Resetting and termination of reentry in a loop-and-tail cardiac model

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Ventricular tachycardia is a type of cardiac arrhythmia that can be associated with a wave circulating around in a loop. Because this rhythm is potentially fatal, its termination is highly desirable. Theoretical approaches have suggested that discontinuity in the phase resetting response to electrical stimuli is indicative of the ability for such termination. We investigate the usefulness of such theoretical predictions when the stimulus site is located at some distance away from the reentrant loop, as would typically be the case during antitachycardia pacing in the heart. We show that there exists a critical tail length below which termination of reentry occurs over a range of stimulus timing values as predicted theoretically by a discontinuous window in the phase resetting curve. Above this critical length, however, a paradoxical situation exists: termination of reentry appears impossible, yet there is a point discontinuity in the phase resetting curve. These findings offer insight into termination using a single stimulus in a loop-and-tail model, an important step toward understanding the mechanism of antitachycardia pacing.

I. INTRODUCTION

Reentrant cardiac arrhythmias occur when tissue is activated repeatedly by a wave that again and again reenters the same anatomical region. Such reentry involving a single reentrant circuit typically leads to monomorphic ventricular tachycardia. Ventricular tachycardia by itself can cause excessively rapid activation of the heart, potentially causing a fatal reduction in the efficiency with which blood is pumped. In addition, ventricular tachycardia may destabilize and break up into the highly disorganized ventricular fibrillation, where the pumping of blood is drastically and lethally reduced. Because of the risks of insufficient pumping associated with ventricular tachycardia, its termination is highly important.

A simple model of ventricular tachycardia is a reentrant wave traveling around a one-dimensional ring. In this model, a single well-timed suprathreshold stimulus may terminate the reentry. This happens when the stimulus induces a wave which is blocked unidirectionally—i.e., it travels only in the direction retrograde to the original reentrant wave because the tissue in the anterograde direction is still refractory. The retrograde wave and the original reentrant wave then collide and mutually annihilate at the antipodal point on the ring.

The time interval in which a stimulus leads to termination of the reentry is termed the vulnerable window (VW). If the stimulus falls prior to the VW, the tissue around the stimulus site is refractory and no waves are induced. If the stimulus is given after the VW, two waves are generated, propagating in opposite directions away from the stimulus site. The retrograde wave will collide with and annihilate the original wave. However, the wave traveling in the anterograde direction will continue to circulate, replacing the original wave, so that the reentry has been phase reset.

In general, phase resetting occurs when the dynamics of an oscillator is shifted in time. This can be accomplished when a stimulus transiently perturbs the state point away from the stable limit cycle associated with the oscillation, followed by the asymptotic return of the state point to the limit cycle. Say that a stimulus delivered to an oscillation at a phase ϕ (the old phase) resets the oscillation to a new phase $g(\phi)$. The function $g(\phi)$ is called the phase transition curve. An important property of the phase transition curve is the continuity theorem [1] (for more detail, please see the Appendix). It states that if a stimulus of a given amplitude delivered at any old phase of a limit-cycle oscillation leaves the state point within the basin of attraction of that asymptotically stable limit cycle, then the phase transition curve will be continuous for that stimulus amplitude. Similarly, if the phase transition curve is truly discontinuous there must be a stimulus phase (or range of phases) that will result in the state point being perturbed outside of the basin of attraction of the limit cycle. This is also true for spatially distributed systems [2].

Thus, on the ring, the VW corresponds to a range of phases of the stimulus timing for which termination occurs because the state point is taken outside the basin of attraction of the limit cycle and the phase transition curve is discontinuous. Also, inversely, the presence of discontinuity in the phase transition curve is predictive of reentry termination [3]. However, when an implanted device attempts to terminate reentry in a patient, the stimulus lead is not necessarily located inside the reentrant circuit. Hence, a more realistic "loop-and-tail model" can be used to study the effects of the stimulus site being located outside the reentrant circuit. In the loop-and-tail model, a tail has been added to a one-dimensional ring, and the stimulus is injected at some location on the tail. The phase transition curve is discontinuous for such a model, predicting that termination of the reentry should be possible for the right stimulus amplitude and timing [4]. However, attempts at terminating reentry in a homogeneous loop-and-tail model have been unsuccessful but did not fully elucidate the reasons for such termination failure. [5,6]. In this paper, we address this paradox and show why a single stimulus cannot terminate reentry unless the tail is very short.

II. METHODS

Simulations were carried out using the Aliev-Panfilov version of the FitzHugh-Nagumo model [7]. The Aliev-Panfilov is a fairly generic model of excitable tissue, but it is modified toward modeling cardiac tissue.

The model equations are

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} - ku(u-a)(u-1) - uv + I,$$

$$\frac{\partial v}{\partial t} = \epsilon(u,v)[-v - ku(u-a-1)], \qquad (1)$$

with t measured in time units (t.u.) and x in space units (s.u.), and where $\epsilon(u,v) = \epsilon_0 + \mu_1 v/(\mu_2 + u)$, $\epsilon_0 = 0.002$, $\mu_1 = 0.2$, $\mu_2 = 0.3$, $k = 8.0$, $a = 0.15$, $D = 1$ s.u.^{2}/t.u., and I is the injected stimulus current (amplitude 30, duration 0.08 t.u.).

For numerical integration we used a finite-difference method with a forward Euler scheme. The values of the temporal and spatial step sizes were $dx = 0.5$ s.u. and $dt = 0.02$ t.u. The loop was 100 s.u. long, as was the tail. The stimulus site was varied systematically between different locations on the tail.

Phase resetting curves were computed at the stimulus site by setting the fiducial point where the phase is zero to be the crossing of 0.5 on the upstroke of u. The intrinsic cycle length is denoted T_0, while T_j, $j \geq 1$, gives the accumulated time of j upstrokes following a stimulus given at a time t_c (the coupling interval; corresponds to the phase $\phi = t_c/T_0$) in the first cycle. Stimuli were applied after a few rotations of the reentrant wave to let transients dissipate.

III. RESULTS

A. Resetting and termination in a loop model

The phase resetting curve[1] for the Aliev-Panfilov model on a one-dimensional (1D) ring without a tail is shown in Fig. 1(a). This curve is quite similar to that of the classic FitzHugh-Nagumo model [3]. The curve has a discontinuous gap for a range of stimulus timing values ($0.288 \lesssim t_c/T_0 \lesssim 0.327$), where termination of the reentry occurs, due to unidirectional conduction of the induced wave as described above.

Extending the analysis of resetting in a ring without a tail [3] to allow for a finite-sized VW, the phase resetting curves are given by

$$T_j \approx \begin{cases} jT_0 & \text{for } 0 \leq t_c < t_r, \\ \varnothing & \text{for } t_r \leq t_c < t_a, \\ (j-1)T_0 + t_c & \text{for } t_a \leq t_c < T_0, \end{cases} \qquad (2)$$

where $\varnothing$ indicates termination, and t_r (t_a) is the time at which the tissue in the retrograde (anterograde) direction has
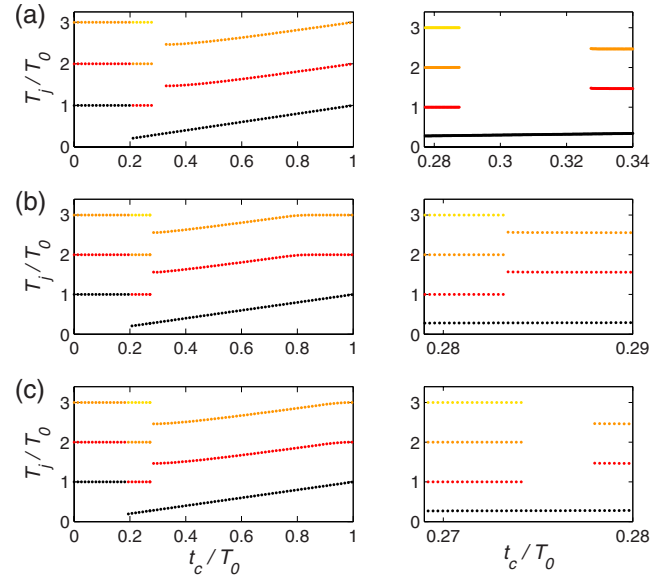

FIG. 1. (Color online) Phase resetting curves for reentry on 1D rings without (a) and with a tail (b) tail length 10 s.u. and (c) tail length 2 s.u. Different colors indicate different values of j [$j = 1$, black; $j = 2$, red (dark gray); $j = 3$, orange (medium gray); $j = 4$, yellow (light gray)]. Right: Closeups around discontinuities. In a loop geometry without a tail (a) there is a discontinuous gap where there is termination of reentry. When the stimulus is given at a distance of 10 s.u. down the tail (b), there is a jump discontinuity and we did not see termination. When the stimulus is given closer to the loop [at a distance of 2 s.u. down the tail (c)], there is again a discontinuous gap where reentry is terminated. The intrinsic cycle length (T_0) is slightly different in the loop geometry (75.88 t.u.) vs the loop-and-tail geometry (77.34 t.u.).

come out of its refractory period and can sustain wave propagation.[2] Notice that $t_a - t_r = $ VW.

B. Resetting and termination in a loop-and-tail model

When a tail is introduced to the ring and stimulating from that tail, the dynamics change qualitatively. When a stimulus is given at a distance of 10 s.u. away from the loop, the phase resetting curve has a discontinuous jump (at $t_c/T_0 \approx 0.283$) as shown in Fig. 1(b).

There are well-known difficulties in determining whether a phase resetting curve is truly discontinuous or merely very steep, but continuous [8]. When we change t_c as finely as 0.02 t.u. (the integration time step), the discontinuity in the phase resetting curve (and the phase transition curve) remains. If the phase transition curve is truly discontinuous, theory predicts that annihilation of the original reentrant rhythm should occur at that point [3,4]. However, we did not see such annihilation in our simulations. This apparent in-

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[1]The phase resetting curve shows T_j as a function of t_c and is a transformation of the phase transition curve. It is discontinuous at the same phase or range of phases as the phase transition curve.

[2]Notice that we do not take into account the fact that for a range of t_c values (0.20–0.29 in the case of the loop), the stimulus induces an upstroke large enough to cross threshold, but not large enough to cause wave propagation in either direction. This effect causes merely a shift in the counting of the waves (from T_{j+1} to T_j) as seen in Fig. 1, not a change in the wave dynamics.
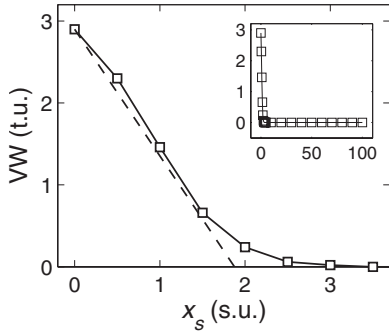
FIG. 2. Decrease in VW for increasing distance x_s of the stimulus site from the loop. Symbols and solid line, simulation results; dashed line, simple model [Eq. (3)]. Inset shows the VW on an x axis extended to the same length as the loop.

ability to terminate reentry in a loop-and-tail geometry has been seen previously in similar model systems [5,6].

To investigate these paradoxical findings, we computed the phase resetting response for a loop-and-tail geometry with the stimulus site being very close (2 s.u.) to the loop. The resulting curve is shown in Fig. 1(c). Indeed, this curve has a range of t_c values for which there is a discontinuous gap (at $0.274 \lesssim t_c/T_0 \lesssim 0.278$), and where reentry is terminated, as predicted by theory.

By systematically varying the location of the stimulus site along the tail, we have computed how the VW for termination depends on the distance of the stimulus from the loop. The results are shown in Fig. 2. The VW decreases when the stimulus is given further from the ring as seen in Fig. 1. For stimulus sites located more than 3.5 s.u. away from the ring, termination of reentry did not occur when changing t_c in steps of 0.02 t.u.

A simple model explains this dependency of VW on stimulus site: the VW is reduced by the sum of (1) the time it takes the reentrant wave to travel up the tail to the stimulus site and (2) the time it takes the stimulus-induced wave to propagate down to the ring. Hence, assuming constant conduction velocity, the VW ($\mathcal{W}$) varies as

$$\mathcal{W}(x_s) = \mathcal{W}_0 - 2x_s/\mathcal{V}, \qquad (3)$$

where $\mathcal{V}$ is the conduction velocity, x_s is the distance from the loop to the stimulus site, and $\mathcal{W}_0$ is the VW at location $x_s=0$, i.e., on the loop. This result (shown as the dashed line in Fig. 2) agrees very well with the simulation results.

Using this model, analytical expressions for the phase resetting curves are readily derived. We consider only situations where the tail is sufficiently short that no more than one action potential at a time propagates up the tail during reentry (i.e., x_s is smaller than the length of the loop). There are then two general cases: one where x_s is sufficiently short that the stimulus-induced activation may reach the loop within the VW; and one where x_s is too large for this to occur.

For $x_s < (1/2)\mathcal{W}_0\mathcal{V}$,

$$T_j \approx \begin{cases} jT_0 & \text{for } 0 \le t_c < t_r, \\ \varnothing & \text{for } t_r \le t_c < t_r + 2x_s/\mathcal{V}, \\ (j-1)T_0 + t_c & \text{for } t_r + 2x_s/\mathcal{V} \le t_c < T_0. \end{cases} \qquad (4)$$
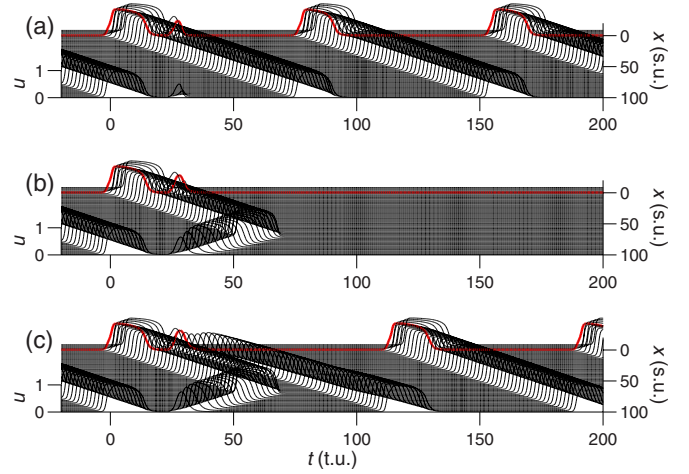

FIG. 3. (Color online) Termination of reentry in loop-and-tail model with the stimulus site close to the loop, $x_s=2$ s.u. The tail is the upper part of each panel, with the red (gray) trace corresponding to the loop-tail branch point. (a) No effect at $t_c=21.1$ t.u. (b) Annihilation at $t_c=21.3$ t.u. (c) Resetting at $t_c=21.5$ t.u.

For $x_s \ge (1/2)\mathcal{W}_0\mathcal{V}$,

$$T_j \approx \begin{cases} jT_0 & \text{for } 0 \le t_c < t_r, \\ (j-1)T_0 + t_c & \text{for } t_r \le t_c < T_0. \end{cases} \qquad (5)$$

Thus, when x_s is small, the phase resetting curve approaches the curve for the loop model with a discontinuous range of values that lead to termination. However, when x_s becomes larger than a certain critical value, $x_c=(1/2)\mathcal{W}_0\mathcal{V}$, a jump discontinuity is predicted. In the following, we investigate the dynamics around this jump discontinuity.

C. Resetting discontinuities and termination in the loop-and-tail model

We showed above that when the stimulus site is close to the ring, e.g., at 2 s.u., the phase resetting curve has a discontinuous gap [Fig. 1(c)], and it is indeed possible to terminate the reentry. The mechanism for termination is similar to that in a ring without a tail: a stimulus given inside the VW [at $t_c=21.3$ t.u. ($t_c/T_0 \approx 0.275$) in Fig. 3(b)] induces a wave that travels down the tail to the loop where it is blocked unidirectionally so that it travels only in the direction retrograde to the original reentry. The stimulus-induced wave then collides with and terminates the original reentrant wave around the antipodal point on the loop [Fig. 3(b)].

A stimulus given earlier [at $t_c=21.1$ t.u. ($t_c/T_0 \approx 0.273$) in Fig. 3(a)] falls in the refractory period of the previous wave traveling up the tail from the loop and has no effect on the reentrant activity. On the other hand, a stimulus given later [at $t_c=21.5$ t.u. ($t_c/T_0 \approx 0.278$) in Fig. 3(c)] induces a wave that travels down the tail to the loop, where it propagates in both directions. The stimulus-induced wave traveling in the retrograde direction collides with and annihilates the original reentrant wave, but the stimulus-induced wave traveling in the anterograde direction persists so that there is still reentry on the loop [Fig. 3(c)], albeit at a reset timing.
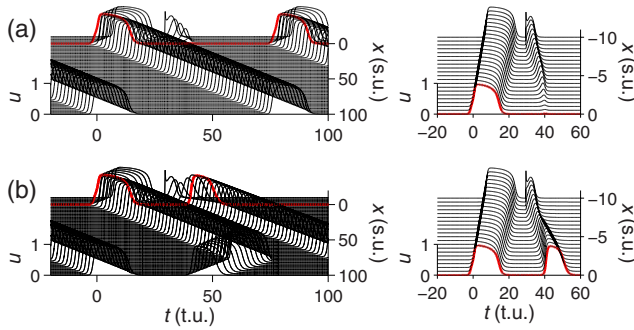
FIG. 4. (Color online) (a) No termination of reentry in the loop-and-tail model when the stimulus site is located further away, x_s =10 s.u. The tail is the upper part of each panel, with the red (gray) trace corresponding to the loop-tail branch point. Right panels show closeups of the dynamics on the tail. No effect at t_c=21.88 t.u. because the action potential is not able to propagate down to the ring. (b) Resetting at t_c=21.90 t.u., the action potential does propagate down to the loop.

When the stimulus site is further away, e.g., at 10 s.u., our simple model predicts a direct transition from no effect to phase resetting [Eq. (5)]. This is shown in Fig. 4: at t_c =21.88 t.u. ($t_c/T_0 \approx 0.2832$), there is no effect of the stimulus, while at t_c=21.90 t.u. ($t_c/T_0 \approx 0.2833$), there is phase resetting, since the VW is over. A closeup of the activity on the tail reveals the mechanism of the transition: the action potential induced at t_c=21.88 t.u. does not propagate all the way down to the ring, while the action potential induced 0.02 t.u. later does. Thus, the discontinuity originates not on the ring, but on the tail. This discontinuity persists when changing t_c in steps as small as 10^{-6} t.u. However, we saw no termination of reentry, which presents a paradoxical disagreement between the predictions of the topological approach [1,2,9] vs the simple model [Eq. (5)] and the simulations.

IV. DISCUSSION

We have shown here that termination of reentry is possible in a loop-and-tail geometry for tail lengths below a certain critical value x_c. In this case, the VW for termination coincides with a discontinuous window in the phase resetting curve. In contrast, when the stimulus site is further away from the loop, there is a point discontinuity in the phase resetting response, yet we saw no termination of the reentrant activity.

This paradox would be resolved if the discontinuity in the phase resetting curve [Fig. 1(b)] disappeared when the stimulus timing t_c was changed in smaller steps. However, FitzHugh-Nagumo models in 1D geometries have two propagating solutions for sufficiently long recovery time: one stable solution with relatively fast propagation speed and one unstable solution with slower propagation speed [10]. At a certain critical recovery time, these two solutions coalesce at a limit point, and for shorter recovery time, no propagating solutions exists. The discontinuity in our simulations thus occurs when the recovery time ahead of the wave drops below the minimum value required to sustain propagation.

Hence, the discontinuity in the resetting response is real in the sense that it does not disappear if t_c is varied more finely—propagation is a true all-or-none phenomenon.

Another possible resolution is that the topological approach is not valid for the quasi-1D geometry of the loop-and-tail model. Although the results shown in the right-hand panels of Fig. 4 suggest this, numerically, the partial differential equation is represented as many coupled ordinary differential equations, for which the topological approach should be valid.

Using our simple model [Eq. (3)], we found that the critical tail length for which termination due to a single stimulus can occur is about 2 s.u. In a physical cardiac system the VW for annihilation due to unidirectional block is on the order of $1-2$ ms [11,12], although there may be considerable variation between species, anatomical regions, etc. Using a typical value for the conduction velocity of 50 cm/s, we can estimate the critical tail length as $x_c = (1/2)\mathcal{W}_0\mathcal{V} \approx (1/2) \times 1$ ms $\times 50$ cm/s ≈ 0.03 cm, which is obviously a very short distance on the centimeter scale of the heart. This agrees with clinical findings that termination of reentry by a single stimulus is a very rare event. It is of interest that simulations have shown that the VW may increase due to intrinsic heterogeneity in conduction [5,6], or due to dynamic instability which develops when giving a pair [12] or a train of stimuli [13]. Additionally, the critical length may be altered in ischemic or diseased hearts, conditions during which arrhythmias and termination attempts often occur. These conditions are often associated with uncoupling of the tissue. Such uncoupling may be simulated by reducing the diffusion constant. Decreasing the diffusion constant by a factor of 2 and 4 reduces the conduction velocity by a factor of $\sqrt{2}$ and 2, respectively (results not shown). However, in our simulations, such uncoupling also increases the VW by a factor of 1.3 and 1.7, respectively. Hence, in this model, the critical tail length is slightly reduced by uncoupling.

We have focused here on a very simple loop-and-tail model of reentry. In the heart, reentry may also occur in the form of spiral waves, which may or may not be pinned to obstacles. In the case of a pinned spiral wave, the reentrant activity may be terminated by application of an electric field which unpins the spiral wave so that it may subsequently drift away [14,15]. Future investigations may focus on theoretical as well as practical aspects of such termination.

Our main conclusion is that discontinuity in phase resetting is indicative of reentry termination in a loop-and-tail geometry only when the stimulus site is very close to the reentrant loop. This in turn questions the extent to which antitachycardia pacing in more complex geometries is amenable to simple analyses based on phase resetting.

APPENDIX: DISCONTINUITY IN PHASE RESETTING

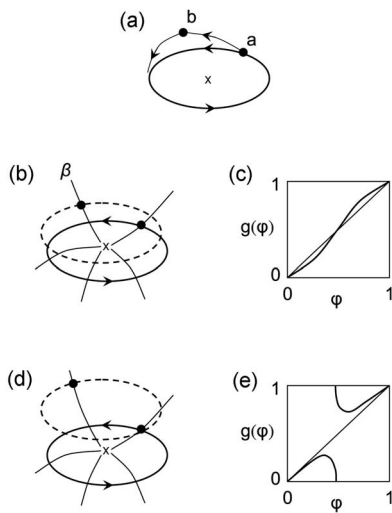In this appendix we give an illustration of the continuity theorem.

FIG. 5. (a) Schematic of phase resetting experiment. (b) Isochrons and shifted cycle for type-1 resetting. (c) Phase transition curve for type-1 resetting. (d) Isochrons and shifted cycle for type-0 resetting. (e) Phase transition curve for type-0 resetting.

Figure 5(a) shows a schematic illustration of a phase resetting experiment. We consider for simplicity a two-dimensional system with an asymptotically stable limit cycle (black oval) and an unstable fixed point (cross) (as done in [16]). The unstable fixed point is the only point outside the basin of attraction of the stable limit cycle.

A stimulus is injected when the state point is at point a on the stable limit cycle (the old phase). The effect of this stimulus is to deliver the state point to point b. Because this location is within the basin of attraction of the stable limit cycle, the state point eventually returns to the limit cycle, albeit at a different (reset) phase. Say that this phase (the new phase) is β; point b is then said to lie on the β W isochron [9]. In a system of continuous differential equations, there exists a locus in the vicinity of point b, with the property that a state point delivered to any one of those points results in the same new phase, i.e., they are on the same W isochron as

b. Notice that this β W isochron must cross the limit cycle at a phase of β.

Figure 5(b) shows examples of W isochrons (there is an infinity of these corresponding to all the possible new phases). The dashed curve in Fig. 5(b) shows the so-called shifted cycle. This curve is the locus of state points at the end of a stimulus for any old phase. Figure 5(c) shows the corresponding phase transition curve. A phase transition curve can be characterized topologically by its winding number, i.e., the number of times that $g(\phi)$ wraps around the unit circle as ϕ goes around the circle once. In Fig. 5(c) the winding number or topological degree is 1. Indeed, for weak stimuli, $g(\phi) \approx \phi$ by continuity, such that all points fall close to the diagonal and the winding number is 1.

In many instances, for stronger stimuli the topological degree is 0 [9]. Such an example is shown in Fig. 5(e), while Fig. 5(d) shows the corresponding shifted cycle. Unlike degree-1 resetting, where the shifted cycle intersects all the W isochrons, if the stimulus is of sufficiently strong amplitude to move the shifted cycle to a location where it no longer intersects all W isochrons, degree-0 resetting will occur. Thus for degree-0 resetting there is a gap in the phase transition curve, consisting of new phases that are unattainable because their W isochrons are not intersected by the shifted cycle. The curve is still continuous however, as the phase is defined using modulus 1.

If the topological degree is 1 for weak stimuli and 0 for strong stimuli, then there must be an intermediate strength (or range of strengths) that results in the state point being perturbed to a location outside the basin of attraction of the stable limit cycle. In this example, this happens when the shifted cycle intersects the unstable fixed point within the stable limit cycle. Recall that this unstable fixed point is outside the basin of attraction of the stable limit cycle. Hence, for the old phase corresponding to that intersection, the oscillation is abolished, the new phase is undefined, and the phase transition curve discontinuous, illustrating the continuity theorem.

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