Intrinsic inhomogeneities and the coexistence of spirals with different periods of rotation

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We propose a mechanism by which wave fronts emanating from a spiral may break far from the spiral core due to intrinsic spatial inhomogeneities. A series of computer simulations are presented to demonstrate how coupling domains, which on their own would not cause breakup, may cause a single spiral to break into many spirals.

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I. INTRODUCTION

Spiral stability in reaction-diffusion systems has been studied in such diverse media as cardiac tissue [1,2], slime model colonies [3], and chemical media [4,5]. The cardiac substrate in particular has been the target of much study as there is evidence to suggest that the transition from tachycardia (a single spiral) to fibrillation (multiple spirals) can be lethal. A number of pathways have been mapped out by which a single spiral breaks up into multiple spirals [1,6–9], but much of the focus has been on the role of dynamic or functional inhomogeneities that may arise in an isotropic and homogeneous medium. In a uniform medium, however, any new spirals will rotate at the same rate as the original spiral and the result is a single dominant spike in the frequency spectrum. Clinical studies of fibrillation, however, reveal not only multiple spirals but a broad spectrum of frequencies. As the heart is known to contain intrinsic inhomogeneities [1,2,5,10–14], the simplest explanation for a broad spectrum is that several stable spirals coexist in regions with different tissue properties, thus enabling rotation at different rates. This multiple domain hypothesis, however, contradicts a well-established finding where a rapidly rotating spiral will unwind all slower spirals and push them toward the medium boundary [5,10].

In this paper we propose a mechanism by which intrinsic inhomogeneities may cause a single spiral to break up into many spirals with different rates of rotation. A stepwise series of computer simulations is presented to unify findings from other media and demonstrates each step in this pathway. Briefly, two domains that support stable spirals of different frequencies may be functionally insulated from one another by a thin region with different tissue properties. Our findings may provide insight into why it is often difficult to shock or pace a patient out of fibrillation and how clinical cardiac mapping of a real heart may enable predictions as to where new breaks may occur in a real heart.

II. RESTITUTION AND DYNAMIC INSTABILITIES

To highlight the difference between our proposed breakup mechanism and the pathways involving dynamic instabilities, we first derive a range of parameters that will not break up on their own. In this way, any breakup that does occur can be assured to be by some other mechanism. Dynamic instabilities may arise near the spiral core when a single spiral collapses in on itself, pinching off a pair of spirals [11]. Subsequent breaks increase the complexity of the dynamics as new spirals form but also annihilate one another [1,15]. A dynamic instability can also occur far from the spiral core if a spiral sends off wave fronts which break on a distant dynamic inhomogeneity caused by previous wave fronts [16–18] or an anatomical obstacle [19].

As an initial step, we created a model that did not exhibit anatomical obstacles or destabilizing functional inhomogeneities. Anatomical obstacles were simple to avoid by simulating uniformly coupled one- and two-dimensional domains.

$$\nabla \cdot (\mathbf{D} \nabla V_m) = -\beta\left(C_m \frac{dV_m}{dt} + I_{\text{ion}} + I_{\text{stim}}\right), \tag{1}$$

where $\mathbf{D}$ (1 ms/cm) is the diffusion coefficient and remains constant, V_m is the potential difference between the inside and outside of a cell, C_m (1 μF/cm^2) is the membrane capacitance, β (2000 cm^{-1}) is the surface to volume ratio, and I_{stim} is an external stimulus.

Functional inhomogeneities arise because cardiac tissue can dynamically change electrical properties [1,6–9], a property known as restitution. Specifically, the time between activation and recovery [Fig. 1(a)], or action potential duration (T_A), is reduced as the cycle length (T_C) is decreased (faster stimulus rate). A similar restitution phenomenon is observed for wave-front propagation velocity (V_P), which also decreases as T_C is reduced. A typical restitution portrait is characterized by a plot of T_A or V_P against the diastolic interval (T_D), which is the time between recovery and the next activation. The property of restitution can result in destabilizing functional heterogeneities if (1) the slope of the T_A-T_D restitution curve is greater than $1+\xi\dot{V}_P/(V_P)^2$, where ξ is proportional to the square of the diffusion coefficient and $\dot{V}_P$ is the slope of the V_P-T_D restitution [20,21], (2) the T_A or V_P restitution portrait has a region of hysteresis [22,23], (3) the T_A or V_P restitution portrait changes over time (e.g., restitution memory) [24], or (4) the T_A or V_P restitution portrait is not monotonically decreasing [23].

Although it is not possible to eliminate functional inhomogeneities entirely, it is possible to choose parameters that will not destabilize a spiral. To eliminate the impact of memory and ensure a monotonic restitution portrait [points (3) and (4) above], we used the Fenton-Karma (FK) model for I_{ion} [1] [Fig. 1(a)]. To eliminate hysteresis and restitution slopes greater than $1+\xi(\dot{V}_P)/(V_P)^2$ [points (1) and (2)

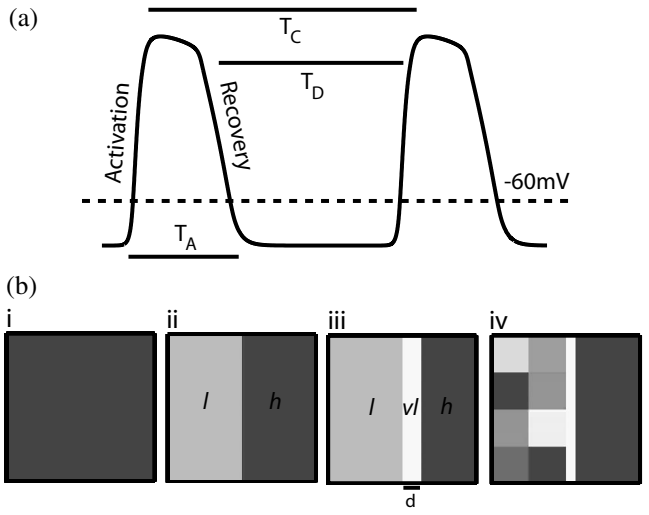

FIG. 1. (a) Activation and recovery for two action potentials. The action potential duration (T_A), diastolic interval (T_D), and activation cycle length (T_C) are computed at crossing of −60 mV. (b) Templates for two-dimensional (8 cm × 8 cm) domains with spatial variation in excitability (g_{fi}). Darker shading indicates greater excitability. (i) A domain with uniform excitability. (ii) Two 8 cm × 4 cm domains coupled together where the right half has high (h) excitability and the left half has low (l) excitability. (iii) High (g_{fi}^{h} = 3.0) and low (g_{fi}^{h}=0.9) excitability regions separated by a variably thick (d) region of very low (vl, $g_{fi}^{vl}<0.9$) excitability. (iv) Similar domain as panel (iii) but where d=0.5 cm and g_{fi}^{vl}=0.7 in the vl region and the l domain has been replaced by eight 2 cm × 2 cm regions of variable excitability.

above], we carefully chose the FK model parameters (Fig. 2). The parameter, g_{fi}, in the FK model controls excitability and was varied from nominal values [Fig. 1(b)(ii)–(iv)] to create spatial inhomogeneities. Since high excitability is destabilizing and very low excitability terminates propagation, a stable range of g_{fi} was found from T_A-T_D and V_P-T_D portraits (not shown). This stable range was found to be $0.5<g_{fi}<3.5$. Based upon these results, g_{fi} for all studies was limited to values between 0.6 and 3.0. Figure 2(a) is an example of T_A restitution. Note that T_A has been plotted against T_C, rather than T_D, to allow for later comparison to spiral rotation rates. The break point (T_B) of a restitution curve was defined as the minimum T_C that elicited a 1:1 stimulus-action potential response. A stimulus cycle length smaller than T_B would therefore result in a 2:1 stimulus-action potential response.

III. SINGLE SPIRAL DYNAMICS

A. Single spiral cycle length

To determine the impact of excitability on the spiral rotation rate, we initiated a single spiral (S1-S2 protocol) in a two-dimensional homogeneous medium [Fig. 1(b)(i)]. Reentry failed for $g_{fi}<0.6$ and spirals would break up for $g_{fi}>3.6$, reinforcing our chosen range of excitability. For g_{fi} between these extremes, the spiral cycle length (T_S) was computed as the average duration between activation wave fronts along the domain boundary. Figure 2(b) demonstrates that for any stable value of excitability it is necessary for $T_B<T_S$. Furthermore, higher excitability decreases the difference between T_B and T_S. It is notable that $T_S=T_B$ at approximately the same value of g_{fi} that results in an unstable core. To ensure that spiral stability and rate were not due to a boundary effect, T_S was computed in a 16 cm × 16 cm domain at two extremes (g_{fi}=0.6 and g_{fi}=3.0).

B. Role of the spiral core

Numerical and experimental studies have demonstrated that T_S is dictated by the properties near the spiral core [5,10]. To ensure that the FK model is no exception, we restarted a spiral from the previous simulation study (g_{fi} =3.0). Next, g_{fi} in a 0.3 cm^2 region surrounding the core was progressively decreased in excitability until the spiral could no longer be sustained. Dots in Fig. 2(b) represent the measured T_S when excitability was changed only near the core. As in previous studies, we found that local properties determine T_S.

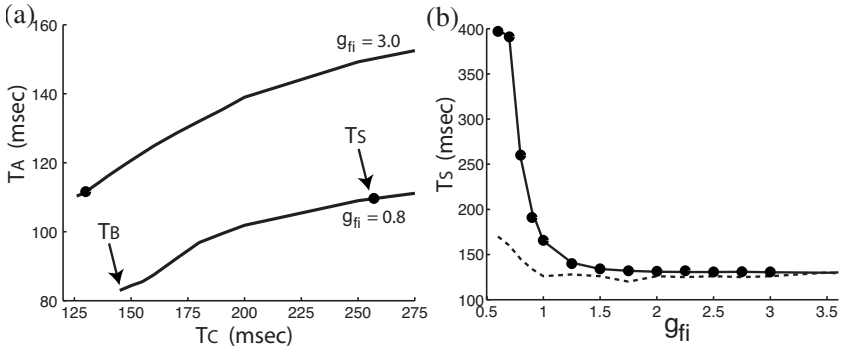

FIG. 2. (a) Restitution portraits for g_{fi}=3.0 and g_{fi}=0.8 generated by pacing a 2 cm homogeneous monodomain [Eq. (1)] one-dimensional cable with Δt=5 ms (Jacobi preconditioned semi-implicit conjugate gradients) and Δx=0.1 cm (finite differences). T_A restitution was measured at the center of the cable (x=1 cm) to account for any electronic effects [8]. Conduction velocity restitution was measured as the delay in activation time (−60 mV crossing) from x=0.5 cm to x=1.5 cm. Other parameters of the Fenton-Karma model were k =240, v_{fi}=15, u_{csi}=0.85, u_v=0.04, u_c=0.13, τ_r=40, τ_{si}=47, τ_0=6, τ_v^+=30, τ_{v1}=30, τ_{v2}=59, τ_w^+=2800, τ_w^-=700, v_{fi}=15 mV, and v_0= −85 mV [1]. Dots represent the single spiral cycle length (T_S). (b) Decreased excitability leads to larger T_B (dashed line) and T_S (solid line). Dots represent data for g_{fi} altered only in the vicinity of the spiral core.

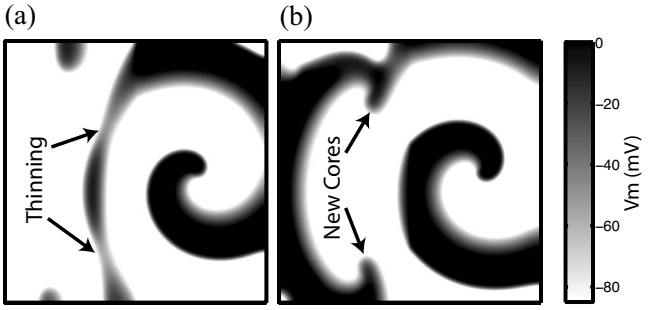

FIG. 3. (a) Thinning of a wave front due to an inhomogeneity in excitability ($g_{fi}^{l}=0.9$, $g_{fi}^{h}=3.0$). (b) Formation of two new spiral cores due to thinning.

IV. MULTISPIRAL INITIATION AND STABILITY

A. Thinning and spiral initiation

In Sec. III B, the excitability at the spiral core was always lower than the excitability of the domain outside of the spiral core. Therefore, the entire domain could respond 1:1 to wave fronts emanating from the spiral. To study how a high frequency spiral may initiate wave breaks in a distant region, we divided the 8 cm×8 cm domain into two halves with high (h) and low (l) excitability [Fig. 1(b)(ii)]. To ensure that a spiral in neither region would break up on its own, $g_{fi}^{h}=3.0$, and $0.7<g_{fi}^{l}<2.5$. Spirals were initiated in one of the half domains and allowed to evolve over 20 s. When a spiral was initiated in l, wave fronts emanating from the spiral would pass 1:1 through h because $T_S^l>T_B^h$. On the other hand, when a spiral was initiated in h, three behaviors were possible. First, if $T_S^h>T_B^l$, wave fronts from h propagated 1:1 into l. Second, $T_S^h \ll T_B^l$ wave fronts from h could propagate 2:1 into l. Third, over a range where $T_S^h<T_B^l$, a change from high to low excitability slowed the speed of the activation wave front but had a smaller impact on recovery. Therefore, the total wave would thin as the activation and recovery wave fronts became closer and closer together [Fig. 3(a)]. If activation and recovery wave fronts collided, a new spiral would form. Due to the slight convex curvature of the wave front [25], singularities always formed in pairs with opposite chirality near the center of the tissue [Fig. 3(b)]. It is important to point out that breakup far from the spiral occurred in the first two revolutions of the fast spiral, before functional inhomogeneities could play a role.

B. Multispirals at different cycle lengths

In Sec. IV A, new slowly rotating spirals in the l domain were driven to the boundary [5,10] by the dominant spiral in the h domain, typically over the course of several rotations of the fast spiral. It was possible for new spirals to remain intact, however, if they were buffered by a region of very low (vl) excitability [Fig. 1(b)(iii)]. Two spirals were simultaneously initiated in both the l and h regions while g_{fi}^{vl} and d were systematically varied. We found that for the slower spiral to be protected, the properties of vl must block alternating wave fronts from the fast spiral. In this way, even if $T_S^l>T_S^h$, both spirals may coexist because $T_B^{vl}>T_S^l>T_S^h$. As $g_{fi}^{vl}\rightarrow 0.5$ (complete block), the width, d, needed to achieve the same insulating effect could be decreased. In the extreme case where a complete block of wave fronts was achieved by vl, the h and l regions were effectively decoupled.

The relationship between g_{fi}^{vl} and d allowed for alternating wave fronts emanating from the fast spiral to be only partially blocked. For example, when $d=0.5$ cm and $g_{fi}^{vl}=0.7$, alternating wave fronts thinned and formed two new cores in the l region in a similar manner to Fig. 3. Unlike the case above, however, the newly formed cores were protected from the fast spiral by the partial block provided by the vl region. By this mechanism, a single fast spiral may initiate multiple new stable spirals of a different T_S.

C. Sustained breakup

Although multiple spirals of different rotation rates may exist in one inhomogeneous domain, the results in Sec. IV B were simply two or three stable spirals. To study breakup to more complex activity, we further subdivided the l domain into eight 2 cm×2 cm regions with randomly assigned $0.6<g_{fi}^{l}<3.0$ [Fig. 1(b)(iv)]. For some cases of randomly distributed g_{fi}, a few stable spirals with small T_S drove other spirals toward the boundaries or forced pairs to annihilate. The surviving spirals typically anchored to the corners of large changes in excitability. Other cases, however, demonstrated many of the hallmarks of fibrillation, including the dynamic creation and annihilation of cores, tip switching [26], and an aperiodic electrogram [Figs. 4(a)–4(c)]. Furthermore, if the fast spiral in the h domain was eliminated [Fig. 4(d)], wave fronts emanating from the l region thinned through the vl region and reinitiated a fast spiral in the h domain [Figs. 4(e) and 4(f)].

D. Inhomogeneities in recovery and coupling

Excitability is a common parameter to vary in studies of dynamic instability because it reliably produces dynamic spiral breakup in many model systems. The basis of our breakup mechanism, however, only relies on the presence of a region that will partially block closely spaced wave fronts. We therefore hypothesized that other parameters could also create an insulating region and lead to breakup by the same mechanism. Two additional simulation studies were performed where g_{fi} remained constant through the domain and a second model parameter was varied.

Changes in recovery strength were varied through τ_r in the FK model to modulate T_B and T_S. By extending the recovery time in the insulating region, the same wave-front thinning, partial block, and breakup were achieved [Fig. 5(a)]. A power spectrum of the electrogram recorded from this simulation [Fig. 5(b)] has a broad range of frequencies characteristic of fibrillation. There is recent experimental evidence to support the idea that regional differences in recovery (e.g., I_{K1}) [12,18] can lead to regional variations in T_B and T_S, and therefore induce breakup by a similar mechanism. An insulating region created by intrinsic inhomogeneities in repolarization is physiologically realistic and known to be present throughout the heart. For example, in the left ventricle the M-cell layer, with a long T_A, is sandwiched

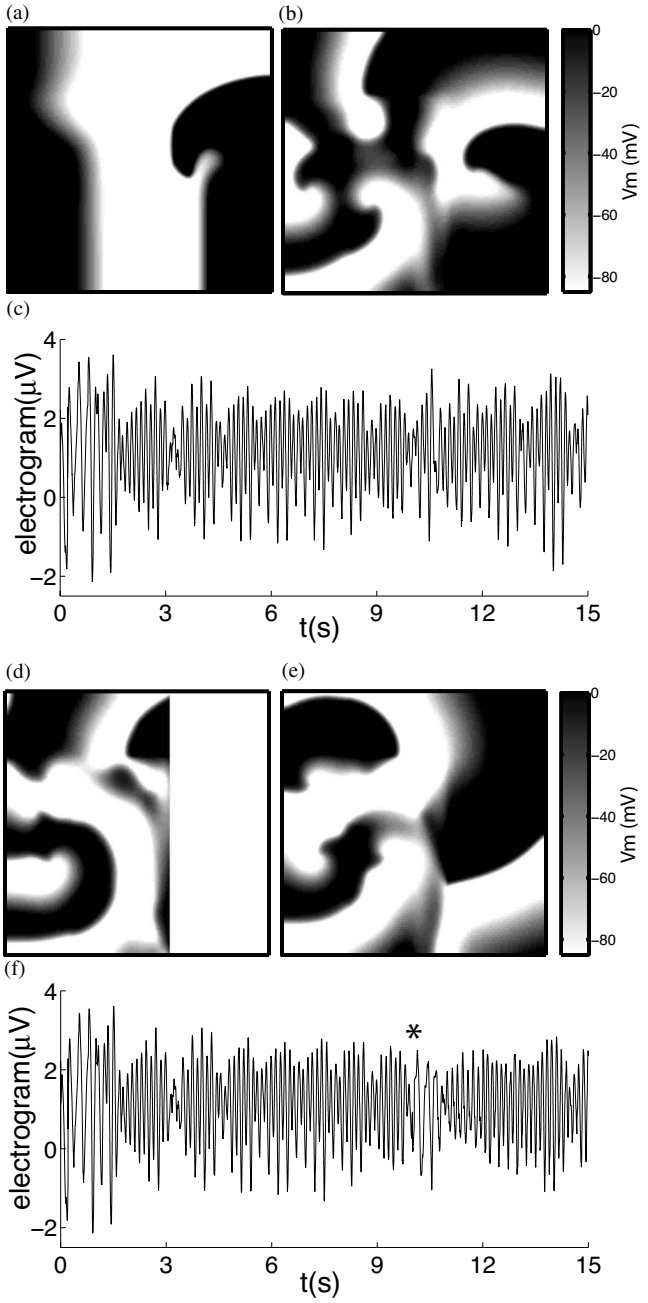

FIG. 4. (a) Single spiral initiation, (b) sustained spiral breakup, (c) 15 s of an aperiodic electrogram computed as a sum of monopoles at an electrode 2 cm above the domain [27]. (d) Elimination of the fast spiral at 10 s, (e) reentry of the fast spiral, (f) 15 s of an electrogram, as in panel (c), but at *, the dominant spiral was eliminated.

between the epicardium and endocardium, both with shorter T_A. The M-cell layer may therefore enable spirals of different rotation rates to exist on the epicardium and endocardium.

Inhomogeneities in coupling [**D** in Eq. (1)] alter both T_B and T_S in a similar manner to g_{fi}. By decreasing coupling in the insulating region, wave fronts were thinned, partially blocked, and resulted in sustained breakup. An insulating region created by intrinsic inhomogeneities in coupling is physiologically realistic in both the healthy and diseased heart. For example, the laminar sheet structure of the healthy

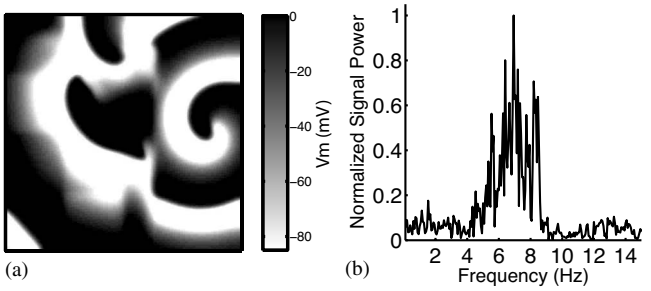

FIG. 5. (a) Sustained spiral breakup due to an inhomogeneity in recovery. (b) Power spectrum of the electrogram recorded from in panel (a).

ventricular wall [28] provides a thin region of low conductivity between two regions of relatively high conductivity. Inhomogeneities in coupling may also occur when gap junctions uncouple around the border of an ischemic region or due to aging [29].

In the study of Xie *et al.* [30], another interesting method of creating an insulating region is reported. The model in these studies was as shown in Fig. 1(b) (ii) and the insulating region was created dynamically by the complex collisions of wave fronts emanating from two spirals rotating at different rates. Although the parameter range required to produce these complex collisions was small and sustained breakup was not shown, the development of a functional insulating barrier also may play a role in sustaining many spirals with multiple periods of rotation.

For simplicity, the studies of Xie *et al.* and those presented here demonstrate the general mechanism of creating an insulating region by varying one parameter. In the ventricles, however, it is known that spatial inhomogeneities in many parameters (e.g., excitability, recovery coupling) are superimposed. In a healthy heart it may be that an intrinsic inhomogeneity in a parameter that would promote insulation is counterbalanced by inhomogeneities in other parameters. The resulting lack of insulating regions means that the entire ventricles are functionally connected and will not easily support multiple spirals of different frequencies. In a diseased state the counterbalance is upset, allowing some regions of the heart to become functionally disconnected, giving rise to a medium that can support multiple spirals of different frequencies.

V. DISCUSSION

Our study demonstrates that intrinsic spatial inhomogeneities may cause breakup even when the restitution parameters are outside of the range predicted to cause dynamic breakup. The general mechanism is that a region of the medium with a large break point (T_B) can functionally separate two regions with different spiral rotation rates (T_S). The development of a thin insulating region may be created through many different parameters of the medium and multiple insulating regions can give rise to the broad frequency spectrum characteristic of fibrillation.

Although simple in concept, the generic mechanism proposed here has practical implications. For example, naturally

occurring intrinsic inhomogeneities in the healthy heart rarely lead to fibrillation. Diseases, on the other hand, typically introduce or magnify inhomogeneities in such a way that spirals more readily form and breakup. As the cardiac community has established a relationship between breakup and dynamic restitution properties, therapies have aimed to revert restitution to predisease conditions. In some cases, this strategy has in fact caused disease symptoms to worsen. Our study demonstrates that some breakup mechanisms involve properties of both the restitution portrait and single spiral rotation rates. Recently, empirical methods have been developed for estimating spatial maps of spiral cycle length (T_S) [31]. Based upon our work, we hypothesize that combining spatial maps of T_S and T_B may enable better estimates of the likelihood and locations of spiral breakup and aid in the design of more effective therapies.

These findings may also shed some light on why pacing and defibrillation is sometimes ineffective in terminating fibrillation. For example, if multiple spirals are buffered from the pacing site by an insulating region, the pacing will be rendered ineffective even if it is faster than the fastest spiral. In defibrillation, Fig. 4 demonstrates that unless all spirals are terminated, a slow spiral may reinitiate faster spirals.

As these studies were phenomenological in nature, there is much room for further study. We expect the general breakup mechanism to be applicable to any medium in which the spiral rotation rate and break point may vary spatially. The authors therefore suggest experimental validation in chemical media because the spiral rate may be controlled by illumination intensity [5]. Although we propose that spiral rotation rate and restitution portrait properties together may be predictors of spiral breakup, these data must currently be derived from separate experiments. A first step toward a more quantitative connection between restitution and spiral rotation rate has been made in [25] in studies on wave-front curvature near the core, but more work remains. Equally important is a quantitative understanding of the nature of wave-front thinning. While these studies have shown that large-scale abrupt intrinsic inhomogeneities can lead to breakup, a separate study where g_{fi} was randomly varied throughout l on a small scale did not lead to complex behavior. This finding is in agreement with previous studies where a random distribution of excitability or coupling, on a fine spatial scale, served to stabilize a single spiral [13,32]. A future study may determine how the spatial extent of inhomogeneities and gradual transitions in properties modulate the stability of a single spiral. The fast spiral in our studies remained nearly stationary, but spiral cores are known to wander due to rapid pacing or intrinsic ionic properties [1]. The drift of a rapidly rotating spiral may lead to two interesting phenomena. First, a spiral core that is approaching a region of tissue will activate that region faster than the actual spiral rotation rate [2]. This Doppler effect may magnify or reduce differences in T_B and T_S depending upon the direction of the spiral drift. Second, it may be possible for a fast spiral to form in one region, induce a global breakup in another region, but then drift into a slower region and be pushed to the boundary.

In summary, our results demonstrate that domains that would not on their own cause spiral breakup, when connected, may cause a single spiral to break into many spirals.

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