Resetting and Annihilation of Reentrant Abnormally Rapid Heartbeat

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Excitable media support circulating waves on a one-dimensional ring. Continuity arguments, developed originally for resetting limit cycle oscillations in finite-dimensional dynamical systems, suggest that there must exist a range of phases and amplitudes for perturbations of the reentrant wave that lead to its annihilation. The annihilation is illustrated in the Fitzhugh-Nagumo equation of excitable media. This phenomenon is related to clinical studies in which reentrant waves in the human heart are reset or annihilated by electrical stimulation delivered directly to the heart.

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In the normal heart the rhythm is set by an autonomous pacemaker, the sinoatrial node [1,2]. Cardiac arrhythmias are heart rhythms in which the generation and/or the propagation of the cardiac impulse are abnormal. In one class of cardiac arrhythmia, called reentrant tachycardias, there is an abnormally rapid heartbeat whose period is set by the time that an excitation takes to travel in a circuitous path [1–3]. A single electrical stimulus delivered to a human heart during reentrant tachycardia can have various effects including termination or resetting of the rhythm [1,4]. In this Letter, we offer an interpretation of these clinical observations by assuming a highly simplified model of reentrant tachycardias in which a nonlinear partial differential equation represents the circulation of a wave of excitation on a one-dimensional ring [5–8]. Numerical simulations and continuity arguments lead us to conjecture that a general property of such models is that there should exist ranges for the amplitude and phases of delivery of a stimulus that will lead to annihilation of the tachycardia.

An excitable medium is characterized by the following two properties. (1) A small but finite perturbation away from a steady state will lead to a large excursion (an excitation) before the steady state is reestablished. This excitation is associated with an action potential in nerve [9] or heart [5,10] and an oxidation wave in the Belousov-Zhabotinsky reaction [11]. The onset of the excitation is called the *excitation time*. (2) Following the start of the excitation there is a time interval during which a perturbation does not induce a new excitation—this interval is called the *refractory period*. Generally, the velocity of an excitation wave will be slowed if it follows too closely after a preceding wave [7,8]. Further, it follows from the refractory properties of excitable media that two waves in an excitable medium will not pass through each other but will annihilate themselves if they collide.

The above notions can be illustrated by consideration of the Fitzhugh-Nagumo equation, a nonlinear partial differential equation that is a prototypical model of excitable media [9,10],

$$\frac{\partial v}{\partial t} = -w - v(v - 0.139)(v - 1) + D\frac{\partial^2 v}{\partial R^2} + I(R),$$

$$\frac{\partial w}{\partial t} = 0.008(v - 2.54w), \qquad (1)$$

where D represents the diffusion coefficient, $I(R)$ represents injected current (the perturbation) at position R, and the parameters are from [9]. In the homogeneous equations ($D = 0$) with no injected current, there is a globally stable steady state at $v = 0, w = 0$. In response to a sufficiently large perturbation a large transient of v and w away from 0 can be elicited. The tracing of v as a function of time is similar to action potentials in biological tissue, and this equation and its variants have been used widely to model excitation in nerve [9] and heart [10].

Although there are no stable oscillations in the homogeneous equations [9], stable oscillations do exist on the ring, Fig. 1 (first column). The successive traces show the value of the v variable around the ring at four different times. We assume the circumference is $2 \times \sqrt{5}$ cm, $D = 1$ cm^2/sec, and cyclic boundary conditions [12]. The excitation travels around the ring with a period $T_0 = 356.1$ msec. The refractory period is about 60 msec. We call the direction of propagation of the wave (here right to left) the *anterograde direction* and the opposite direction the *retrograde* direction.

We assume that stimuli are applied over a small segment of the ring. The effects of perturbation depend on the amplitude of the stimulus and the location of the stimulus relative to the wave front. Stimuli that fall in the refractory period do not lead to new excitations. Stimuli that fall outside of the refractory period are called *suprathreshold* if they lead to the generation of excitation wave(s) and *subthreshold* if they do not. We are principally concerned with the effects of suprathreshold stimuli.

To discuss resetting the oscillation by perturbations it is necessary to define the phase of a stimulation. We assume a stably circulating excitation wave with intrinsic cycle length T_0. Because of the circular symmetry of the ring, the definition of phase of the stimulus is arbitrary.

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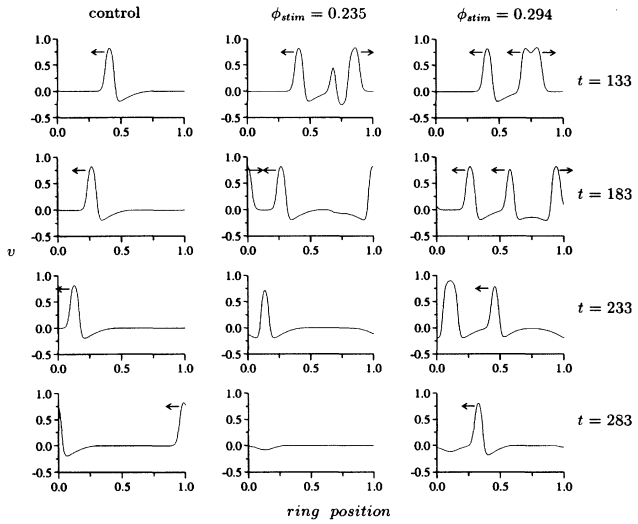

FIG. 1. Simulation of the Fitzhugh-Nagumo equation showing propagation of excitation around a ring. The ring circumference is about 4.47 cm. We display the normalized position from an arbitrary origin. In each panel the v variable is displayed as a function of ring position. Each row corresponds to the activity shown at the time shown to the right of the row, where $t = 0$ corresponds to the time the excitation is at position 0.75 before stimulation. Column 1: no stimulus; column 2: stimulus delivered at position 0.75 at $\phi_{\text{stim}} = 0.235$. A single wave is generated that propagates in a retrograde direction. The collision of this wave with the original reentrant wave leads to annihilation of the reentrant wave. Column 3: stimulus delivered at position 0.75 at $\phi_{\text{stim}} = 0.294$. Two waves are generated. The retrogradely propagated wave collides with the original wave and leads to its annihilation. The anterogradely propagated wave continues, leading to resetting of activation times at position 0.75.

For purposes of convenience and display, we associate $t = 0$ and $\phi = 0$ with the time when v increases through 0.5 at a position 3/4 of the way around the ring circumference, ring position = 0.75. Subsequent times $t > 0$ are identified with phase $\phi = (t/T_0) \,(\text{mod } 1)$. We assume that the stimulus is injected at a single grid point ($\Delta R \approx 0.022$ cm) at position 0.75 with a magnitude $I = 1$ for 10 time units. Figure 2 summarizes the results. We plot the subsequent excitation times (the time when v increases through 0.5), normalized by T_0 at position 0.75 as a function of the phase of the stimulus, ϕ_{stim}.

During the refractory period (here between $0 \leq \phi < 0.16$) there is little effect on the subsequent circulation of the excitation around the ring, and subsequent activations occur at the times they would have been expected if there was no stimulus.

Stimuli delivered later in the cycle lead to one of two different behaviors. If the stimulus occurs at a phase $0.28 < \phi < 1$, two waves are generated that travel in opposite directions on the ring, Fig. 1, column 3. There will be a collision between the original wave and the

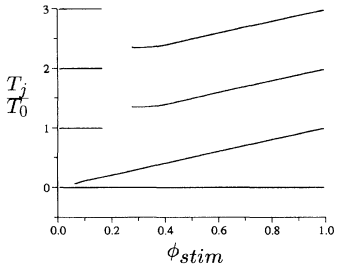

FIG. 2. Summary of resetting data for reentrant excitation using a suprathreshold stimulus. The normalized excitation times T_j/T_0 at position 0.75 are displayed as a function of the phase of stimulation of the reentrant wave. Stimuli either have little effect $0 \leq \phi < 0.16$, lead to annihilation, $0.16 < \phi < 0.28$, or reset the oscillation, $0.28 < \phi < 1$.

retrogradely propagated wave generated by the stimulus, leading to the annihilation of both waves. This leaves only a single wave traveling in the anterograde direction. The oscillation is reset so that subsequent activations at position 0.75 now occur at different times from what would have been observed if there was no perturbation. Stimuli delivered between $0.16 < \phi < 0.28$ generate a single wave traveling retrogradely, Fig. 1, column 2. This wave collides with the original wave leading to an annihilation of the reentrant wave.

These results are consistent with previous numerical and analytical studies that showed that either 0, 1, or 2 waves will be generated as a consequence of electrical stimulation delivered in the wake of a propagating wave in a one-dimensional excitable medium (see [5,10] and references therein) and provide a mechanism for the resetting and annihilation of reentrant tachycardias similar to clinical observations [4]. We conjecture that the annihilation of reentrant waves by a spatially localized suprathreshold stimulus delivered over a range of phases should be a generic property of partial differential equations modeling excitable media.

Our argument in support of this conjecture rests on extending results of resetting limit cycle oscillations in finite-dimensional dynamical systems to resetting oscillations in infinite-dimensional systems. The results on resetting oscillations in finite dimensions are developed at length elsewhere [13,14].

A stable limit cycle is an oscillation in a set of differential equations that is always reestablished following any small perturbation. The *basin of attraction* of a limit cycle consists of all states that will approach the limit cycle in the limit $t \to \infty$. In some situations a perturbation will lead to a state that lies outside of the basin of attraction of a limit cycle leading to qualitatively different behavior as $t \to \infty$. Other perturbations reset the oscillation. As above, we call the time when the oscillation reaches an arbitrary fiducial point the excitation time and use this point to set $t = 0$ and $\phi = 0$. Assume that, following a

perturbation delivered at phase ϕ, we remain in the basin of attraction of the oscillation and that successive excitation times occur at $T_1(\phi)$, $T_2(\phi),\ldots,T_j(\phi)$. If there is no resetting we have $T_j(\phi) = jT_0$. If there is resetting, then the limit cycle is approached for long times so that for j sufficiently large we have $T_j(\phi) - T_{j-1}(\phi) = T_0$. Taking a sufficiently large value of j so that the limit cycle is asymptotically approached, the *phase transition curve* $g(\phi)$ is defined to be

$$g(\phi) = \phi - \frac{T_j(\phi)}{T_0} \pmod 1. \tag{2}$$

The following mathematical result follows directly from Guckenheimer [14] for resetting limit cycle oscillations in finite dimensions. *Continuity rule: Provided a perturbation delivered at any phase of the cycle leaves one in the basin of attraction of the oscillation, the phase transition curve $g(\phi)$ is a continuous circle map.* We conjecture that the result also holds for resetting in infinite-dimensional systems [15].

We now apply the continuity rule to resetting the reentrant wave in the infinite-dimensional partial differential equations. We assume that the stimulus delivery and the subsequent measurements of the excitation times are at the same position, and that the ring is sufficiently large but of finite circumference. Based on the properties of excitable media described above, the timing of successive activations following a stimulus should be at

$$T_j(\phi) = jT_0, \quad \text{for} \quad 0 \le \phi \le \phi_{\text{refr}}, \tag{3a}$$

$$T_j(\phi) \approx \phi + (j-1)T_0, \quad \text{for} \quad \phi_{\text{refr}} < \phi, \tag{3b}$$

where ϕ_{refr} is the phase at the end of the refractory period. If the velocity of the excitation waves was always a constant, the approximation sign in Eq. (3b) would be replaced by an equal sign. Since the velocity of the wave propagation is typically reduced for waves that follow in the wake of a previous excitation, the subsequent activations may be delayed (see the slight flattening of the times of successive activations in Fig. 2 for $\phi \approx 0.28$). For large rings, the intrinsic period T_0 of the reentrant excitation is proportional to the circumference, but the magnitude of the delay will reach a constant value for stimuli that follow in the wake of a previous wave. Consequently, the timing of successive activations is increasingly better approximated by the linear functions in Eq. (3) as the ring size increases. Equation (3) implies a discontinuity in the phase transition curve at ϕ_{refr}. As the ring size shrinks, the magnitude of the discontinuity will change, but, in general, should still persist. However, discontinuities in the phase transition curve are forbidden by the continuity rule. Consequently, if the continuity rule holds, there must be a time interval following the refractory period that leads to a transition outside of the basin of attraction of the original oscillation [16]. Thus, based on the above argument, a general property of reentry waves in a one-dimensional ring in excitable media is that suprathreshold stimuli falling in a range of phases of the cycle will lead to annihilation of the reentrant wave [17]. This result is only based on continuity and generic properties of excitable media, and therefore it should hold in a wide range of physical and biological systems displaying reentrant waves, or in mathematical models of these systems formulated as partial differential equations.

Since reentrant tachycardias are often associated with significant sickness or death, understanding the mechanism for their initiation and termination is of crucial importance in medicine. Although previous theoretical and experimental papers have documented the role of a single stimulus delivered in the wake of a propagating excitation wave in the initiation and termination of reentrant tachycardias in particular cases [4,5,10], we have argued that the mechanism of tachycardia termination observed here should hold for a large class of systems. We suggest that assessment of clinically measured phase transition curves during tachycardias may help in the analysis of their mechanisms and may eventually help in the treatment of these dangerous arrhythmias.

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[16] This argument cannot exclude the possibility of inducing another rhythm (e.g., a rhythm with two waves circulating at the same time).
[17] In this theoretical model we have also observed annihilation of reentrant waves by subthreshold stimuli by a different mechanism. In the current case, a stimulus of $I = 0.3$ delivered at a single grid point ($\Delta R = 0.005$) at position 0.75 for 10 time units leads to annihilation in the range $0.85 < \phi < 0.91$.