12. THE TOPOLOGY OF PHASE
RESETTNG AND THE
ENTRAINMENT OF LIMIT
CYCLES

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12.1 INTRODUCTION

Biological rhythms are ubiquitous. Their periods of oscillation range
from fractions of a second to a year. Independent of the period of the oscil-
lation 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 without the stimulus. Occasionally, a stimulus delivered during an oscil-
lation will terminate the oscillation, or lead to a different oscillation. Determin-
ing the response of an oscillator to perturbations administered at different
phases of the cycle can give important information about the oscillator, and
also may be useful in determining its behavior in the fluctuating environment.
It is likely that in every subarea of biology in which oscillations are observed,
there is a literature analyzing the oscillations from the idiosyncratic perspec-
tive of the particular discipline. Yet, from a mathematical perspective there is
a commonality of ideas and approaches (Pavlidis 1973; Guckenheimer 1975;
Glass and Winfree 1984; Winfree 1987; Glass and Mackey 1988).

The main notions are:

- Resetting can be measured experimentally as a function of the phase of
  the stimulus.

- Continuity and topological properties of the dynamical systems generat-
ing the oscillations are probed by the resetting experiments.

- If one assumes that the effects of a single stimulus are known as a func-
tion of its phase, then provided the stimulus does not change the prop-
ties of the oscillator, and there is rapid relaxation back to the original
oscillation, the effects of periodic stimulation at different frequencies can
be computed.
My object in this chapter is to sketch out the basic mathematical concepts pointing out a number of open problems and difficulties. The actual applications of the mathematics in concrete biological situations are widespread. Applications stressed here involve cardiac electrophysiology, but the same methods are equally applicable to perturbation of neural rhythms with electrical shocks, modulation of respiration by lung inflation, resetting the circadian rhythms of plants and animals by light (e.g., Winfree (1980); Winfree (1987); Glass and Mackey (1988)). However, only rarely is there a critical testing of the theory by comparing experimental observations with theoretical computations. Thus, there is a need for combined theoretical and experimental studies testing the applicability of these methods in specific applications.

12.2 MATHEMATICAL BACKGROUND

12.2.1 Isochrons and the perturbation of biological oscillations by a single stimulus

Since biological oscillations often have "stable" periods and amplitudes (coefficient of variation of the order of 3%), it is usual to associate the oscillation with a stable limit cycle in some appropriate nonlinear theoretical model (Winfree 1980). Recall 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 the neighborhood of the limit cycle (see Appendix B). 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 $\phi = t/T_0 \mod 1$. The phase here is defined to lie between 0 and 1; to convert it to radians, multiply it by $2\pi$.

An illustration of the concept of a limit cycle in a concrete experimental setting is shown in Figure 12.1. A single stimulus delivered to a spontaneously beating aggregate of cells from embryonic chick heart leads to a rapid reestablishment of the original oscillation. This is experimental evidence that the rhythm is being generated by a stable-limit-cycle oscillation.

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 $\phi$. Then, if in the limit $t \to \infty$,

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

the latent or asymptotic phase of $y(t)$ is also $\phi$. We say that $y(t)$ is on the same isochron as $x(t)$.

The development of the concept of isochrons and the recognition of their significance is due to Winfree (1980). Many important mathematical results concerning 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 isochron. Moreover, the dimension of the frontier of the basin of attraction is $\geq n - 2$. 
Figure 12.1. 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 $j$th 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 et al. (1992).)

We now consider the effects of perturbations delivered to the biological oscillation. Assume that a perturbation delivered to an oscillation at phase $\phi$ shifts the oscillation to the latent phase $g(\phi)$. The function $g(\phi)$ is called the phase transition curve. The following continuity rule summarizes important aspects of the effects of perturbations on limit-cycle oscillations: Provided the perturbation always leaves the system in the basin of attraction of the limit cycle, then the phase-transition curve $g(\phi)$ is a continuous circle map so that $g : S^1 \to S^1$. The continuity rule seems obvious, but as far as I know, a proof of it has not yet been published.

Since $g(\phi)$ is a circle map, it is characterized by its (topological) degree or winding number. The degree of $g(\phi)$ measures the number of times $g(\phi)$ wraps around the unit circle as $\phi$ goes around the circle once. For example, if the perturbation is very weak, $g(\phi) \approx \phi$, and the degree is 1. In many situations, as Winfree (1980) discusses, the degree is 0 when the stimulation is strong. If the degree 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.

These notions are directly related to experiment. The phase-transition 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 $\phi$ 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.
The phase-transition curve can be determined from the data given in Figure 12.2. It is given by

$$g(\phi) = \phi - \frac{T_j(\phi)}{T_0} \quad \text{(mod 1)}$$  

(12.1)

Winfree (1980) gives many examples of resetting biological oscillators. The degree of the experimentally measured phase-transition curve is usually 1 or 0, though in some cases it was discontinuous, see, for example, pages 172, 318, 383, 438, 456 in Winfree (1980). Though most experimentalists are not much bothered by discontinuities in resetting experiments, understanding their origin is a challenge (Glass and Winfree 1984). I return to a discussion of the significance of discontinuities in resetting experiments in a later section.

### 12.2.2 Phase locking of limit cycles by periodic stimulation

The effects of periodic stimulation of a nonlinear oscillator can be modeled by a nonlinear map. Earliest studies involved the computation of the effects of periodic stimulation on a stretch receptor (Perkel et al. 1964) and circadian rhythms (Pavlidis 1973). The methods have been applied to a broad range of other problems subsequently. For an introduction to the basic theory and extensive references, see Glass and Mackey (1988).

Consider the effects of periodic stimulation with period $t_s$ of a limit cycle with intrinsic period $T_0$. We assume that the stimulus instantaneously resets the oscillation, that the properties of the limit cycle are not affected by the stimulus, and that following the stimulus, the limit cycle is reestablished on a time scale that is fast compared to the period of stimulation $t_s$. Call $\phi_i$ the phase of stimulus $i$. Then, if the phase-transition curve is $g(\phi_i)$, the effects of
periodic stimulation are given by
\[ \phi_{i+1} = g(\phi_i) + \tau \mod 1 \equiv f(\phi_i, \tau) . \tag{12.2} \]
where \( \tau = t_i / T_0 \). Starting from an initial condition \( \phi_0 \), we generate the sequence of points \( \phi_1, \phi_2, \ldots, \phi_n \).

The sequence \( \{\phi_i\} \) is well defined, provided no stimulus results in a resetting to a point outside the basin of attraction of the limit cycle. If \( \phi_n = \phi_0 \) and \( \phi_i \neq \phi_0 \) for \( 1 \leq i < n \), where \( i \) and \( n \) are positive integers, there is a periodic cycle of period \( n \). A periodic cycle of period \( n \) is stable if
\[ \left| \frac{\partial f^n(\phi_0)}{\partial \phi} \right| = \left| \prod_{i=0}^{n-1} \left| \frac{\partial f}{\partial \phi} \right| \right| < 1. \tag{12.3} \]

The rotation number, \( \rho \), gives the average increase in \( \phi \) per iteration. Calling
\[ \Delta_{i+1} = g(\phi_i) + \tau - \phi_i, \tag{12.4} \]
we have
\[ \rho = \lim_{N \to \infty} \frac{1}{N} \sum_{i=1}^{N} \Delta_i. \tag{12.5} \]

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

### 12.3 THE POINCARÉ OSCILLATOR

We 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. However, it has been presented under a variety of other names in its 100-year history (Glass and Mackey 1988).

The Poincaré oscillator is probably the simplest differential equation that displays a stable-limit-cycle oscillation (Figure 12.3), and it has been considered many times as a model of biological oscillations (Winfree 1980; 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 help one 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 \( \phi \) is the angular coordinate. The equations are written
\[ \frac{dr}{dt} = kr(1 - r), \tag{12.6} \]
where \( k \) is a positive parameter. Starting at any value of \( r \), except \( r = 0 \), the solution approaches the circle \( r = 1 \). The parameter \( k \) controls the relaxation rate. To make the connection with experiments in cardiac electrophysiology, such as the one shown in Figure 12.1, I assume that the phase, \( \phi = 0 \), corresponds to the upstroke of the action potential or the onset of the contraction.

Since the rate of change of \( \phi \) 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 \( \geq (n-2) \), in accord with Guckenheimer’s theorem (see Figure 12.4(a)).

**Figure 12.3.** The phase plane for the Poincaré oscillator. (Reprinted from Glass and Mackey (1988).)

**Figure 12.4.** (a) Isochrons in the Poincaré oscillator. (b) A stimulus is assumed to induce a horizontal translation \( b \). Poincaré oscillator. (Reprinted from Glass and Mackey (1988).)

We assume that perturbations are modeled by a horizontal translation to the right by a distance \( b \) (Figure 12.4 (b)). In the experimental setting shown in Figure 12.1, the perturbation is an electrical stimulus that depolarizes the membrane. At stimulation time (afterwards), a triggering potential if it is
computed and is given by

$$g(\phi) = \frac{1}{2\pi} \arccos \frac{\cos 2\pi \phi + b}{(1 + b^2 + 2b \cos 2\pi \phi)^{1/2}} \text{(mod 1).} \quad (12.8)$$

In computations using (12.8), in evaluating the arccosine function, take $0 < g(\phi) < 0.5$ for $0 < \phi < 0.5$, and $0.5 < g(\phi) < 1$ for $0.5 < \phi < 1$. In Figure 12.5, I plot the perturbed cycle length and the phase-transition curve for the Poincaré oscillator. The results in Figure 12.5 should be compared with the experimental data in Figure 12.2.

\[\text{Figure 12.5. Perturbed cycle length and phase-transition curves for the Poincaré oscillator for weak and strong stimuli. (Reprinted from Glass and Winfree (1984).)}\]

The effects of periodic stimulation can now be computed by application of (12.2) and (12.8). The geometry of the locking zones is very complicated; a partial representation is shown in Figure 12.6. Here I summarize several important properties. For further details, the original references are recommended.
There are symmetries in the organization of the locking zones as originally derived in Guevara and Glass (1982). The symmetries are:

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

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

Symmetry 1 is satisfied in Figure 12.6. Using the translational symmetry, symmetry 2, the zones in Figure 12.6 can be expanded to cover the region $\tau > 1$.

I now summarize the 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.

$0 \leq b < 1$. The map is an invertible differentiable map of the circle (Arnold 1983). An *Arnold tongue of rotation number* $m/n$ is defined as the union of values in parameter space for which there is unique attracting $n : m$ cycle.
locking for $\tau'$, then there exists a value $\tau < \tau* < \tau'$, leading to $n + n': m + m'$ phase locking. Usually, the range of values of $\tau$ 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 quasi-periodicity. The organization of phase-locking zones for $0 \leq b < 1$ shown in Figure 12.6 for $b < 1$ is typical and is called the classic Arnold-tongue structure. The periodic orbits lose stability via a tangent bifurcation.

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 $\partial \phi_{i+1}/\partial \phi_i = 1$. This implies that at the boundary we have

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

from which we compute

$$b = | \sin 2\pi \tau | .$$  \hspace{1cm} (12.9)

The fixed point at the stability boundary is at

$$\phi_0 = \tau + \frac{1}{4}, \quad \text{for} \quad 0 < \tau < \frac{1}{4},$$  \hspace{1cm} (12.10)

and

$$\phi_0 = \tau + \frac{3}{4}, \quad \text{for} \quad \frac{3}{4} < \tau < 1.$$  \hspace{1cm} (12.11)

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

$$2 + b^2 + 3b \cos 2\pi \phi_0 = 0.$$  \hspace{1cm} (12.12)

Carrying through the trigonometry, we find the stability boundary

...
The fixed point at the boundary is given by

\[
\phi_0 = \tau + \frac{1}{2\pi} \sin^{-1} \sqrt{\frac{4 - b^2}{3b^2}}.
\] (12.14)

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 \(2 < b\), there is a change from 1:0 phase locking to 1:1 phase locking along the line \(\tau = 0.5\).

### 12.4 PERIODIC STIMULATION OF A CARDIAC PACEMAKER

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. The object 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. 1990b; Kowtha et al. 1994). The results of these studies are shown in Figure 12.7, which summarizes computations of the different locking regions by 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 which 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 \(n:m\), where \(n\) and \(m\) are 4 or less, can usually be observed near the theoretically predicted region in Figure 12.7.

- For several different sets of stimulation amplitude and frequency there are aperiodic dynamics (Guevara et al. 1981). A particular zone, using moderate stimulation amplitude and frequencies slightly less than the intrinsic frequency, leads to period-doubling bifurcations and deterministic chaos. In this region, plots of \(\phi_{i+1}\) as a function of \(\phi_i\) based on the experimental data are approximately one dimensional with characteristic shape associated with one-dimensional maps that give chaotic dynamics (Figure 12.8.)

### 12.5 BEYOND THE ONE-DIMENSIONAL MAP
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Figure 12.7. Locking zones for periodically stimulated heart-cell aggregates. The computations are based on experimentally measured resetting curves. The time bar is 1 sec. (Based on Glass et al. (1987).)

Figure 12.8. Return map for data obtained during aperiodic dynamics during periodic stimulation of spontaneously beating aggregates of chick-heart 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 et al. (1984).)
The relaxation of the cardiac pacemakers to the limit cycle is not instantaneous. Although the relaxation rate is rapid, estimated to be of the order of 100 msec (Zeng et al. 1992), it is nevertheless finite. This makes it of interest to consider the Poincaré oscillator in the finite-relaxation-time limit.

Entrainment of cardiac pacemakers at a rate different from their intrinsic frequency leads to changes in the intrinsic beating frequency (Vassalle 1977; Zeng et al. 1990a; Zeng et al. 1991; Kunysz et al. 1995; Kunysz et al. 1996). If the aggregate is phase locked to a frequency more rapid than its intrinsic rate, then, when the stimulator is turned off, the oscillation is slower than its intrinsic rate. This is called overdrive suppression. If the aggregate is phase locked to a rate slower than its intrinsic frequency, then, when the stimulator is turned off, the frequency is higher than the intrinsic frequency. This is called underdrive acceleration.

In this section, I briefly recount the ways we have been incorporating these factors into theoretical and experimental work. I first consider the effects of finite relaxation times on the Poincaré oscillator. I then consider overdrive during the stimulation of heart-cell aggregates.

### 12.5.1 Entrainment of the Poincaré oscillator with finite relaxation times

As before, assume that a stimulus is schematically represented by a horizontal translation of magnitude $b$ (Figure 12.4 (b)). The stimulus takes point $(r, \phi_i)$ to point $(r'_i, \phi'_i)$, where

\[ r'_i = (r_i^2 + b^2 + 2br_i \cos 2\pi \phi_i)^{1/2}, \]  
\[ \phi'_i = \frac{1}{2\pi} \arccos \frac{r_i \cos 2\pi \phi_i + b}{r'_i}. \]

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

\[ r_{i+1} = \frac{r'_i}{(1 - r_i') \exp(-k\tau) + r_i'}. \]
\[ \phi_{i+1} = \phi'_i + \tau \pmod{1}. \]

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 for the map, i.e., a period $\tau$ orbit for the flow. In contrast, in the infinite relaxation limit, for $b < 1$, inside the Arnold tongues associated with locking of period $n \neq 1$, there is no
Figure 12.9. Locking zones for periodically stimulated Poincaré oscillator with finite relaxation times, \( k = 10 \). Based on Glass and Sun (1994).

the Brouwer fixed-point theorem. Consequently, the result is also applicable to a broad class of periodically stimulated oscillators and excitable systems, provided there is a sufficiently large 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. After the 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 that occur at the intersection of the Arnold tongues with the line \( b = 1 \) have *not* “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 (1983); (see Fig. 153, p. 312 in Arnold (1983)).

### 12.5.2 Overdrive suppression

Phase locking of the heart-cell aggregates in a 1:1 fashion to periodic stimulation at a frequency faster than its intrinsic frequency leads to changes in the intrinsic frequency (Vassalle 1977; Zeng et al. 1990a; Zeng et al. 1991; Kunysz et al. 1995). When the stimulation is turned off, the intrinsic frequency of the aggregate is only weakly dependent on the duration of
the locking at the faster rate and on the rate itself. A simple theoretical model for overdrive suppression is that Na⁺ builds up inside cells during the rapid stimulation. When the stimulation is turned off, the excess Na⁺ is pumped out of the cells. The resulting (hyperpolarizing) current counteracts the pacemaker current slowing the beating rate until the normal Na⁺ level is reestablished (Kunysz et al. 1995; Kunysz et al. 1996).

The presence of overdrive suppression raises a difficult question concerning the application of the theory to concrete situations. How should we determine the phase of a stimulus? In the earlier work it was assumed that the phase of a stimulus is simply the time interval from the start of an action to the start of the stimulus divided by the intrinsic cycle length. But if the intrinsic cycle length changes as a consequence of the stimulation, what cycle length should be used? Moreover, if the properties of the oscillator are changed as a consequence of the stimulation, does this also induce changes in the resetting curves?

Although the answers to these questions are not yet satisfactorily understood, some advances have been made. In computing the phase of a stimulus, it is necessary to take in the current value of the cycle length as it has been altered as a consequence of the periodic stimulation.

Consider what happens during stimulation at a rapid rate, but at a rate which still leads to a 1:1 locking rhythm. During the course of the stimulation, the intrinsic frequency of the oscillator will gradually decrease — it will beat at a slower rate. Consequently, the effective phase of the stimulus will fall earlier and earlier in the cycle. However, if the phase falls too early, it can no longer lead to an immediate action potential and there will be a missed beat. Such behavior is observed and has been analyzed by consideration of the points discussed here (Kunysz et al. 1996).

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**Figure 12.10.** Bursting rhythms as a consequence of overdrive suppression during stimulation at a rate faster than the intrinsic rate. The time bar is 1 sec. (Based on Zeng et al. 1995.)
potential. The original theory would assume that each stimulus has an identical effect. However, even for the Poincaré oscillator in the finite relaxation limit, stimulation at a fixed delay can lead to complex bifurcations. In work recently completed (Kunysz et al. 1996), complex dynamics were observed during fixed-delay stimulation — particularly for stimuli of moderate amplitude delivered at phases near the transition from shortening to lengthening in the plots of the perturbed cycle time. Development of a theory necessarily entails consideration of both the scaling of the cycle length and the resetting curves.

12.6 INFINITE-DIMENSIONAL SYSTEMS

Until recently, the preceding theory had been applied solely to finite-dimensional systems. However, some of the results might be equally applicable to infinite-dimensional systems. I consider two different problems: the resetting of a delay differential equation for negative feedback, and resetting of a reentrant rhythm in a ring of excitable media.

12.6.1 Resetting oscillations in delay differential equations modeling negative feedback

In physiology, time delays often are an essential feature of the control systems. It is well known that time delays in negative-feedback systems can lead to oscillations. A familiar example is the cycling on and off of a furnace during a cold Canadian winter. There is a long delay between the time the furnace turns on and the time the temperature at the thermostat is raised. Similarly, when the furnace turns off, there is a subsequent time lag until the temperature at the thermostat falls beneath the set point. Negative feedback in a delay differential equation was presented as a model for haematopoiesis in Chapter 8 (see also Mackey and Glass (1977) and Glass and Mackey (1979)). In this context, let $x$ be the level of circulating blood cells, and $\tau$ a delay. Assuming that the destruction of the blood cells takes place at a rate proportional to their concentration in the blood, but that the production is a nonlinear monotonically decreasing sigmoidal function $f(x_{\tau})$ of the number of circulating cells $x_{\tau}$ at time $(t - \tau)$, we find

$$\frac{dx}{dt} = f(x_{\tau}) - x.$$  \hspace{1cm} (12.19)

From a purely mathematical perspective, there are many open questions concerning the properties of this class of delay differential equations, see Hale and Lunel (1993). For computations, I assume

$$f(x_{\tau}) = \frac{1}{1 + x_{\tau}^6}. \hspace{1cm} (12.20)$$

For $\tau = 10$ there is a stable oscillation of length about 21.9.

The start of the cycle is arbitrarily defined as $x = 0.75$, $dx/dt > 0$. The end is determined by $x_{\tau} = x_{\tau}$. Then, the asynchronous cycle is the time $t$ when $x(t) = x_{\tau}$.
shown in Figure 12.11. Notice that there is a long transient — so that it takes approximately 10 cycles for the transients to dissipate. This is not surprising in view of the time delays in this system. However, the phase-transition curve, defined from (12.1), is type 0 — a strong resetting curve. I am aware of only one prior computation of resetting of limit cycles in a delay differential equation (Johnsson and Karlsson 1971). In view of the extremely long transients in this system, it is unlikely that one could accurately predict the effects of periodic stimulation by iteration of the phase-transition curve. Since delay differential equations are often appropriate models for blood disorders (Mackey and Glass 1977; Glass and Mackey 1979); also see Chapter 8 in this volume for a detailed discussion and references), which are sometimes treated by periodic administration of drugs, additional study of the effects of periodic stimulation of delay differential systems would seem of interest.

![Graphs showing resetting behavior](image)

**Figure 12.11.** Resetting a limit cycle in a delay differential equation modeling negative feedback. The lefthand panel shows the time of successive starts of the cycle as a function of the phase of the stimulus. The righthand panel shows the associated phase-transition curve computed after all the transients are dissipated.

### 12.6.2 Resetting and entrainment of oscillations in partial differential equations

A second example of stable limit cycles in infinite-dimensional systems can be found in partial differential equations modeling excitable media. An excitable medium is one in which there is a large excursion from steady state in response to a small stimulus which 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 1980; 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 1990; Rudy 1995; Courtemanche et al. 1993). They have a special importance to
been recognized in cardiology that the methods developed to study resetting and phase locking might also be applicable to cardiology.

An initial attempt to apply this theory to a model system is given in two recent papers (Glass and Josephson 1995; Nomura and Glass 1996). I briefly summarize the main arguments and refer the reader to the original papers for full details.

The model system is the FitzHugh-Nagumo equations for excitable media (FitzHugh 1969):

\[
\begin{align*}
\frac{\partial v}{\partial t} &= -v(v - 0.139)(v - 1) - w + I + D \frac{\partial^2 v}{\partial x^2}, \\
\frac{\partial w}{\partial t} &= 0.008(v - 2.54w).
\end{align*}
\]  

(12.21)

where \( D \) is a diffusion coefficient, \( I \) is a time- and space-dependent injected current, and the parameters are from Rinzel (1977). Parameters consistent with values appropriate for cardiac conduction are: the circumference is \( L = 2 \times \sqrt{5} \) cm, \( D = 1 \) cm\(^2\)/sec, and cyclic boundary equations (Glass and Josephson 1995). The equations are integrated using the Euler method with \( \Delta t = 0.1 \) msec and \( \Delta x = 0.005L \). These equations support a single circulating wave rotating around a ring with a period of about \( T_0 = 356.1 \) msec. The stimulation (injected current) is applied at a single grid point of the discretized equations with a magnitude \( I \) for 10 iteration steps (1 msec). Let \( x_{\text{stim}} = 0.5 \) be the locus where current is injected. This stimulus has one of three different effects, depending on the phase of the stimulus in the cycle.

- **No effect.** This will happen if the stimulus falls in the excited region. The time interval during which the stimulus has little effect is called the refractory period.

- **Initiation of two waves.** This will occur if the stimulus falls during the time the tissue is excitable. This time interval is sometimes called the excitable gap by cardiologists. The waves will propagate in both directions around the ring. Collision of one of these waves with the original wave will lead to an apparent resetting of the original oscillation.

- **Initiation of a single wave traveling in an opposite direction to the original wave.** This will occur when the stimulus falls in a narrow window just after the excitation. This window is sometimes called the vulnerable window by cardiologists (Starmer et al. 1993). Initiation of a single wave will lead to an annihilation of the original wave following collision of the two waves.

The resulting resetting curves and phase-transition curves for stimulation of an excitation in a ring of tissue are shown in Figure 12.12. Although the above results were found from computer simulation, a recent paper has argued that there must be a range of stimuli that lead to annihilation of the original wave based purely on the continuity principle discussed earlier and the arguments and the basic properties of reentrant excitation (Glass and Josephson...
of periodic stimulation on a limit-cycle oscillation can be determined by iteration of the phase-transition curve just as was carried out in ordinary differential equations. Depending on the amplitude, the initial phase, the period of a train of stimuli, and the number of stimuli there can be either entrainment, resetting, or annihilation of a circulating wave. The dependence of these behaviors on the parameters in the model has a delicate structure that was not anticipated before the theory was carried out. The details are given in Nomura and Glass (1996). What is still missing is a clear demonstration that the theory really works in an experimental setting. I am confident that things will work out, but it is essential to carry out the experiments anyway.

One interesting aspect of this work is that resetting of reentrant excitations will always tend to be associated with discontinuous resetting curves. In view of the earlier observations that discontinuous resetting curves are often observed in experiments, it is possible that reentrant mechanisms might be a basic mechanism for a larger number of biological oscillators than is currently appreciated.

### 12.7 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 quasi-periodicity, entrainment, chaos, and annihilation. The origin of all these different behaviors can be found in the iterations of low-dimensional maps. The number of examples that have been worked out carefully is still small.

In this review I have tried to cover a broad range, discussing the effects of single and periodic stimulation on nonlinear oscillations in biological systems.
• The stimulation can change the properties of the oscillator. For example, I have mentioned the phenomenon of overdrive suppression, in which the intrinsic period of the oscillation is increased as a consequence of rapid stimulation. Further work is needed to determine the best methods to include these effects in theoretical models.

• The relaxation time to the limit cycle may be long. Even in the Poincaré oscillator, when the relaxation time is finite, a host of theoretical problems have been barely analyzed. For example, multistability, chaos, and the bifurcations by which the stable periodic orbits lose stability have not yet been carefully investigated.

• There is little analysis of geometrical aspects of resetting and entrainment of limit-cycle oscillation in infinite-dimensional systems. For example, the structure of isochrons in infinite-dimensional systems has not been studied. Experiments are needed to focus the theory.

In order 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 often yield unambiguous 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. Since the detailed biochemical and physiological mechanisms generating rhythms are certainly different in different systems, a global geometric approach based on the mathematics of oscillations is essential.

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