5

Resetting and Entraining Biological Rhythms

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5.1 Introduction

Biological rhythms are ubiquitous. Their periods of oscillation range from fractions of a second to a year. Independent of the period of the oscillation, and the precise mechanism underlying the generation of the oscillation, certain underlying mathematical concepts are broadly applicable. Appropriate stimuli delivered to the oscillators usually induce a resetting of the oscillation, so that the timing of the oscillation will be different from what it would have been if the stimulus were not delivered. Occasionally, a stimulus delivered during an oscillation will terminate the oscillation, or lead to a different oscillation. Determining the response of oscillators to perturbations administered at different phases of the cycle can give important information about the oscillator, and also may be useful in determining the behavior of the oscillator in the fluctuating environment. It is likely that in every branch of biology in which oscillations are observed, there is a literature analyzing the oscillations from the idiosyncratic perspective of the particular discipline. Yet, from a mathematical perspective there is a commonality of ideas and approaches (Pavlidis 1973; Guckenheimer 1975; Kawato and Suzuki 1978; Kawato 1981; Winfree 2000; Guevara, Glass, and Shrier 1981; Glass and Winfree 1984; Winfree 1987; Glass and Mackey 1988).

Resetting can be measured experimentally by delivering a stimulus to an oscillating system and determining the resulting dynamics. By delivering stimuli at different phases of an oscillation and with different magnitudes, the underlying dynamical system generating the oscillation can be probed. I give a dramatic clinical example to illustrate the approach. Figure 5.1 shows an example of a stimulus delivered by an electrode directly in a person's heart during the course of a serious cardiac arrhythmia, ventricular tachycardia (Josephson et al. 1993). The different traces represent the simultaneously recorded activity from several different sites both on the

body surface and also in the heart itself. The sharp deflections represent the times when waves of electrical activation pass a given location. In the top panel, the stimulus was delivered at 270 ms following an activation recorded in the right ventricular apex, and in the bottom panel, the stimulus was delivered 260 ms after an activation from the right ventricular apex. The effects were completely different. A pulse at 270 ms reset the rhythm, whereas when a pulse was delivered 10 ms earlier, the abnormal tachycardia was abolished and the original rhythm was reestablished. Cardiologists often take this type of result to indicate that the original rhythm was generated by an excitation traveling in a reentrant circuit, in which the excitation repeatedly circulates like a toy train going around a circular track. From a mathematical perspective, we are led to inquire exactly what one can infer about underlying physiological mechanisms based on experimental data concerning resetting.

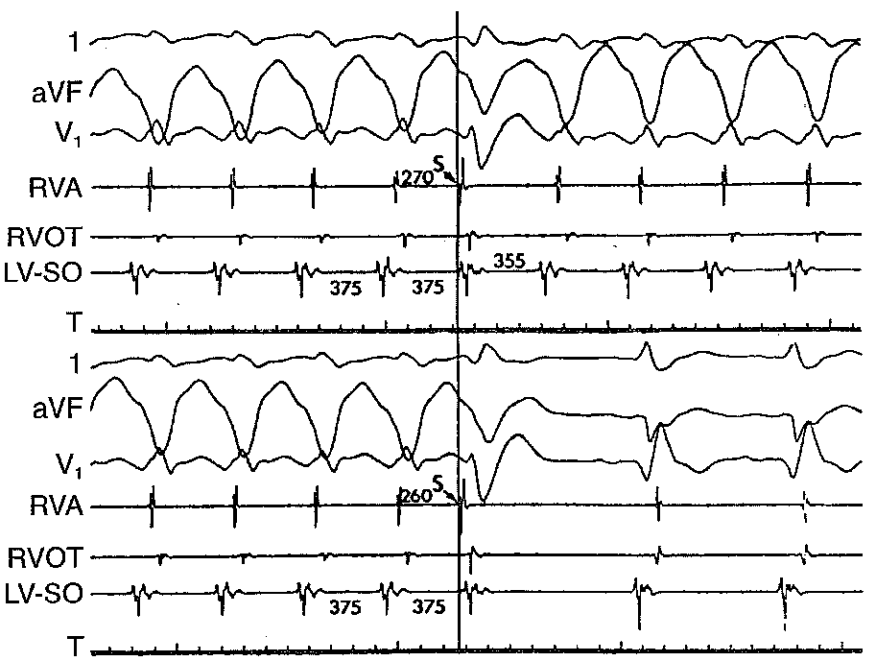

Figure 5.1. Resetting and annihilation of ventricular tachycardia. In each panel the traces labeled 1, aVF, V_1 are surface electrocardiograms, and the other traces are from the right ventricular apex (RVA), right ventricular outflow tract (RVOT), and the site of origin of the tachycardia in the left ventricle (LV-SO). In the top panel a stimulus (S) delivered 270 ms after a complex in the RVA resets the tachycardia, whereas in the lower panel, a stimulus delivered 260 ms after a complex in the RVA annihilates the tachycardia. From Josephson, Callans, Almendral, Hook, and Kleiman (1993).

Stimuli need not be delivered as single isolated pulses, but can also be delivered as periodic trains. In general, the observed rhythms will depend on the frequency and amplitude of the periodic pulse train. In some cases regular rhythms are set up, whereas in other cases, there are complex aperiodic rhythms. A formidable experimental challenge is to determine experimentally the dynamics as a function of stimulation parameters. Another issue is whether we can predict the effects of periodic stimulation based on knowledge about the resetting induced by a single stimulus.

Because of our knowledge about the mathematical properties of equations generating oscillations, we have expectations concerning the results of resetting and entrainment experiments. The presence of stable oscillations in mathematical models of oscillations enables us to make theoretical predictions concerning resetting and entrainment experiments. Since predictions may be quite different for oscillations generated by different mechanisms, knowledge about the results of resetting and entrainment experiments may be helpful in determining underlying mechanisms.

In this chapter, I will summarize the application of these ideas in idealized situations as well as in concrete experimental settings. I will also mention recent advances and open problems.

5.2 Mathematical Background

5.2.1 W-Isochrons and the Perturbation of Biological Oscillations by a Single Stimulus

Since biological oscillations often have "stable" periods and amplitudes (coefficient of variation on the order of 3%), it is usual to associate the oscillation with a stable limit cycle in some appropriate nonlinear theoretical model of the oscillation (Winfree 2000). Recall from Chapter 2 that a **stable limit cycle** is a periodic solution of a differential equation that is attracting in the limit of $t \to \infty$ for all points in a neighborhood of the limit cycle. Say that the period of the oscillation is T_0. We will designate a particular event to be the fiducial event, designated as phase, $\phi = 0$. The **phase** at any subsequent time $t > 0$ is defined to be $\phi = t/T_0 \pmod 1$. The phase here is defined to lie between 0 and 1; to convert it to radians multiply it by 2π.

The set of all initial conditions that attract to the limit cycle in the limit $t \to \infty$ is called the **basin of attraction** of the limit cycle. Let $x(t)$ be on a limit cycle at time t and $y(t)$ be in the basin of attraction of the limit cycle. Denote the distance between a and b by $d[a, b]$. Let the phase of x at $t = 0$ be ϕ. Then if in the limit $t \to \infty$,

$$d[x(t), y(t)] = 0,$$

the **latent** or **asymptotic phase** of $y(t)$ is also ϕ. We say that $y(t)$ is on the same **W-isochron** as $x(t)$.

The development of the concept of W-isochrons and the recognition of their significance is due to Winfree (2000). Many important mathematical results concerning W-isochrons were established by Guckenheimer (1975), who considered dynamical systems in n-dimensional Euclidean space. He proved the existence of isochrons and showed that every neighborhood of every point on the frontier of the basin of attraction of a limit cycle intersects every W-isochron. Moreover, the dimension of the frontier of the basin of attraction is greater than or equal to $n - 2$.

We now consider the effects of perturbations delivered to the biological oscillation. Assume that a perturbation delivered to an oscillation at phase ϕ shifts the oscillation to the latent phase $g(\phi)$. The function $g(\phi)$ is called the **phase resetting curve**. The following **continuity theorem** summarizes important aspects of the effects of perturbations on limit cycle oscillations in ordinary differential equations (Guckenheimer 1975) and partial differential equations (Gedeon and Glass 1998). *If a perturbation delivered at any phase of a limit cycle oscillation leaves the state point in the basin of attraction of the asymptotically stable limit cycle, then the resetting curves characterizing the effects of the stimuli will be continuous.* In general, the phase resetting curve $g(\phi)$ is a circle map $g : S^1 \to S^1$.

Circle maps can be continuous or discontinuous. Continuous circle maps can be characterized by their **(topological) degree** or **winding number**. The degree of a continuous circle map measures the number of times the latent phase $g(\phi)$ wraps around the unit circle as ϕ goes around the circle once. For example, for oscillations associated with stable limit cycle oscillations in differential equations and for very weak perturbations in general, $g(\phi) \approx \phi$ and the degree is 1. In many instances, as Winfree discusses (Winfree 2000), the degree of the resetting curve is 0 when the stimulation is strong. If the degree of the resetting curve is 1 for weak stimuli and 0 for strong stimuli, there must be an intermediate stimulus (or stimuli) that will perturb the system outside of the basin of attraction of the limit cycle, though whether the limit cycle is eventually reestablished depends on whether the stimulus perturbs the system to the basin of attraction of another stable attractor. Similarly, if the resetting curve is discontinuous, there must be a stimulus phase or range of stimulus phases that will perturb the system outside of the basin of attraction of the limit cycle (Gedeon and Glass 1998).

These abstract notions are directly related to experiment. The phase resetting curve can be measured experimentally. Assume once again that the marker event of an oscillation is defined as $t = 0$, $\phi = 0$. Assume that in response to a perturbation delivered at phase ϕ, marker events recur at successive times $T_1(\phi), T_2(\phi), \ldots, T_n(\phi)$. Let us assume that for all j sufficiently large, the limit cycle is asymptotically approached, so that $T_j(\phi) - T_{j-1}(\phi) = T_0$, where T_0 is the control cycle length.

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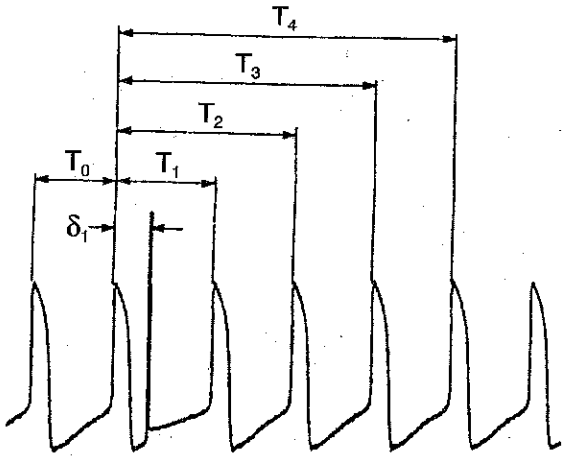

Figure 5.2. Resetting the intrinsic rhythm in a spontaneously beating aggregate of cells from embryonic chick heart. A single stimulus delivered at a phase $\phi = \delta_1/T_0$ leads to a resetting of the oscillation. The time from the action potential before the stimulus to the jth action potential after the stimulus is designated T_j. The reestablishment of an oscillation with the same amplitude and period as before the stimulus is evidence for a stable limit cycle oscillation in this preparation. From Zeng, Glass, and Shrier (1992).

Figure 5.2 shows the effects of a single stimulus delivered to a spontaneously beating aggregate of cells from embryonic chick heart. There is a rapid reestablishment of the original oscillation. This is experimental evidence that the rhythm is being generated by a stable limit cycle oscillation.

Figure 5.3 shows the results of a resetting experiment in an aggregate of cells from embryonic chick heart. A single stimulus is delivered at different phases of the oscillation. The panel on the left is typical of weak stimulation, and the panel on the right is typical of strong stimulation.

The phase resetting curve can be determined from the data in Figure 5.3. It is given by

$$g(\phi) = \phi - \frac{T_j(\phi)}{T_0} \pmod 1. \tag{5.1}$$

Winfree (2000) gives many examples of resetting biological oscillators. The degree of the experimentally measured phase resetting curve is usually 1 or 0, though in some cases it was discontinuous (Winfree 2000). Though most are not much bothered by discontinuities in resetting experiments, understanding their origin is a challenge (Glass and Winfree 1984).

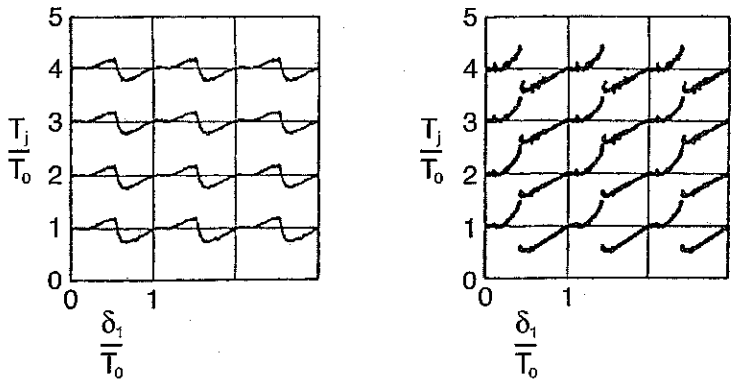

Figure 5.3. Resetting curves derived from an experiment in which a single stimulus is delivered to spontaneously beating heart cell aggregates. The results are triple plotted. A stimulus of 13 nA gives weak resetting, and a stimulus of 26 nA gives strong resetting. The time from the action potential before the stimulus to the jth action potential after the stimulus is plotted as a function of the phase of the stimulus. From Zeng, Glass, and Shrier (1992).

5.2.2 Phase Locking of Limit Cycles by Periodic Stimulation

The earliest studies drawing a connection between the resetting and the entrainment of limit cycles involved the computation of the effects of periodic stimulation on a stretch receptor (Perkel et al. 1964) and the entrainment of circadian rhythms (Pavlidis 1973). This connection can be developed mathematically using the concept of the W-isochron introduced in the last section (Glass and Mackey 1988).

In general, the effect of a single stimulus is to shift an oscillator from one W-isochron to a new W-isochron. Consequently, it is possible to define a one-dimensional map that relates the phase of an oscillation before a stimulus to the phase of an oscillation before the following stimulus. Iteration of such a map enables prediction of the dynamics during periodic stimulation. Although iteration of a one-dimensional map determined from resetting experiments can offer excellent insight into dynamics observed in real systems (Perkel et al. 1964; Guevara et al. 1981), there are many underlying assumptions. First, it is necessary to assume that the stimulation does not change the properties of the oscillation, so that the same resetting curve that is found using single pulses is also applicable under periodic stimulation. In addition, it is necessary to assume that the resetting induced by a single isolated stimulus is the same as the resetting induced by a single stimulus at the same phase delivered during a periodic train of stimuli. Even if the properties of the oscillation are not changed by the periodic stimulation protocol, there are at least two different reasons why knowing the effects of a single stimulus would not be adequate to predict the results of a periodic

train of stimuli. First, it is possible that the oscillation did not relax back to its asymptotic attractor before the next stimulus was applied. Such an effect would be particularly important if there were slow relaxation to the limit cycle oscillation following a stimulus. In addition, for limit cycles that are associated with circulating oscillations in excitable media in space, the effects of a single stimulus might be blocked by a propagating wave associated with the oscillation, whereas a pulse during a periodic train of stimuli might penetrate the circuit and lead to resetting of the circulating wave.

From the assumptions above, we can derive an appropriate one-dimensional map to predict the effects of periodic stimulation with period t_s of a limit cycle with intrinsic period T_0. Call ϕ_n the phase of stimulus n. Then, if the phase resetting curve is $g(\phi_n)$, the effects of periodic stimulation are given by

$$\phi_{n+1} = g(\phi_n) + \tau \pmod 1 \equiv f(\phi_n, \tau), \tag{5.2}$$

where $\tau = t_s/T_0$. Starting from an initial condition ϕ_0 we generate the sequence of points $\phi_1, \phi_2, \ldots, \phi_n$.

The sequence $\{\phi_n\}$ is well-defined, provided no stimulus results in a resetting to a point outside the basin of attraction of the limit cycle. If $\phi_p = \phi_0$ and $\phi_n \neq \phi_0$ for $1 \leq n < p$, where n and p are positive integers, there is a periodic cycle of period p. A periodic cycle of period p is stable if

$$\left|\frac{\partial f^p(\phi_0)}{\partial \phi}\right| = \prod_{n=0}^{p-1} \left|\frac{\partial f}{\partial \phi}\right|_{\phi_n} < 1. \tag{5.3}$$

The **rotation number**, ρ, gives the average increase in ϕ per iteration. Calling

$$\Delta_{n+1} = g(\phi_n) + \tau - \phi_i, \tag{5.4}$$

we have

$$\rho = \limsup_{N\to\infty} \frac{1}{N} \sum_{n=1}^{N} \Delta_i. \tag{5.5}$$

Stable periodic orbits are associated with **phase locking**. In $p : m$ phase locking, there is a periodic orbit consisting of p stimuli and m cycles of the oscillator leading to a rotation number m/p. For periodically forced oscillators neither the periodicity nor the rotation number alone is adequate to characterize the dynamics.

To illustrate the application and limitations of this basic theory we consider two simple theoretical models: the Poincaré oscillator and excitation circulating in a two-dimensional reentrant circuit.

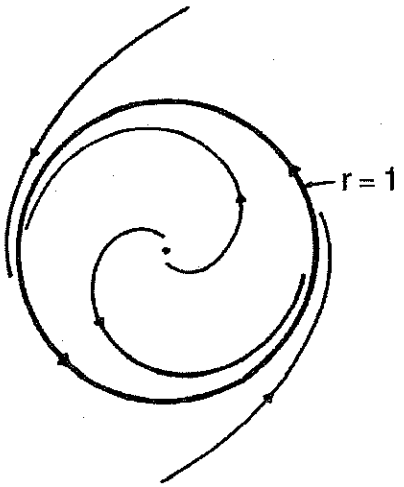

Figure 5.4. The phase plane portrait for the Poincaré oscillator. From Glass and Mackey (1988).

5.3 The Poincaré Oscillator

We first illustrate these concepts in a very simple ordinary differential equation that has been used extensively as a theoretical model in biology. Since this prototypical example of a nonlinear oscillation was first used by Poincaré as an example of stable oscillations, it has been called the Poincaré oscillator (Glass and Mackey 1988).

The Poincaré oscillator has been considered many times as a model of biological oscillations (Winfree 2000; Guevara and Glass 1982; Hoppensteadt and Keener 1982; Keener and Glass 1984; Glass and Mackey 1988; Glass and Sun 1994). The model has uncanny similarities to experimental data and has been useful as a conceptual model to think about the effects of periodic stimulation of cardiac oscillators.

The Poincaré oscillator is most conveniently written in a polar coordinate system where r is the distance from the origin and ϕ is the angular coordinate; see Chapter 2. The equations are written

$$\begin{aligned} \frac{dr}{dt} &= kr(1-r), \\ \frac{d\phi}{dt} &= 2\pi, \end{aligned} \tag{5.6}$$

where k is a positive parameter. Starting at any value of r, except $r = 0$, there is an evolution until $r = 1$. The parameter k controls the relaxation rate. The phase, $\phi = 0$, corresponds to the upstroke of the action potential or the onset of the contraction.

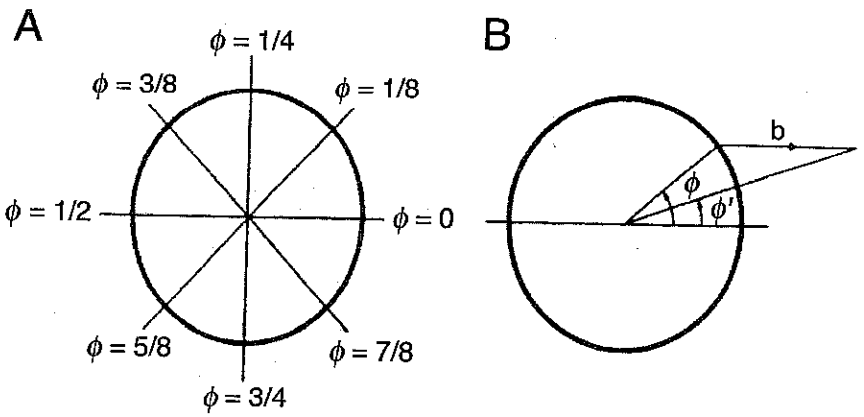

Figure 5.5. (a) Isochrons in the Poincaré oscillator. (b) A stimulus is assumed to induce a horizontal translation b. From Glass and Mackey (1988).

We show the phase plane portrait in Figure 5.4. Since the rate of change of ϕ is not a function of r, the isochrons are open sets lying along radii of the coordinate system. In this case the frontier of the basin of attraction of the limit cycle is the origin. The dimension of the frontier of the isochrons is 0, which is $\geq (n-2)$ (see p. 126), Figure 5.5.

We assume that perturbations are modeled by a horizontal translation to the right by a distance b, Figure 5.5. In the experimental setting, perturbations are an electrical stimulus that depolarizes the membrane. A stimulus induces (after a delay) a new action potential if it is delivered in the latter part of the cycle.

This theoretical model facilitates analytical work because of its comparatively simple analytical form. The phase resetting curve, $g(\phi)$, is readily computed and is given by

$$g(\phi) = \frac{1}{2\pi} \arccos \frac{\cos 2\pi\phi + b}{(1 + b^2 + 2b\cos 2\pi\phi)^{1/2}} \pmod 1. \qquad (5.7)$$

In computations using equation (5.7), in evaluating the arccosine function, take $0 < \phi_i' < 0.5$ for $0 < \phi_i < 0.5$, and $0.5 < \phi_i' < 1$ for $0.5 < \phi_i < 1$.

In Figure 5.6, I plot the perturbed cycle length and the phase resetting curve for the Poincaré oscillator.

The effects of periodic stimulation can now be computed by application of equations (5.2) and (5.7). The geometry of the locking zones is very complicated; a partial representation is shown in Figure 5.7. Here I summarize several important properties. For further details the original references (Guevara and Glass 1982; Keener and Glass 1984; Glass and Sun 1994) should be consulted.

There are symmetries in the organization of the locking zones as originally derived in Guevara and Glass (1982). The symmetries are:

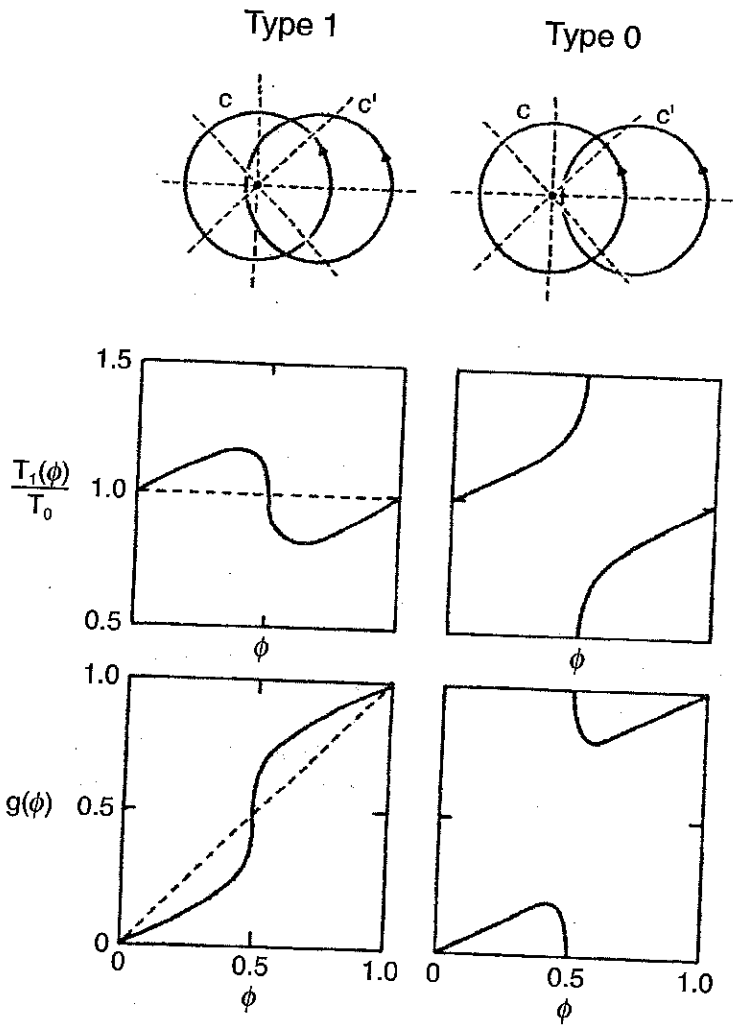

Figure 5.6. Perturbed cycle length and phase resetting curves for the Poincaré oscillator for weak, Type 1 (left panels) and strong, Type 0 (right panels) stimuli. From Glass and Winfree (1984).

- *Symmetry 1.* Assume that there is a stable period p cycle with fixed points $\phi_0, \phi_1, \ldots, \phi_{p-1}$ for $\tau = 0.5 - \delta$, $0 < \delta < 0.5$, associated with $p : m$ phase locking. Then for $\tau = 0.5 + \delta$, there will be a stable cycle of period p associated with a $p : p - m$ phase locking ratio. The p fixed points are $\psi_0, \psi_1, \ldots, \psi_{p-1}$ where $\psi_i = 1 - \phi_i$.
- *Symmetry 2.* Assume that there is a stable period p cycle with fixed points $\phi_0, \phi_1, \ldots, \phi_{p-1}$ for $\tau = \delta$, $0 < \delta < 1.0$, associated with $p : m$ phase locking. Then for $\tau = \delta + k$, where k is a positive integer,

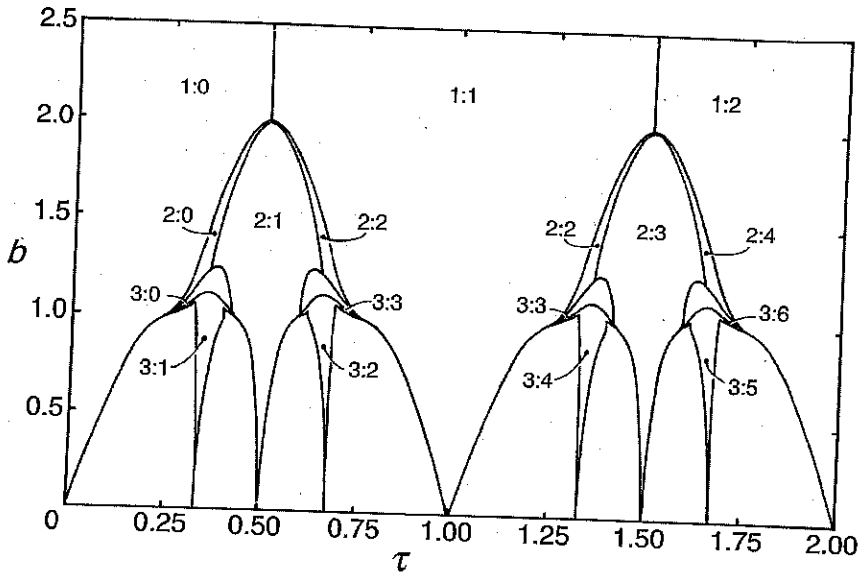

Figure 5.7. Locking zones for the Poincaré oscillator. Adapted from Glass and Sun (1994).

there will be a stable cycle of period p associated with a $p : m + pk$ phase locking ratio. The p fixed points are $\psi_0, \psi_1, \ldots, \psi_{p-1}$ where $\psi_i = 1 - \phi_i$.

These symmetries can be confirmed in Figure 5.7.

I now summarize main features of the organization of the locking zones. The topology of $g(\phi)$ changes at $b = 1$, and this has profound effects on the organization of the locking zones.

Case: $0 \leq b < 1$. The map is an invertible differentiable map of the circle (Arnold 1983). An **Arnold tongue of rotation number** m/p is defined as the union of values in parameter space for which there is unique attracting $p : m$ phase locking for all initial conditions. For invertible differentiable maps of the circle of the form in equation (5.2), if there is $p : m$ phase locking for τ and $p' : m'$ phase locking for τ', then there exists a value $\tau < \tau* < \tau'$, leading to $p + p' : m + m'$ phase locking. Usually, the range of values of τ associated with a given Arnold tongue covers an open interval in parameter space. For a given set of parameters the rotation number is unique. If it is rational, there is phase locking, and if it is irrational, there is **quasiperiodicity**. The organization of phase locking zones for $0 \leq b < 1$ shown in Figure 5.7 for $b < 1$ is typical, and is called the **classic Arnold tongue structure**. The periodic orbits lose stability via a tangent bifurcation.

Case: $1 < b$. The map now has two local extrema. For any set of parameter values there is no longer necessarily a unique attractor. It is possible

to have **bistability** in which there exist two stable attractors for a given set of parameter values. The attractors are either periodic or chaotic. A **superstable cycle** is a cycle containing a local extremum. Such cycles are guaranteed to be stable. One way to get a good geometric picture of the structure of the zones is to plot the locus of the superstable cycles in the parameter space. The structure of bimodal interval maps and circle maps has been well studied and shows complex cascades of bifurcations in the two-dimensional parameter space. As b decreases in this zone, new phase locking zones arise; however, almost all these zones disappear into the discontinuities of the circle map at $b = 1$. There are accumulation points of an infinite number of periodic orbits at the junction of the Arnold tongues with the line $b = 1$.

Analytic expressions for some of the bifurcations can be derived. For $0 < b < 1$ the stability is lost by a tangent bifurcation for which $\partial\phi_{n+1}/\partial\phi_n = 1$. This implies that at the boundary we have

$$b + \cos 2\pi\phi_0 = 0,$$

from which we compute

$$b = |\sin 2\pi\tau|. \tag{5.8}$$

The fixed point at the stability boundary is at

$$\phi_0 = \tau + \frac{1}{4}, \text{ for } 0 < \tau < \frac{1}{4},$$

and

$$\phi_0 = \tau + \frac{3}{4}, \text{ for } \frac{3}{4} < \tau < 1.$$

For $1 < b < 2$ stability of the period-1 fixed point is lost by a period-doubling bifurcation for which $\partial\phi_{n+1}/\partial\phi_n = -1$. From this we compute that at the boundary we have

$$2 + b^2 + 3b\cos 2\pi\phi_0 = 0.$$

Carrying through the trigonometry we find the stability boundary

$$b = \sqrt{4 - 3\sin^2 2\pi\tau}. \tag{5.9}$$

The fixed point at the boundary is given by

$$\phi_0 = \tau + \frac{1}{2\pi}\sin^{-1}\sqrt{\frac{4-b^2}{3b^2}}.$$

It is not generally appreciated that in this system there can be changes in the rotation number without a change in periodicity (Guevara and Glass 1982). For example, for $2 < b$ as τ increases with b fixed there is a change from 1:0 phase locking to 1:1 phase locking along the line $\tau = 0.5$.

The analysis above assumes instantaneous relaxation back to the limit cycle. Although this idealization is clearly not obeyed in real systems (Zeng,

Glass, and Shrier 1992), it can nevertheless provide a good approximation to the dynamics of real systems, particularly for the case in which the stimulation frequency is roughly comparable to the intrinsic period of the limit cycle.

We now consider the consequences of a finite relaxation time in the Poincaré oscillator (Glass and Sun 1994). We again assume that a stimulus is schematically represented by a horizontal translation of magnitude b; Figure 5.5. The stimulus takes point (r, ϕ_n) to point (r'_n, ϕ'_n), where

$$r'_n = (r_n^2 + b^2 + 2br_n \cos 2\pi\phi_n)^{1/2},$$
$$\phi'_n = \frac{1}{2\pi} \arccos \frac{r_n \cos 2\pi\phi_n + b}{r'_n}. \tag{5.10}$$

Following the stimulus, the equations of motion take over, so that by direct integration, we find that immediately before stimulus $(n+1)$ delivered at a time τ after the first stimulus, we have

$$r_{n+1} = \frac{r'_n}{(1 - r'_n)\exp(-k\tau) + r'_n},$$
$$\phi_{n+1} = \phi'_n + \tau (\text{mod } 1). \tag{5.11}$$

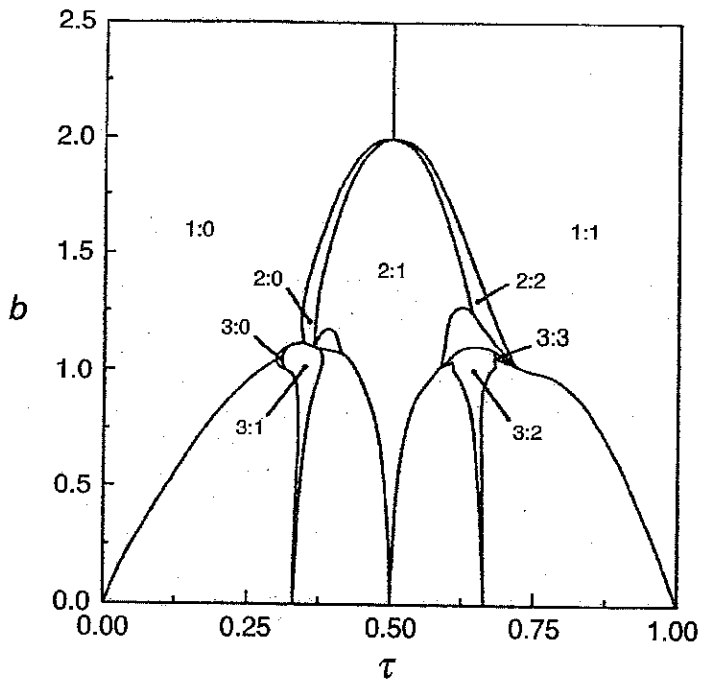

Figure 5.8. Locking zones for periodically stimulated Poincaré oscillator with finite relaxation times, $k = 10$. Adapted from Glass and Sun (1994).

An important difference is present in the organization of locking zones; even for low stimulation amplitudes the classic Arnold tongue structure described earlier does **not** apply. This fact does not seem to be widely appreciated. Even for low–amplitude stimulation, for any amplitude and frequency of stimulation, there will always be a period-1 orbit. In contrast, in the infinite relaxation limit, for $b < 1$, inside the Arnold tongues associated with locking of period $p \neq 1$, there is no period-1 cycle. The existence of period-1 cycles follows immediately from an application of the Brouwer fixed point theorem (Guillemin and Pollack 1975, p. 65). Consequently, the result is also applicable to a broad class of periodically stimulated oscillators and excitable systems, provided there is a sufficient contraction for large excursions from the limit cycle (Glass and Sun 1994). Of course, the period-1 cycle is not always stable, so that in experimental work, it will often appear as though the classic Arnold tongue structure is being observed. Subsequent to publication of this result I found a similar result in Levinson (1944). The result deserves to be better known.

Finite relaxation to the limit cycle will also destroy the symmetries in the infinite relaxation case. Moreover, the fine details of the locking zones change in subtle ways not yet well understood. For example, the points of accumulation of an infinite number of locking zones, which occur at the intersection of the Arnold tongues with the line $b = 1$, need to "unfold" in some natural way. In Glass and Sun (1994), we observe that this unfolding appears to occur in a manner similar to that envisioned earlier by Arnold (see Figure 153 on p. 312 in Arnold 1983).

5.4 A Simple Conduction Model

An excitable medium is a medium in which there is a large excursion from steady state in response to a small stimulus that is greater than some threshold. Nerve cells, cardiac tissue, and the Belousov–Zhabotinsky reaction are examples of excitable media and share many similar properties (Winfree 2000; Winfree 1987). A ring of excitable medium can support a circulating excitation, often called a reentrant wave. Reentrant waves have been demonstrated in a large number of experimental and theoretical systems (Quan and Rudy 1990b; Rudy 1995; Courtemanche, Glass, and Keener 1993). They have a special importance to human health, since it is believed that many cardiac tachyarrhythmias (abnormally fast heart rhythms) are associated with reentrant mechanisms (see Chapter 7). There is a large cardiological literature that involves the resetting and entrainment of cardiac arrhythmia (Josephson et al. 1993; Gilmour 1990).

The previous section dealt with the resetting of a highly simplified model containing a stable limit cycle oscillation in a nonlinear ordinary differential equation. In this section we describe a highly simplified model to illustrate

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some of the main features as well as the subtleties that arise in the analysis of resetting and entrainment of periodic reentrant waves in nonlinear partial differential equations.

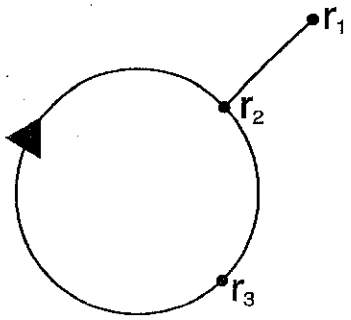

Figure 5.9. A simple model for reentrant excitation. The excitation travels at a fixed velocity around the ring and along the tail. From Glass, Nagai, Hall, Talajic, and Nattel (2002).

We assume that a wave circulates on a one-dimensional ring to which a "tail" has been added; Figure 5.9. The basic cycle length T_0 is given by

$$T_0 = \frac{L}{c},$$

where L is the circumference of the ring and c is the velocity of propagation. At any point on the ring, for a time interval of R after passage of the wave, the tissue is refractory. Otherwise, the medium is excitable. A stimulus delivered during the refractory period has no effect, whereas a stimulus delivered during the excitable period will generate waves propagating into the excitable medium. In the current presentation, I consider only the resetting as measured from a single site, which might be the same or different from the stimulation site. The current discussion is based on the analysis in Glass et al. (2002), which should be consulted for more details.

First, assume that the stimulus and recording site are both directly on the ring. We select this point as a fiducial point and assume that the circulating wave crosses the fiducial point at time t_0. The phase is $\phi(t) = (t - t_0)/T_0 \pmod 1$. The ring is parameterized by an angular coordinate, θ. We set $\theta = 0$ at the fiducial point so that the angular position of the wave around the ring at time t is $\theta(t) = \phi(t)$. This example has been set up so that the location of the wave on the ring is the same as the phase of the oscillation. This example is an interesting contrast to the Poincaré oscillator in which the trajectory was a closed circular path in the two-dimensional phase space. In this example, the trajectory is a closed circular path in two-dimensional physical space.

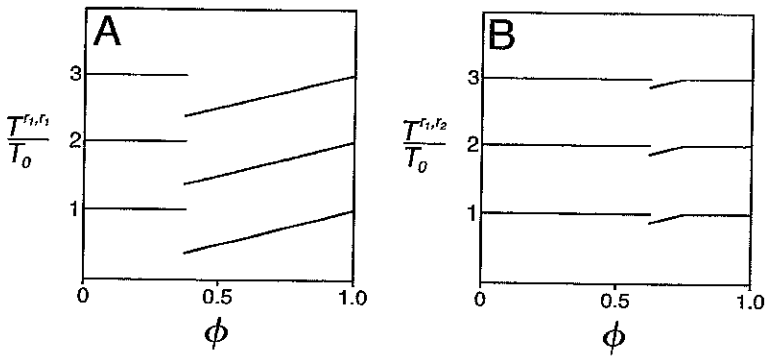

Figure 5.10. Resetting a reentrant wave in the simple geometry shown in Figure 5.9. The refractory period is $3T_0/8$, and the distance from r_1 to r_2 is $\frac{1}{4}$ the circumference of the circle. Panel A shows the effects of stimulation and measurement from point r_2, and panel B shows the effects of stimulation from point r_1 and measurement from point r_2.

If the stimulus is delivered during the refractory period, then it has no effect. If the stimulus is delivered outside the refractory time, then it will induce two waves, one traveling in the opposite (antidromic) and the other in the same direction (orthodromic) to the original wave. The antidromic wave will collide with it and be annihilated, whereas the orthodromic wave will continue to propagate, leading to a resetting of the original rhythm. The perturbed cycle length $T_j(\phi(t))$ is

$$\frac{T_j(\phi(t))}{T_0} = \begin{cases} j-(1-\phi(t)), & 1>\phi(t)>\frac{R}{T_0}, \\ j, & \frac{R}{T_0}>\phi(t)>0. \end{cases} \tag{5.12}$$

Using equation (5.1) we obtain the phase transition curve

$$g(\phi(t)) = \begin{cases} 0, & 1>\phi(t)>\frac{R}{T_0}, \\ \phi(t), & \frac{R}{T_0}>\phi(t)>0. \end{cases} \tag{5.13}$$

The time interval during which the stimulus resets the rhythm is called the **excitable gap**. The excitable gap is $G = T_0 - R$.

Iteration of equation (5.2) is easily carried out. Provided the stimulation period falls in the range $R < t_s < T_0$, there is a stable fixed point on the period-1 map, associated with entrainment of the reentrant excitation to the periodic stimulation. The phase of the fixed point is t_s/T_0.

Now consider the effect of stimulating the excitation from a point r_1 off the ring that lies at a distance l from the fiducial point r_2 on the ring and on the same radius as r_2; see Figure 5.9. Measurements are carried out at the point r_2. Because the conduction from the reentrant pathway can collide with the excitation from the stimulating electrode before it resets the reentrant excitation, the range of phases over which resetting is observed

is reduced. The perturbed cycle length is

$$\frac{T_j(\phi(t))}{T_0} = \begin{cases} j - 1 + \phi(t) + \frac{l}{cT_0}, & 1 - \frac{l}{cT_0} > \phi(t) > \frac{R}{T_0} + \frac{l}{cT_0}, \\ j, & \text{otherwise,} \end{cases} \tag{5.14}$$

and the associated resetting curve becomes

$$g(\phi(t)) = \begin{cases} 1 - \frac{l}{cT_0}, & 1 - \frac{l}{cT_0} > \phi(t) > \frac{R}{T_0} + \frac{l}{cT_0}, \\ \phi(t), & \text{otherwise.} \end{cases} \tag{5.15}$$

The range of values over which resetting occurs due to a single pulse decreases as the distance of the stimulus from the ring increases. Specifically, the excitable gap is $(T_0 - R - 2l/c)$. From this it follows that for $l > c(T_0 - R)/2$, there is no resetting. If the phase transition curve is used to predict the effects of periodic stimulation, then one theoretically predicts that there will be 1:1 entrainment for stimulation periods in the range $T_0 > t_s > R + 2l/c$. However, this is not correct, and in this case the resetting curve can no longer be used to predict the effects of periodic stimulation. The reason for this is that the collisions between the wave from the stimulus and the reentrant wave lead to a reduced range of values for the resetting. During periodic stimulation at a rate t_s in the range $T_0 > t_s > R$, the collisions between the waves originating from the periodic stimulation and the reentrant wave will occur successively closer to the reentrant circuit and the waves originating from the periodic forcing will eventually penetrate the reentrant circuit and entrain the reentrant wave (Krinsky and Agladze 1983; Biktashev 1997). Therefore, the theoretical prediction of the entrainment zone based on the resetting curve will underestimate the range of values leading to entrainment by a value of $2l/c$ for $l < c(T_0 - R)/2$. Thus, one can estimate the distance of a stimulus from the reentrant circuit by multiplying the discrepancy between the predicted and observed high-frequency boundaries of the 1:1 locking by the velocity of propagation of the wave, provided the stimulus is not very distant from the reentrant circuit.

Just as the Poincaré oscillator captures important aspects of nonlinear oscillators generated by ordinary differential equations, the current model captures some important aspects of dynamics in nonlinear partial differential equations that support reentrant excitation. The resetting curves shown in Figure 5.10 are discontinuous, similar to resetting curves observed from stimulation of the nonlinear FitzHugh–Nagumo equation of a pulse circulating on a one-dimensional ring (Glass and Josephson 1995; Nomura and Glass 1996) or a two-dimensional annulus (Glass, Nagai, Hall, Talajic, and Nattel 2002). By the continuity theorem discussed in Section 5.2.1 (p. 126), the observation of a discontinuity in the resetting curves has an important implication: that there should exist stimulation parameters that would lead to a transition so that the system no longer displays a single reentrant circulating wave (Glass and Josephson 1995; Gedeon and Glass 1998; Glass, Nagai, Hall, Talajic, and Nattel 2002). This type of annihilation is observed

in numerical studies. Further, the observation of the annihilation of ventricular tachycardia by a single pulse, shown in Figure 5.1, is consistent with this theoretical concept and also the theoretical interpretation that the ventricular tachycardia in the patient whose record is displayed in Figure 5.1 was generated by a reentrant excitation.

5.5 Resetting and Entrainment of Cardiac Oscillations

The computational machinery outlined above can be applied in practical situations. I will very briefly recount work from our group, and give references to more complete descriptions.

Extensive studies of the effects of single and periodic stimulation on spontaneously beating aggregates of embryonic chick heart cells have been carried out by Michael Guevara, Wanzhen Zeng, and Arkady Kunysz working in Alvin Shrier's laboratory at McGill University. The objective has been to determine the phase resetting behavior under single stimuli and to apply these results to compute the effects of periodic stimulation (Guevara et al. 1981; Guevara et al. 1986; Glass et al. 1983; Glass et al. 1984; Glass et al. 1987; Guevara et al. 1988; Zeng et al. 1990; Kowtha et al. 1994).

The results of the studies on the entrainment of the spontaneously beating aggregates of heart cells are summarized in Figure 5.11, which shows the different main locking regions using numerical iteration of experimentally determined resetting curves using the methods described above and shows examples of representative rhythms. The main findings of the experimental studies are:

- There are many different phase locking regions. For low to moderate stimulation amplitudes, the largest zones that can be readily observed in every experiment, are 1:1, 1:2, 3:2, 2:1, 3:1, 2:3. In addition, other zones corresponding to rational ratios $p : m$, where p and m are 4 or less, can usually be observed near the theoretically predicted region in Figure 5.11.

- For several different sets of stimulation amplitude and frequency there are aperiodic dynamics (Guevara, Glass, and Shrier 1981). There is a particular zone, using moderate stimulation amplitude and frequencies slightly less than the intrinsic frequency, that leads to period-doubling bifurcations and deterministic chaos. In this region, plots of ϕ_{i+1} as a function of ϕ_i based on the experimental data are approximately one-dimensional with characteristic shape associated with one-dimensional maps that give chaotic dynamics.

As a second example, I briefly recount more recent results from experiments in which reentrant excitation in an animal was subjected to single

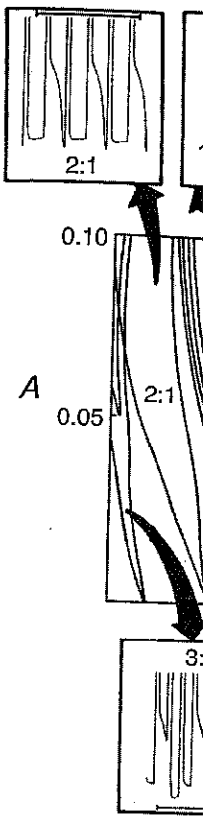

Figure 5.11. Locking
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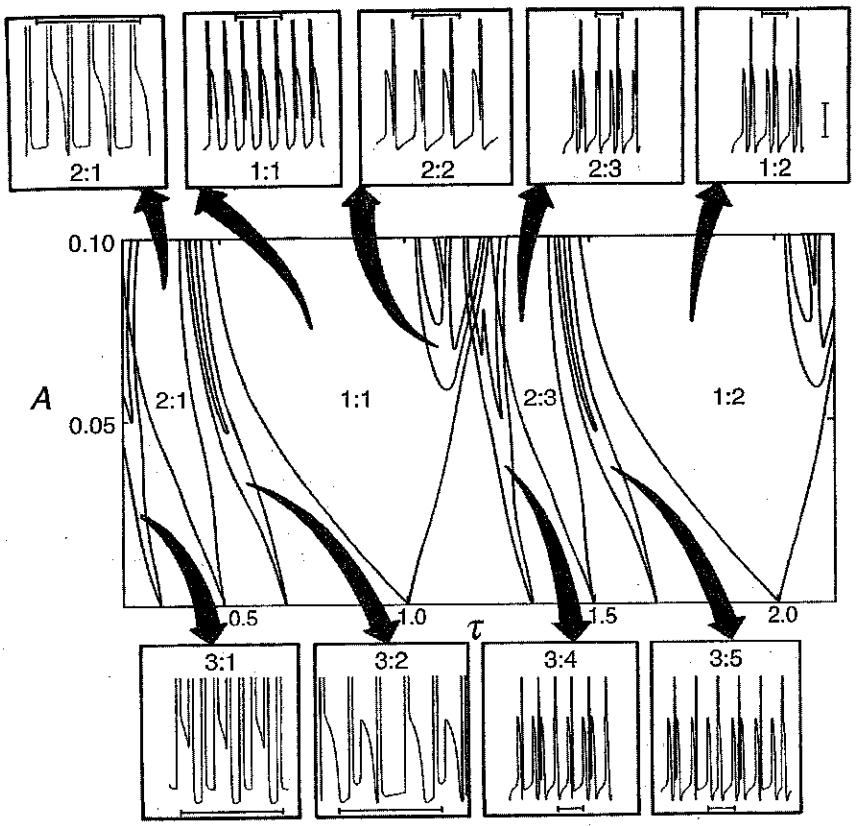


Figure 5.11. Locking zones for periodically stimulated heart cell aggregates. The computations are based on experimentally measured resetting curves. The time bar is 1 sec. Adapted from Glass, Guevara, and Shrier (1987).

and periodic stimuli carried out in the laboratory of Stanley Nattel at the Montreal Heart Institute; see Glass, Nagai, Hall, Talajic, and Nattel (2002), which should be consulted for full details.

Experiments were carried out in anesthetized dogs. One of the upper chambers of the heart, the right atrium, had incisions made that result in the establishment of a circulating excitation similar to the clinical arrhythmia atrial flutter. During the course of this rhythm, both single and periodic stimuli could be delivered from different places on the heart's surface, and the dynamics could be measured at other sites on the heart's surface. Figure 5.13 shows a schematic diagram of the surgery and the observed activity during the tachycardia.

During periodic stimulation the activity could be entrained in a 1:1 fashion over a broad range of stimulation periods ranging from 115 ms to 145 ms; Figure 5.14. However, the experimental determination of the reset-

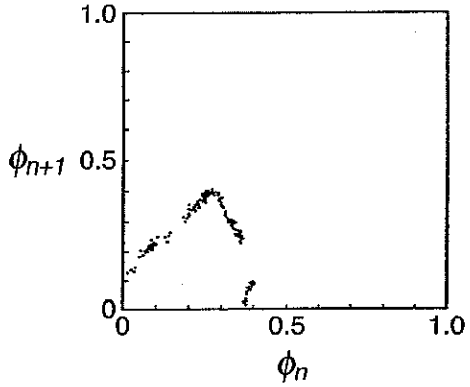


Figure 5.12. Return map for data obtained during aperiodic dynamics during periodic stimulation of spontaneously beating aggregates of chick hearts cells. The return map shows the phase of one stimulus plotted as a function of the phase of the preceding stimulus. This form for the map is similar to the quadratic map, which is known to give chaotic dynamics. Adapted from Glass, Guevara, Bélair, and Shrier (1984).

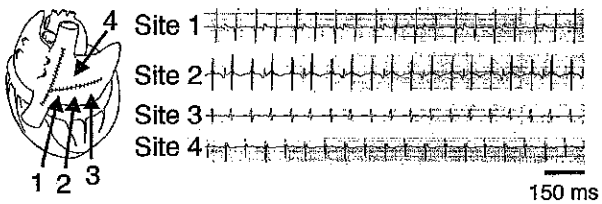
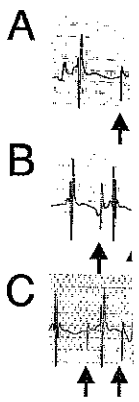


Figure 5.13. Schematic diagram of surgical procedures that led to the establishment of a reentrant rhythm in a canine model of human atrial flutter and electrical recordings from different sites in the heart during atrial flutter. From Glass, Nagai, Hall, Talajic, and Nattel (2002).

ting curve followed by the application of the theory in Section 5.2.2 led to the conclusion that 1:1 entrainment should be possible over a more limited range of stimulation periods from 130 ms to 145 ms. The failure of the resetting curve to predict the range of entrainment in this example likely arises because the stimulus is some distance away from the circuit responsible for the reentrant tachycardia.

5.6 Conclusions

Single stimuli reset or annihilate stable nonlinear oscillations. Periodic stimuli delivered during the course of nonlinear oscillations can lead to a wide range of different behaviors including quasiperiodicity, entrainment, chaos,



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Glass, Nagai, Hall, Talajic

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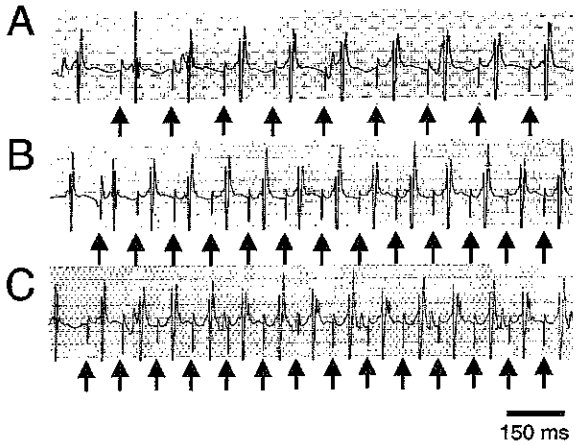

Figure 5.14. Experimental studies of the entrainment of atrial flutter with stimulation at site 4 and recording from site 2 in Figure 5.13. A. $t_s = 145$ ms, $t_s/T_0 = 0.97$; B. $t_s = 130$ ms, $t_s/T_0 = 0.0.87$; C. $t_s = 115$ ms, $t_s/T_0 = 0.77$. From Glass, Nagai, Hall, Talajic, and Nattel (2002).

and annihilation. Although the origin of all these different behaviors can be interpreted using the iteration of low-dimensional maps, our studies have shown that a number of different factors that exist in the real world tend to limit our ability to predict the effects of periodic stimulation using iteration of low-dimensional maps.

- *Stimulation can change the properties of the oscillation.* Although in numerical models, time constants are often very fast and the ongoing activity does not modify system properties, in experiments and in clinical circumstances the parameters of cardiac oscillations are modified under the rapid repetitive activity. Thus, the idealizations that the properties of oscillators are not affected by the stimulation need to be modified for a more complete analysis. Though such modifications have been implemented occasionally (Kunysz, Glass, and Shrier 1997; Vinet 1999), the simplicity of the one-dimensional circle map as a model for periodically forced biological oscillators is lost in the process, and the resulting models, though more realistic, are often less esthetically pleasing.

- *There can be slow relaxation times to the limit cycle.* Following a stimulus, the limit cycle is not necessarily reestablished prior to the time of the next stimulus (Zeng, Glass, and Shrier 1992). At fast stimulation rates, the finite relaxation time to the limit cycle may make it difficult to predict the effects of periodic stimulation based on resetting curves. Even in the Poincaré oscillator, when the relaxation time is finite, there are still only limited results on the fine

structure of the dynamics as a function of the stimulation frequency and amplitude (Glass and Sun 1994).

- *For systems distributed in space, the resetting may depend on the spatial location of the stimulus.* For limit cycle oscillations associated with reentrant excitation in space, the failure of an excitation to reset the oscillation may result from the blocking of a wave originating from the stimulus by a wave generated by the reentrant excitation. Since periodic stimulation from the same location might entrain the oscillation, there would be a failure to predict the effects of periodic stimulation using the information about resetting (Glass, Nagai, Hall, Talajic, and Nattel 2002).

To understand the resetting and entrainment of limit cycle oscillations in biological systems, there needs to be a mix of theory and experiment. Experimental studies of the effects of single and multiple stimuli delivered to biological oscillators yield beautiful data in which the timing of key events can be measured over time. Since the rhythms that are observed depend on the parameters of the stimulation (amplitude of stimuli, frequency of stimuli, number of stimuli, initial phase of stimuli), systematic studies are essential. This chapter has sketched out the basic mathematics that I believe is essential for understanding these experiments, and has given some examples where the methods have yielded unexpected results.

5.7 Acknowledgments

This chapter reviews work carried out with a number of colleagues. I have benefited greatly from these collaborations and give particular thanks to Michael Guevara, Alvin Shrier, Arthur T. Winfree, Zeng Wanzhen, Jiong Sun, Arkady Kunysz, Taishin Nomura, Stanley Nattel, Yoshihiko Nagai. This material has been presented at a number of summer schools held in a variety of locales including Salt Lake City, Montreal, Saō Paulo, Maribor, and Warsaw. I appreciate the feedback and interactions from the students which have helped me understand this work. The work has been supported by the Natural Sciences and Engineering Council of Canada, the Canadian Heart and Stroke Foundation, the Mathematics of Information Technology and Complex Systems Centre of Excellence (Canada), and the Research Resource for Complex Physiologic Signals funded by the National Institutes of Health, USA. Some of current chapter is based on an earlier presentation of the same material in (Glass 1997).

5.8 Problems

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5.8 Problems

Analysis of the following problems will facilitate understanding and may be useful for those who wish to do further research on these topics.

1. Suppose that you observe a biological oscillation with a period of oscillation that is quite stable; say there is a coefficient of variation of about 3%. Also assume that you have found a stimulus that can reset the oscillation, as measured by a marker event of the oscillation. For example, the stimulus might be a current pulse delivered to a neural or cardiac oscillation, and the marker event would be the onset of an action potential. How can the new phase induced by the stimulus be measured experimentally?

2. Annihilation of a limit cycle oscillation by a single stimulus can be fatal, if the oscillation is essential for life, or helpful, if the oscillation is a dangerous arrhythmia. Discuss the circumstances under which knowledge about the resetting curves of biological systems can be used to predict whether annihilation of a stable limit cycle oscillation using a single stimulus is possible. Critically discuss and contrast the postulated mechanisms for annihilation of limit cycles presented in Jalife and Antzelevitch (1979), Paydarfar and Buerkel (1995), and Glass and Josephson (1995).

3. The Poincaré oscillator provides a simple model that is amenable to significant algebraic analysis. The text gives the algebraic expression for the resetting curve, equation (5.7), and also the boundaries of the 1:1 locking regions in equations (5.8) and (5.9). Derive these equations.

4. Extending the results in the problem above to the finite relaxation case is difficult; the current state of the art is in Glass and Sun (1994). The problem is to analyze the loss of stability of the period-1 fixed points in the Poincaré oscillator with finite relaxation times as a function of the stimulation strength b and the relaxation k. It is necessary to keep in mind that there can be more than one fixed point for given parameter values, and that the initial condition is important. Good results would merit publication.

5. Experimental project. Select any biological or physical oscillation that can be reset using brief pulsatile stimuli. Determine the phase resetting curves for a range of stimuli and amplitudes, and the phase locking for a range of amplitudes and periods. Can the resetting curves be used to predict the effects of periodic stimulation? Careful studies would merit publication.

5.9 Computer Exercises: Resetting Curves for the Poincaré Oscillator

One of the simplest models of a limit cycle oscillation is the Poincaré oscillator. The equations for this model are

$$\frac{dr}{dt} = kr(1-r),$$
$$\frac{d\phi}{dt} = 2\pi, \tag{5.16}$$

where k is a positive parameter. Starting at any value of r, except $r = 0$, there is an evolution until $r = 1$. The parameter k controls the relaxation rate. In these exercises, we consider the relaxation in the limit $k \to \infty$.

Software

There are 2 `Matlab`* programs you will use for this exercise:

resetmap(b) This program computes the resetting curve (new phase versus old phase) for a stimulus strength **b**. The output is a matrix with 102 columns and 2 arrays. The first array is the old phase ranging from 0 to 1. There are two points just less than and just greater than $\phi = 0.5$. These points are needed especially for the case where $b > 1$. The second array is the new phase.

poincare(phizero,b,tau,niter) This program does an iteration of the periodically stimulated Poincaré oscillator, where **phizero** is the initial phase, **b** is the stimulation strength, **tau** is the period of the stimulation, and **niter** is the number of iterations. It is valid for $0 < \tau < 1$. The output consists of two arrays:

The first array (called **phi** in the following) is a listing of the successive phases during the periodic stimulation.
The second array (called **beats** in the following) is a listing of the number of beats that occur between successive stimuli.

How to Run the Programs

- To compute the resetting curve for $b = 1.10$, type

```
[phi,phiprime]=resetmap(1.10);
```

- To plot out the resetting curve just computed, type

```
plot(phi,phiprime,'*')
```

*See Introduction to `Matlab` in Appendix B.

- To simulate per

```
[phi,beat
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Exercises

Ex. 5.9-1. **Compute**
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Ex. 5.9-2. **Test the p**
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(a) Refer to Figu
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- To simulate periodic stimulation of the Poincaré oscillator, type

```
[phi,beats]=poincare(.3,1.13,0.35,100);
```

This will generate two time series of 100 iterates from an initial condition of $\phi = 0.3$, with $b = 1.13$ and $\tau = 0.35$. The array **phi** is the successive phases during the stimulation. The array **beats** is the number of beats between stimuli.

- To display the output as a return map, type

```
plot(phi(2:99),phi(3:100),'*')
```

This plots out the successive phases of each stimulus as a function of the phase of the preceding stimulus. The points lie on a one-dimensional curve. The dynamics in this case are chaotic. In fact, what is observed here is very similar to what is actually observed during periodic stimulation of heart cell aggregates described in the first chapter.

- To display the number of beats between stimuli, type

```
plot(beats,'*')
```

- The rotation number gives the ratio between the number of beats and the number of stimuli during a stimulation. This is the average number of beats per stimulus. To compute the rotation number, type

```
sum(beats)/length(beats)
```

Exercises

Ex. 5.9-1. **Compute resetting curves for varying values of b.** Use the program **resetmap** to compute the resetting curves for several values of b in the range from 0 to 2. In particular, determine the value of b at which the topology of the resetting curve changes. **Note:** The value $b = 1$ is a singular value, and the program does not work for that value. You could try to compute the analytic form for $b = 1$, or you could consult (Keener and Glass 1984) for the surprising answer.

Ex. 5.9-2. **Test the periodicity of iterates of phi.** Use the program **poincare** to compute the succesive iterates of **phi** for different values of (b, τ) and use the program **testper** (see lab 2.8) to determine whether or not the successive iterates of **phi** are periodic. You might wish to modify the programs so that they loop through several values of (b, τ). Stable periodic points correspond to stable patterns of entrainment between the stimulus and the oscillator.

(a) Refer to Figure 5.7. Select values of b and τ that are expected to give 1:1, 2:1, 3:2, 2:2 phase locking and try to confirm that these behaviors are in fact observed in the simulations. In doing this,

you should realize that the rotation number is given by the ratio of the number of action potentials to the number of stimuli.

(b) Find values for which there are different asymptotic behaviors depending on the initial condition.

(c) Find values of b and τ that give quasiperiodicity. How many iterates do you need to carry out to convince yourself that the behavior is quasiperiodic rather that periodic with a long period? Choose a value of $b > 0$.

(d) Find a period-doubling route to chaos.

Ex. 5.9-3. **Dynamics over the (b,τ) plane.** (Hard): Determine the dynamics over the (b, τ) parameter plane and draw a diagram with the results. You should get the diagram in Figure 5.7.

Ex. 5.9-4. **Dynamics of 2-D Poincaré oscillator with finite relaxation time.** (Research level). Consider the two-dimensional Poincaré oscillator, equation (5.16), with finite relaxation time (k is finite). Investigate the dynamics of this equation. What has been found out so far is in (Glass and Sun 1994).
Any good results on the following questions merit a research publication:

(a) What are the dynamics where the period-1 orbit becomes unstable? You need to get some analytic results giving particular consideration to the presence of subcritical and supercritical Hopf bifurcations.

(b) How many stable orbits can exist simultaneously? Describe the different stable periodic orbits for some subset of parameter space.

(c) For what range of parameter values are there chaotic dynamics?

(d) Give an analytic proof of chaos in this example and explore the routes to chaos.

Do you agree that it is important to understand this example as well as the ionic mechanisms of heart cell aggregates to understand the effects of periodic stimulation of the aggregates?

6

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