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Nathan W. Schultheiss
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# Phase Response Curves in Neuroscience

## Theory, Experiment, and Analysis

Springer

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Editors

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# Preface

The two decades leading up to this year's twentieth annual Computational Neuroscience conference (CNS) have seen a dramatic upswing in applications of quantitative and analytical methods taken from mathematics, physics, and engineering (among others) to the traditionally more biological approaches to Neuroscience. Much of the progress in the Computational Neurosciences, as in the broader field of Neuroscience, has taken the form of advancements in our understanding of neural systems at two key levels: the cellular processes underlying the dynamic electrical and chemical behaviors of individual neurons and the complex interactions among neurons in networks of varying composition and size, ranging from two reciprocally connected neurons, to detailed local microcircuitry, to large scale networks of thousands or more. One of the most difficult challenges, however, has been (and remains) to bridge the cellular and network levels of computation, i.e., to identify and understand how the properties of individual neurons contribute to the behaviors of functional networks underlying perception, motor performance, memory, and cognition. Given that neurons, like people, communicate with and influence one another through a variety of means, this problem is quite a bit like relating the individual personalities of two or more people to the interactions between them; or more generally, it is like relating the psychology of individuals to the sociology of a community.

One of the most fruitful means of addressing the interface between cellular and network computation has been the application of phase response analysis to neuronal systems. Neuronal phase response curves (PRCs) describe the pattern of shifts in the timing of action potentials (spikes) that are caused by inputs to a neuron arriving at different times within that neuron's spike cycle. The degree to which an input can affect spike timing depends not only on the properties of the neuron but also on the characteristics of the input, and the relationship between the PRCs of individual neurons and the behavior of a neuronal network additionally depends on the connectivity structure within the network. Consequently, many of the complexities of computation at the cellular and network levels are embodied in the variety of applications of phase response analyses to neuronal systems. This book provides a cross section of the considerable body of work by many of the

prominent theoreticians and experimentalists in the Computational Neurosciences which make use of PRCs to further our understanding of neurons and networks, more generally, the brain, and more abstractly, ourselves. Part 1 introduces the theoretical underpinnings of phase response analysis and presents the central concepts and context for the rest of the book; Part 2 surveys techniques for estimating neuronal phase response curves and many of the technical considerations necessary to do so; Part 3 presents many of the key investigations relating the phase response properties of neurons to their cellular characteristics; and finally, the chapters in Part 4 illustrate how phase response curves can be used to understand and predict patterning of network activity in neuronal systems.

To make this text exciting and accessible to a diverse audience, the contributors to this book were asked to write "across the aisle," so-to-speak, such that the more theoretical or "mathy" authors considered more biologically-minded readers in preparing their contributions, and vice versa. Although this text generally proceeds from more theoretical to more applied topics, and major themes are partitioned into the book's four major parts, readers are not expected to move purely linearly through the content from start to finish. Rather, we encourage readers to familiarize themselves with the general concepts and perspectives and then move from one chapter to another as curiosity and perhaps relevance to their own interests dictate.

We, the editors, dedicate this volume to our mentors, in particular among them Drs. Dieter Jaeger, Eve Marder, Jack Byrne, John Clark, Ron Calabrese, and Terry Blumenthal, and to our families.

# Contents

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# Part I
# Foundations of Phase Response Analysis

## Introduction

The first section of this text provides an overview of the basic principles of applying phase response analysis to the study of neurons and neuronal networks. Each chapter describes general strategies by which phase response curves can be used for the prediction of phase-locked states among neuronal oscillators. Chapter 1 by Schwemmer and Lewis details the theory of weakly coupled oscillators. This theory entails the reduction of high dimensional descriptions of neurons to phase equations, and the authors describe three approaches for obtaining such phase model descriptions: the "seat of the pants" approach, the geometric approach, and the singular perturbation approach. Chapter 2 by Krogh–Madsen and colleagues presents the topological approach to phase response analysis. This is the earliest developed method of phase response analysis. It simply assumes that biological oscillations are stable limit cycles and considers the effects of perturbations of a neuron's spiking limit cycle within the surrounding phase space. Chapter 3 by Remme and colleagues combines cable theory, used to describe the dynamics of voltage spread in the dendritic processes of neurons, with weak coupling theory to characterize the interactions of dendritic oscillations in different regions of a neuron's dendritic tree. This chapter takes a broader view of the integrative properties of individual neurons by considering the contribution of dendrites to neuronal computation which will be addressed further in later chapters. Finally, in Chap. 4, Canavier and Achuthan introduce analyses of pulse-coupled networks wherein the constituent neuronal oscillators interact at discrete times, perturbing one another away from their respective limit cycles. This approach makes use of maps to describe the evolution of individual neurons' phases across network cycles and to predict stable periodic firing modes. In some cases perturbations among pulse-coupled networks can be significant, violating the weak-coupling assumptions described in the first chapter. Thus, the conditions or systems that can be analyzed with weak-coupling and pulse-coupling methods are relatively distinct.

# Chapter 1
# The Theory of Weakly Coupled Oscillators

**Michael A. Schwemmer and Timothy J. Lewis**

**Abstract** This chapter focuses on the application of phase response curves (PRCs) in predicting the phase locking behavior in networks of periodically oscillating neurons using the theory of weakly coupled oscillators. The theory of weakly coupled oscillators can be used to predict phase-locking in neuronal networks with any form of coupling. As the name suggests, the coupling between cells must be sufficiently weak for these predictions to be quantitatively accurate. This implies that the coupling can only have small effects on neuronal dynamics over any given cycle. However, these small effects can accumulate over many cycles and lead to phase locking in the neuronal network. The theory of weak coupling allows one to reduce the dynamics of each neuron, which could be of very high dimension, to a single differential equation describing the phase of the neuron.

The main goal of this chapter is to explain how a weakly coupled neuronal network is reduced to its phase model description. Three different ways to derive the phase equations are presented, each providing different insight into the underlying dynamics of phase response properties and phase-locking dynamics. The technique is illustrated for a weakly coupled pair of identical neurons. We then show how the phase model for a pair of cells can be extended to include weak heterogeneity and small amplitude noise. Lastly, we outline two mathematical techniques for analyzing large networks of weakly coupled neurons.

## 1 Introduction

A phase response curve (PRC) (Winfree 1980) of an oscillating neuron measures the phase shifts in response to stimuli delivered at different times in its cycle. PRCs are often used to predict the phase-locking behavior in networks of neurons

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and to understand the mechanisms that underlie this behavior. There are two main techniques for doing this. Each of these techniques requires a different kind of PRC, and each is valid in a different limiting case. One approach uses PRCs to reduce neuronal dynamics to firing time maps, e.g., (Ermentrout and Kopell 1998; Guevara et al. 1986; Goel and Ermentrout 2002; Mirollo and Strogatz 1990; Netoff et al. 2005b; Oprisan et al. 2004). The second approach uses PRCs to obtain a set of differential equations for the phases of each neuron in the network.

For the derivation of the firing time maps, the stimuli used to generate the PRC should be similar to the input that the neuron actually receives in the network, i.e., a facsimile of a synaptic current or conductance. The firing time map technique can allow one to predict phase locking for moderately strong coupling, but it has the limitation that the neuron must quickly return to its normal firing cycle before subsequent input arrives. Typically, this implies that input to a neuron must be sufficiently brief and that there is only a single input to a neuron each cycle. The derivation and applications of these firing time maps are discussed in Chap. 4.

This chapter focuses on the second technique, which is often referred to as the theory of weakly coupled oscillators (Ermentrout and Kopell 1984; Kuramoto 1984; Neu 1979). The theory of weakly coupled oscillators can be used to predict phase locking in neuronal networks with any form of coupling, but as the name suggests, the coupling between cells must be sufficiently "weak" for these predictions to be quantitatively accurate. This implies that the coupling can only have small effects on neuronal dynamics over any given period. However, these small effects can accumulate over time and lead to phase locking in the neuronal network. The theory of weak coupling allows one to reduce the dynamics of each neuron, which could be of very high dimension, to a single differential equation describing the phase of the neuron. These "phase equations" take the form of a convolution of the input to the neuron via coupling and the neuron's infinitesimal PRC (iPRC). The iPRC measures the response to a small brief ($\delta$-function-like) perturbation and acts like an impulse response function or Green's function for the oscillating neurons. Through the dimension reduction and exploiting the form of the phase equations, the theory of weakly coupled oscillators provides a way to identify phase-locked states and understand the mechanisms that underlie them.

The main goal of this chapter is to explain how a weakly coupled neuronal network is reduced to its phase model description. Three different ways to derive the phase equations are presented, each providing different insight into the underlying dynamics of phase response properties and phase-locking dynamics. The first derivation (the "Seat-of-the-Pants" derivation in Sect. 3) is the most accessible. It captures the essence of the theory of weak coupling and only requires the reader to know some basic concepts from dynamical system theory and have a good understanding of what it means for a system to behave linearly. The second derivation (The Geometric Approach in Sect. 4) is a little more mathematically sophisticated and provides deeper insight into the phase response dynamics of neurons. To make this second derivation more accessible, we tie all concepts back to the explanations in the first derivation. The third derivation (The Singular

Perturbation Approach in Sect. 5) is the most mathematically abstract but it provides the cleanest derivation of the phase equations. It also explicitly shows that the iPRC can be computed as a solution of the "adjoint" equations.

During these three explanations of the theory of weak coupling, the phase model is derived for a pair of coupled neurons to illustrate the reduction technique. The later sections (Sects. 6 and 7) briefly discuss extensions of the phase model to include heterogeneity, noise, and large networks of neurons.

For more mathematically detailed discussions of the theory of weakly coupled oscillators, we direct the reader to (Ermentrout and Kopell 1984; Hoppensteadt and Izhikevich 1997; Kuramoto 1984; Neu 1979).

## 2 Neuronal Models and Reduction to a Phase Model

### 2.1 General Form of Neuronal Network Models

The general form of a single or multicompartmental Hodgkin–Huxley-type neuronal model (Hodgkin and Huxley 1952) is

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X), \tag{1.1}$$

where $X$ is a $N$-dimensional state variable vector containing the membrane potential(s) and gating variables[1], and $F(X)$ is a vector function describing the rate of change of the variables in time. For the Hodgkin–Huxley (HH) model (Hodgkin and Huxley 1952), $X = [V, m, h, n]^{\mathrm{T}}$ and

$$F(X) = \begin{bmatrix} \frac{1}{C}(-g_{\mathrm{Na}} m^3 h(V - E_{\mathrm{Na}}) - g_K n^4 (V - E_K) - g_L (V - E_L) + I) \\ \frac{m_\infty(V) - m}{\tau_m(V)} \\ \frac{h_\infty(V) - h}{\tau_h(V)} \\ \frac{n_\infty(V) - n}{\tau_n(V)}, \end{bmatrix}, \tag{1.2}$$

In this chapter, we assume that the isolated model neuron (1.1) exhibits stable $T$-periodic firing (e.g., top trace of Fig. 1.2). In the language of dynamical systems, we assume that the model has an asymptotically stable $T$-periodic *limit cycle*. These oscillations could be either due to intrinsic conductances or induced by applied current.

[1]The gating variables could be for ionic membrane conductances in the neuron, as well as those describing the output of chemical synapses.

A pair of coupled model neurons is described by

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = F(X_1) + \varepsilon I(X_1, X_2) \tag{1.3}$$

$$\frac{\mathrm{d}X_2}{\mathrm{d}t} = F(X_2) + \varepsilon I(X_2, X_1), \tag{1.4}$$

where $I(X_1, X_2)$ is a vector function describing the coupling between the two neurons, and $\varepsilon$ scales the magnitude of the coupling term. Typically, in models of neuronal networks, cells are only coupled through the voltage ($V$) equation. For example, a pair of electrically coupled HH neurons would have the coupling term

$$I(X_1, X_2) = \begin{bmatrix} \frac{1}{C}\left(g_C(V_2 - V_1)\right) \\ 0 \\ 0 \\ 0 \end{bmatrix}. \tag{1.5}$$

where $g_C$ is the coupling conductance of the electrical synapse (see Chap. 14).

## 2.2 Phase Models, the G-Function, and Phase Locking

The power of the theory of weakly coupled oscillators is that it reduces the dynamics of each neuronal oscillator in a network to single phase equation that describes the rate of change of its relative phase, $\phi_j$. The phase model corresponding to the pair of coupled neurons (1.3)–(1.4) is of the form

$$\frac{\mathrm{d}\phi_1}{\mathrm{d}t} = \varepsilon H(\phi_2 - \phi_1) \tag{1.6}$$

$$\frac{\mathrm{d}\phi_2}{\mathrm{d}t} = \varepsilon H(-(\phi_2 - \phi_1)). \tag{1.7}$$

The following sections present three different ways of deriving the function $H$, which is often called the interaction function.

Subtracting the phase equation for cell 1 from that of cell 2, the dynamics can be further reduced to a single equation that governs the evolution of the phase difference between the cells, $\phi = \phi_2 - \phi_1$

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \varepsilon(H(-\phi) - H(\phi)) = \varepsilon G(\phi). \tag{1.8}$$

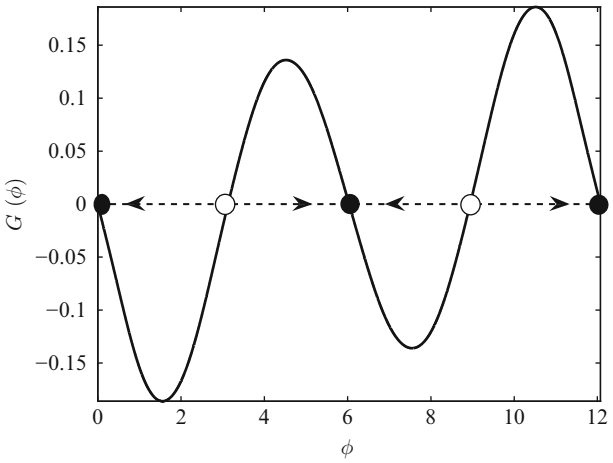


**Fig. 1.1** *Example G function*. The G function for two model Fast–Spiking (FS) interneurons (Erisir et al. 1999) coupled with gap junctions on the distal ends of their passive dendrites is plotted. The arrows show the direction of the trajectories for the system. This system has four steady state solutions $\phi_S = 0, T$ (synchrony), $\phi_{\text{AP}} = T/2$ (antiphase), and two other nonsynchronous states. One can see that synchrony and antiphase are stable steady states for this system (*filled in circles*) while the two other nonsynchronous solutions are unstable (*open circles*). Thus, depending on the initial conditions, the two neurons will fire synchronously or in antiphase

In the case of a pair of coupled Hodgkin–Huxley neurons (as described above), the number of equations in the system is reduced from the original 8 describing the dynamics of the voltage and gating variables to a single equation. The reduction method can also be readily applied to multicompartment model neurons, e.g., (Lewis and Rinzel 2004; Zahid and Skinner 2009), which can render a significantly larger dimension reduction. In fact, the method has been applied to real neurons as well, e.g., (Mancilla et al. 2007).

Note that the function $G(\phi)$ or "$G$-function" can be used to easily determine the phase-locking behavior of the coupled neurons. The zeros of the G-function, $\phi^*$, are the steady state phase differences between the two cells. For example, if $G(0) = 0$, this implies that the synchronous solution is a steady state of the system. To determine the stability of the steady state note that when $G(\phi) > 0$, $\phi$ will increase and when $G(\phi) < 0$, $\phi$ will decrease. Therefore, if the derivative of G is positive at a steady state ($G'(\phi^*) > 0$), then the steady state is unstable. Similarly, if the derivative of $G$ is negative at a steady state ($G'(\phi^*) < 0$), then the steady state is stable. Figure 1.1 shows an example $G$-function for two coupled identical cells. Note that this system has 4 steady states corresponding to $\phi = 0, T$ (synchrony), $\phi = T/2$ (antiphase), and two other nonsynchronous states. It is also clearly seen that $\phi = 0, T$ and $\phi = T/2$ are stable steady states and the other nonsynchronous states are unstable. Thus, the two cells in this system exhibit bistability, and they will either synchronize their firing or fire in antiphase depending upon the initial conditions.

In Sects. 3, 4, and 5, we present three different ways of derive the interaction function $H$ and therefore the $G$-function. These derivations make several approximations that require the coupling between neurons to be sufficiently weak. "Sufficiently weak" implies that the neurons' intrinsic dynamics dominate the effects due to coupling at each point in the periodic cycle, i.e., during the periodic oscillations, $|F(X_j(t))|$ should be an order of magnitude greater than $|\varepsilon I(X_1(t), X_2(t))|$. However, it is important to point out that, even though the phase models quantitatively capture the dynamics of the full system for sufficiently small $\varepsilon$, it is often the case that they can also capture the qualitative behavior for moderate coupling strengths (Lewis and Rinzel 2003; Netoff et al. 2005a).

## 3 A "Seat-of-the-Pants" Approach

This section will describe perhaps the most intuitive way of deriving the phase model for a pair of coupled neurons (Lewis and Rinzel 2003). The approach highlights the key aspect of the theory of weakly coupled oscillators, which is that neurons behave linearly in response to small perturbations and therefore obey the principle of superposition.

### *3.1 Defining Phase*

$T$-periodic firing of a model neuronal oscillator (1.1) corresponds to repeated circulation around an asymptotically stable $T$-periodic limit cycle, i.e., a closed orbit in state space $X$. We will denote this $T$-periodic limit cycle solution as $X_{\mathrm{LC}}(t)$. The phase of a neuron is a measure of the time that has elapsed as the neuron's moves around its periodic orbit, starting from an arbitrary reference point in the cycle. We define the phase of the periodically firing neuron $j$ at time $t$ to be

$$\theta_j(t) = (t + \phi_j) \mod T, \tag{1.9}$$

where $\theta_j = 0$ is set to be at the peak of the neurons' spike (Fig. 1.2).[2] The constant $\phi_j$, which is referred to as the *relative phase* of the $j$th neuron, is determined by the position of the neuron on the limit cycle at time $t = 0$. Note that each phase of the neuron corresponds to a unique position on the cell's $T$-periodic limit cycle, and any solution of the uncoupled neuron model that is on the limit cycle can be expressed as

$$X_j(t) = X_{\mathrm{LC}}(\theta_j(t)) = X_{\mathrm{LC}}(t + \phi_j). \tag{1.10}$$

[2]Phase is often normalized by the period $T$ or by $T/2\pi$, so that $0 \leq \theta < 1$ or $0 \leq \theta < 2\pi$ respectively. Here, we do not normalize phase and take $0 \leq \theta < T$.

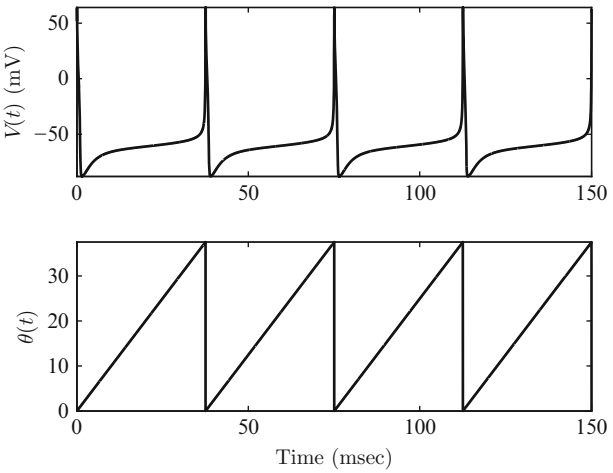


**Fig. 1.2** *Phase*. (**a**) Voltage trace for the Fast-Spiking interneuron model from Erisir et al. (1999) with $I_{\text{appl}} = 35\ \mu\text{A/cm}^2$ showing $T$-periodic firing. (**b**) The phase $\theta(t)$ of these oscillations increases linearly from 0 to $T$, and we have assumed that zero phase occurs at the peak of the voltage spike

When a neuron is perturbed by coupling current from other neurons or by any other external stimulus, its dynamics no longer exactly adhere to the limit cycle, and the exact correspondence of time to phase (1.9) is no longer valid. However, when perturbations are sufficiently weak, the neuron's intrinsic dynamics are dominant. This ensures that the perturbed system remains close to the limit cycle and the interspike intervals are close to the intrinsic period $T$. Therefore, we can approximate the solution of neuron $j$ by $X_j(t) \simeq X_{\text{LC}}(t + \phi_j(t))$, where the relative phase $\phi_j$ is now a function of time $t$. Over each cycle of the oscillations, the weak perturbations to the neurons produce only small changes in $\phi_j$. These changes are negligible over a single cycle, but they can slowly accumulate over many cycles and produce substantial effects on the relative firing times of the neurons.

The goal now is to understand how the relative phase $\phi_j(t)$ of the coupled neurons evolves slowly in time. To do this, we first consider the response of a neuron to small abrupt current pulses.

## *3.2 The Infinitesimal Phase Response Curve*

Suppose that a small brief square current pulse of amplitude $\varepsilon I_0$ and duration $\Delta t$ is delivered to a neuron when it is at phase $\theta^*$. This small, brief current pulse causes the membrane potential to abruptly increase by $\delta V \simeq \varepsilon I_0 \Delta t / C$, i.e., the change in voltage will approximately equal the total charge delivered to the cell by

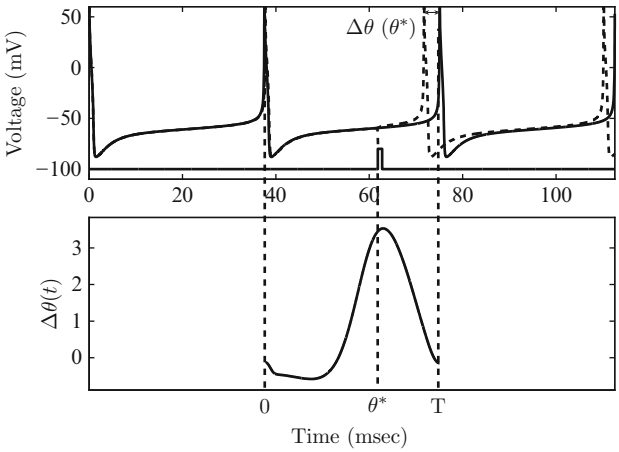


**Fig. 1.3** *Measuring the Phase Response Curve from Neurons*. The voltage trace and corresponding PRC is shown for the same FS model neuron from Fig. 1.2. The PRC is measured from a periodically firing neuron by delivering small current pulses at every point, $\theta^*$, along its cycle and measuring the subsequent change in period, $\Delta\theta$, caused by the current pulse

the stimulus, $\varepsilon I_0 \Delta t$, divided by the capacitance of the neuron, $C$. In general, this perturbation can cause the cell to fire sooner (phase advance) or later (phase delay) than it would have fired without the perturbation. The magnitude and sign of this *phase shift* depends on the amplitude and duration of the stimulus, as well as the phase in the oscillation at which the stimulus was delivered, $\theta^*$. This relationship is quantified by the Phase Response Curve (PRC), which gives the phase shift $\Delta\phi$ as a function of the phase $\theta^*$ for a fixed $\varepsilon I_0 \Delta t$ (Fig. 1.3).

For sufficiently small and brief stimuli, the neuron will respond in a linear fashion, and the PRC will scale linearly with the magnitude of the current stimulus

$$\Delta\phi(\theta^*) \simeq Z_V(\theta^*)\, \delta V = Z_V(\theta^*) \left(\frac{1}{C}\varepsilon I_0 \Delta t\right), \quad 0 \le \theta^* < T, \tag{1.11}$$

where $Z_V(\theta^*)$ describes the proportional phase shift as a function of the phase of the stimulus. The function $Z_V(\theta)$ is known as the infinitesimal phase response curve (iPRC) or the phase-dependent sensitivity function for voltage perturbations. The iPRC $Z_V(\theta)$ quantifies the normalized phase shift due to an infinitesimally small $\delta$-function-like voltage perturbation delivered at any given phase on the limit cycle.

## *3.3 The Phase Model for a Pair of Weakly Coupled Cells*

Now we can reconsider the pair of weakly coupled neuronal oscillators (1.3)–(1.4). Recall that, because the coupling is weak, the neurons' intrinsic dynamics dominate

the dynamics of the coupled-cell system, and $X_j(t) \simeq X_{\mathrm{LC}}(\theta_j(t)) = X_{\mathrm{LC}}(t + \phi_j(t))$ for $j = 1, 2$. This assumes that the coupling current can only affect the speed at which cells move around their limit cycle and does not affect the amplitude of the oscillations. Thus, the effects of the coupling are entirely captured in the slow time dynamics of the relative phases of the cells $\phi_j(t)$.

The assumption of weak coupling also ensures that the perturbations to the neurons are sufficiently small so that the neurons respond linearly to the coupling current. That is, (i) the small phase shifts of the neurons due to the presence of the coupling current for a brief time $\Delta t$ can be approximated using the iPRC (1.11), and (ii) these small phase shifts in response to the coupling current sum linearly (i.e., the principle of superposition holds). Therefore, by (1.11), the phase shift due to the coupling current from $t$ to $t + \Delta t$ is

$$\begin{aligned}\Delta\phi_j(t) &= \phi_j(t + \Delta t) - \phi_j(t)\\ &\simeq Z_V(\theta_j(t))\ (\varepsilon I(X_j(t), X_k(t)))\Delta t.\\ &= Z_V(t + \phi_j(t))\ \left(\varepsilon I(X_{\mathrm{LC}}(t + \phi_j(t)), X_{\mathrm{LC}}(t + \phi_k(t)))\right)\Delta t. \qquad (1.12)\end{aligned}$$

By dividing the above equation by $\Delta t$ and taking the limit as $\Delta t \to 0$, we obtain a system of differential equations that govern the evolution of the relative phases of the two neurons

$$\frac{\mathrm{d}\phi_j}{\mathrm{d}t} = \varepsilon\, Z_V(t+\phi_j)\ I(X_{\mathrm{LC}}(t+\phi_j), X_{\mathrm{LC}}(t+\phi_k)), \quad j,k = 1,2;\ j \neq k. \qquad (1.13)$$

Note that, by integrating this system of differential equations to find the solution $\phi_j(t)$, we are assuming that phase shifts in response to the coupling current sum linearly.

The explicit time dependence on the right-hand side of (1.13) can be eliminated by "averaging" over the period $T$. Note that $Z_V(t)$ and $X_{\mathrm{LC}}(t)$ are $T$-periodic functions, and the scaling of the right-hand side of (1.13) by the small parameter $\varepsilon$ indicates that changes in the relative phases $\phi_j$ occur on a much slower timescale than $T$. Therefore, we can integrate the right-hand side over the full period $T$ holding the values of $\phi_j$ constant to find the average rate of change of $\phi_j$ over a cycle. Thus, we obtain equations that approximate the slow time evolution of the relative phases $\phi_j$,

$$\begin{aligned}\frac{\mathrm{d}\phi_j}{\mathrm{d}t} &= \varepsilon\frac{1}{T}\int_0^T Z_V(\tilde{t})\left(I(X_{\mathrm{LC}}(\tilde{t}), X_{\mathrm{LC}}(\tilde{t} + \phi_k - \phi_j))\right)\mathrm{d}\tilde{t}\\ &= \varepsilon H(\phi_k - \phi_j), \quad j,k = 1,2;\ j \neq k, \qquad (1.14)\end{aligned}$$

i.e., the relative phases $\phi_j$ are assumed to be constant with respect to the integral over $T$ in $\tilde{t}$, but they vary in $t$. This averaging process is made rigorous by averaging theory (see Ermentrout and Kopell 1991; Guckenheimer and Holmes 1983).

We have reduced the dynamics of a pair of weakly coupled neuronal oscillators to an autonomous system of two differential equations describing the phases of the neurons and therefore finished the first derivation of the equations for a pair of weakly coupled neurons.[3] Note that the above derivation can be easily altered to obtain the phase model of a neuronal oscillator subjected to $T$-periodic external forcing as well. The crux of the derivation was identifying the iPRC and exploiting the approximately linear behavior of the system in response to weak inputs. In fact, it is useful to note that the interaction function $H$ takes the form of a convolution of the iPRC and the coupling current, i.e., the input to the neuron. Therefore, one can think of the iPRC of an oscillator as acting like an impulse response function or Green's function.

### 3.3.1 Averaging Theory

Averaging theory (see Ermentrout and Kopell 1991; Guckenheimer and Holmes 1983) states that there is a change of variables that maps solutions of

$$\frac{\mathrm{d}\phi}{\mathrm{d}\tilde{t}} = \varepsilon g(\phi, \tilde{t}), \tag{1.15}$$

where $g(\phi, \tilde{t})$ is a $T$-periodic function in $\phi$ and $\tilde{t}$, to solutions of

$$\frac{\mathrm{d}\varphi}{\mathrm{d}t} = \varepsilon \bar{g}(\varphi) + \mathcal{O}(\varepsilon^2), \tag{1.16}$$

where

$$\bar{g}(\varphi) = \frac{1}{T}\int_0^T g(\varphi, \tilde{t})\mathrm{d}\tilde{t}, \tag{1.17}$$

and $\mathcal{O}(\varepsilon^2)$ is Landau's "Big O" notation, which represents terms that either have a scaling factor of $\varepsilon^2$ or go to zero at the same rate as $\varepsilon^2$ goes to zero as $\varepsilon$ goes to zero.

## 4 A Geometric Approach

In this section, we describe a geometric approach to the theory of weakly coupled oscillators originally introduced by Kuramoto (1984). The main asset of this approach is that it gives a beautiful geometric interpretation of the iPRC and deepens our understanding of the underlying mechanisms of the phase response properties of neurons.

[3] Note that this reduction is not valid when $T$ is of the same order of magnitude as the timescale for the changes due to the weak coupling interactions (e.g., close to a SNIC bifurcation), however an alternative dimension reduction can be performed in this case (Ermentrout 1996).

## 4.1 The One-to-One Map Between Points on the Limit Cycle and Phase

Consider again a model neuron (1.1) that has a stable $T$-periodic limit cycle solution $X_{\mathrm{LC}}(t)$ such that the neuron exhibits a $T$-periodic firing pattern (e.g., top trace of Fig. 1.2). Recall that the phase of the oscillator along its limit cycle is defined as $\theta(t) = (t + \phi) \mod T$, where the relative phase $\phi$ is a constant that is determined by the initial conditions. Note that there is a one-to-one correspondence between phase and each point on the limit cycle. That is, the limit cycle solution takes phase to a unique point on the cycle, $X = X_{\mathrm{LC}}(\theta)$, and its inverse maps each point on the limit cycle to a unique phase, $\theta = X_{\mathrm{LC}}^{-1}(X) = \Phi(X)$.

Note that it follows immediately from the definition of phase (1.9) that the rate of change of phase in time along the limit cycle is equal to 1, i.e., $\frac{\mathrm{d}\theta}{\mathrm{d}t} = 1$. Therefore, if we differentiate the map $\Phi(X)$ with respect to time using the chain rule for vector functions, we obtain the following useful relationship

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = \nabla_X \Phi(X_{\mathrm{LC}}(t)) \cdot \frac{\mathrm{d}X_{\mathrm{LC}}}{\mathrm{d}t} = \nabla_X \Phi(X_{\mathrm{LC}}(t)) \cdot F(X_{\mathrm{LC}}(t))) = 1, \tag{1.18}$$

where $\nabla_X \Phi$ is the gradient of the map $\Phi(X)$ with respect to the vector of the neuron's state variables $X = (x_1, x_2, \ldots, x_N)$

$$\nabla_X \Phi(X) = \left[ \left( \frac{\partial \Phi}{\partial x_1}, \frac{\partial \Phi}{\partial x_2}, ..., \frac{\partial \Phi}{\partial x_N} \right) \Big|_X \right]^{\mathrm{T}}. \tag{1.19}$$

(We have defined the gradient as a column vector for notational reasons).

## 4.2 Asymptotic Phase and the Infinitesimal Phase Response Curve

The map $\theta = \Phi(X)$ is well defined for all points $X$ on the limit cycle. We can extend the domain of $\Phi(X)$ to points off the limit cycle by defining *asymptotic phase*. If $X_0$ is a point on the limit cycle and $Y_0$ is a point in a neighborhood of the limit cycle[4], then we say that $Y_0$ has the same asymptotic phase as $X_0$ if $||X(t; X_0) - X(t; Y_0)|| \to 0$ as $t \to \infty$. This means that the solution starting at the initial point $Y_0$ off the limit cycle converges to the solution starting at the point $X_0$ on the limit cycle as time goes to infinity. Therefore, $\Phi(Y_0) = \Phi(X_0)$. The set of

[4]In fact, the point $Y_0$ can be anywhere in the basin of attraction of the limit cycle.

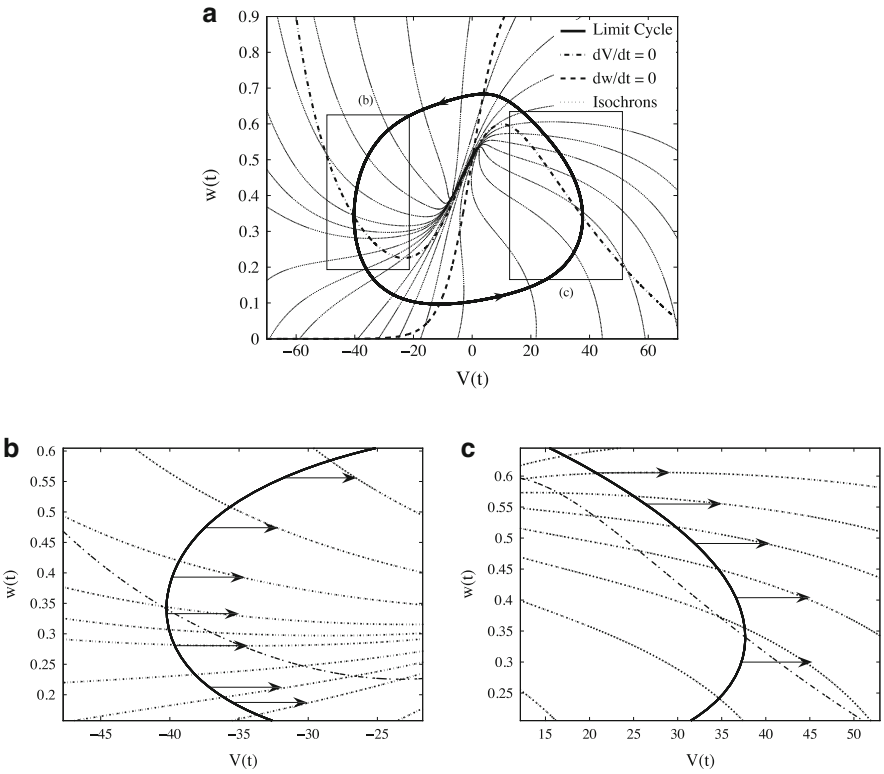


**Fig. 1.4** *Example Isochron Structure.* (**a**) The limit cycle and isochron structure for the Morris–Lecar neuron (Morris and Lecar 1981) is plotted along with the nullclines for the system. (**b**) Blow up of a region on the left-hand side of the limit cycle showing how the same strength perturbation in the voltage direction can cause different phase delays or phase advances. (**c**) Blow up of a region on the right-hand side of the limit cycle showing also that the same size voltage perturbation can cause phase advances of different sizes

all points off the limit cycle that have the same asymptotic phase as the point $X_0$ on the limit cycle is known as the *isochron* (Winfree 1980) for phase $\theta = \Phi(X_0)$. Figure 1.4 shows some isochrons around the limit cycle for the Morris–Lecar neuron (Morris and Lecar 1981). It is important to note that the figure only plots isochrons for a few phases and that *every* point on the limit cycle has a corresponding isochron.

Equipped with the concept of asymptotic phase, we can now show that the iPRC is in fact the gradient of the phase map $\nabla_X \Phi(X_{\mathrm{LC}}(t))$ by considering the following phase resetting "experiment". Suppose that, at time $t$, the neuron is on the limit cycle in state $X(t) = X_{\mathrm{LC}}(\theta^*)$ with corresponding phase $\theta^* = \Phi(X(t))$. At this time, it receives a small abrupt external perturbation $\varepsilon U$, where $\varepsilon$ is the magnitude of the perturbation and $U$ is the unit vector in the direction of the perturbation in

state space. Immediately after the perturbation, the neuron is in the state $X_{\rm LC}(\theta^*) + \varepsilon U$, and its new asymptotic phase is $\tilde{\theta} = \Phi(X_{\rm LC}(\theta^*) + \varepsilon U)$. Using Taylor series,

$$\tilde{\theta} = \Phi(X_{\rm LC}(\theta^*) + \varepsilon U) = \Phi(X_{\rm LC}(\theta^*)) + \nabla_X \Phi(X_{\rm LC}(\theta^*)) \cdot (\varepsilon U) + \mathcal{O}(\varepsilon^2). \quad (1.20)$$

Keeping only the linear term (i.e., $\mathcal{O}(\varepsilon)$ term), the phase shift of the neuron as a function of the phase $\theta^*$ at which it received the $\varepsilon U$ perturbation is given by

$$\Delta\phi(\theta^*) = \tilde{\theta} - \theta^* \simeq \nabla_X \Phi(X_{\rm LC}(\theta^*)) \cdot (\varepsilon U). \quad (1.21)$$

As was done in Sect. 3.2, we normalize the phase shift by the magnitude of the stimulus,

$$\frac{\Delta\phi(\theta^*)}{\varepsilon} \simeq \nabla_X \Phi(X_{\rm LC}(\theta^*)) \cdot U = Z(\theta^*) \cdot U. \quad (1.22)$$

Note that $Z(\theta) = \nabla_X \Phi(X_{\rm LC}(\theta))$ is the iPRC. It quantifies the normalized phase shift due to a small delta-function-like perturbation delivered at any given on the limit cycle. As was the case for the iPRC $Z_V$ derived in the previous section [see (1.11)], $\nabla_X \Phi(X_{\rm LC}(\theta))$ captures only the linear response of the neuron and is quantitatively accurate only for sufficiently small perturbations. However, unlike $Z_V$, $\nabla_X \Phi(X_{\rm LC}(\theta))$ captures the response to perturbations in any direction in state space and not only in one variable (e.g., the membrane potential). That is, $\nabla_X \Phi(X_{\rm LC}(\theta))$ is the vector iPRC; its components are the iPRCs for every variable in the system (see Fig. 1.5).

In the typical case of a single-compartment HH model neuron subject to an applied current pulse (which perturbs only the membrane potential), the perturbation would be of the form $\varepsilon U = (u, 0, 0, \ldots, 0)$ where $x_1$ is the membrane potential $V$. By (1.20), the phase shift is

$$\Delta\phi(\theta) = \frac{\partial \Phi}{\partial V}(X_{\rm LC}(\theta))\ u = Z_V(\theta)\ u, \quad (1.23)$$

which is the same as (1.11) derived in the previous section.

With the understanding that $\nabla_X \Phi(X_{\rm LC}(t))$ is the vector iPRC, we now derive the phase model for two weakly coupled neurons.

## 4.3 A Pair of Weakly Coupled Oscillators

Now consider the system of weakly coupled neurons (1.3)–(1.4). We can use the map $\Phi$ to take the variables $X_1(t)$ and $X_2(t)$ to their corresponding asymptotic phase, i.e., $\theta_j(t) = \Phi(X_j(t))$ for $j = 1, 2$. By the chain rule, we obtain the change in phase with respect to time

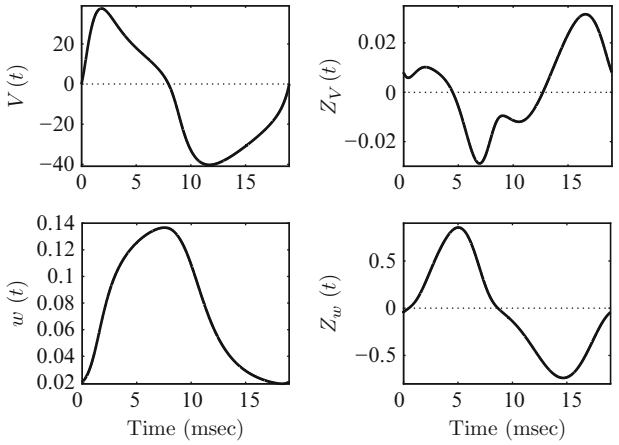


**Fig. 1.5** *iPRCs for the Morris–Lecar Neuron*. The voltage, $V(t)$ and channel, $w(t)$, components of the limit cycle for the same Morris–Lecar neuron as in Fig. 1.4 are plotted along with their corresponding iPRCs. Note that the shape of voltage iPRC can be inferred from the insets of Fig. 1.4. For example, the isochronal structure in Fig. 1.4c reveals that perturbations in the voltage component will cause phase advances when the voltage is ∼30 to 38 mV

$$\begin{aligned}\frac{\mathrm{d}\theta_j}{\mathrm{d}t} &= \nabla_X \Phi(X_j(t)) \cdot \frac{\mathrm{d}X_j}{\mathrm{d}t} \\ &= \nabla_X \Phi(X_j(t)) \cdot \left[F(X_j(t)) + \varepsilon I(X_j(t), X_k(t))\right] \\ &= \nabla_X \Phi(X_j(t)) \cdot F(X_j(t)) + \nabla_X \Phi(X_j(t)) \cdot \left[\varepsilon I(X_j(t), X_k(t))\right] \\ &= 1 + \varepsilon \nabla_X \Phi(X_j(t)) \cdot I(X_j(t), X_k(t)), \end{aligned} \tag{1.24}$$

where we have used the "useful" relation (1.18). Note that the above equations are exact. However, in order to solve the equations for $\theta_j(t)$, we would already have to know the full solutions $X_1(t)$ and $X_2(t)$, in which case you wouldn't need to reduce the system to a phase model. Therefore, we exploit that fact that $\varepsilon$ is small and make the approximation $X_j(t) \sim X_{\mathrm{LC}}(\theta_j(t)) = X_{\mathrm{LC}}(t + \phi_j(t))$, i.e., the coupling is assumed to be weak enough so that it does not affect the amplitude of the limit cycle, but it can affect the rate at which the neuron moves around its limit cycle. By making this approximation in (1.24) and making the change of variables $\theta_j(t) = t + \phi_j(t)$, we obtain the equations for the evolution of the relative phases of the two neurons

$$\frac{\mathrm{d}\phi_j}{\mathrm{d}t} = \varepsilon \nabla_X \Phi(X_{\mathrm{LC}}(t + \phi_j(t))) \cdot I(X_{\mathrm{LC}}(t + \phi_j(t)), X_{\mathrm{LC}}(t + \phi_k(t))). \tag{1.25}$$

Note that these equations are the vector versions of (1.13) with the iPRC written as $\nabla_X \Phi(X_{\mathrm{LC}}(t))$. As described in the previous section, we can average these equations over the period $T$ to eliminate the explicit time dependence and obtain the phase model for the pair of coupled neurons