COMPLEX DYNAMICS RESULTING FROM REPEATED STIMULATION
OF NONLINEAR OSCILLATORS AT A FIXED PHASE

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Repeated stimulation of nonlinear oscillators at a fixed phase of the cycle leads to complex rhythms. This is illustrated using a theoretical example and a biological experiment.

Periodic stimulation with brief pulsatile stimuli of nonlinear systems exhibiting stable limit cycle oscillations generates a rich diversity of regular and irregular rhythms as stimulation frequency and amplitude are changed. Under the assumption that the limit cycle is strongly attracting and that there is a rapid (relative to the time interval between stimuli) return to the limit cycle following a single pulse, the dynamics can be analyzed using one-dimensional circle maps. Such a formalism has been applied to biological oscillators [1–3], chemical oscillators [4], and theoretical models [5–9].

An alternate approach to study nonlinear oscillators is to give repeated stimuli at a fixed phase of the cycle. If the limit cycle is very rapidly reestablished following a stimulus, then each stimulus will have the same effects as the preceding one, and a simple periodic rhythm with one stimulus per cycle of the perturbed oscillator will be found. If, however, there is not a rapid relaxation back to the limit cycle, a much more complicated situation arises. Although the phase resetting effects of a single stimulus have been intensively studied [10], the effects of repeated stimulation at a single phase have to the best of our knowledge only been examined in the context of neural stimulation of the heart [11,12]. In the following we show that repeated stimulation of nonlinear oscillators at a fixed phase leads to complex bifurcations and dynamics. This is illustrated by considering two different examples: a simple math-

ematical model and an experiment involving perturbation of the respiratory rhythm.

We consider the effects of stimulation at fixed phase of the simple limit cycle oscillation [6,8,10]

$$\frac{d\phi}{dt} = 1, \quad \frac{dr}{dt} = kr(1-r) . \tag{1}$$

This equation displays a stable limit cycle at $r=1$, which is globally attracting in the limit $t \to \infty$, for all points with the exception of $r=0$. In eq. (1) ϕ is normalized to lie between 0 and 1 and the period of the limit cycle is 1. A stimulus is assumed to be a horizontal translation of length S, fig. 1A. Therefore if a stimulus is delivered when the system is at (r_0, ϕ_0), there is an immediate displacement to (r', ϕ') where

$$r' = (r_0^2 + S^2 + 2r_0 S \cos 2\pi\phi_0)^{1/2} ,$$

$$\phi' = \frac{1}{2\pi} \cos^{-1} \left(\frac{r_0 \cos 2\pi\phi_0 + S}{r'} \right) . \tag{2}$$

The marker event, taken to be $\phi=0$, will occur following a time interval of $1-\phi'$. Thus, if a stimulus is given at a phase ϕ_0 with n cycles between stimuli, the time between stimuli is $t_s = 1 - \phi' + \phi_0 + n$. By integrating (1), for a time t_s we obtain

$$\phi_1 = \phi_0 + t_s \pmod 1 ,$$

$$r_1 = \frac{r'}{(1-r') \exp(-kt_s) + r'} , \tag{3}$$

where $(r_1, \phi_1) = (r_1, \phi_0)$ gives the coordinates at the
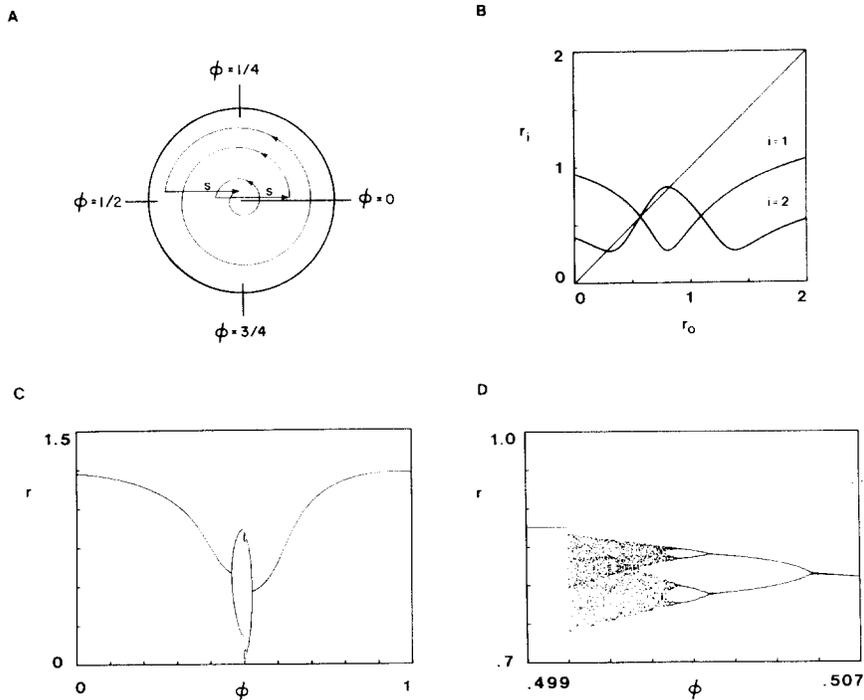
Fig. 1. (A) Graphical representation of the model. The limit cycle at $r=1$ is shown in the (r, ϕ) plane. The marker event is defined at $\phi=0$ (with ϕ ranging between 0 and 1). A stimulus consists of a horizontal translation of length S. A stable cycle of period two is shown. (B) One-dimensional map $(r_i=f(r_0))$ of (2) and (3) showing the first and second iterates, r_1 and r_2. Parameter values $\phi_0=0.48$, $S=0.8$, $k=1$, $n=0$ show a stable period-2 orbit. (C) Bifurcation diagram of solutions of (2) and (3) where r is the radius of the next stimulus as the phase, ϕ, is varied, at an increment of 0.001, from 0 to 1, with $s=0.8$, $k=1$, $n=0$. (D) The window of the bifurcation diagram in (C), between $\phi=0.499$ and $\phi=507$ with an increment $=0.00001$.

next stimulus. Note that by giving stimuli at a fixed phase the two-dimensional problem can be reduced to the one-dimensional map $r_{i+1}=f(r_i)$. In fig. 1b we show r_1 and r_2 as a function of r_0 for $\phi_0=0.48$, $S=0.8$, $k=1$, $n=0$. In this case, there is a stable cycle of period two. A bifurcation diagram showing r as a function of ϕ_0 for (2) and (3) for $S=0.8$, $k=1$, $n=0$ is shown in fig. 1C. In the region between $\phi_0=0.5$ and $\phi_0=0.506$ cascades of period-doubling bifurcations are seen, fig. 1D, but the global organization of the bifurcations is not fully understood. Similarly, if several cycles are skipped between stimuli, one can also obtain complex bifurcations as the stimulus phase is changed provided the relaxation rate, k, is not too large. In general, for any limit cycle oscillation in n dimensions, the effect of repeated stimulation at fixed phase can be described by an $(n-1)$-dimensional map. This example shows that even the simplest possible cases of two-dimensional limit cycles leads to

unexpectedly rich dynamics using this stimulation protocol.

We now consider a second example in which stimulation at fixed phase was undertaken in a physiological experiment. A complete report of these results will be published elsewhere. Experiments were performed on midcollicular decerebrate and paralyzed cats which were mechanically ventilated. The vagus nerves and the carotid sinus nerves were sectioned to eliminate feedback from the lungs and arterial baroreceptors to the respiratory rhythm generators in the brainstem. The respiratory rhythm is monitored from integrated (time constant $=100$ ms) phrenic nerve activity. The onset of phrenic activity (corresponding to the onset of inspiration in an unparalyzed animal) is taken as zero phase. The control cycle length, T_0, is the time between successive onsets, fig. 2A. Perturbation of the respiratory cycle is accomplished via stimulation of the superior lar-

Fig. 2. Experimental traces of integrated phrenic activity. Onset of inspiration is marked by the onset of the phrenic activity and expiration occurs while the phrenic is quiescent. One cycle consists of an inspiration followed by an expiration. Panel (A) shows unstimulated control cycles. Panels (B) to (F) show the effect of varying the delay of the SLN stimuli from the onset of phrenic activity (0.098 V pulses at 100 Hz, 50 ms trains). (B) 100 ms, (C) 200 ms, (D) 350 ms, (E) 650 ms, and (F) 825 ms. The bottom trace of each panel shows the stimuli. Time bar is 10 s for (A)–(F). Panel (G) shows control cycles for a different experiment in which alternans was observed with 9 unstimulated cycles between stimuli (panel (H)). The bottom trace of panel (H) shows SLN stimuli (100 ms delay, 0.1 V pulses at 200 Hz, 50 ms trains). Time bar is 30 s for (G) and (H). The delays were measured with an oscilloscope. The records were obtained on curvilinear paper (Grass Model 7D polygraph).

yngeal nerve (SLN). This nerve contains sensory axons originating in the larynx which have a marked effect on the respiratory rhythm [13]. An SLN stimulus of sufficient strength given during a phrenic burst will terminate it, and advance the onset of the nex burst resulting in a shortening of the cycle. SLN stimulation during the period when the phrenic nerve is quiescent delays the onset of the next burst and a consequent prolongation of the cycle.

When stimuli are delivered every cycle at fixed delay after phrenic onset (and hence at fixed phase), a number of different rhythms result which depend

on the stimulus strength and the delay at which the stimulus is delivered. Figs. 2B–2F show a sequence of rhythms observed as delay is increased. Typically, some of the phrenic bursts are shortened, whereas other are not markedly affected by the SLN activation. In some circumstances there is no evidence of a stable rhythm (figs. 2C, 2E). In other circumstances a stable rhythm is found. However, a period of time of up to a minute or more may be needed before the activity pattern stabilizes. In fig. 2D we show a segment of an alternating rhythm which was maintained stably for over three minutes, following a transient of 75 seconds. The last cycle before the stable alternans is shown at the start of the record. Alternans could also be observed even when stimulus was delivered regularly every several cycles (2–10). In fig. 2H we show an alternans found with stimuli delivered every 10 cycles with the 9 intervening unstimulated cycles having a cycle time approximately equal to control (fig. 2G).

The theoretical model and the experiments both show complex bifurcations which depend on the stimulus phase, stimulus magnitude and the number of cycles intervening between stimuli. Although it is tempting to associate the alternans in the experimental systems with period-doubling bifurcations observed in the model, no clear evidence of period-doubling bifurcations has yet been found in these experiments. The sequence of bifurcations in figs. 1C, 1D and fig. 2 are not the same. Therefore, the theoretical computations cannot be taken as a model for this experimental system. However, the experimental and theoretical results show that variables which do not affect the frequency of the rhythm (and are thus hidden) may nevertheless play an important role in characterizing the response of the oscillators to stimulation. Finally, this study shows that stimulation of nonlinear oscillators at fixed phase is expected to yield complex dynamics, and provides a further tool for theoretical and experimental analysis.

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