

# Chapter 2

## Phase Resetting Neural Oscillators: Topological Theory Versus the Real World

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**Abstract** Biological oscillations, despite their vast range of periodicities, can be described mathematically by stable limit cycles. Therefore, a general theory characterizing the effects of perturbations applied to such limit cycles allows predictions of qualitative features of a particular oscillation subject to perturbation. In this chapter, we summarize this topological approach and discuss ways in which the theory breaks down, mainly for neuronal and cardiac oscillators. In particular, we describe experimental and computational studies that demonstrate apparent discontinuities in the response to perturbations, and others where there is not a rapid return to the limit cycle following a perturbation. Finally, we discuss differences between the topological and the excitability-type descriptions of neuronal oscillators.

### 1 Introduction

Biological systems display stable oscillations. These oscillations have periods that range over many orders of magnitude: milliseconds in the case of some neural oscillations; seconds for cardiac and respiratory rhythms; days for circadian and

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menstrual rhythms; a year for the rhythms underlying hibernation. However, to fulfill its physiological role, any particular biological oscillation must be controlled by various feedbacks, and it must appropriately interact with the rich dynamics generated from other cells and organs that might affect it.

The fundamental concept underlying the mathematical study of biological rhythms is that they can be associated with stable limit cycle oscillations in some appropriate dynamical system – typically an ordinary, partial or time delay differential equation. A stable limit cycle is a periodic cycle in state space that will be reestablished in the limit of  $t \rightarrow \infty$  for all initial conditions in the neighborhood of the cycle. The set of points in state space that attract to the limit cycle is called its *basin of attraction*. Since many biological rhythms, such as the heartbeat or respiration, must be robust to perturbation, the basin of attraction of biological oscillations may often be quite large, and amenable to experimental study by delivering appropriate perturbations. Further, because of this presumed underlying mathematical structure, based solely on mathematical analysis, all biological rhythms will be expected to display some similar characteristics (Canavier 2006; Glass and Mackey 1998; Winfree 2000).

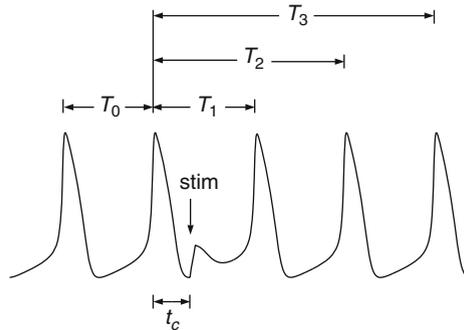
In particular, Winfree described basic features that could be theoretically predicted during phase resetting experiments in which perturbations were delivered to biological oscillations under controlled circumstances that vary the phase and amplitude of the delivery of the perturbation. Subsequent studies by others, particularly in the field of neurophysiology, have carried out further theoretical and experimental studies of resetting biological oscillations, which in some cases have used similar terminology to that introduced by Winfree to reflect different concepts. Winfree championed the notion that the underlying limit cycle structure of biological oscillations will lead to certain universal characteristics amenable to classification and mathematical analysis (Glass and Mackey 1998; Winfree 2000). Our point in the following is to examine the robust predictions of the topological theory of resetting of limit cycle oscillations in light of subsequent experimental and theoretical studies. In Sect. 2, we briefly present the main predictions of the topological theory with regard to resetting and show how in the limit of very fast return to the limit cycle following a perturbation, the effects of periodic forcing can be mathematically analyzed from iteration of circle maps determined from resetting experiments. In Sect. 3, we describe two ways in which the theory in Sect. 2 breaks down. First, we show circumstances in which the resetting curves differ in a fundamental sense from the topological predictions. Then, we describe experimental and theoretical studies that demonstrate circumstances in which there is not a rapid convergence to a limit cycle, so that iteration of a circle map cannot be used to predict dynamics. In Sect. 4, we discuss the main concepts of phase oscillator models and weak coupling as commonly used in the computational neuroscience community.

## 2 Topology of Phase Resetting

A very large number of investigators, coming from different disciplines, have investigated the resetting of biological oscillators experimentally. Since in many instances, investigators were not aware of similar questions being asked in different areas, there are a great many different notations and conventions for describing phase resetting. In the following, we present the topological theory of phase resetting as introduced by Winfree, and present appropriate terminology and notation. This topological perspective on phase-resetting predates most applications of phase-response theory in neuroscience, and has been more commonly used in cardiac electrophysiology. Furthermore, the notions of both strong vs. weak resetting within this topological theory are quite distinct from notions of coupling strength using other theoretical frameworks in computational neuroscience, which we will discuss in Sect. 4.

In general, phase resetting occurs when the dynamics of an oscillator is shifted in time. This can be accomplished when a stimulus transiently perturbs the state point away from the stable limit cycle associated with the oscillation, followed by the asymptotic return of the state point to the limit cycle. An example of such a resetting experiment is shown in Fig. 2.1. The unperturbed limit cycle oscillation (here of a model of spontaneous cardiac pacemaking activity) is of period  $T_0$ . All points within this cycle can be assigned a phase; we assign it values from 0 to 1 and set the fiducial point where the phase is zero to be on the upstroke of the action potential.

A stimulus delivered at a time  $t_c$  after the previous action potential upstroke is therefore applied at a phase



**Fig. 2.1** Notation for resetting protocol in a schematic cardiac pacemaker cell. A depolarizing stimulus is given at a coupling interval  $t_c$  after the crossing of 0 mV on the upstroke of the second action potential. The (old) phase of the cycle at which the stimulus is delivered is  $t_c/T_0$ . This stimulus causes a delay, with the first perturbed cycle length,  $T_1$ , being larger than the unperturbed period,  $T_0$

$$\phi = \frac{t_c}{T_0}, \quad (2.1)$$

which we term the *old phase*.

Following the perturbation by the applied stimulus, the asymptotic return to the limit cycle can be measured from the timing of the subsequent action potential upstrokes, i.e.,  $T_1, T_2, \dots$ . Mathematically, this return occurs in the limit  $i \rightarrow \infty$ . In general, the state point will return to a point on the limit cycle that is different from the point it would have been had there been no perturbation. From the timing of the subsequent action potential upstrokes, we quantify this as the *new phase*:

$$g(\phi) = \phi + \frac{iT_0 - T_i}{T_0} \pmod{1}, \quad i \rightarrow \infty. \quad (2.2)$$

The degree to which the value of  $T_i - T_{i-1}$  differs from  $T_0$  depends on the rate at which the rhythm returns to the limit cycle oscillation. Although many use the change of phase (sometimes designated  $\Delta\phi$ ) to measure the resetting, since both the new and old phases are represented by points on the circle the concept of advance and delay is not always well defined – this is particularly the case when a single stimulus can cause a pause greater than the intrinsic cycle length before the cycle is reestablished. Further, if there is a transient longer than the intrinsic cycle length until the asymptotic behavior is established the timing of the next beat following a stimulus cannot be used to accurately determine the resetting. However, for the sake of easier comparison to the neural literature, in many plots we will show both the phase response curve (also called the phase resetting curve), which plots  $\Delta\phi$  vs.  $\phi$ , and the phase transition curve, which plots  $g(\phi)$  vs.  $\phi$ . The relationship between these two functions is

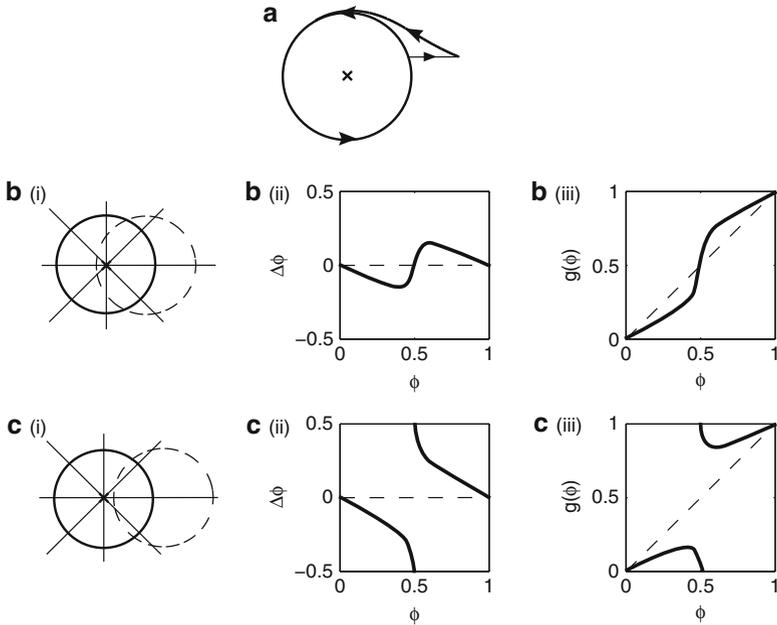
$$g(\phi) = \phi + \Delta\phi. \quad (2.3)$$

Figure 2.2 shows resetting in a two-dimensional system called the Poincaré oscillator (also called the radial isochron clock or the Andronov–Hopf oscillator). This system is governed by the equations

$$\frac{d\theta}{dt} = 1, \quad (2.4)$$

$$\frac{dr}{dt} = kr(1 - r^2), \quad (2.5)$$

where  $k$  is a positive parameter. The system has an asymptotically stable limit cycle with  $|r| = 1$  (black circle in Fig. 2.2) and an unstable fixed point at  $r = 0$  (cross). This unstable fixed point is the only point outside of the basin of attraction of the stable limit cycle. The rate of convergence to the limit cycle is determined by  $k$ . Let  $x(t = 0), x'(t = 0)$  be the initial conditions of a point on the cycle and a point not on the cycle, respectively, and  $x(t), x'(t)$  be the coordinates of the trajectories at time  $t$ . Then, if  $\lim_{t \rightarrow \infty} d[x(t), x'(t)] = 0$ , where  $d$  is the Euclidean distance, we say that the latent, or asymptotic, phase of  $x'(0)$  is the same as the phase of  $x(0)$ .



**Fig. 2.2** Phase resetting of the Poincaré oscillator. **(a)**: Example of phase-resetting experiment with  $k = 2.0$ . The state point is removed from the limit cycle by a perturbation of amplitude  $b$  in the horizontal direction (*thin line*), and then converges back to the limit cycle (*thick trajectory*). “x” designates the unstable fixed point. **(b)**: Type 1 resetting ( $b = 0.8$ ). **(i)** Isochrons (*thin lines*) and shifted cycle (*dashed curve*); **(ii)** phase response curve; and **(iii)** phase transition curve. **(c)**: Same as **(b)**, but for type 0 resetting ( $b = 1.2$ )

A *W-isochron* consists of all points with the same latent phase (for example, see radial lines in Fig. 2.2b(i)). Thus, every point in the basin of attraction of a limit cycle, lies on an isochron (Winfrey 2000).

A phase resetting experiment probes the effect of stimuli delivered at different phases of the cycle. For example, the dashed curves in Figs. 2.2b(i) and c(i) shows the *shifted cycle*, which consists of the locus of points resulting from stimuli delivered at all phases of the cycle. The stimulus delivered in Fig. 2.2b is a weak stimulus, whereas the stimulus in Fig. 2.2c is strong, resulting in a larger shift. The resulting phase transition curves in Fig. 2.2b(ii) and c(ii), can be thought of as circle maps, i.e., they map a circle into itself;  $g: S^1 \rightarrow S^1$ . If continuous, a circle map can be characterized topologically by its winding number, i.e., the number of times that  $g(\phi)$  wraps around the unit circle as  $\phi$  goes around the circle once. Geometrically, the winding number equals the average slope of  $g(\phi)$ . In Fig. 2.2b(iii) the winding number is 1. Indeed, for very weak stimuli,  $g(\phi) \approx \phi$  by continuity, such that all points fall close to the diagonal and the winding number is 1, leading to “weak” or “type 1” resetting. However, in this example, for stronger stimuli the winding number of  $g(\phi)$  is 0, Fig. 2.2c(iii). Unlike weak resetting, where

the shifted cycle intersects all the W-isochrons, if the stimulus is of sufficiently strong amplitude to move the shifted cycle to a location where it no longer intersects all W-isochrons, degree 0 resetting will occur (Winfree 2000). The curve  $g(\phi)$  is still continuous however, as the phase is defined using *modulus* 1. The example here shows a typical situation for cardiac pacemaker systems subjected to a depolarizing stimulus: an early stimulus causes a delay, while a late stimulus leads to an advance in the rhythm.

If the winding number is 1 for weak stimuli and 0 for strong stimuli, then there must be an intermediate strength (or range of strengths) that results in the state point being perturbed to a location outside of the basin of attraction of the stable limit cycle. In this example, this happens when the shifted cycle intersects the unstable fixed point within the stable limit cycle. Hence, for the old phase corresponding to that intersection, the oscillation is abolished, the new phase is undefined, and the phase transition curve discontinuous.

An important property of the phase transition curve is the Continuity Theorem (Gedeon and Glass 1998; Guckenheimer 1975). It states that if a stimulus of a given amplitude delivered at any phase of a limit-cycle oscillation leaves the state point within the basin of attraction of that asymptotically stable limit cycle, then the phase transition curve will be continuous for that stimulus amplitude. Similarly, if the phase transition curve is truly discontinuous there must be a stimulus phase (or range of phases) that will result in the state point being perturbed outside of the basin of attraction of the limit cycle. In the next section, we discuss situations where apparent discontinuities occur in phase resetting.

Although the determination of properties of the phase resetting curve of biological oscillators has a certain intrinsic interest, perhaps the major reason for investigating phase resetting is to understand the interaction of a biological oscillator with inputs from other oscillators or the environment. In the simplest circumstance there is a brief perturbation delivered to an oscillator, for example, as delivered by a stimulus from a microelectrode or from an action potential from another nerve cell. In that case, and assuming a rapid return to the limit cycle following a perturbation, the phase transition curve can be used to predict the effects of a train of stimuli. Indeed, if a series of periodic stimuli is delivered to a limit cycle oscillator with phase transition curve  $g(\phi)$ , then successive phases are given by

$$\phi_{j+1} = g(\phi_j) + \tau \pmod{1}, \quad (2.6)$$

where  $\tau = t_s/T_0$ , and  $t_s$  is the interval between successive stimuli and the phase transition curve  $g$  depends on the strength of the stimuli (Guevara and Glass 1982; Guevara et al. 1983).

This equation thus shows how the circle map defining the phase transition curve may be iterated to predict the effect of periodic forcing. Indeed, since the resulting Eq. (2.6) involves a circle map with two parameters, corresponding to the period and strength of the stimuli, there has been significant analysis of the periodic stimulation of biological oscillators in the context of theoretical studies of the bifurcation of circle maps (Arnol'd 1965; Glass and Mackey 1998). In particular,

following early studies on a spiking neuron by Perkel and colleagues (1964), there were descriptions of experimentally observed dynamics such as complex bifurcations and chaos in cardiac (Guevara et al. 1981) and neuronal oscillators (Kaplan et al. 1996; Matsumoto et al. 1984). In some cases, the one dimensional circle map, Eq. (2.6), is able to predict the dynamics under periodic stimulation as frequency and amplitude change (Guevara et al. 1981, 1983).

### 3 Discrepancies Between Theoretical Predictions and Experimental and Computational Results

Although the topological theory of phase resetting reviewed in the previous section has a certain simplicity and elegance, current experimental and theoretical studies of resetting and entrainment of biological (especially neural) oscillators are largely focused in other directions. We can think of three possible reasons.

*Experimental studies of resetting and entrainment using the theory are tedious and require experimental systems with low noise, comparatively short period, and a sufficiently long experimental duration.* Any real experimental system will be subjected to noise, and in some cases, there can be significant fluctuations in the period of biological oscillators. If the period is not constant, then there is necessarily uncertainty in measuring both the phase of the stimulus and the resetting induced by the stimulus. To carry out resetting experiments using a variety of amplitudes of stimulus requires very stable oscillations and sufficiently fast oscillations that repeated resetting experiments can be carried out. Furthermore, higher resolution phase response curves require a longer duration of experiment, which is often limited for acute single cell *in vitro* experimentation. There is an extensive literature on resetting circadian rhythms, but resetting experiments take very long times and are difficult due to the difficulty of measuring the phase of the oscillation. In neuroscience, it is commonly observed that experimental phase response curves from invertebrate neurons (Pinsker 1977; Preyer and Butera 2005; Sieling et al. 2009) are much less noisy than those from mammalian neurons (Mancilla et al. 2007; Netoff et al. 2005).

*The topological predictions about resetting oscillations are of limited interest to most biologists and are not particularly relevant to understanding biological oscillations.* Although the topological analysis makes robust predictions about continuity and winding numbers of phase resetting, these predictions have not proven useful for scientists studying mechanisms of oscillations. Indeed, there have been few studies that relate the ionic mechanisms to the phase response curve itself (Canavier et al. 1997; Demir et al. 1997; Kunysz et al. 1995). (See also Part 3 of this book, particularly Chaps. 9, 12, and 13.) Recently, the use of the phase response curve to infer predictions about synchrony has been an active area of study in neuroscience, particularly using dynamic clamp techniques (Butera et al. 2001;

Dorval et al. 2001; Sharp et al. 1993) to study controlled interactions among pairs of cells (Bem et al. 2005; Mancilla et al. 2007; Netoff et al. 2005; Sharp et al. 1996).

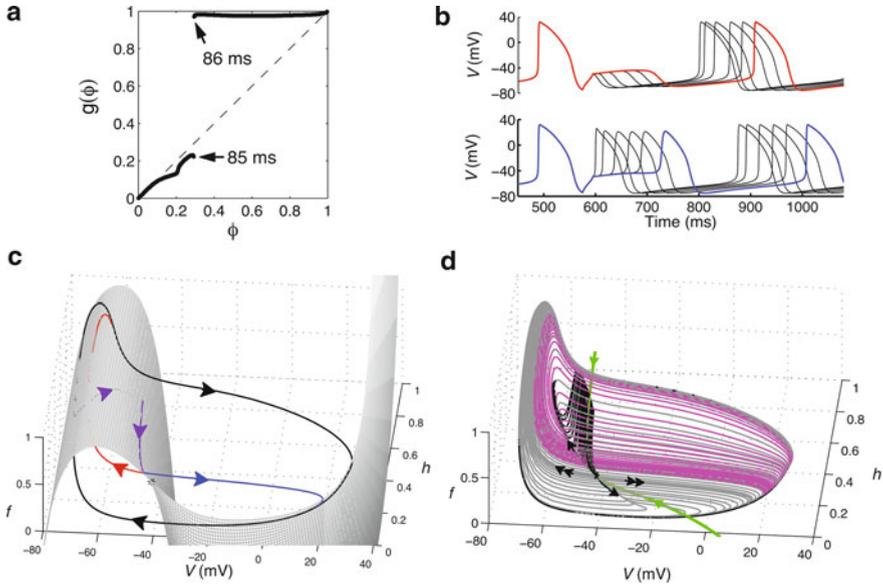
*Actual properties of real biological oscillators and the ways in which they interact differ substantially from the simple properties outlined in Sect. 2.* The basic theory above assume very brief stimuli. Although there are certainly circumstances that correspond to this paradigm in experimental systems, the relevance in networks of interacting cells is less clear. Further, there really has been very little systematic testing of the predictions in Sect. 2, even assuming very brief stimuli. However, in the remainder of this section we discuss two ways in which the predictions break down: experimentally measured resetting curves may not be continuous except for low level stimuli; and relaxation rates to the limit cycle may be sufficiently slow to preclude rapid return to the limit cycle for realistic stimuli.

### 3.1 Discontinuities in Phase Resetting

According to the topological theory discussed in Sect. 2, the phase transition curve will be continuous for any stimulus amplitudes that does not lead to a transition outside the basin of attraction of the limit cycle. However, in many studies, the phase transition curve is very steep or even discontinuous for some combinations of stimulus amplitude and stimulus timing, but only in some of these situations was the oscillation abolished (Clay et al. 1984; Glass and Winfree 1984; Guevara et al. 1986; Vanmeerwijk et al. 1984). In this section, we reconcile this observation with the theoretical analysis.

*Apparent discontinuities.* In experiments on a cardiac pacemaker preparation, fine probing of the dynamics close to the transition between delay and advance of the next action potential showed that for a certain value of the coupling interval, either advance or delay occurred in different trials (Guevara et al. 1986). A slightly smaller (larger) value of the coupling interval caused only delays (advances) in multiple trials [Fig. 4 of Guevara et al. (1986)]. Further, this separation was maintained during several subsequent cycles. Thus, if one were to construct the phase transition curve for this preparation, it would be bi-valued at one value of the old phase (the one corresponding to the coupling interval where both advance and delay were seen) and these two values would be separated by a large gap. Clearly, this curve would be discontinuous. However, no annihilation of the intrinsic rhythm was seen, contradicting the Continuity Theorem.

The abrupt transition between advance and delay of the oscillation is related to the “all-or-none” dynamics typical of neuronal and some cardiac cells due to the fast positive feedback dynamics of the sodium current generating the action potential upstroke. Using a simplified three-variable model, Krogh-Madsen et al. showed that between the trajectories that lead to “all” or “none” responses lies a family of exceptionally sensitive solutions that secure the continuity of the phase transition curve (Fig. 2.3, Krogh-Madsen et al. (2004)). These so-called canard solutions hug the unstable branch of the slow manifold (Fig. 2.3c) before diverging

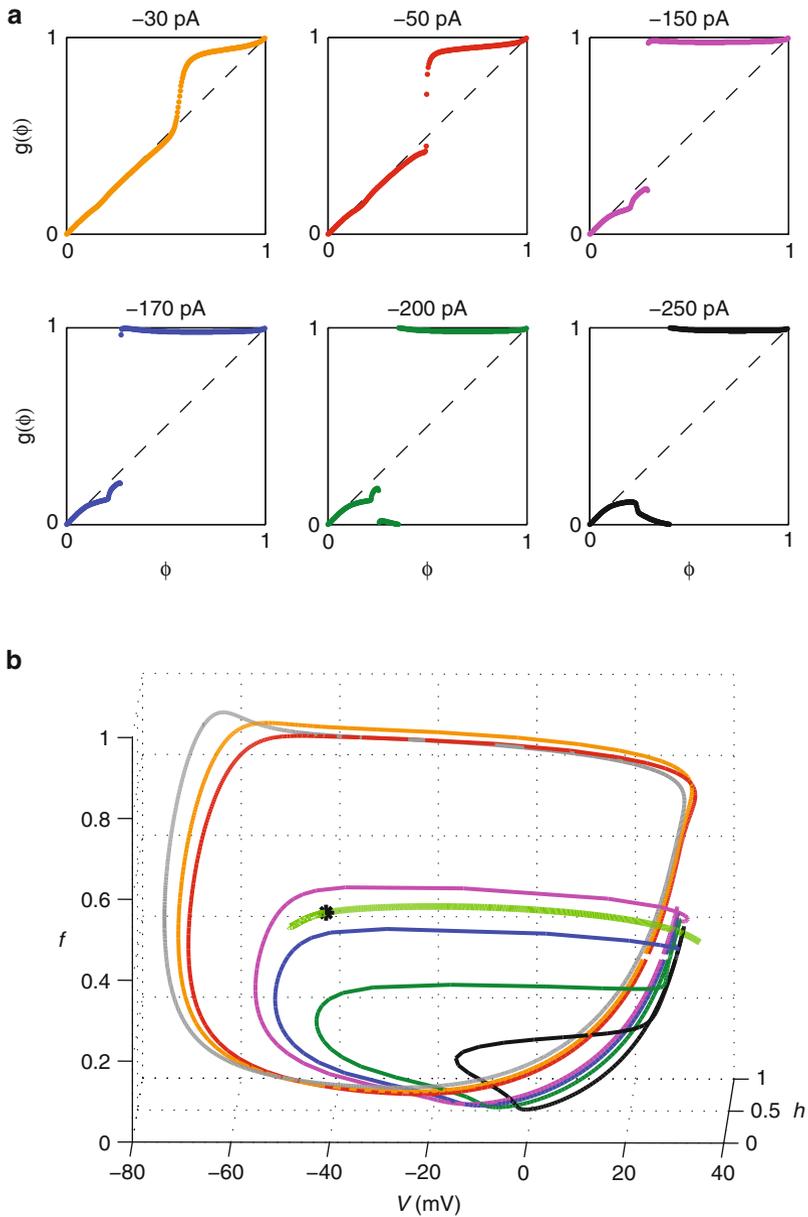


**Fig. 2.3** (a): Discontinuous phase transition curve with  $t_c$  sampled every 1.0 ms. (b): Voltage waveforms close to the abrupt transition between delay and advance. Red trace obtained for  $t_c = 85.336376727283$  ms, blue trace is for  $85.336376727284$  ms. (c): Trajectories in phase space travel along the slow manifold (gray structure, defined as  $dV/dt = 0$ ). (d): Quasi-threshold structure (black, defined as the stable manifold of the trajectories following the slowest direction away from the fixed point). (c) and (d) are reprinted with modifications from Krogh-Madsen et al. (2004) with permission

off a quasi-threshold structure (Fig. 2.3d). Because these solutions are so sensitive, a tiny amount of noise such as that stemming from the stochastic gating of even a single ion channel, can provide sufficient perturbation to convert the “all” to the “none” response and vice versa (Krogh-Madsen et al. 2004). Similar sensitivity can occur in the neuronal Hodgkin-Huxley model (Clay 1977).

*Type 1 to type 0 transition.* The transition from type 1 to type 0 resetting is well defined theoretically. It may be direct as in the example in Fig. 2.2, where for one exact value of the stimulus amplitude, the shifted cycle crosses the unstable fixed point causing annihilation of the oscillation and an undefined topological degree. A direct transition has been observed in a model of a cardiac pacemaker cell with a slow action potential upstroke (Guevara and Jongsma 1990). Alternatively, the transition may be indirect if there is a range of intermediate stimulus amplitudes for which the state point is taken outside of the basin of attraction of the limit cycle.

However, in experimental and even computational studies, apparent discontinuities can make it very difficult to distinguish between type 1 and type 0 topologies (Krogh-Madsen et al. 2004). An example is shown in Fig. 2.4a (same model as in Fig. 2.3), where  $t_c$  was sampled in intervals of 1 ms. For a low stimulus amplitude ( $-30$  pA), the phase transition curve is clearly of type 1 and with a very large



**Fig. 2.4** Type 1 to type 0 transition. **(a)**: Phase transition curves for a range of stimulus amplitudes. **(b)**: Location of shifted cycles corresponding to the curves in **(a)** relative to the stable manifold of the fixed point (light green)

stimulus amplitude ( $-250$  pA), it is evidently of type 0. However, for some of the intermediate stimulus amplitudes (in particular  $-150$  and  $-170$ ) the degree is indeterminate.

In a noise-free model, the location of the transition may be determined by much finer sampling of the stimulus timing. Alternatively, in a model where one has access to all the variables, the shifted cycle is readily computed and the topological transition determined from the location of a range of shifted cycles relative to the phaseless set. In our example, the transition from type 1 to type 0 resetting occurs for a stimulus amplitude between  $-150$  and  $-170$  pA (Fig. 2.4b). However, due to intrinsic noise in experimental preparations, this inherent difficulty in assigning a topological degree for intermediate stimulus amplitudes persists (Guevara et al. 1986; Vanmeerwijk et al. 1984). Noise is particularly prevalent in the phase response curves of many mammalian spiking neurons (Galan et al. 2005; Netoff et al. 2005).

There are only a limited number of studies examining the existence of a type 1 to type 0 transition in single neurons. In one study where both type 1 and type 0 resetting was found by systematic variation of the stimulus amplitude, the two types occurred for both excitatory and inhibitory inputs to a bursting neuron (Prinz et al. 2003). Further, the type transition was hypothesized to occur in spiking neurons also (Prinz et al. 2003). Except for this case, the published phase response curves from spiking neurons of which we are aware [e.g., Cui et al. (2009); Galan et al. (2005); Mancilla et al. (2007); Netoff et al. (2005); Perkel et al. (1964); Preyer and Butera (2005)] all appear to be type 1. It is quite likely that the experimental rationale never required a sufficiently strong input to elicit a type 1 to type 0 transition. Conversely, the published phase response curves of bursting neurons (Pinsker 1977; Sieling et al. 2009) in response to inhibitory input almost always appear to be type 0. This response is also supported by modeling studies (Demir et al. 1997). In the case of these bursting neurons, this type 0 response is due to an all-or-none like effect (see Sect. 3.1) – inhibitory inputs during a burst (when the neuron is spiking) either have a negligible effect on the burst trajectory (and thus the phase) or cause an immediate hyperpolarization to a different portion of the limit cycle. A type 1 topology in bursting neurons in response to excitatory input is only possible for extremely weak inputs, and is difficult to achieve in practice. These phenomena are discussed in (Sieling et al. 2009). In essence, the existence and nature of the type 1 to type 0 transition has not been extensively studied in spiking or bursting neurons and is an open area of investigation.

### 3.2 *Finite Relaxation Times and the Limits of the Circle Map*

One of the important applications of resetting experiments is the use of the resetting curves to determine dynamics set up between an oscillator and the environment (including other oscillations). The notions of weak interactions have played an important role in the development and application of the infinitesimal resetting curve (see Sect. 4). However, a major conclusion of Sect. 2 is that if the phase transition

curve  $g(\phi)$  is known, and a stimulation protocol is adapted, then the effects of the stimulation can be determined provided there is a rapid return to the limit cycle. For example, Eq. (2.6) can be used to predict the effects of periodic stimulation. Indeed, work from several groups has shown the applicability of this approach to predict the effects of periodic stimulation of cardiac tissue (Guevara et al. 1981). However, there have been limited experimental and theoretical studies that have explored the consequences if the time to relax back to the limit cycle is not fast compared to the cycle length.

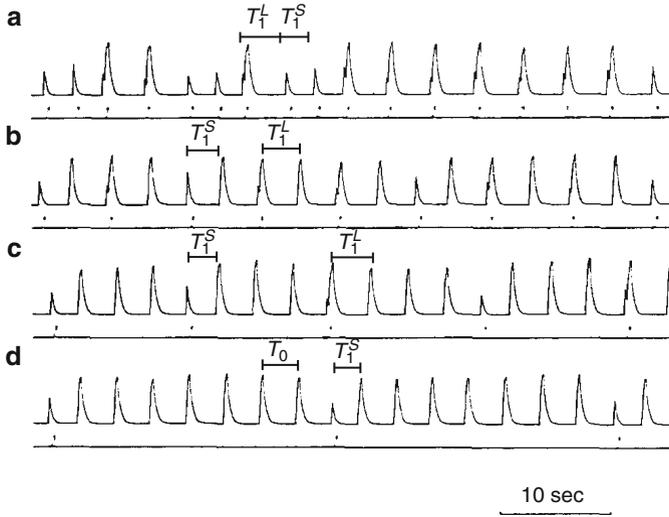
Perhaps the most direct way to explore the notion of instantaneous relaxation back to the limit cycle is to deliver stimuli at a fixed time delay after a fiducial event. By definition, Eq. (2.1), the phase of a stimulus is  $t_c/T_0$ , so provided there is rapid relaxation to the limit cycle, the effect of a stimulus will only depend on the phase of the stimulus and not on the previous history. From an experimental perspective, it is straightforward to deliver a stimulus at fixed delays and to determine the effects.

We mention several examples.

Lewis et al. determined the effects of stimulation of the superior laryngeal nerve (SLN) on the respiratory rhythm in anesthetized decerebrate cats (Lewis et al. 1989). These experiments were initially undertaken to apply the theory of Sect. 2 to measure the resetting of the respiratory rhythm by SLN stimulation, and then to predict the effects of periodic SLN stimulation. Normally, a pulse of SLN activity delivered at a time delay of 200 ms after the onset of phrenic activity (associated with the onset of inspiration) would lead to a termination of the inspiratory phase. However, in the course of doing these experiments, it became clear that the SLN stimulation had long lasting effects, and that consequently Eq. (2.6) would not hold. The SLN stimuli were delivered every phrenic burst, or after some specified fixed number of phrenic bursts. The stimulus would either shorten or prolong the respiratory cycle. If the stimulus was given every 8 cycles, each stimulus would lead to a shortening of the respiratory cycle, but if the stimulus was given at every 1st, 2nd, or 4th cycle, some stimuli would lead to shortening of the cycle, whereas others would lead to lengthening of the cycle (Fig. 2.5).

Kunysz et al. carried out similar experiments on spontaneously beating aggregates of chick heart cells, but used a depolarizing current that would normally induce an action potential if given after a sufficiently long delay after an action potential (Kunysz et al. 1997). If each stimulus induced a new action potential, then there would be a resulting burst of activity, at a faster rate than normal, a finding that could provide a physiological basis for some types of rapid heart rhythms (tachycardias). However, over a range of delays, each stimulus would not give rise to an action potential, so that after a short burst of activity the stimulus would not be effective, and there would be a long delay until there would again be a spontaneous action potential. Thus, this would lead to bursts of activity and could also provide a potential physiological mechanism for paroxysmal tachycardias that are observed clinically.

Another approach for this situation is to quantify the effects of the perturbation on subsequent limit cycles (Oprisan and Canavier 2004; Reyes and Fetz 1993). This approach defines each limit cycle by measurement of spike times and separates



**Fig. 2.5** Phrenic nerve activity during SLN stimulation. (a): Stimulus train delivered every cycle; (b): every 2 cycles; (c): every 4 cycles; (d): every 8 cycles.  $T_0$ ,  $T_1^S$ , and  $T_1^L$  mark examples of the intrinsic period, stimulus-induced cycle shortening, and stimulus-induced cycle lengthening, respectively. Reproduced from Lewis et al. (1989) with permission

the effect of the stimulus into a first order phase response curve (effect on first limit cycle), second order phase response curve (effect on second period after the limit cycle with the perturbation), and so forth. Oprisan et al. (2004) showed that incorporating second order resetting improved the prediction of the synchronous state between a bursting neuron and a bursting neuron model synaptically coupled via a dynamic clamp.

More recently, Cui et al. have explored similar effects associated with adaptation of spontaneously spiking neurons in *Aplysia* (Cui et al. 2009). While the neurons display adaptation that occurs over several cycles, their method was to characterize a phase response curve calculated by repetitive stimulation of the neuron after a fixed delay from phase 0. After a sufficient number of cycles the phase relationship between the delayed stimulus and the spike oscillation stabilized. The rationale for this approach is that adapting neurons participating in a rhythm-generating network frequently lock into stable phase relationships among multiple oscillators, with an input arriving at approximately the same phase each cycle. Thus this method of characterizing a phase response curve represents the phase response curve of the neuron under a “steady-state” level of adaptation.

From a theoretical perspective, there has been some work. Given the Poincaré oscillator with periodic or fixed delay stimulation, extremely interesting dynamics can be obtained by simply assuming a finite relaxation time to the limit cycle. For example, a detailed mathematical study of the entrainment rhythms for different relaxation rates would be warranted, but we know of only one study at some selected

relaxation rates (Glass and Sun 1994). Similarly, stimulation of the Poincaré oscillator at a fixed phase can lead to chaotic dynamics and interesting bifurcations as the phase of the stimulus is changed (Lewis et al. 1987).

## 4 Topological Analysis of Neural Models Near the Saddle Node Bifurcation

Although some studies of pulse coupling of neural oscillators use phase response curves in a similar fashion to those used in the present chapter (also see Chap. 4), most previous studies of resetting of neural oscillators have not been strongly influenced by the topological approach. Rather, studies of resetting neural oscillators emphasize the classification “class I” and “class II” oscillators (in this chapter, we use the terminology of type I/0 for the topological classification and class I/II for the traditional neural classification). This classification was initially based on experimental observations of different classes of excitability by Alan Hodgkin (1948) and has subsequently been extended by many [see Izhikevich (2000, 2007)]. In class I neurons the firing frequency codes an input intensity, whereas in class II neurons the firing frequency is largely independent of a (suprathreshold) input. There are many examples of published phase response curves from single repetitive spiking neurons that are predominantly class I and also apparently type I [e.g., Cui et al. (2009); Galan et al. (2005); Mancilla et al. (2007); Netoff et al. (2005); Perkel et al. (1964); Preyer and Butera (2005)]. Consideration of the class I/II neurons from a dynamical perspective by Ermentrout, Izhikevich and others (Rinzel and Ermentrout (1989); Izhikevich (2000, 2007)) has led to the recognition that class I neurons may arise from a saddle node bifurcation on an invariant circle, whereas class II neurons may more likely arise from an Andronov–Hopf bifurcation. The concept of class I/II neurons has been particularly fruitful in analysis of weak coupling which is assumed when using phase-oscillator model approaches to studying interacting oscillations (Ermentrout and Kopell 1990).

In the current theoretical neurophysiological literature, there is often a common statement “class I neurons will exhibit a phase-advance, whereas class II neurons exhibit both advance and delay” [e.g., Abouzeid and Ermentrout (2009)]. However, based on the topological description in Sect. 2, continuity of the underlying dynamical system ensures the existence of isochrons corresponding to all real values of the new phase between 0 and 1 (or 0 and  $2\pi$  if measured in radians). Hence, the topological approach predicts both delay and advance, making the above assertion regarding class I neurons appear at odds with the topological description. We thought it worthwhile to analyze the source of the apparent discrepancies. In order to carry out the computations, we first assume an equation for a model oscillator that displays a saddle-node bifurcation on an invariant cycle, and consider a parameter value “close” to the bifurcation point.

We analyze the equation

$$\frac{d\theta}{dt} = 1 - ar \cos(\theta - \Phi_{\text{SN}}), \quad (2.7)$$

$$\frac{dr}{dt} = r(1 - r^2). \quad (2.8)$$

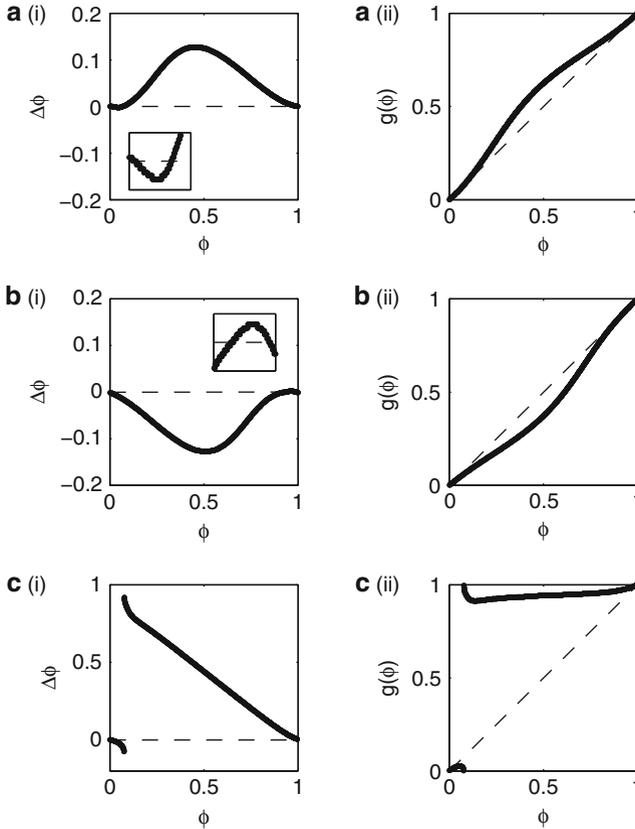
For  $a < 1$  there is a stable limit cycle with  $|r| = 1$  and when  $a = 1$  there is a saddle node bifurcation on the invariant circle at  $\Phi_{\text{SN}}$ . Again, stimuli of amplitude  $b$  are applied to perturb the state point in the direction of  $\theta = 0$ . We show the results of three simulations of resetting curves with  $a = 0.97$ , representing a value that is near the saddle node bifurcation. Notice that when  $a = 0$  we have the Poincaré oscillator discussed in Sect. 2 with an oscillation period of  $2\pi$ . When  $a = 0.97$  the period increases to  $\approx 25.85$  reflecting the slowing of the angular derivative near the point  $\Phi_{\text{SN}}$ .

Figure 2.6a shows the phase transition and phase response curve curves for  $b = 0.1$  and  $\Phi_{\text{SN}} = 3\pi/2$ . In this case the phase response curve is almost entirely positive. This arises from (a) the slowing of the trajectory near the point  $\Phi_{\text{SN}} = 3\pi/2$ ; and (b) the observation that stimuli near the phase  $\phi = 3\pi/2$  in the Poincaré oscillator will lead to positive phase response curve (see Fig. 2.2). However, there is also a region in which the phase response curve is negative, as would be expected from the topological analysis. Because of isochron clustering, the region of delay in the phase response curve is small and might easily be missed or even be unmeasurable in experiments. This situation represents the typical situation in most neuron models, where the location of saddle node bifurcation, the orientation of the limit cycle trajectory, and the direction of the perturbation occurs in a region of phase space where stimuli generally lead to a phase advance. Others have observed that the phase response curve of class I neurons models appears to have at least a small portion of the limit cycle where the phase response curve is negative (Oprisan et al. 2002; Rinzel and Ermentrout 1989).

Now consider the situation when  $\Phi_{\text{SN}} = \pi/2$  (Fig. 2.6b). In contrast to the situation in Fig. 2.6a, the phase response curve is now almost entirely negative. The explanation for this behavior is clear and it is a consequence of a slowing of the trajectory near a point in phase space that will lead to a negative phase response curve. Once again, the phase response curve is bimodal, though now most of the phase response curve is negative and only a small region is positive.

For completeness, in Fig. 2.6c we illustrate the phase transition curve and phase response curve for  $a = 0.97$ ,  $\Phi_{\text{SN}} = 3\pi/2$ , and  $b = 1.1$  for which we have topological type 0 resetting.

In conclusion, these examples show that (a) limit cycles that arise as a consequence of a saddle node bifurcation will show bimodal phase response curves and (b) the relative ranges over which the curves are advancing or delaying depends on the location of the incipient bifurcation relative to the fiducial point and the imposed perturbation.



**Fig. 2.6** Phase response curves (*left*) and phase transition curves (*right*) for the simple model close to the SNIC Eq. (2.7). **(a)** (i and ii):  $b = 0.1$ ,  $\Phi_{\text{SN}} = 3\pi/2$ ; **(b)** (i and ii):  $b = 0.1$ ,  $\Phi_{\text{SN}} = \pi/2$ ; **(c)** (i and ii):  $b = 1.1$ ,  $\Phi_{\text{SN}} = 3\pi/2$ ; where  $b$  is the stimulus amplitude. Inserts in **(a)** (i) and **(b)** (i) show zoom-ins of negative and positive going parts of the phase response curves. Axes range is 0.1 in the horizontal direction and 0.06 in the vertical direction

## 5 Summary and Conclusions

In summary, we have reviewed the general theory of topological phase resetting and shown how it can be applied to experimental analysis. The method is straightforward to apply to experimental data and relies upon testable assumptions. These methods are similar to the pulse-coupled approaches used for neuronal oscillators as described in Chap. 4. Although some of the statements that have been made with regard to phase resetting appear to contradict the topological theory, there is no inconsistency between the two approaches. In particular, phase response curves will in general be bimodal for both class I and class II neurons. However, in the limit when one is infinitesimally close to the bifurcation point, the phase response curve

can be positive for class I neurons. In addition, the assertion that class I neurons will display principally positive phase response curves, results both from the occurrence of a stable limit cycle near a saddle node bifurcation *and* the actual spatial location of the incipient saddle-node in the phase space. In typical mathematical models of neurons, the saddle node bifurcation is located in a region of the phase space where a depolarization would lead to an action potential sooner than expected in the absence of a perturbation causing a positive phase response curve.

The use of phase oscillator models and the assumption of weak coupling (Ermentrout and Kopell 1990) is an alternative approach for studying the phase response of neuronal oscillators. The advantage of such theory is the ability to separate the input waveform from the intrinsic phase response properties of the neuron. A disadvantage of this theory is that the estimation of phase response curves using this method is less straightforward [e.g., Galan et al. (2005); Preyer and Butera (2005)] and requires a degree of numerical estimation, optimization, or deconvolution. A type 0 phase response curve is not possible within the paradigm of weak coupling, as the assumptions of weak coupling are inclusive of (and more stringent than) the assumptions of type 1 resetting described herein. These assumptions include that the perturbation is weak and relatively close to the limit cycle. Topological theory may be a useful adjunct for weak coupling in situations where sufficiently strong inputs occur such that the weak coupling assumptions are violated. We are currently investigating more completely the relationship between the influence of the bifurcation (class I or II) on the topology of the phase space and its implications on topological phase resetting.

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