2} \frac{dm_{K2}}{dt} = m_{K2}^\infty(V) - m_{K2}. \tag{B.1}
\]

Here, \( C = 0.5nF \) is the membrane capacitance; \( V \) is the membrane potential in mV; \( I_{Na} \) is the sodium current with slow inactivation \( h_{Na} \) and fast activation \( m_{Na} \); \( I_{K2} \) is the slow persistent potassium current with activation \( m_{K2} \); \( I_L \) is the leak current and \( I_{app} = 0.006 \) is an applied current. The values of maximal conductances are set as \( \bar{g}_{K2} = 30nS \), \( \bar{g}_{Na} = 200nS \) and \( g_L = 8nS \). The reversal potentials are \( E_{Na} = 0.045V \), \( E_K = -0.07V \) and \( E_L = -0.046V \). The time constants of gating variables are \( \tau_{K2} = 0.9sec \) and \( \tau_{Na} = 0.0405sec \). The steady state values of gating variables, \( h_{Na}^\infty(V) \), \( m_{Na}^\infty(V) \), \( m_{K2}^\infty(V) \), are given by the following Boltzmann equations:

\[
h_{Na}^\infty(V) = \left[1 + \exp(0.5(V + 0.325))\right]^{-1}
\]

\[
m_{Na}^\infty(V) = \left[1 + \exp(-0.15(V + 0.0305))\right]^{-1}
\]

\[
m_{K2}^\infty(V) = \left[1 + \exp(-0.083(V + 0.018 + V_{shift}))\right]^{-1}. \tag{B.2}
\]

The synaptic current is modeled through the fast threshold modulation paradigm as follows:

\[
I_{syn} = -\sum_{j=1}^{n} g_{syn}(1 \pm g_{as})(E_{syn}^{inh} - V_i) \Gamma(V_j - \Theta_{syn}). \tag{B.3}
\]
The reversal potential $E_{inh}^{syn} = -0.0625$ is set to be smaller than $V_i(t)$, i.e. the synapse is inhibitory. The synaptic coupling function is modeled by the sigmoidal function $\Gamma(V_j) = \frac{1}{1 + \exp\{-1000(V_j - \Theta_{syn})\}}$ [91]. The threshold $\Theta_{syn} = -0.03$ V is chosen so that every spike within a burst of the neuron burst can reach it. This implies that the synaptic current from the $j$-th neuron is initiated as soon as this neuron becomes active after its membrane potential exceeds the synaptic threshold.

The intrinsic bifurcation parameter $V_{shift}^{K2}$ of the model is a deviation from $V_{1/2} = -0.018$ mV corresponding to the half-activated potassium channel at $m_{K2}^\infty = 1/2$. In the model (B.1), decreasing $V_{shift}^{K2}$ elevates the slow nullcline $\frac{dm_{K2}}{dt} = 0$ in the $V$-direction, thereby delaying the activation of $m_{K2}$. In this study, the values $V_{shift}^{K2} = -0.01895$ mV, $V_{shift}^{K2} = -0.021$ mV and $V_{shift}^{K2} = -0.0225$ mV, correspond to short (~20%), medium (~50%), and long (~80%) bursting, respectively. We provide additional phase-lag mappings for $V_{shift}^{K2} \in [-0.01895, -0.0225]$ in the Appendix B.2 for a thorough examination. More negative/positive values of $V_{shift}^{K2}$ correspond to the interneuron spiking tonically or quiescent, respectively. It becomes bursting through the blue sky bifurcation that can make the bursting period arbitrarily long [92]. Bursting becomes shorter when the parameter is increased, and vanishes through a saddle-node bifurcation at the hyperpolarized equilibrium state [90].

B.2 Phase-lag Mappings for 3 cell motifs

We provide numerous phase-lag return mappings for the 3 interneuron network with reciprocal inhibitory synaptic connections. The phase-lag return mappings are made for $V_{shift}^{K2} \in [-0.01895, -0.0225]$ and specified $g_{as} \in [0, 1]$, such that: $g_C = g_{syn}(1 \pm g_{as})$. 

B.2.1 Phase-lag mappings for $V_{K2}^{\text{shift}} = -0.01895 V$

Figure B.1: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895 V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.1$ (right)

Figure B.2: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895 V$: $g_{as} = 0.2$ (left) and $g_{as} = 0.25$ (right)
Figure B.3: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895V$: $g_{as} = 0.35$ (left) and $g_{as} = 0.4$ (right)

Figure B.4: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895V$: $g_{as} = 0.42$ (left) and $g_{as} = 0.5$ (right)
B.2.2 Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.019V$

Figure B.5: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.019V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.1$ (right)

Figure B.6: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.019V$: $g_{as} = 0.12$ (left) and $g_{as} = 0.2$ (right)
Figure B.7: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.019V$: $g_{as} = 0.4$ (left) and $g_{as} = 0.5$ (right)

B.2.3 Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01912V$

Figure B.8: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01912V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.1$ (right)
Figure B.9: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01912V$: $g_{as} = 0.15$ (left) and $g_{as} = 0.2$ (right)

Figure B.10: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01912V$: $g_{as} = 0.3$ (left) and $g_{as} = 0.4$ (right)
B.2.4 Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01925 V$

Figure B.11: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01925 V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.1$ (right)

Figure B.12: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01925 V$: $g_{as} = 0.3$ (left) and $g_{as} = 0.6$ (right)
B.2.5 Phase-lag mapping for $V_{K2}^\text{shift} = -0.02V$

Figure B.13: Phase-lag mapping for $V_{K2}^\text{shift} = -0.02V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.04$ (right)

Figure B.14: Phase-lag mapping for $V_{K2}^\text{shift} = -0.02V$: $g_{as} = 0.27$ (left) and $g_{as} = 0.5$ (right)
B.2.6 Phase-lag mapping for $V_{\text{shift}}^{K2} = -0.021 V$

Figure B.15: Phase-lag mapping for $V_{\text{shift}}^{K2} = -0.021 V$: $g_{\text{as}} = 0.0$ (left) and $g_{\text{as}} = 0.1$ (right)

Figure B.16: Phase-lag mapping for $V_{\text{shift}}^{K2} = -0.021 V$: $g_{\text{as}} = 0.13$ (left) and $g_{\text{as}} = 0.14$ (right)
Figure B.17: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$: $g_{as} = 0.149$ (left) and $g_{as} = 0.151$ (right)

Figure B.18: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$: $g_{as} = 0.16$ (left) and $g_{as} = 0.2$ (right)
Figure B.19: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$: $g_{as} = 0.3$ (left) and $g_{as} = 0.6$ (right)

B.2.7 Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.022V$

Figure B.20: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.022V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.1$ (right)
Figure B.21: Phase-lag mapping for $V^{\text{shift}}_{K2} = -0.022V$: $g_{as} = 0.12$ (left) and $g_{as} = 0.2$ (right)
Figure B.22: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.022V$: $g_{as} = 0.25$ (left) and $g_{as} = 0.4$ (right)

B.2.8 Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V$

Figure B.23: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V$: $g_{as} = 0.0$ (left) and $g_{as} = 0.1$ (right)
Figure B.24: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V$: $g_{as} = 0.2$ (left) and $g_{as} = 0.5$ (right)

Figure B.25: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V$: $g_{as} = 0.7$ (left) and $g_{as} = 1$ (right)
Appendix C

A BIFURCATION STUDY FOR 3 INTERNEURON NETWORK MODEL

C.1 Model

A CPG motif is comprised of three interneurons connected reciprocally across by non-delayed fast inhibitory/excitatory synapses with arbitrarily though weekly coupling strengths. Time evolution of the membrane potential, $V$, of each interneuron is modeled within a framework of the Hodgkin-Huxley formalism:

$$CV' = -I_{Na} - I_{K2} - I_L - I_{app} - I_{syn},$$

$$\tau_{Na} h'_{Na} = h_{Na}(V) - h,$$

$$\tau_{K2} m'_{K2} = m_{K2}(V) - m_{K2}.$$  \hspace{1cm} (C.1)

The dynamics of the above reduced leech heart interneuron model are based on the fast sodium current, $I_{Na}$ with the activation described by the voltage dependent gating variables, $m_{Na}$ and $h_{Na}$, the slow potassium current $I_{K2}$ with the inactivation from $m_{K2}$, and the ohmic leak current, $I_{leak}$ respectively:

$$I_{Na} = \bar{g}_{Na} m_{Na}^3 h_{Na} (V - E_{Na}),$$

$$I_{K2} = \bar{g}_{K2} m_{K2}^2 (V - E_K),$$

$$I_L = \bar{g}_L (V - E_L).$$ \hspace{1cm} (C.2)

In the model, $C = 0.5\text{nF}$ is the membrane capacitance and $I_{app} = 0.006\text{nA}$ is an applied current. The values of maximal conductances are set as $\bar{g}_{K2} = 30\text{nS}$, $\bar{g}_{Na} = 160\text{nS}$ and $g_L = 8\text{nS}$. The reversal potentials are $E_{Na} = 0.045\text{V}$, $E_K = -0.07\text{V}$ and $E_L = -0.046\text{V}$. The time constants of gating variables are $\tau_{K2} = 0.9\text{sec}$ and $\tau_{Na} = 0.0405\text{sec}$.
The steady state values, \(h^\infty_{\text{Na}}(V)\), \(m^\infty_{\text{Na}}(V)\), \(m^\infty_{\text{K}_2}(V)\), of the gating variables are given by the following Boltzmann equations:

\[
\begin{align*}
    h^\infty_{\text{Na}}(V) &= \left[1 + \exp(500(V + 0.325))\right]^{-1} \\
    m^\infty_{\text{Na}}(V) &= \left[1 + \exp(-150(V + 0.0305))\right]^{-1} \\
    m^\infty_{\text{K}_2}(V) &= \left[1 + \exp(-83(V + 0.018 + V_{\text{shift}}_{\text{K}_2}))\right]^{-1}.
\end{align*}
\]  

(C.3)

The reduced leech heart interneuron has turned out to be dynamically rich. It can demonstrate a plethora of regular and irregular activity types, including hyper and depolarized quiescent, tonic spiking and bursting oscillations of the membrane potential.

Fast, non-delayed synaptic currents in this study are modeled using the fast threshold modulation (FTM) paradigm as follows [101]:

\[
I_{\text{syn}} = g_{\text{syn}}(E_{\text{syn}} - V_{\text{post}})\Gamma(V_{\text{pre}} - \Theta_{\text{syn}}),
\]

\[
\Gamma(V_{\text{pre}} - \Theta_{\text{syn}}) = 1/[1 + \exp\{-1000(V_{\text{pre}} - \Theta_{\text{syn}})\}];
\]

(C.4)

here \(V_{\text{post}}\) and \(V_{\text{pre}}\) are voltages of the post- and the pre-synaptic interneurons; the synaptic threshold \(\Theta_{\text{syn}} = -0.03V\) is chosen so that every spike within a burst in the presynaptic cell crosses \(\Theta_{\text{syn}}\), see Fig. 3.1. This implies that the synaptic current, \(I_{\text{syn}}\), is initiated as soon as \(V_{\text{pre}}\) exceeds the synaptic threshold. The type, inhibitory or excitatory, of the FTM synapse is determined by the level of the reversal potential, \(E_{\text{syn}}\), in the post-synaptic interneuron. In the inhibitory case, it is set as \(E_{\text{syn}} = -0.0625V\) so that \(V_{\text{post}}(t) > E_{\text{syn}}\). In the excitatory case the level of \(E_{\text{syn}}\) is raised to zero to guarantee that \(\langle V_{\text{post}}(t) \rangle\) remains below the reversal potential on average over the period of the bursting interneuron. We point out that until the synapses remain fast and non-delayed, alternative ways of their modeling, such as \(\alpha\)- or dynamics representations, do not essentially change the dynamical interactions between the interneurons. [102].
The following numerical methods presented here differs from the methods in the text in wording only. The methods employed in the study are the same, we merely provide an alternate explanation in case additional explanation is desired. In order to explore the phenomena of multistability among bursting rhythms generated by the 3-cell motif, as well as to give a detailed examination of their transformations and bifurcations in non-homogenous motif with asymmetric and mixed synapses, we propose and develop an effective computational toolkit. The underlying idea is based on reducing the problem of the existence and stability of attainable bursting rhythms in plausible networks to the bifurcation analysis of fixed points and invariant curves of Poincaré return mappings for phase lags between the interneurons. In this study, we consider only weakly coupled motifs. Unlike the phase resetting technique, this is not a limitation of the toolkit. We treat the weakly coupled case as a pilot study, which lets us test the tools and uncover all limiting rhythms, including stable and unstable, which can possibly occur in the network. Using a single 64Bit Tesla CUDA card reduces the simulation time from 3+ hours to about 15 minutes for less weakly coupled networks with a faster convergence to phase-locked states.

The idea underlying the computational tool is inspired by real recordings in wet experiments. As such, it requires only the voltage recording from the mathematical interneurons and does not explicitly rely other variables, including gating. We intentionally choose the phases in relation to the voltage trace as often the voltage is the only experimentally measurable variable. Moreover, like in wet experiments, we can control the initial phase distribution by releasing the interneurons from inhibitions at specific times, chasing the chosen reference interneuron 1.

The phase relationships between the coupled interneurons are defined through specific events, \( \{ \tau_1^{(n)}, \tau_2^{(n)}, \tau_3^{(n)} \} \), when their voltages hit an auxiliary threshold, \( \Theta_{th} \), thus indicating the initiation of n-th burst in the interneurons, see Fig. C.1. We set the threshold to \( \Theta_{th} = -0.04V \), above the hyperpolarized voltage and below the spike oscillations within bursts.

We define a sequence of phase-lags through the delays in burst initiations in the reference cell 1 and the other two interneuron on the motif, which are normalized over the current
Figure C.1: Sample voltage traces depicting phase measurements. The phase of the reference neuron 1 (blue) is reset when $V_1$ reaches an auxiliary threshold, $\Theta_{\text{th}} = -40 \text{ mV}$, at $\tau_1^{(n)}$. The recurrent time delays, $\tau_{21}^{(n)}$ and $\tau_{31}^{(n)}$ between the burst onsets in the reference interneuron 1 and interneurons 2 (green) and 3 (red), normalized over the motif period, $[\tau_{1}^{(n+1)} - \tau_{1}^{(n)}]$, define a sequence of phase lags: $\{\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)}\}$.

network period or the burst recurrent times for the reference interneuron, as follows:

$$
\Delta \phi_{21}^{(n)} = \frac{\tau_{21}^{(n+1)} - \tau_{21}^{(n)}}{\tau_{1}^{(n+1)} - \tau_{1}^{(n)}} \quad \text{and} \quad \Delta \phi_{31}^{(n)} = \frac{\tau_{31}^{(n+1)} - \tau_{31}^{(n)}}{\tau_{1}^{(n+1)} - \tau_{1}^{(n)}}, \quad \text{mod } 1. \quad (C.5)
$$

An ordered pair, $M_n : (\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)})$, defines a forward iterate, or a phase point, $M_n$, of the Poincaré return mapping for the phase lags:

$$
T : (\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)}) \rightarrow (\Delta \phi_{21}^{(n+1)}, \Delta \phi_{31}^{(n+1)}). \quad (C.6)
$$

A sequence, $\{(\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)})\}_{n=0}^{N}$, yields a forward phase-lag trajectory, $\{M_n\}_{n=0}^{N}$, of the Poincaré return mapping on a 2D torus $[0, 1) \times [0, 1)$ with phases defined on mod 1, see Fig. ???. Typically, such a trajectory is run for $N=90$ bursting cycles in our simulations. The run can be stopped when the distance between two successive iterates, $\{(\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)})\}$ and $\{(\Delta \phi_{21}^{(n+1)}, \Delta \phi_{31}^{(n+1)})\}$, becomes less than some preset value, say $||M_n - M_{n+1}|| < 10^{-3}$. This means that the trajectory has converged to a fixed point, $M^*$ of the mapping, which corresponds to a phase-locked rhythm with specific constant delays between the bursting
interneurons. By varying the initial delays between the interneurons 2 and 3 with respect to the reference interneuron 1, we can detect all fixed points, if any, of the mapping and identify corresponding attraction basins and boundaries in between.

![Poincaré return mapping](image)

Figure C.2: Poincaré return mapping for the phase-lags \( \{\Delta \phi_{21}^{(n)}, \Delta \phi_{31}^{(n)}\} \) between the bursting (50\%DC) interneurons on a 2D torus \([0,1) \times [0,1)\) in the case of the homogeneous motif. Different colors denote attraction basins of several fixed points corresponding to phase locked states of distinct bursting rhythms.

We say that coupling is weak between the interneurons of the given motif when the convergence rate to any stable fixed point of the return mapping is slow. This implies if the gap between any two iterates of a forward trajectory of the return mapping remains smaller than some bound: \( 10^{-3} < ||M_n - M_{n+1}|| \leq 1/N \). Therefore, we can say that coupling is strong if a transient converges to a fixed point of the mapping after just a few iterates. We point out that it does follow from our definition of strong coupling that amplitude perturbations due to synaptic interactions have to be visible on the bursting trajectory in Fig. 3.1. As soon as they become actually noticeable, the coupling is too strong for properly defined phases to be between the bursting interneurons.

We conclude this section with some technical remarks concerning computational derivations of the Poincaré return mapping for phase lags defined above in (C.5,C.6).

A priori, the initial period or a recurrence time of the motif was unknown due to interneural interactions; furthermore, it varies over the course of bursting transient until it converges to a fixed value on the phase locked state. We can estimate (in a first order
approximation) the initial phase-lag, \((\Delta \phi^{(0)}_{21}, \Delta \phi^{(0)}_{31})\) between the networked interneurons, as the phase lags \((\Delta \phi_{21}^{**}, \Delta \phi_{31}^{**})\) on the periodic synchronous solution of period \(T_{\text{synch}}\). Note that \(\Delta \phi_{21}^{**}\) is shifted away from \(\Delta \phi_{31}^{**}\), i.e. advanced or delayed. Notice that in the weakly coupled case the recurrent times of the reference cell 1 are close to \(T_{\text{synch}}\), which implies \((\Delta \phi_{21}^{**}, \Delta \phi_{31}^{**}) \approx (\Delta \phi^{(0)}_{21}, \Delta \phi^{(0)}_{31})\). By setting \(\Delta \phi_{21} = \Delta \phi_{31} = 0\) and \(t_{1j} = 0\) at \(V_1 = \Theta_{th}\) we can parameterize the synchronous solution by a time shift, \(\{0 \leq \tau_{1j} < T_{\text{synch}}\}\), or, alternatively by phase-lags, \(\{0 \leq \Delta \phi_{j1} < 1\}\). Thus, we can create the initial phase-lags by releasing the reference interneuron and having the interneuron 2 and 3 suppressed by external inhibition pulses for \(\tau_{12} = \Delta \phi^{(0)}_{21}T_{\text{synch}}\) and \(\tau_{13} = \Delta \phi^{(0)}_{31}T_{\text{synch}}\) from the same initial point, given by \(V_i = \Theta_{th} = -0.04V\), on the synchronous bursting orbit. In essence, this means that initial phases between the reference interneuron and another neuron can be set by releasing the latter from inhibition at various delays; this algorithm is meant to realistically resemble and fit to experimental recordings.

To complete a single phase-lag mapping we choose the initial phase-lags being uniformly distributed on \(40 \times 40\) (more points) grid over the \([0, 1) \times [0, 1)\) torus. We point out that the initial guess for the phase lag distribution may differ from the case of interacting networked interneurons, especially with coupling strength variations, which is also affected by variations of the network period from \(T_{\text{synch}}\). In computations, this may result in fast non-linear jumps from the set of guessed initial phases. As such to avoid jumps, we begin recording the phase lag trajectory settled from the second bursting cycle. Due to weakly coupling, transients do not evolve fast, and we connect phase-lag trajectories of the mapping in order to demonstrate and preserve the forward order of iterates, just like in the case of time continuous vector fields in a plane. Topologically the phase-lag state space resides on the surface of a torus, and we skin the torus for the sake of a visibility.

The numerical simulations and phase analysis were accomplished utilizing the freely available software PyDSTool (version 0.88) [99]. Additional files and instructions are available upon request.
C.3 Phase-lag Mappings for asymmetric connections

A thorough set of phase-lag mappings for asymmetric connections are presented here. Above each phase-lag mapping is a caricature of the motif set up for that particular mapping. The thicker and darker the connection is, indicates a stronger connection and vice versa. The mappings are specified for specific $V_{k2}^{\text{shift}} \in [-0.01895, -0.021, -0.0225]$ and $g_{ij}$ as a percentage of $g_{\text{syn}}$. The mappings are provided to inform the reader of all intermediate findings not expressly discussed in Chapter 3. Note, mappings provided here are for diagnostic purposes. We do not provide a detailed explanation for each mapping as we feel that would be superfluous, since the mappings are self-explanatory and can be used to test the readers understanding.

Figure C.3: Enlargement of complex dynamics near the origin for $V_{k2}^{\text{shift}} = -0.021V$. At least 5 unstable FPs can be found and several saddles including a degenerate saddle at $\approx (0.2, 0.2)$. 
C.3.1 3-cell variations to Individual connections

Figure C.4: Phase-lag mapping for $V^{\text{shift}}_{K2} = -0.01895V; g_{21} = 1.1g_{syn}$ (left) and $V^{\text{shift}}_{K2} = -0.01895V; g_{21} = 1.5g_{syn}$ (right).

Figure C.5: Phase-lag mapping for $V^{\text{shift}}_{K2} = -0.01895V; g_{21} = 2g_{syn}$ (left) and $V^{\text{shift}}_{K2} = -0.01895V; g_{21} = 2.5g_{syn}$ (right).
Figure C.6: Phase-lag mapping for $V_{K2}^{shift} = -0.01895V; g_{31} = 2g_{syn}$ (left) and $V_{K2}^{shift} = -0.01895V; g_{31} = 2.5g_{syn}$ (right).

Figure C.7: Phase-lag mapping for $V_{K2}^{shift} = -0.021V; g_{12} = 0.9g_{syn}$ (left) and $V_{K2}^{shift} = -0.021V; g_{12} = 0.95g_{syn}$ (right).
Figure C.8: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.05g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.1g_{\text{syn}}$ (right).

Figure C.9: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{13} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{21} = 1.05g_{\text{syn}}$ (right).
Figure C.10: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{21} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{21} = 1.5g_{\text{syn}}$ (right).

Figure C.11: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{21} = 2g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{21} = 2.5g_{\text{syn}}$ (right).
Figure C.12: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{21} = 0.95g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{23} = 1.05g_{\text{syn}}$ (right).

Figure C.13: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{31} = 0.85g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{31} = 0.9g_{\text{syn}}$ (right).
Figure C.14: Phase-lag mapping for $V_{K_2}^{\text{shift}} = -0.021V; \ g_{31} = 0.0 g_{\text{syn}}$ (left) and $V_{K_2}^{\text{shift}} = -0.021V; \ g_{31} = 1.1 g_{\text{syn}}$ (right).

Figure C.15: Phase-lag mapping for $V_{K_2}^{\text{shift}} = -0.021V; \ g_{32} = 1.1 g_{\text{syn}}$ (left) and $V_{K_2}^{\text{shift}} = -0.021V; \ g_{31} = 1.1 g_{\text{syn}}$ (right).
Figure C.16: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V; g_{31} = 0.85g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.0225V; g_{31} = 0.9g_{\text{syn}}$ (right).

Figure C.17: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V; g_{21} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.0225V; g_{21} = 1.5g_{\text{syn}}$ (right).
Figure C.18: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V; g_{21} = 2.0g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.0225V; g_{21} = 2.5g_{\text{syn}}$ (right).

C.3.2 3-cell variations to 2 connections

Figure C.19: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895V; g_{12} = 1.6g_{\text{syn}}$ and $g_{21} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.01895V; g_{12} = 1.6g_{\text{syn}}$ and $g_{21} = 1.2g_{\text{syn}}$ (right).
Figure C.20: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895V; g_{12} = 1.5g_{\text{syn}}$ and $g_{13} = 1.5g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.01895V; g_{12} = 2.0g_{\text{syn}}$ and $g_{13} = 2.0g_{\text{syn}}$ (right).

Figure C.21: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.01895V; g_{12} = 1.3g_{\text{syn}}$ and $g_{23} = 1.3g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.01895V; g_{12} = 2.0g_{\text{syn}}$ and $g_{13} = 2.0g_{\text{syn}}$ (right).
Figure C.22: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.1g_{\text{syn}}$ and $g_{21} = 1.1g_{\text{syn}}$ (left), $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.2g_{\text{syn}}$ and $g_{21} = 1.1g_{\text{syn}}$ (right).

Figure C.23: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.225g_{\text{syn}}$ and $g_{21} = 1.225g_{\text{syn}}$ (left), $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.235g_{\text{syn}}$ and $g_{21} = 1.235g_{\text{syn}}$ (right).
Figure C.24: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.25g_{\text{syn}}$ and $g_{21} = 1.25g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.3g_{\text{syn}}$ and $g_{21} = 1.3g_{\text{syn}}$ (right).

Figure C.25: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.35g_{\text{syn}}$ and $g_{21} = 1.35g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$ and $g_{21} = 1.5g_{\text{syn}}$ (right).
Figure C.26: Phase-lag mapping for $V_{V_{K2}}^{\text{shift}} = -0.021V$; $g_{12} = 2g_{\text{syn}}$ and $g_{21} = 2g_{\text{syn}}$ (left) and $V_{V_{K2}}^{\text{shift}} = -0.021V$; $g_{12} = 3g_{\text{syn}}$ and $g_{21} = 3g_{\text{syn}}$ (right).

Figure C.27: Phase-lag mapping for $V_{V_{K2}}^{\text{shift}} = -0.021V$; $g_{12} = 1.6g_{\text{syn}}$ and $g_{21} = 1.1g_{\text{syn}}$ (left) and $V_{V_{K2}}^{\text{shift}} = -0.021V$; $g_{12} = 1.6g_{\text{syn}}$ and $g_{21} = 1.2g_{\text{syn}}$ (right).
Figure C.28: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.5g_{\text{syn}}$ and $g_{13} = 1.5g_{\text{syn}}$ (left), $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.6g_{\text{syn}}$ and $g_{21} = 1.2g_{\text{syn}}$ (right).

Figure C.29: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.1g_{\text{syn}}$ and $g_{23} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V; g_{12} = 1.15g_{\text{syn}}$ and $g_{32} = 1.15g_{\text{syn}}$ (right).
Figure C.30: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V; g_{12} = 1.6g_{\text{syn}}$ and $g_{21} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.0225V; g_{12} = 1.6g_{\text{syn}}$ and $g_{32} = 1.2g_{\text{syn}}$ (right).

Figure C.31: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.0225V; g_{12} = 1.5g_{\text{syn}}$ and $g_{13} = 1.5g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.0225V; g_{12} = 1.5g_{\text{syn}}$ and $g_{13} = 2.0g_{\text{syn}}$ (right).
3-cell variations to 3 or more connections

Figure C.32: Phase-lag mapping for $V_{K_2}^{\text{shift}} = -0.01895V; g_{12} = 0, g_{23} = 0$ and $g_{31} = 0$ (left) and $V_{K_2}^{\text{shift}} = -0.01895V; g_{13} = 0, g_{32} = 0$ and $g_{21} = 0$ (right).

Figure C.33: Phase-lag mapping for $V_{K_2}^{\text{shift}} = -0.01895V; g_{12} = 1.5g_{\text{syn}}, g_{21} = 1.5g_{\text{syn}}, g_{13} = 1.5g_{\text{syn}}$ and $g_{23} = 1.5g_{\text{syn}}$ (left) and $V_{K_2}^{\text{shift}} = -0.01895V; g_{12} = 2g_{\text{syn}}, g_{21} = 2g_{\text{syn}}, g_{13} = 2g_{\text{syn}}$ and $g_{23} = 1.5g_{\text{syn}}$ (right).
Figure C.34: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 0$, $g_{23} = 0$ and $g_{31} = 0$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{13} = 0$, $g_{32} = 0$ and $g_{21} = 0$ (right).

Figure C.35: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$ and $g_{23} = 0.9g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$ and $g_{23} = 1.25g_{\text{syn}}$ (right).
Figure C.36: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$ and $g_{13} = 1.5g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$ and $g_{23} = 1.25g_{\text{syn}}$ (right).

Figure C.37: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$, $g_{31} = 0.8g_{\text{syn}}$ and $g_{13} = 0.8g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$, $g_{31} = 0.85g_{\text{syn}}$ and $g_{13} = 0.85g_{\text{syn}}$ (right).
Figure C.38: Phase-lag mapping for $V_{K2}^{shift} = -0.021V; g_{12} = 1.5g_{syn} , g_{21} = 1.5g_{syn} , g_{31} = 0.9g_{syn}$ and $g_{13} = 0.9g_{syn}$ (left) and $V_{K2}^{shift} = -0.021V; g_{12} = 1.5g_{syn} , g_{21} = 1.5g_{syn} , g_{31} = 1.5g_{syn}$ and $g_{13} = 1.5g_{syn}$ (right).

Figure C.39: Phase-lag mapping for $V_{K2}^{shift} = -0.021V; g_{12} = 1.25g_{syn} , g_{21} = 1.25g_{syn} , g_{31} = 0.6g_{syn}$ and $g_{32} = 0.6g_{syn}$ (left) and $V_{K2}^{shift} = -0.021V; g_{12} = 1.25g_{syn} , g_{21} = 1.25g_{syn} , g_{31} = 0.8g_{syn}$ and $g_{32} = 0.8g_{syn}$ (right).
Figure C.40: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{23} = 1.25g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 2.0g_{\text{syn}}$, $g_{23} = 1.5g_{\text{syn}}$ (right).

Figure C.41: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{23} = 1.1g_{\text{syn}}$ (left) and $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 2.0g_{\text{syn}}$, $g_{23} = 1.5g_{\text{syn}}$ (right).
Figure C.42: Phase-lag mapping for $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$, $g_{31} = 0.5g_{\text{syn}}$, $g_{13} = 0.5g_{\text{syn}}$, and $g_{23} = 0.5g_{\text{syn}}$ (left), $V_{K2}^{\text{shift}} = -0.021V$; $g_{12} = 1.5g_{\text{syn}}$, $g_{21} = 1.5g_{\text{syn}}$, $g_{31} = 1.5g_{\text{syn}}$, $g_{13} = 1.5g_{\text{syn}}$, and $g_{23} = 1.5g_{\text{syn}}$ (right).

C.4 Excitation

Here we present mappings for the excitatory case. We changed all connections to excitatory by letting the parameter $E_{\text{syn}} = 0$. As expected attractors become repellors, and repellors become attractors. Stability changes do occur for saddles in terms of the incoming and outgoing separatrices, but they are still saddles.
Figure C.43: Phase-lag mapping for the excitatory case $V_{K2}^{\text{shift}} = -0.01895\, \text{V}$; $E_{\text{syn}} = 0$, and $V_{K2}^{\text{shift}} = -0.021\, \text{V}$; $E_{\text{syn}} = 0$.,