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Anomalous drift of spiral waves in heterogeneous excitable media

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We study the drift of spiral waves in a simple model of heterogeneous excitable medium, having gradients in the distribution of ion-channel expression or cellular coupling. We report the anomalous drift of spiral waves toward regions having shorter period or stronger coupling, in reaction-diffusion models of excitable media. Such anomalous drift can promote the onset of complex spatiotemporal patterns, e.g., those responsible for life-threatening arrhythmias in the heart.

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Spatial patterns of activity, spiral waves in particular, are observed in a broad class of physical, biological and chemical excitable systems [1]. One of the most important contexts in which spiral waves occur is that of electrical activity in the heart, where they can act as local sources of high-frequency excitations. This disrupts the rhythmic pumping action of the heart, leading to irregularities known as arrhythmias [2]. Understanding the dynamics of spiral waves may potentially result in improved methods for controlling such arrhythmias [3–6]. Spiral wave dynamics, primarily characterized by the motion of its core (i.e., the trajectory of the spiral wave tip, defined to be a phase singularity) can be either stationary rotation or evolving with time as in the case of meandering and drift [7]. Drift, which has a significant linear translational component, is a possible underlying mechanism for polymorphic ventricular tachycardia [7,8]. This arrhythmia, which is characterized by an aperiodic electrocardiogram, can be a precursor of fully disordered activity that characterizes potentially fatal ventricular fibrillation [9]. Therefore, understanding the mechanisms leading to spiral wave drift is not only a problem of central interest for physics of excitable media, but also has potential clinical significance [10].

One of the most important causes of spiral drift is the heterogeneous nature of the excitable medium. This was first predicted in cellular automata models with steplike or discontinuous inhomogeneity [11], which was later confirmed by experiments [12,13]. Subsequently, drift has been shown to be induced by a smooth gradient of excitability in both simple and biologically realistic ionic models of cardiac tissue [14,15]. Theoretical arguments indicate that the direction of the transverse component of the spiral drift (i.e., orthogonal to the gradient) depends on model parameters [16]. On the other hand, the longitudinal component is always directed toward the region with longer spiral rotation period [15]. This phenomenon has been seen in a variety of excitable media models of different complexity [14,15]. However, till date there is no satisfactory understanding of the reasons behind the spiral wave drift toward regions with longer rotation period. Although earlier kinematic studies suggested the possibility of drift toward region with shorter period [17], it has never actually been observed in a model of excitable tissue. The occurrence of drift in the direction of shorter period may have clinical significance, as it moves the spiral core to a section where it rotates faster. This increases the likelihood of additional wave breaks in regions where the wave has a relatively slower period of rotation. Thus, it is a possible generation mechanism for "mother rotor" fibrillation [18], characterized by a stationary persistent source of high-frequency excitations giving rise to turbulent activity in the heart.

Electrophysiological heterogeneities in cardiac tissue may arise, in general, through spatial variation in the distribution of ion-channel expression in excitable tissue [19]. There can also be gradients in the intercellular coupling as a result of the inhomogeneous distribution of the conductances of gap junctions connecting neighboring cells [20]. In this paper, we use a simple model of cardiac tissue to investigate the role of both these types of heterogeneities in governing the direction of the spiral wave drift. We report the existence of a regime where the spiral wave core moves toward the region having (a) shorter period (due to higher expression of ionic channels), and/or (b) higher intercellular coupling. As reduction in either the ion-channel density or the intercellular coupling can impede wave propagation, it can be qualitatively regarded as decreasing the excitability of the medium. Thus, both of the cases mentioned above may be considered as a drift toward region of higher excitability, a result that may increase our understanding of how heterogeneities affect spiral wave dynamics in the heart.

A generic model of excitable media that describes the dynamics of transmembrane potential V in cardiac tissue has the form

$$\partial V/\partial t = \nabla \gamma D \nabla V + \alpha I_{ion}(V, g_i), \tag{1}$$

$$\partial g_i/\partial t = F(V, g_i). \tag{2}$$

Here, I_{ion} is the total ionic current traveling through the channels on the cellular membrane, D accounts for the intercellular coupling and g_i describes the dynamics of gating variables for the various ion-channels. In this paper, we study the effects of a heterogeneous distribution of ion-channel expression and intercellular coupling. For this purpose, we introduce the parameters α and γ, which represent the spatial variation in ion-channel expression and conduction properties (respectively) for an inhomogeneous medium. Parameter α directly scales the value of ion-channel expression in Eq. (1), while γ scales the diffusion coefficient as $D = D_0 + \gamma(x)$ ($D_0 = 1$ for the rest of the paper). In this study, we have used the Barkley model [21], where the several gating variables are aggregated into a single variable g that controls the slow recovery dynamics of the medium with $F(V,g)=V-g$. The nonlinear dependence of the ionic current on the fast variable V is represented by the cubic function $I_{ion}=[V(1-V)\{V-[(g+b)/a]\}]/\epsilon$, where a and b are parameters governing the local kinetics and ϵ is the relative time scale between the local dynamics of V and g. The spatial heterogeneity of ion-channel expression and cellular coupling are assumed to have linear functional form, *viz.*, $\alpha(x)=\alpha_0+\Delta\alpha x$ and $\gamma(x)=\gamma_0+\Delta\gamma x$. The variable x $(=-d/2,\ldots,d/2)$ represents the spatial position along the principal direction of the inhomogeneity gradient, where d is the length of the domain measured along this direction and the origin (i.e., $x=0$) is at the midpoint of the simulation domain. At this point, $\alpha=\alpha_0$, $\gamma=\gamma_0$, and $\Delta\alpha$, $\Delta\gamma$ measure their rate of change along the gradient. For all the figures in this paper, we have used $\alpha_0=1.15$, $\gamma_0=1.3$, and $\epsilon=0.02$.

The two-dimensional system is discretized on a square spatial grid of size $L\times L$ ($L=200$ for the figures shown here). The values of space step Δx and time step Δt used are 0.5 and 0.005, respectively. A sample of simulations has been repeated for $\Delta x=0.25$ to verify numerical accuracy. The model equations are solved using forward Euler scheme with a standard five-point stencil for the spatial second derivatives and central differences for the spatial first derivatives. No-flux boundary conditions are implemented at the edges of the simulation domain. The initial condition for all simulations is a stable spiral wave generated in a homogeneous medium with $\alpha=\alpha_0$ and $\gamma=\gamma_0$.

To investigate the role of heterogeneity in spiral drift, we have considered spatial gradients in α or γ individually (keeping the other parameter constant). After extensive numerical simulations that scan over the (a,b) parameter space of the Barkley model, we have found that it is indeed possible to observe *anomalous drift* of the spiral, i.e., a drift toward regions with shorter period or higher intercellular coupling. Examples of such anomalous drift are shown in Figs. 1(A) and 1(C). In both of these cases, anomalous drift is toward the region of higher excitability (in the qualitative sense) because increase in either α or γ enhances wave propagation. For comparison, in Figs. 1(B) and 1(D) we show the normal drift of the spiral, i.e., toward regions of lower excitability. This is seen for a set of (a,b) values which is farther from the boundary with the subexcitable region of the Barkley model [22] than the (a,b) parameter set for which anomalous drift is observed in Figs. 1(A) and 1(C).

To analyze the genesis of anomalous drift, we first look at how the parameters γ and α affect the spiral wave in a *homogeneous* medium. As γ is only a scaling factor for the diffusion coefficient, the period of the spiral wave does not depend on it. Thus, neither normal nor anomalous drift is associated with a significant change in the period. However, due to the discrete nature of wave propagation in real systems such as cardiac tissue, there is a small decrease in the period when the spiral wave moves toward regions having higher cellular coupling during anomalous drift. Figure 2(A) shows the variation of the spiral period as a function of the parameter α, which decreases as α increases [24]. Thus, for normal drift in the presence of α gradient, the period of the spiral increases as the core moves toward lower α regions. On the other hand, we see a decrease in the period in the case of anomalous drift toward regions having higher values of α. In contrast, the wavelength does not appear to be a determinant of the drift. For anomalous drift in presence of a gradient in γ, the wavelength increases (as $\sqrt{\gamma}$), while it decreases for an α gradient, as it moves toward regions of higher α [Fig. 2(B)].

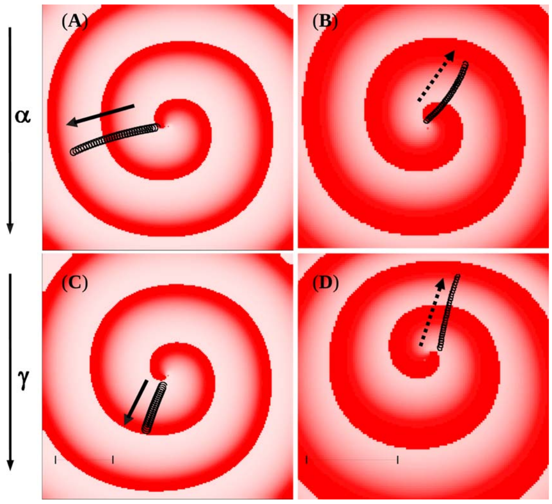

FIG. 1. (Color online) Anomalous and normal drift of spiral wave. Pseudocolor images of spiral wave at the instant when the gradient in ion-channel expression α (top row) and cellular coupling (bottom row) is applied. (A, C) Anomalous drift toward increasing values of α (A) or γ (C), the direction being shown by solid arrows. (B, D) Normal drift in α (B) or γ (D) gradient, the direction being shown by broken arrows. Parameter values are $a=0.82$, $b=0.13$ (for A, C) and $a=1.02$, $b=0.15$ (for B, D). The gradients applied are (A, B) $\Delta\alpha=0.0025$, $\Delta\gamma=0$, and (C, D) $\Delta\alpha=0$, $\Delta\gamma=0.020$. In all cases, the gradient is along the vertical direction, with α or γ increasing from top to bottom. In (B,D) the region around the core is magnified to make the wavelength of the spiral comparable to that in (A,C). The trajectories shown correspond to 100 time units and are obtained using the algorithm given in Ref. [23]. The bar indicates a scale of 25 space units.

Next, we study the effect of the magnitude of spatial gradient in α or γ on the velocity of spiral drift. Figure 3 shows the longitudinal component of the drift velocity, v_L, i.e., along the gradient, as a function of the spatial variation in α or γ. Note that, positive v_L corresponds to anomalous, while, negative v_L corresponds to normal drift of the spiral wave. Figure 3 shows that, for normal drift, increasing either of the gradients results in a monotonic increase of v_L (broken lines). However, in the case of anomalous drift as a result of α gradient, we see a *nonmonotonic* behavior in v_L, which first increases but then decreases and becomes negative [Fig. 3(B)]. Thus, the anomalous drift of the spiral toward shorter period in α gradient is seen only for small $\Delta\alpha$. For higher $\Delta\alpha$, there is a reversal of direction and the spiral exhibits normal drift. On the other hand, Fig. 3(A) shows that for a gradient in γ, the anomalous drift is observed for the entire range of $\Delta\gamma$ that is investigated.

We have also studied the effect of the local kinetics on anomalous drift by varying the Barkley model parameter a

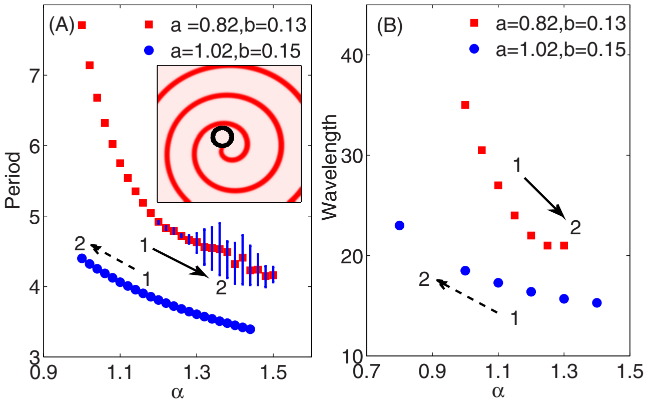

FIG. 2. (Color online) The variation of spiral period (A) and wavelength (B) as a function of the parameter α. The symbols "1" and "2" correspond to the values of α in the region around the initial and final positions (respectively) of the spiral waves in Fig. 1, with the same sets of Barkley model parameters being used. The solid and broken arrows represent the directions of anomalous and normal drift, respectively, in presence of a gradient in α. Results shown are obtained by averaging over multiple values recorded from symmetrically placed points in the simulation domain to smooth variations arising from spiral wave meandering at high values of α. Error bars are indicated when the standard deviation is larger than the symbol size used. The inset in (A) is a pseudocolor image of a spiral wave showing its trajectory in a *homogeneous* medium with parameters $a=0.82$, $b=0.13$ and $\alpha=1.275$.

[Fig. 4(A)]. Increasing a (keeping b fixed) decreases the activation threshold of the medium, and thus makes the system more excitable. We observe that for both α and γ gradients, the variation of v_L as a function of a is nonmonotonic. For the cellular coupling (γ) gradient, the presence of anomalous regime clearly correlates with excitability. The drift is anomalous at lower excitability, but becomes normal at higher excitability. However, for the gradient in α, the anomalous drift occurs only over an intermediate range of a. For lower and higher excitabilities, the drift becomes normal. Note that arguments put forth in Ref. [25] suggest that in the *large core limit* (corresponding to very low excitability), the longitudinal component of drift velocity resulting from a parameter gradient in α should disappear.

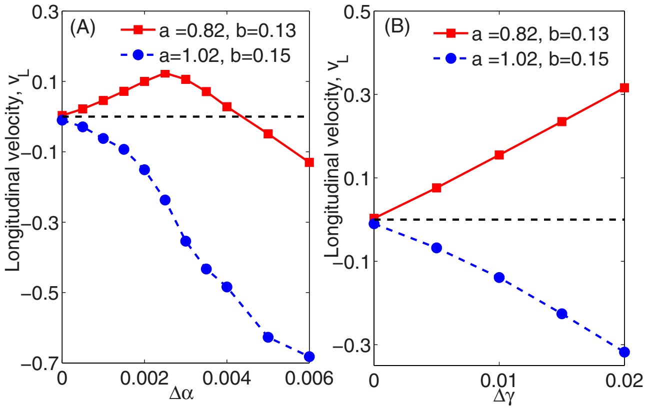

FIG. 3. (Color online) Drift velocity depends on the gradient in parameters α and γ. (A) Nonmonotonic variation (solid curve) of the longitudinal component of spiral wave drift velocity v_L as a function of the gradient in ion-channel expression, $\Delta\alpha$, for a model system with parameters $a=0.82$, $b=0.13$. Positive values of v_L indicate anomalous drift. For a different set of parameters ($a=1.02$, $b=0.15$), normal drift is seen for the entire range of gradients used (broken curve). (B) Variation of v_L with the gradient in cellular coupling, $\Delta\gamma$. Solid and broken curves represent the anomalous and normal drift seen for the two parameter sets mentioned earlier (respectively), and are observed throughout the range of gradients used.

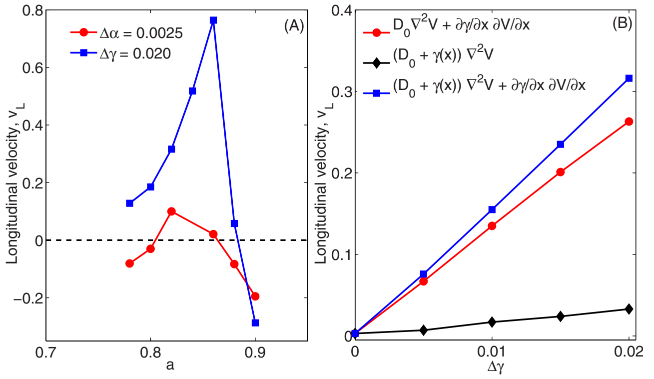

FIG. 4. (Color online) (A) Nonmonotonic variation of the longitudinal component of drift velocity, v_L, as a function of the model parameter a ($b=0.13$). The two curves correspond to media having a constant gradient in excitability (circles: $\Delta\alpha=0.0025$, $\Delta\gamma=0$) and cellular coupling (squares: $\Delta\alpha=0$, $\Delta\gamma=0.020$). (B) The contribution to v_L from the different components in the diffusion term as a function of the gradient in cellular coupling, $\nabla\gamma$. The circles and diamonds correspond to the linear and second-order contributions, and, squares correspond to the complete Laplacian term, respectively. All data points shown are for $a=0.82$, $b=0.13$.

The mechanism of anomalous drift in α gradient remains unclear. However, we can understand the anomalous drift for the cellular coupling (γ) gradient, by relating it to other drift phenomena in excitable media. Note that the Laplacian term in Eq. (1) can be expanded as

$$\nabla\gamma(x)D\nabla V=[D_0+\gamma(x)]\nabla^2V+\partial\gamma/\partial x\,\partial V/\partial x. \tag{3}$$

Therefore, the heterogeneous cellular coupling $\gamma(x)$ contributes to both the gradient ($\partial\gamma/\partial x\,\partial V/\partial x$), as well as, second-order $[\gamma(x)\nabla^2V]$ terms. The relative contributions of these terms to the longitudinal component of drift velocity is shown in Fig. 4(B). We observe that the principal effect on v_L is due to the $\partial\gamma/\partial x\,\partial V/\partial x$ term, while $\gamma(x)\nabla^2V$ accounts only for about 10% of the observed drift. This allows us to propose the following explanation for anomalous drift in the presence of a gradient in γ. If we do not consider the $\gamma(x)\nabla^2V$ term in the Laplacian, the spatial operators in Eq. (3) are seen to be identical to those in equations describing drift of a spiral wave in the presence of an electric field [26]. This latter, in turn, is similar to the Laplacian describing the drift of radially symmetric filaments of a scroll ring in three dimensions excitable media [27,28]. As shown in Refs. [29,30], the drifts observed in these two kinds of systems are induced by the same instabilities. We see from Fig. 4(B) that the gradient $\partial\gamma/\partial x\,\partial V/\partial x$, which determines the drift in an electric field and that of scroll wave filaments, also determines the drift as a result of γ gradient. Therefore, we infer that the anomalous drift direction (toward stronger cellular coupling) observed by us is also a result of the same long-wavelength instabilities determining the drift of scroll wave filaments. This suggests that the occurrence of scroll expansion in three-dimensional implies the existence of anomalous drift in γ gradient in two dimensions. Conversely, observation of anomalous drift might suggest parameter regions where scroll wave expansion is possible.

In this paper, we have explicitly demonstrated in a simple model of smoothly varying heterogeneous excitable medium that spiral waves can drift toward regions with shorter rotation period (corresponding to larger expression of ion-channels) and/or stronger cellular coupling. Both can be broadly considered to be drift toward a more excitable region. Our analysis can be easily extended to biologically realistic models, such as Luo-Rudy I (LR1) or ten Tusscher-Noble-Panfilov (TNNP) [31,32], which have the same form as Eq. (1), and to types of heterogeneity inferred from direct experimental measurements [33], although gradients in ion-channel expression may not affect all ion channels and do not always affect excitability. It might be possible to infer the parameter range in realistic models where anomalous drift may occur by using the relation between the cellular coupling gradient induced drift and scroll ring expansion. Note that the latter phenomenon has recently been seen in the LR1 model [28].

Spiral waves are not only relevant for cardiac tissue, but are also observed in many different excitable media. Thus, it may be possible to relate our observation with results of kinematic studies [17] and models of cyclic catalysis in replicating entities [34], which predict drift toward region with shorter periods. From a clinical perspective, anomalous drift is important as it may result in fibrillation by promoting wave-breaks away from the spiral core. Spiral drift in presence of a cellular-coupling gradient maybe a key factor giving rise to abnormal wave activity in regions of the heart where conductivity changes, e.g., at Purkinje-muscle cell junctions or in an infarct border zone [35]. It can also be studied experimentally and numerically in many model systems, such as, heterogeneous monolayers of neonatal rat cardiomyocytes [36].

To conclude, we have observed that spiral waves in heterogeneous excitable media, having linear gradient in ion-channel expression or cellular coupling, can drift toward regions having shorter spiral rotation period or stronger cellular coupling. It appears to be related to regimes where expansion of three-dimensional scroll wave filaments is observed. Such anomalous drift of spiral waves may increase the likelihood of complex spatiotemporal patterns in excitable medium, e.g., turbulent electrical activity in the heart.

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