Entrainment and termination of reentrant wave propagation in a periodically stimulated ring of excitable media

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Excitable media, such as nerve, heart, and the Belousov-Zhabotinsky reaction, exhibit a large excursion from equilibrium in response to a small but finite perturbation. Assuming a one-dimensional ring geometry of sufficient length, excitable media support a periodic wave of circulation. In analogy with earlier results found from the periodic stimulation of oscillations in ordinary differential equations, the effects of periodic stimulation of the periodically circulating wave can be described by a one-dimensional map called the Poincaré map. Depending on the period and intensity of the stimulation as well as its initial phase, either entrainment or termination of the original circulating wave is observed. These phenomena are directly related to clinical observations concerning periodic stimulation of a class of cardiac arrhythmias caused by reentrant wave propagation in the human heart. [S1063-651X(96)08606-0]

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I. INTRODUCTION

Cardiac tachycardias are abnormal cardiac rhythms in which the heartbeat is too rapid [1,2]. It is believed that some tachycardias are caused by circulating excitation waves in the heart. Such waves are often called reentrant. In cardiology, it is common to imagine a reentrant wave as circulating on a one-dimensional ring [3–7]. This is the simple model of reentrant tachycardias that we adopt, though other geometries may prevail in some circumstances [8–11]. The prevention of the occurrence of tachycardia is a key objective in cardiology. A secondary objective is termination of tachycardias when and if they arise. A generation of implantable medical devices called ''antitachycardia pacers'' delivers a sequence of periodic electrical pulses directly to the hearts of patients who suffer from tachycardias. The effect of the implantable pacemaker depends on the location of the stimulating electrode in the heart, the number of pulses, the current in each pulse, the frequency of the periodic pulses, the initial phase of the first stimulus, and whether or not the rate of pulse delivery changes during the sequence [6,12]. Despite the importance of these questions to human health, the vast majority of clinical studies in this area are based on empirical evaluation of pacing algorithms, rather than an analysis of the fundamental theory.

We place this clinical problem in a more general context. The current paper deals with single and periodic stimulation of oscillations in nonlinear partial differential equations that can be used to model excitable media. Excitable media are defined by the following two properties [13–16]: (1) A small but finite perturbation away from a steady state will lead to a large excursion (an excitation or an action potential) before the steady state is reestablished; (2) following the onset of the excitation, there is an interval during which a perturbation does not induce a new excitation. The interval is called the refractory period. A consequence of the refractory period is that colliding waves annihilate each other.

Examples of excitable media include chemical media such as the Belousov-Zhabotinsky reaction [8,17], nerve [13–16], and heart [5,8,9,18]. We consider one of the simplest theoretical models for excitable media, the FitzHugh-Nagumo equation, which supports a periodically circulating wave of excitation if the excitable medium is in the form of a one-dimensional ring [15,16,18–20]. Although we could have selected a theoretical model that is more realistic for some particular setting [5,21], there should be broad similarities between dynamics in excitable media under single and periodic stimulation, independent of the details of the equations.

Analysis of the effects of single and periodic stimulation on spontaneously oscillating systems has played an important role in the development of modern dynamics [22]. Periodic stimulation of spontaneously oscillating systems can often be approximated by low-dimensional maps. For example, maps of the circle into itself f: $S^1 \rightarrow S^1$ often arise in the context of periodic stimulation of oscillating systems described by ordinary differential equations if the oscillating system displays a stable limit cycle that is strongly attracting. Extensive studies of periodic forcing of oscillations in biological and physical systems and in models formulated as ordinary differential equations demonstrated a variety of dynamical phenomena including entrainment, quasiperiodicity, and chaos [23–27].

Theoretical analysis of the effects of single and periodic stimulation of spatially distributed systems is much less developed. However, one important result is that a single stimulus delivered to a reentrant excitation on a one-dimensional ring will either reset or annihilate the excitation depending on the phase and amplitude of the stimulus [5,9,18]. In recent work, we used continuity arguments to show that annihilation of a reentrant wave in a one-dimensional ring by an appropriate single stimulus should be a general phenomenon, independent of the particular details of the nonlinear partial differential equation or physical or biological system supporting the excitation [20]. The current

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paper shows how these earlier results can be used to predict the effects of periodic stimulation.

The plan of this paper is as follows. In Sec. II, we discuss the mathematical foundation for this work. We discuss resetting of nonlinear oscillations using isolated stimuli, and the prediction of the effects of periodic stimulation using one-dimensional maps. In Sec. III, we study the resetting and annihilation of reentrant excitation in a one-dimensional ring by a single pulse. In Sec. IV we use these results to predict the effects of multiple stimuli. We compare the results found from iteration of one-dimensional maps to the results found from numerical integration of the appropriate nonlinear partial differential equation. The results are discussed in Sec. V.

II. MATHEMATICAL BACKGROUND

Single and periodic stimuli delivered to oscillating nonlinear systems have a range of effects. Most studies focus on perturbation of finite-dimensional systems that can be described by low-dimensional maps. In this section we review the basic theory and discuss its extension to reentrant waves in one-dimensional rings of excitable media. More detailed discussions of the theory as applied to ordinary differential equations are in [23–30].

A. Resetting of oscillations

Following a single perturbation of relatively short duration delivered to an oscillating system, the oscillation is often reestablished with the same period as before, but with altered timing of subsequent oscillations. This shift in the phase of the oscillation is called phase resetting or simply resetting.

Assume a dynamical system with a stable limit cycle γ with period T_0. We choose a marker event on the cycle. The phase at the marker event is taken as 0. The phase at any subsequent time $0<t<T_0$ is defined to be $\phi=t/T_0$. If a stimulus is delivered at a time δ following a marker event, the phase of the stimulus is δ/T_0.

The basin of attraction of γ corresponds to all states that approach γ in the limit $t\to\infty$. Each point $x\in\gamma$ has a stable set $W^s(x)$ defined as the set $\{y:\|x-\Psi(y,t)\|\to 0\}$ as $t\to\infty$, where $\|\cdot\|$ represents some metric defined on the solution space, and Ψ represents a flow of the system. For a state $y_0\in W^s(x)$, we can construct a sequence $\{y_0,y_1,\ldots,y_n,\ldots\}$ as $y_n=\Psi(y_0,nT_0)$. All the states are on $W^s(x)$, and the sequence converges to x as $n\to\infty$. The latent phase for all $y\in W^s(x)$ is ϕ where the phase of x is ϕ. The stable sets $W^s(x)$ are called isochrons. In finite-dimensional systems, Guckenheimer has proven that the stable set $W^s(x)$ of each $x\in\gamma$ is a cross section of γ and a manifold diffeomorphic to Euclidean space. Moreover, the union of the stable manifolds $W^s(x)$ for $x\in\gamma$ is an open neighborhood of γ and the stable manifold of γ [28].

An example may be useful in visualizing these ideas. Consider a two-dimensional ordinary differential equation with a single unstable steady state and stable limit cycle that is globally attracting for all points except the steady state. The isochrons are line segments that cut transversely across the limit cycle. The steady state is a singular point. All isochrons approach the neighborhood of the steady state.

In the current setting, the state of the system is associated with functions that give the values of the variables in the partial differential equation at all points along the ring. Nevertheless, we conjecture that the basic concepts from the finite-dimensional systems described above should still prevail.

The effect of a perturbation delivered during the course of the cycle is to shift the state off $x\in\gamma$ on isochron $W^s(x)$ to a perturbed state. If the perturbed state is in the basin of attraction of γ, the effects of the perturbation can be represented by a phase transition curve, $g(\phi)$, where ϕ is the phase of the initial state x at which the stimulus is presented, and $g(\phi)$ is the latent phase at the termination of the stimulus. If the differential equations for the perturbed system satisfy certain regularity conditions, and if all perturbed states for all $x\in\gamma$ are in the basin of attraction of γ, $g(\phi)$ is a continuous circle map g: $S^1\to S^1$ [28,29]. In some circumstances, the effect of a single stimulus is to shift the system outside the basin of attraction of γ. Although, in principle, stimulation may lead to a different periodic or aperiodic rhythm, the most usual finding is that if the oscillation is annihilated, and the system approaches a stable steady state. The phase transition curve $g(\phi)$ is not defined for those phases which lead to shifting an oscillation outside of its basin of attraction.

B. Periodic stimulation of oscillations

The phase transition curve can be used to predict the effects of periodic stimulation provided the following two conditions hold [23–27]: (1) The stimulation does not affect the parameters of the underlying system or the equation which may model it; and (2) the period of the stimulation is sufficiently long that following stimulation there is a return to the limit cycle.

We use the intrinsic cycle length T_0 to set the scale of time. Let τ be the normalized period of stimulation, d be the normalized duration of the stimulation, and I be the stimulation intensity. Suppose the first stimulation is applied at phase ϕ. The stimulus shifts the phase to $g(\phi)$ at the end of the stimulation. After an additional time $(\tau-d)$, the second stimulation is applied at phase ϕ'. Then ϕ' is

$$\phi'=g(\phi)+\tau-d(\mathrm{mod}\ \ 1)\equiv f_I(\phi;\tau). \tag{2.1}$$

$f_I:S^1\to S^1$ is a one-dimensional Poincaré map under the two assumptions above. We usually abbreviate $f_I(\phi;\tau)$ as $f(\phi)$.

For any given initial phase ϕ_0, we define inductively the sequence $\{\phi_i\}$ using the map $f(\phi)$:

$$\phi_i=f(\phi_{i-1})=f^2(\phi_{i-2})=\cdots=f^n(\phi_0).$$

The sequence ϕ_i is well defined, provided no stimulus falls in the range of values of (ϕ) that leads to annihilation of the oscillation. If $\phi_n=\phi_0$ and $\phi_i\neq\phi_0$ for $1\leqslant i<n$ with i and n being positive integers, ϕ_i is a periodic cycle of period n. We also say that the rhythm is entrained or phase-locked with period n. A periodic point of period n is stable if

$$\left|\frac{\partial f^n(\phi_0)}{\partial\phi}\right|=\prod_{i=0}^{n-1}\left|\frac{\partial f}{\partial\phi}\bigg|_{\phi_i}\right|<1. \tag{2.2}$$

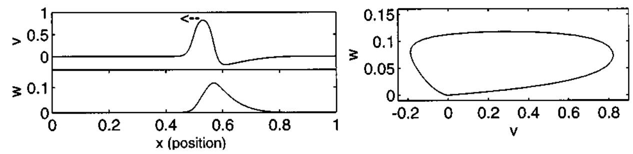

FIG. 1. (left panel) Numerically computed solution of the FitzHugh-Nagumo equation (3.1) as a function of ring position x (normalized to unit length). A single pulse propagates from right to left. We assume parameters in the text and cyclic boundary conditions. This represents $\phi=0$ (right panel). The projection of the solution into the (v,w) plane (right panel). As x increases, the coordinates of v and w as a function of x trace out a closed loop that is traversed in a counterclockwise direction. By rotational symmetry of the ring, this loop is invariant over time provided the wave is rotating stably.

III. RESETTING AND ANNIHILATION OF REENTRANT EXCITATIONS OF REENTRANT WAVES BY A SINGLE STIMULUS

In this section we consider the effects of a single stimulus on a reentrant wave. We consider the FitzHugh-Nagumo equations [13]

$$\frac{\partial v}{\partial t}=-v(v-0.139)(v-1)-w+I+D\frac{\partial^2 v}{\partial x^2},$$
$$\frac{\partial w}{\partial t}=0.008(v-2.54w), \tag{3.1}$$

where D is a diffusion coefficient, I is a time- and space-dependent injected current, and the parameters are from [15]. The FitzHugh-Nagumo equation is a generic model of excitable media. We choose parameters consistent with values appropriate for cardiac conduction. We assume the circumference is $L=2\times\sqrt{5}$ cm, $D=1$ cm^2/sec, and cyclic boundary equations [20]. The equations are integrated using the Euler method with $\Delta t=0.1$ msec and $\Delta x=0.005L$. We initiate a reentrant rhythm in which a single wave propagates by appropriate choice of initial conditions [20]. Figure 1 shows the numerically computed solutions of (3.1). In the left-hand panels, v and w are shown as a function of ring position x. In the biological context, v is analogous to the membrane voltage, and w is a variable that determines the refractory time. The projection of the solution into the (v,w) plane is shown in the right-hand panel. Because of the circular symmetry the projection in the (v,w) plane remains invariant over time. As x increases the projection in the (v,w) plane traces out a closed curve that is traversed once in the counterclockwise direction. As time evolves, the wave propagates from right to left in the left-hand panels. This direction of propagation is called the anterograde direction and the opposite direction of propagation is called the retrograde direction. The intrinsic cycle length of the reentrant excitation, is $T_0=356.1$ msec [20].

Let x_{rec} be a specific position in the ring. Since the ring has circular symmetry, $x_{rec}\in S^1$ is arbitrary. We choose $x_{rec}=0.5$. We define the phase as follows. Suppose the reentrant rhythm is stably circulating on the ring. Then we associate $t=0$, $\phi=0$ with the time when $v(x_{rec},t)$ increases through 0.5. This is the case shown in Fig. 1. Subsequent times $t>0$ are identified with phase $\phi=t/T_0$ (mod 1) of the reentrant rhythm.

We will apply stimulation (injected current) at a single grid point of the discretized equations with a magnitude I for 10 iteration steps (1 msec). Let $x_{stim}=0.5$ be the locus where current is injected.

If a stimulation is delivered at phase ϕ and if the reentrant rhythm is reestablished after the stimulation, successive excitations are observed at x_{rec} at times $T_1(\phi)$, $T_2(\phi),\ldots,T_j(\phi)$. If there is no resetting, we have $T_j=jT_0$. If there is resetting, then T_j-T_{j-1} should converge to T_0 for sufficiently large j since the reentrant rhythm is stable. For sufficiently large values of j, we define the phase transition curve based on the sequence T_j. We find

$$g(\phi)=\phi-\frac{T_j}{T_0}\ (\mathrm{mod}\ 1). \tag{3.2}$$

This means that the phase of the reentrant rhythm is shifted from ϕ to $g(\phi)$ when the stimulation is applied at ϕ [20,29,30]; see Sec. II. If the reentrant rhythm is reestablished following stimulation at any phase, the curve $g(\phi)$ is continuous. If the reentrant rhythm is annihilated for some stimulus phases, $g(\phi)$ is not defined for those phases leading to discontinuities in $g(\phi)$.

In excitable media, if stimulation is delivered when the system is at its steady state there will be an excitation induced if the stimulation is suprathreshold. If the stimulation intensity is decreased, a critical magnitude will be reached that will fail to generate a new excitation. Such a stimulus is called subthreshold. During the course of stimulation, the threshold separating subthreshold and suprathreshold stimuli, depends on the past history of the excitation. A medium that has recently been excited usually has a higher threshold than a fully recovered medium.

A. Suprathreshold stimulation

In a previous paper [20], we considered the effects of a single suprathreshold stimulus. Since these results form the foundation for this paper, we briefly review them here.

The effect of a stimulus depends on its phase in the cycle. If the stimulus is applied during the action potential it has negligible effect. The excitation continues to circulate and is not reset by the stimulus.

Suprathreshold stimuli delivered after the medium has fully recovered from a wave of excitation lead to two waves, one propagating in the anterograde direction and the other propagating in the retrograde direction. The dynamics in this case is illustrated in Fig. 2(a) which shows a series of traces at successive times following a stimulation at phase $\phi=0.70$. At $t=45$, there is a collision between the retrogradely propagating wave and the original wave. The collision leads to an annihilation of the original wave and the retrogradely propagating wave, leaving only the anterogradely propagating wave initiated by the stimulus. The projections in the (v,w) plane (right panels) show a complex progression eventually leaving only a single wave. The timing of the reentrant excitation is reset.

A stimulus that occurs in a narrow interval of phases following the action potential leads to annihilation of the reen-

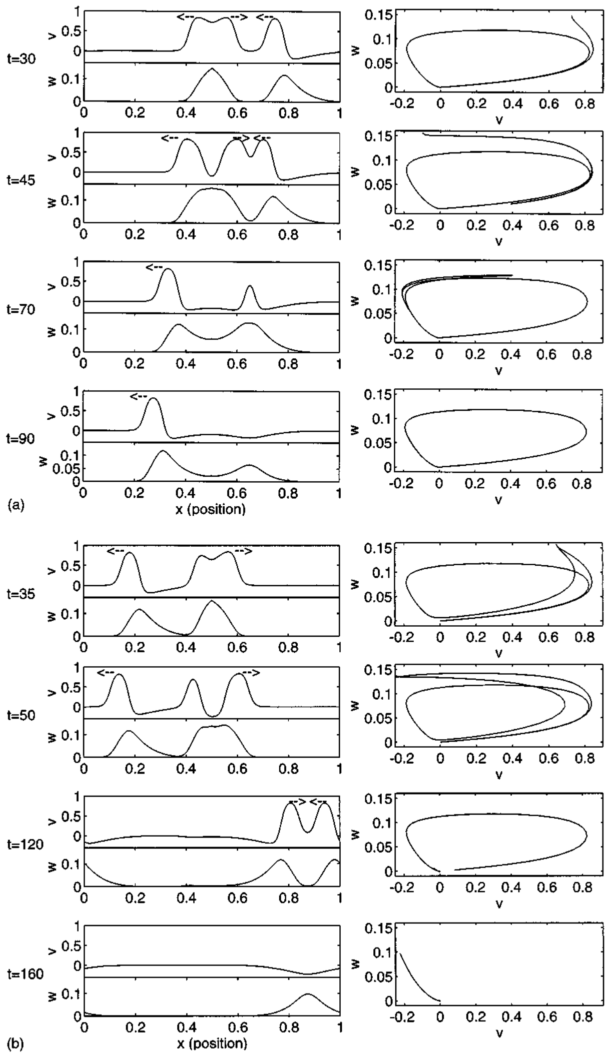

FIG. 2. Dynamics of phase resetting and annihilation using suprathreshold stimuli ($I=5.0$; duration of the stimulus is always 1 msec or 10 iteration steps). The panels are presented using the same format as in Fig. 1. The time following the onset of the stimulus is given at the left side of the figure. (a) Resetting with a pulse delivered at phase $\phi=0.70$. (b) Annihilation by a pulse delivered at phase $\phi=0.25$.

trant excitation [Fig. 2(b)]. A stimulus delivered at phase $\phi=0.25$ induces a wave that propagates only in the retrograde direction. When the retrograde wave collides with the original wave at $t=120$, the two waves annihilate each other and the medium returns to a resting state $t=160$. The projection of the dynamics to the (v,w) plane, Fig. 2(b) (right panels), gives insight into this process. The projection at $t=35$ shows a small gap opened up just above the origin. The curve is nevertheless continuous. As time progresses, the projection smooths out due to collisions of the waves, but the whole curve shrinks to a point. For analytic approaches to the phenomena described above see [16,18].

Figure 3(a) shows the resetting curve and Fig. 3(b) illustrates the associated phase transition curve for a suprathreshold stimulation intensity ($I=5.0$) based on Eq. (3.2). The curve has been shifted up by 0.5 to improve clarity. The curve is discontinuous, with the critical window around the

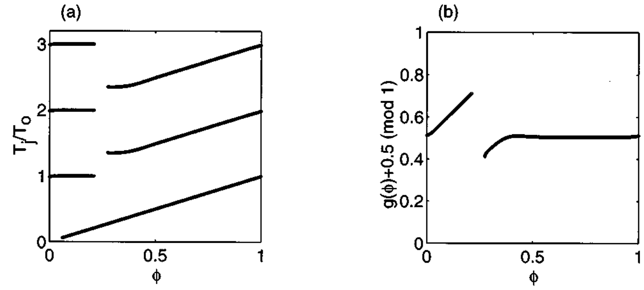

FIG. 3. (a) The normalized times of successive occurrences of action potentials T_j as a function of the phase of the stimuli with a suprathreshold stimulus ($I=5$). The wave circulation is annihilated if a stimulus is delivered within a critical window of phases. (b) Phase transition curve defined by Eq. (3.2). The curve has been shifted up by 0.5 to clarify presentation.

phase 0.25. The reentrant rhythm is terminated by stimulation applied at phases within the window. In [20] we argued that for suprathreshold stimuli, the same basic shape of the phase transition curve should be observed for a broad class of excitable media even though the detailed kinetics will differ from case to case.

B. Subthreshold stimulation

The situation is different for a subthreshold stimulation, $I=2.0$. For subthreshold stimulation, there is little effect for stimuli delivered over most of the cycle. However, a stimulus delivered in the time interval preceding the invasion of the reentrant wave will lead to its termination; see Fig. 4. The membrane potential in the neighborhood of the stimulation site is increased by the stimulation. Following the stimulation, the membrane potential decreases since the stimulation intensity is subthreshold. In parallel with this process, w at the stimulation site also increases; see the left-hand panels for $t=9.5$, $t=29.5$. This makes the tissue less excitable and the wave fails to propagate. In the right-hand panels, we see

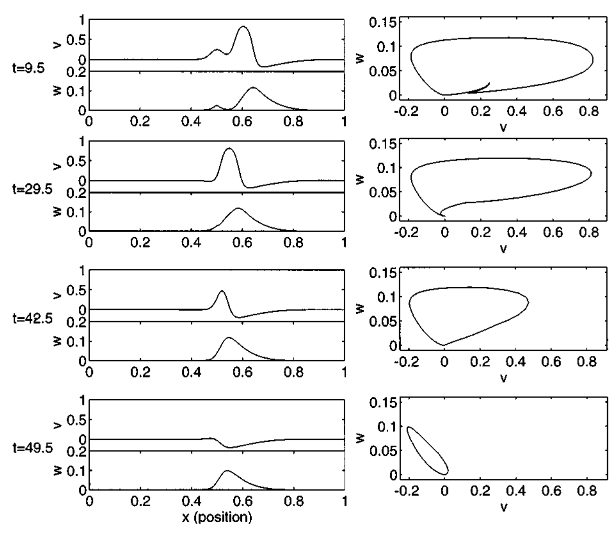

FIG. 4. Dynamics of annihilation using subthreshold stimulus ($I=2.0$) applied at the phase $\phi=0.90$. The same format as in Fig. 2 is used.

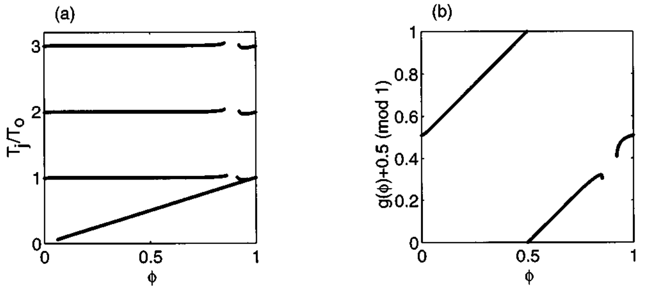

FIG. 5. Representation of resetting by a single stimulus using a subthreshold stimulus ($I=2$). The same format as in Fig. 4.

that the projections in the (v,w) plane develop a small kink near the origin, and the continuous curve is shifted slightly above the origin. The projection in the (v,w) plane shrinks to a point at the origin as time proceeds. The associated resetting curve is in Fig. 5(a). There is again a critical window that leads to annihilation but this window is around phase 0.9. Figure 5(b) illustrates the discontinuous phase transition curve for a subthreshold stimulation intensity. For clarity the curve is shifted up by 0.5.

IV. PERIODIC STIMULATION

In this section, we investigate the response of the reentrant wave in the FitzHugh-Nagumo equation to periodic stimulation. Then we show how these results can be accounted for using simple considerations based on iteration of the phase transition curves.

Periodic stimulation with suprathreshold stimuli leads to either leads to entrainment of the reentrant wave to the stimulus or annihilation of the reentrant wave. If there is entrainment of the reentrant wave there is a periodic rhythm in which the ratio of the number of stimuli to the number of rotations of the reentrant wave is a rational number.

A. Numerical studies of the FitzHugh-Nagumo equation

Stimulation is delivered at position x_{stim} with suprathreshold stimuli. I is taken to be 5.0 since this gives a typical form of the phase transition curve for suprathreshold stimulation intensities. Figure 6 shows examples of several different types of entrainment. When $\tau=0.402$ there is period 1 entrainment, when $\tau=0.285$ there is period 3 entrainment, and when $\tau=0.193$ there is period 2 entrainment. The basic cycle length of the reentrant wave is perturbed from the value it would have had without the periodic stimulation. Following cessation of the stimulation the original wave is reestablished with propagation in the same (anterograde) direction and period as before the stimulation. During the stimulation, the local appearance of the waveforms will depend on the site at which the activity is measured.

Stimulation can also lead to annihilation of the reentrant wave. As described in Sec. III, the annihilation will always be immediate if the initial stimulus falls in the critical window. However, if the first stimulus does not lie in the critical window, it is possible that a subsequent stimulus will nevertheless lead to annihilation. In Fig. 7(a) we show stimulation with a period of 1.293 with an initial phase of 0.9. Two stimuli (left panel) do not annihilate the reentrant wave,

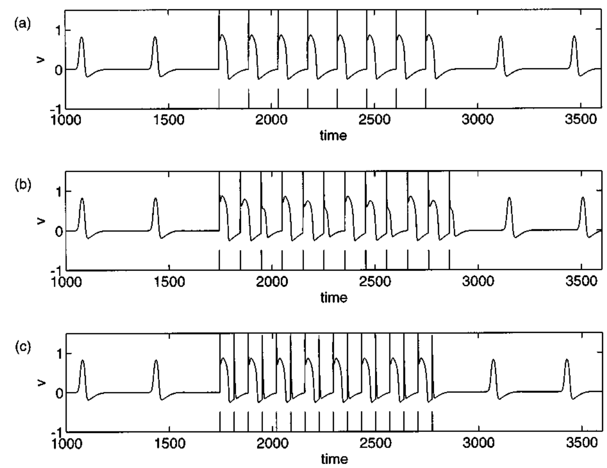

FIG. 6. Entrained reentrant waves by periodic stimuli. For each trace, the stimulus is suprathreshold ($I=5.0$), and the first stimulus is applied at $\phi=0.9$. When the periodic stimuli are terminated, the original reentrant wave is reestablished. (a) $\tau=0.402$. Period 1 entrainment. (b) $\tau=0.285$. Period 3 entrainment. (c) $\tau=0.193$. Period 2 entrainment. Time units are in sec.

whereas three stimuli do annihilate it (right panel). In Fig. 7(b), using a stimulus period of 0.293 [which is the same period as in panel (a) if the period is taken modulo 1], it also takes three stimuli to annihilate the oscillation.

For stimulation frequencies that lead to entrainment, some initial phases will nevertheless lead to annihilation of the reentrant wave. This annihilation can occur after either one stimulus or multiple stimuli. For example, in Fig. 6(b), we showed an entrainment rhythm with three stimuli for each circulating wave where the initial phase of stimulation was 0.9 and the period of stimulation was 0.285. However, had we selected the initial phase as 0.298, with the same period of stimulation, there would have been annihilation after two stimuli, Fig. 7(c).

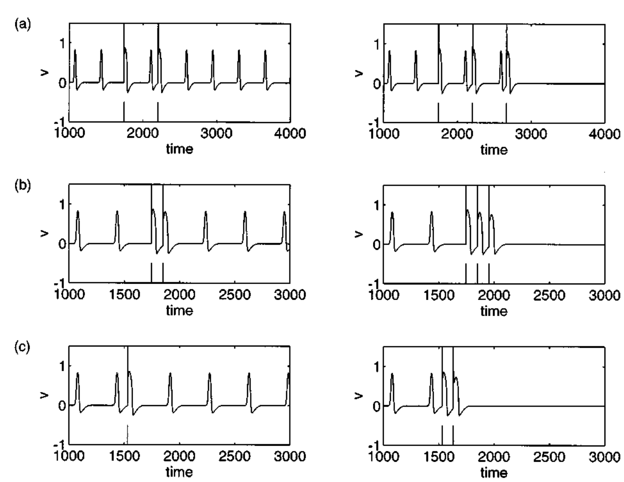

FIG. 7. Annihilation of reentrant waves using several stimuli. In the left-hand columns the periodic stimuli do not terminate the reentry. Adding an additional pulse (right-hand columns) leads to annihilation of the excitation. (a) $\tau=1.293$, $\phi_0=0.9$. (b) $\tau=0.293$, $\phi_0=0.9$. (c) $\tau=0.285$, $\phi_0=0.298$. Time units are in sec.

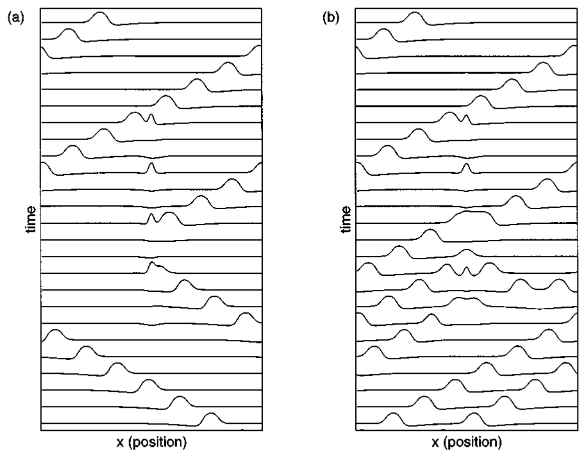

FIG. 8. Transitions out of the basin of attraction of the reentrant wave to basins of attraction of different attractors using high-frequency stimulation and suprathreshold stimuli ($I=5.0$). Successive traces shown show v as a function of x. Earliest time is at the top of the figure. Initially the wave is propagating from right to left. 20 stimuli of $\tau \approx 0.084$ are applied to the ring with an initial phase of $\phi_0 \approx 0.1$ starting at a time between the sixth and seventh traces. The initial phase of the simulations in the right- and left-hand panels differed by $\approx 1/3561$. (a) The original leftward propagating wave is annihilated and is replaced by a wave propagating to the right. (b) The original leftward propagating wave is replaced by a wave with two action potentials propagating to the left.

Although annihilation of the reentrant wave almost always led to the quiescent steady state, the theory does not exclude the possibility of initiation of a different oscillation [20]. This behavior was observed in the simulations but only rarely. In Fig. 8(a) we show the effects of 20 stimuli with period 0.084. The successive traces show the value of v along the ring at equal time intervals (the earliest time is at the top of the figure). Initially the wave is travelling from right to left (this is the anterograde direction). Stimulation is initiated between the sixth and seventh traces. Following cessation of stimulation, there is again a single reentrant wave on the ring—but it is traveling in the opposite (retrograde) direction to the initial wave. This case arose as a consequence of a complex sequence, in which the initial wave was first annihilated (ceasing stimulation after 10 stimuli leads to cessation of all activity), but then a new wave traveling in the opposite direction is initiated as a consequence of the interaction of the stimuli with the medium. In Fig. 8(b), 20 stimuli are again delivered with the same parameters as in Fig. 8(a), but with slightly different initial phase. In this case double wave reentry, in which two pulses are on the ring at the same time, is initiated by the stimuli. We show these traces because they pose interesting theoretical questions, and similar phenomena are observed in experimental and clinical settings. Experimental studies have demonstrated reversal of rotation of reentrant waves and initiation of double wave reentry following rapid periodic stimulation of reentrant waves [7].

Finally, using subthreshold stimuli, it is difficult to obtain entrainment. Rather, the usual circumstance is that there will be annihilation following some number of stimuli.

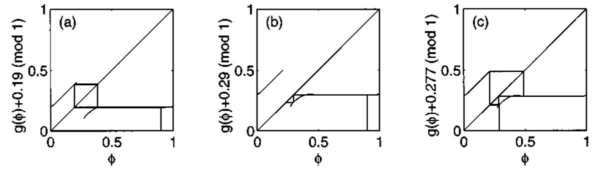

FIG. 9. Numerical iteration of the one-dimensional Poincaré determined from the resetting experiments. The maps can be used to predict the qualitative dynamics arising from periodic stimulation of the FitzHugh-Nagumo equation ($d \approx 0.003$). (a) $\tau=0.193$, $\phi_0=0.9$. This corresponds to the period 2 cycle in Fig. 6(c). (b) $\tau=0.293$, $\phi_0=0.9$. This corresponds to the annihilation in Fig. 7(b). (c) $\tau=0.285$. Starting from a phase of $\phi_0=0.9$ the orbit converges to a periodic orbit with period 3 [compare with Fig. 6(b)]. Starting from a phase of $\phi_0=0.298$ the orbit reaches the critical window after two iterations and is annihilated; compare with Fig. 7(c).

B. Analysis using the Poincaré map

The Poincaré map, Eq. (2.1), provides a basis for understanding the results presented above. The following two rules summarize the effects of periodic stimulation.

(1) If there is a stable periodic point in the Poincaré map, there will be stable entrainment of the periodically stimulated reentrant wave. All initial phases which approach the steady state of the map will lead to entrainment. The period of the entrainment is associated with the period of the steady state in the map.

(2) If the iterates of the Poincaré map land in the critical window after j iterates, then the reentrant wave will be annihilated after j stimuli.

The application of these rules is illustrated in Fig. 9. Figure 9(a) shows a period 2 orbit following a transient responses ($I=5.0$, $\tau=0.193$, $\phi_0=0.9$). The parameters correspond to those of Fig. 6(c). In this case, the phase of the stimuli alternate. Figure 9(b) corresponds to Fig. 7(b) ($I=5.0$, $\tau=0.293$, and $\phi_0=0.9$). The iterates land in the critical window after three stimuli leading to termination of the reentry. In this map, periodic stimulation starting from different initial phases will lead to different dynamics. Figure 9(c) illustrates an example in which $\tau=0.285$. The parameters are associated with those of Figs. 6(b) and 7(c). Starting from $\phi_0=0.9$ we obtain stable entrainment with period 3, while $\phi_0=0.298$ leads to termination after two iterates.

For a fixed stimulus intensity ($I=5.0$) the dynamics depend on both the period and the initial phase of the periodic stimuli. Figure 10 summarizes these dependencies found from numerical iteration of the Poincaré map. The horizontal axis is $\tau-d$ (mod 1), and the vertical axis is the initial phase ϕ_0 of the iteration. The symbols $p1$ and $p2$ designate period 1 and period 2 entrainment. Similarly, the numbers 1,...,5 in the regions indicate the number of stimuli that are needed to annihilate the reentrant rhythm. For example, the horizontal band labeled with a 1 represents annihilation by a single stimulus falling in the critical window. In the heavily shaded region around $\tau-d \approx 0.27$, period 3 entrainment regions and terminations by different numbers of stimuli are mixed in a complicated manner. The boundaries in this figure are simple consequences of the iteration of the one-dimensional map. For example, the region labeled 2 represents all combinations of period and initial phase that map to the critical win-

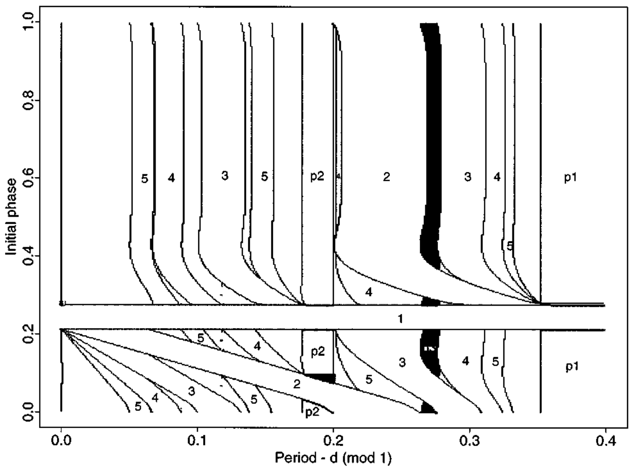

FIG. 10. Summary of dynamics of the periodically stimulated FitzHugh-Nagumo equation based on numerical iteration of the Poincaré map found for suprathreshold stimuli $I=5.0$. The symbols $p1$ and $p2$ designate periodic 1 and 2 entrainment. The numbers 1,...,5 in the regions designate the number of stimuli that are needed to annihilate the reentrant rhythm. In the heavily shaded region around $\tau-d\approx0.27$, period 3 entrainment region and terminations by several different numbers of stimuli are mixed.

dow in two iterations. Because of the simple structure of the map, this and other regions can be readily computed.

The results in Fig. 10 are based on iteration of the Poincaré map. Although we have not carried out a systematic analysis, these results also give an accurate representation of the periodic stimulation of the partial differential equation over a broad frequency range for which we have done sample computations. However, for high-frequency stimulation (Fig. 8) the dynamics do not have time to relax to the attractor between stimuli, and the predictions of the map are not accurate.

Thus, periodic stimulation of a nonlinear partial differential equation supporting stable oscillations caused by a circulating reentrant wave on a one-dimensional ring can be understood to a first approximation by the iteration of a one-dimensional map based on the resetting of the reentrant wave by a single pulse.

V. DISCUSSION

A ring of excitable medium can support a circulating reentrant wave which will either be reset or annihilated by a single stimulus. In this paper we have shown that once we know the effects of a single stimulus as a function of its phase, we can predict the effects of multiple stimuli by iteration of an appropriate one-dimensional map. In most circumstances, annihilation or entrainment will result depending on the initial phase of the stimulus, the amplitude of the stimulus, the number of stimuli, and the period of the stimuli. There is close agreement between the numerical integration of a nonlinear partial differential modeling excitable media, and iteration of the associated Poincaré map. These results are interesting from a perspective of the underlying theory as well as medical applications.

The basic theory that is sketched out in Sec. II was developed specifically for the periodic forcing of limit cycle oscillators in finite-dimensional systems [23–30]. In ordinary differential equations, it is often easy to get a complete picture of the flow in phase space. When the limit cycle is strongly attracting and the stimulation does not affect the properties of the limit cycle oscillation, the one-dimensional map provides a good description of the dynamics under periodic stimulation.

For infinite-dimensional systems such as we have here, the current state is defined by functions defined on the ring. The ring can support many attractors. For example, the different attractors include the steady state, a single wave propagating clockwise or counterclockwise around the ring, and solutions with two or more propagating pulses traveling simultaneously in the same direction. Each of the different attractors has its own basin of attraction. The basins of attraction of the oscillating systems are foliated by isochrons. The boundaries between the basins is of crucial importance in determining the stability of oscillations and steady states to perturbations. We conjecture that oscillating solutions can be characterized by an index, e.g., $+1$, -2, which indicates the number of propagating pulses in the ring at a given time and their direction. The index would be an invariant of all functions in the basin of attraction of a given attractor. Although we have been unable to find an appropriate definition of the index, we expect the projection of the functions on the ring to the (v,w) plane, e.g., right-hand panels in Figs. 2 and 4 are a good place to start. We have tried to define an index by computing the winding number of the projections in the (v,w) plane about points slightly displaced from the origin, but have been unable to come up with a suitable definition that is appropriate for the many trials we have tested.

In medicine, it is well known that it is possible to terminate and entrain reentrant tachycardias by single or periodic stimulation and many of the simulations here are similar to clinical recordings [1,2,4,6,7,11]. There is a family of implantable cardiac devices that terminate tachycardias [12]. Although some theoretical modeling of these phenomena has been carried out [5,9,11] we are not aware of earlier studies that use resetting of tachycardias to predict the effects of multiple stimuli. Thus, although it is well known in cardiology that a train of stimuli will lead to resetting, entrainment, or annihilation of tachycardias, it is not recognized that this range of phenomena can be captured by very simple iterative models.

The current work therefore suggests quantitative cardiological studies in which data from resetting experiments is used to predict the effects of multiple stimuli. Such studies might have practical utility if they could lead to better fine tuning of medical devices since battery life is an important factor in implantable devices. In this regard it is interesting that low-amplitude–low-frequency stimulation should also be able to annihilate reentrant excitation, since this might be desirable in many settings. Also, better means of interpreting clinical protocols that use resetting and entrainment, might lead to better localization of anatomical sites involved in tachycardia generation.

However, it is inevitable that quantitative tests of the theoretical approach outlined here will lead to some discrepancies with experimental and clinical studies. Since the real heart is a complex three-dimensional structure with anatomical and physiological heterogeneity, it might seem preposterous to believe that these methods will have any applicability. However, the many correspondences between the theoretical results and the clinical results invite further investigation. A better understanding of the basic physics and mathematics of resetting and entrainment of reentrant tachycardias in a one-dimensional ring should help the cardiologist to understand the mechanisms of tachycardia and to develop better therapies for these dangerous rhythms.

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[1] M. E. Josephson, *Clinical Cardiac Electrophysiology: Techniques and Interpretation,* 2nd ed. (Lea & Febiger, Philadelphia, 1993).

[2] E. N. Prystowsky and G. J. Klein, *Cardiac Arrhythmias: An Integrated Approach for the Clinician* (McGraw-Hill, New York, 1994).

[3] G. R. Mines, Trans. R. Soc. Can. **4**, 43 (1914).

[4] R. Ruffy, K. J. Friday, and W. F. Southworth, Circulation **67**, 457 (1983); J. M. Almendral *et al.*, J. Am. Coll. Cardiol. **8**, 294 (1986); W. G. Stevenson *et al.*, Circulation **80**, 793 (1989); M. Malik and A. J. Camm, PACE **13**, 103 (1990); R. C. Bernstein and L. H. Frame, Circulation **81**, 267 (1980).

[5] W. Quan and Y. Rudy, Circ. Res. **66**, 367 (1990); PACE **14**, 1700 (1991); Y. Rudy, J. Cardiovasc. Electrophysiol. **6**, 294 (1995).

[6] M. E. Josephson *et al.*, in *Tachycardia: Mechanisms and Management,* edited by M. E. Josephson and H. J. J. Wellens (Futura, Mount Kisco, 1993), pp. 505–536; D. J. Callans, B. G. Hook, and M. E. Josephson, Circulation **87**, 1229 (1993).

[7] L. Boersma, J. Brugada, C. Kirchof, and M. Allessie, Circulation **88**, 1852 (1993).

[8] A. T. Winfree, Science **175**, 634 (1972); *When Time Breaks Down* (Princeton University Press, Princeton, 1987); Nature **371**, 233 (1994).

[9] V. I. Krinsky, V. N. Biktashev, and A. M. Pertsov, Ann. N. Y. Acad. Sci. **591**, 232 (1990).

[10] J. M. Davidenko, A. M. Pertsov, R. Salmonsz, W. Baxter, and J. Jalife, Nature **355**, 349 (1992).

[11] J. M. Davidenko, R. Salomonsz, A. M. Pertsov, W. T. Baxter, and J. Jalife, Circ. Res. **77**, 1166 (1995).

[12] J. D. Fisher, S. G. Kim, J. A. Matos, and L. E. Waspe, in *Cardiac Electrophysiology and Arrhythmias,* edited by D. P. Zipes and J. Jalife (Grune and Stratton, Orlando, 1985), pp. 507–511; J. D. Fisher, in *Electrical Therapy for Cardiac Arrhythmias: Pacing, Antitachycardia Devices, Catheter Ablation,* edited by S. Saksena and N. Goldschlager (Saunders, Philadelphia, 1990), pp. 411–423. These papers summarize the clinical literature concerning antitachycardia pacers and give extensive references to the clinical literature.

[13] R. FitzHugh, in *Biological Engineering,* edited by H. P. Schwan *et al.* (McGraw-Hill, New York, 1969).

[14] J. Rinzel and J. B. Keller, Biophys. J. **13**, 1313 (1973).

[15] J. Rinzel, *Research Notes in Mathematics. Nonlinear Diffusion,* edited by W. E. Fitzgibbon III and H. R. Walker (Pitman, London, 1977), pp. 186–212.

[16] J. P. Keener, SIAM J. Appl. Math. **39**, 528 (1980).

[17] Z. Noszticzius, W. Horsthemke, W. D. McCormick, H. L. Swinney, and W. Y. Tam, Nature **329**, 619 (1987). Rotating waves, similar to those described here, were observed in an annular chemical reactor.

[18] C. F. Starmer *et al.*, Biophys. J. **65**, 1775 (1993); J. Starobin, Y. I. Zilberter, and C. F. Starmer, Physica D **70**, 321 (1994).

[19] K. Maginu, J. Math. Biol. **6**, 49 (1978); **10**, 133 (1980).

[20] L. Glass and M. E. Josephson, Phys. Rev. Lett. **75**, 2059 (1995).

[21] M. S. Courtemanche, L. Glass, and J. P. Keener, Phys. Rev. Lett. **70**, 2182 (1993); A. Vinet and F. Roberge, Ann. Biomed. Eng. **22**, 568 (1994).

[22] J. Guckenheimer and P. Holmes, *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields* (Springer-Verlag, New York, 1986); see in particular pp. 67–82.

[23] M. R. Guevara, L. Glass, and A. Shrier, Science **214**, 1350 (1981); M. R. Guevara and L. Glass, J. Math. Biol. **14**, 1 (1982); L. Glass, M. R. Guevara, J. Bélair, and A. Shrier, Phys. Rev. A **29**, 1348 (1984).

[24] D. L. Gonzalez and O. Piro, Phys. Rev. Lett. **50**, 870 (1983).

[25] T. Bohr, P. Bak, and M. H. Jensen, Phys. Rev. A **30**, 1970 (1984).

[26] N. Takahashi, Y. Hanyu, T. Musha, R. Kubo, and G. Matsumoto, Physica D **43**, 318 (1990).

[27] T. Nomura, S. Sato, S. Doi, J. P. Segundo, and M. D. Stiber, Biol. Cybern. **69**, 429 (1993); **72**, 55 (1994); **72**, 93 (1994).

[28] J. Guckenheimer, J. Math. Biol. **1**, 259 (1975).

[29] M. Kawato and R. Suzuki, Biol. Cybern. **30**, 241 (1978); M. Kawato, J. Math. Biol. **12**, 13 (1980).

[30] A. T. Winfree, *The Geometry of Biological Time* (Springer-Verlag, New York, 1980).