

Emergence of Spiral Wave Activity in a Mechanically Heterogeneous Reaction-Diffusion-Mechanics System

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We perform a numerical study of emergent spiral wave activity in a two-dimensional reaction-diffusion-mechanics medium with a regional inhomogeneity in active and passive mechanical properties. We find that self-sustaining spiral wave activity emerges for a wide range of mechanical parameters of the inhomogeneity via five mechanisms. We classify these mechanisms, relate them to parameters of the inhomogeneity, and discuss how these results can be applied to understand the onset of cardiac arrhythmias due to regional mechanical heterogeneity.

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Spiral waves occur in various important excitable media. The most studied examples include spiral waves in the Belousov-Zhabotinski (BZ) reactions [1] and in the cardiac muscle where they underpin dangerous cardiac arrhythmias [2,3].

Excitation waves can be described by reaction-diffusion (RD) partial differential equations; however, the excitation process is often coupled to deformation of the underlying medium, such as motion of amoebae of *Dictyostelium discoideum* [4] or swelling of a gel caused by BZ reactions [5]. The heart's pumping is governed by electrical waves of excitation; yet, its deformation also feeds back on the excitation processes of the cardiomyocytes. This phenomenon, which is known as “mechanoelectrical feedback” (MEF), has been shown to be able to cause, but also to abolish, dangerous cardiac arrhythmias [6]. To study basic effects of MEF the reaction-diffusion mechanics (RDM) framework has been introduced [7], which couples RD to mechanical equations. Using the RDM framework, important phenomena were identified, such as self-organized pacemakers [8], initiation [9], drift, and breakup [10] of spiral waves.

The most important problem in the theory of spiral waves is to understand mechanisms of their initiation, as it is a key to understanding the onset of cardiac arrhythmias. So far, the main known mechanisms of spiral wave initiation are related to electrophysiological heterogeneity of cardiac tissue [11–14], for example, in duration of the refractory period of cardiac cells. Many forms of cardiac disease also cause mechanical heterogeneity in the heart. Although mechanical heterogeneity has been linked to the onset of arrhythmias, the mechanisms of spiral initiation due to mechanical heterogeneity have not been studied yet. Here we perform a generic study with the aim to understand how regional heterogeneity in passive and in active mechanical properties may cause

spiral wave activity using a discrete RDM (dRDM) model.

Model.—The dRDM model is described in detail in [15]. Here, we provide a short description of its main features. The dRDM model couples a two-variable FitzHugh–Nagumo-type RD model for cardiac excitation [16] with mechanics equations describing a finite-elastic, isotropic material,

$$\frac{\partial u}{\partial t} = \nabla^2 u - ku(u - a)(u - 1) - uv - I_s, \quad (1)$$

$$\frac{\partial v}{\partial t} = \epsilon(u)(ku - v), \quad (2)$$

$$\frac{\partial T_a}{\partial t} = \epsilon(u)(k_T u - T_a), \quad (3)$$

$$\mathbf{F}_{12} = p \left(\frac{T_a(1) + T_a(2)}{2} \right) \frac{\mathbf{l}_{12}}{\|\mathbf{l}_{12}\|}, \quad (4)$$

$$\mathbf{f}_{1a} = \left[c \left(\frac{\|\mathbf{l}_{12}\| - r_0}{r_0} \right) - d \frac{(\dot{\mathbf{l}}_{12} \cdot \mathbf{l}_{12})}{\|\mathbf{l}_{12}\|} \right] \frac{\mathbf{l}_{12}}{\|\mathbf{l}_{12}\|} + \mathbf{F}_{12}, \quad (5)$$

$$\mathbf{f}_{1p} = \frac{1}{2} \left[c \left(\frac{\|\mathbf{l}_{13}\| - \sqrt{2}r_0}{\sqrt{2}r_0} \right) - d \frac{(\dot{\mathbf{l}}_{13} \cdot \mathbf{l}_{13})}{\|\mathbf{l}_{13}\|} \right] \frac{\mathbf{l}_{13}}{\|\mathbf{l}_{13}\|}, \quad (6)$$

$$\sum_{\alpha=1}^N \mathbf{f}_{i\alpha} = m\ddot{\mathbf{x}}_i = 0, \quad (7)$$

$$I_s = G_s(\sqrt{A} - 1)(u - E_s), \quad (8)$$

where step function $\epsilon(u)$ sets time scales of recovery and contraction processes: $\epsilon(u) = 1$ for $u < 0.05$, and $\epsilon(u) = 0.1$ for $u \geq 0.05$. For undeformed tissue, Eqs. (1) and (2), with transmembrane potential u and conductance

of repolarizing current v , describe nonoscillatory cardiac tissue ($a = 0.08$, $k = 8$). We set up the mechanical model on a square lattice of mass points connected to up to $N = 8$ direct neighboring mass points with springs (see Fig. 1 in [15]). Equation (3) describes the development of active tension T_a as a function of tissue depolarization (term $\epsilon(u)k_T u$, with $k_T = 1.5$). Active contraction force is generated at each node and mediated via vertical and horizontal (“active”) springs. Equation (4) describes the contraction force \mathbf{F}_{12} generated by an active spring \mathbf{I}_{12} connecting mass points 1 and 2. In Eq. (5), \mathbf{F}_{12} is added to the elastic force mediated by the active spring \mathbf{I}_{12} . Diagonal “passive” springs account only for passive forces. Equation (6) describes the force \mathbf{f}_{1p} mediated at mass point 1 through a passive spring connecting mass points 1 and 3. Time derivatives of spring vectors are $\dot{\mathbf{I}}_{12}$ and $\dot{\mathbf{I}}_{13}$; c and d are the stiffness and damping constants (in bulk medium: $c = 1$, $m = 1$, and $d = 30 \times c$, in inhomogeneity: $d = 10 \times c$). Following previous studies on cardiac electromechanics [7–10,15], we assumed elastostatics [see Eq. (7)]. As in [8–10,15], we describe MEF as depolarizing stretch-activated currents I_s [6] given by Eq. (8) with ($E_s = 1$ and $G_s = 2.5$), where variable A is the normalized surface area (relative to undeformed reference surface area) of a square formed by 4 direct neighboring mass points connected with active springs. Stretch-activated current I_s is active if $A > 1$ (stretch).

The model was solved with the explicit Euler method for the RD system and the Verlet integration scheme for the mechanical model with time step $m\tau = 0.01$, convergence threshold $\text{thr} = 2 \times 10^{-5}$, Euler time step $\Delta t = 0.001$ (time units [t.u.]), and space step of $\Delta x = \Delta y = 0.3$ (space units [s.u.]) [15]. We used a quadratic deforming grid of 101×101 mass points and 202×202 finite difference points using no-flux boundary conditions. The boundaries of the medium were fixed in space to mimic isovolumic phases in the cardiac cycle, an assumption that has been made also in previous electromechanical studies [8–10,15].

We used a 60×60 s.u.² model with a regional mechanical inhomogeneity of size 18×30 s.u.² located close to the center of the medium (see Fig. 1). We altered the passive (parameter c) and active (parameter p) mechanical properties in this region for different simulations, where we initiated a traveling wave from one side of the medium (see Fig. 1) and computed for 200 t.u.

Results.—We found that self-sustaining spiral waves emerge in the model via several mechanisms in a large range of parameters c and p of the inhomogeneity. We will first illustrate the phenomenon of emergent spiral wave patterning and sketch underlying mechanisms. Figure 1 and movies submitted as Supplemental Material [17] illustrate the mechanisms of spiral wave initiation. Figure 1 I illustrates the first mechanism of spiral wave formation. An extra pulse ② forms in the heterogeneous region in the

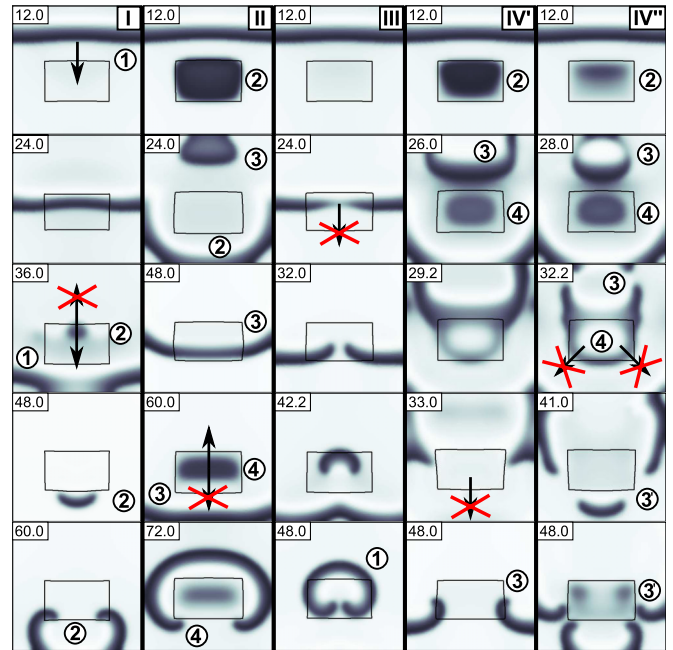


FIG. 1 (color online). Mechanisms (I–IV’’) of spiral wave formation caused by a mechanical inhomogeneity. The mechanical parameters (p , c) in the inhomogeneity are I: (1.00, 0.51), II: (0.00, 0.75), III: (0.50, 1.20), IV’: (0.25, 0.68), and IV’’: (0.25, 0.92). Wave blocks are indicated by crossed arrows. Waves are labeled by order of appearance. Simulation time [t.u.] of a snapshot is shown in its upper left corner.

back of the initially stimulated wave ① at time 36 t.u. Then the propagation of this new wave ② is blocked counter to the propagation direction of wave ① [Fig. 1 I, 36 t.u.], and as a result a pair of counter rotating spiral waves is formed [Fig. 1 I, 48 t.u., 60 t.u.]. Figure 1 II illustrates the second mechanism of spiral wave formation. Following initial wave ①, waves ② and ③ are formed, but they do not cause spirals. At time 63 t.u. a pulse ④ forms in the inhomogeneity which is blocked toward a previous wave ③ inducing a pair of counter-rotating spiral waves (72 t.u.). Note, that in contrast to mechanism I, wave block occurs in accordance with a classical pinwheel protocol for spiral wave formation, when conduction block occurs at the recovery tail of the preceding wave [18]. Figure 1 III illustrates the third mechanism of spiral wave formation. At time 24 t.u. a wave breaks at the inhomogeneous region and forms two rotating spiral waves (36 t.u., 48 t.u., 60 t.u.).

Furthermore, we found mechanisms that are related to an incomplete excitation in the inhomogeneous region. Figure 1 IV’ illustrates the fourth mechanism of spiral wave formation. At time 26 t.u., we see that a pulse ④ forms in the inhomogeneity that does not result in a traveling wave but disappears (29.2 t.u.). However, it produces a temporarily inexcitable region (29.2 t.u.), and another wave ③ breaks at this region at time 33.0 t.u. producing a

pair of spiral waves (48.0 t.u.). If this wave (4) is stronger and can exit the inhomogeneity partially, it can result in formation of spiral waves by another fifth mechanism [Fig. 1 IV'']. At time 28 t.u., we see that a pulse (4) forms in the inhomogeneity similar to the previous case, and here this wave forms a traveling wave. However, it gets blocked in diagonal directions to form pairs of spiral waves (41 t.u., 48 t.u.). Note, that we initiated only one propagating “initial wave,” and all other waves emerged in the medium due to MEF. Waves can emerge prior to the initial wave, which we will call a “premature beat” (wave (2) in Figs. 1 II, IV', IV'' the upper row) or behind the initial wave (wave (2) in Fig. 1 I at 36.0 t.u., and wave (4) in Fig. 1 II at 60.0 t.u.). Furthermore, we found that pacemakers can form in the medium.

We find that most mechanisms for spiral wave initiation are caused by MEF and accommodation. Accommodation is the phenomenon of a decrease of excitability caused by a relatively weak depolarizing current, which has been studied in electrophysiology since 1936 [19,20]. In our model, accommodation is caused by stretch of the tissue which causes a depolarization via I_s .

We will now outline the mechanisms of spiral wave formation. In mechanism I, stretch behind the traveling wave initiates a secondary wave at the region of maximal local excitability [9]. As this wave propagates towards regions of lower excitability, it is blocked as is illustrated in Fig. 1 I. This mechanism for spiral formation was reported for a homogeneous tissue in [9]. In mechanism II, a pulse is also caused via stretch behind the traveling wave; however, here wave block occurs in the opposite direction due to proximity of this pulse to the refractory tail of the preceding traveling wave. In mechanism III, the initial wave stretches the inhomogeneous region in front of itself, decreasing its excitability due to accommodation. As a result,

the traveling wave breaks at the inhomogeneous region. This mechanism was first reported in [10] in two-dimensional (2D) and in whole heart models in [21,22]. In new mechanisms IV' and IV'' a stretch of the inhomogeneous region causes a wave response. However, accommodation causes decreased excitability, and thus, it may result in an overall block of propagation and, thus, a temporary inexcitable region in the inhomogeneity (mechanism IV') which can break other waves or result in a partial exit of the wave from the inhomogeneity causing local breaks (mechanism IV''). Note, that mechanisms III and IV are similar to an important mechanism of spiral wave formation in which wave block happens due to an inhomogeneity with a prolonged refractory period [11]; however, in our case these breaks occur only due to mechanical inhomogeneity.

We will now report the regimes as a function of (p, c) . Figure 2 illustrates emergent wave patterning as a function of mechanical properties of the inhomogeneity. The white region in Fig. 2 illustrates the parametric space (p, c) where the initial wave does not produce any secondary waves. Black dots in Fig. 2(a) indicate simulations when a premature beat was induced, remaining dots when no premature beat but other wave patterning occurred. The boundary of the “patterning region” is given by two straight lines [23], which reflects the linearity of the elastic model. The positive and negative slopes reflect different mechanisms of patterning. During the formation of a premature beat, active tension p counteracts the passive tension c during formation of a pulse in the heterogeneity, while for a wave originating behind the initial wave, a stronger contraction of the heterogeneity itself (p) increases the stretch behind that wave and thus favors formation of this additional pulse. Figure 2(b) shows spiral wave formation in the experiment for a large parametric range. We studied the (p, c) -space with resolution $(\Delta p = 0.05, \Delta c = 0.05)$ and found 425 simulations that lead to emergent wave patterning. In 239

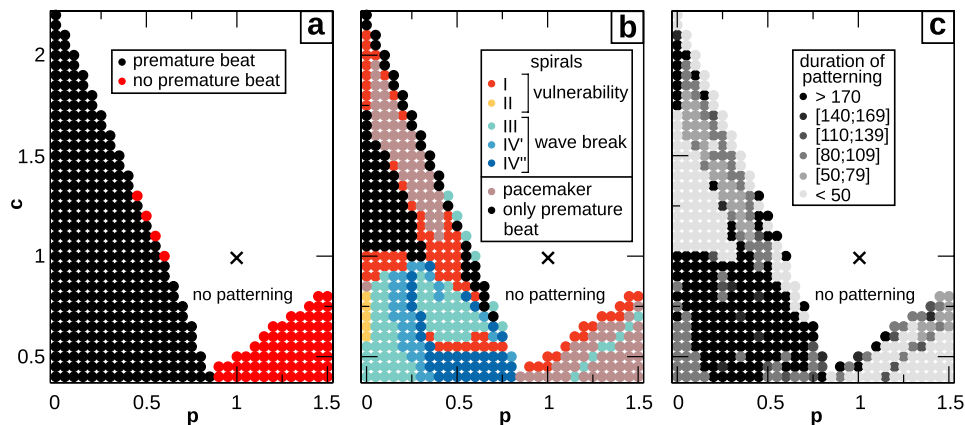


FIG. 2 (color online). Wave patterning as a function of mechanical parameters p and c of the inhomogeneity. Black crosses indicate condition $(p = c = 1)$. Colored dots indicate the wave patterning regime. “No patterning” labels the white region where the initially stimulated traveling wave propagates through the medium without producing new waves. (a) Patterning with and without premature pulse. (b) Patterning regimes: single premature beat, pacemaker, spiral formation due to vulnerability, and spiral formation due to wave break. (c) Duration of wave patterning [t.u.].

of these 424 patterning cases, spiral waves emerge (56%), in 99 simulations (23%) pacemaking activity [8] occurs, and in 87 simulations (20%) a single premature beat happens. In the 239 cases that cause spiral wave activity, mechanism III occurs 81 times (34%), mechanism I happens 80 times (33%), mechanism IV'' 41 times (17%), mechanism IV' 32 times (13%), and mechanism II occurs 5 times (2%). Figure 2(c) shows the observed duration of wave patterning as a function of (p, c) in the inhomogeneity. We see that spiral wave patterning can often sustain in the model for a long simulation time: in 160 of the 239 cases (67%) patterning sustained longer than 200 t.u. (≈ 10 spiral periods). For mechanism I, it was 85% (51 of 60 cases), for mechanism II (2 of 5), 64% for mechanism III (52 of 81), 97% for mechanism IV' (31 of 32), and 56% for mechanism IV'' (23 of 41).

We have also studied the longer-term dynamics of wave patterning on representative examples for each of the mechanisms (see Fig. 3 and movies submitted as Supplemental Material [17]). We see that for the examples for mechanisms I, II, III, and IV' [Figs. 3(a)–3(d)], the activity sustained beyond the simulation time, whereas for example IV'' activity eventually terminated. For mechanisms II, III, and IV' [Figs. 3(b)–3(d)], wave patterning included spirals and pacemakers. We see in all examples dynamic appearance and disappearance of spiral waves via various mechanisms; however, most frequently it occurs by mechanism III (accommodation).

Now, we will use our results to make predictions. Mechanical heterogeneity can occur due to different processes in the heart. The most common is myocardial ischaemia, where a region of the heart receives insufficient blood flow which can result in infarction, when a part of

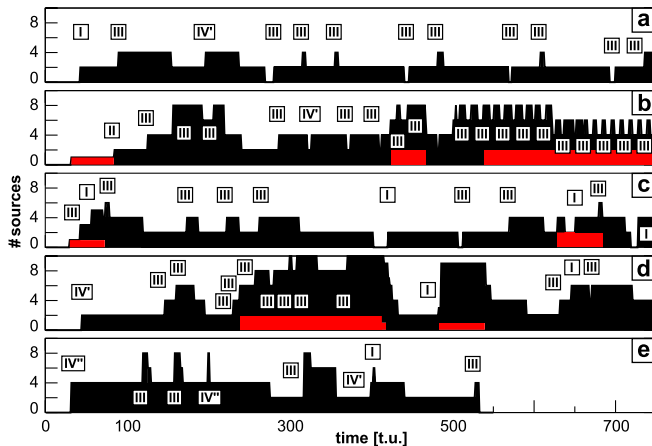


FIG. 3 (color online). Self-sustaining spiral wave activity. Number of wave sources (“#sources” shown as black line, number of pacemakers shown as bars) and mechanisms of spiral formation (I–IV'') are plotted against simulation time. Mechanical parameters (p, c) in the inhomogeneity are (a): (0.90, 0.45), (b): (0.00, 0.80), (c): (0.50, 0.70), (d) (0.40, 0.80), (e) (0.70, 0.45).

cardiac muscle tissue is damaged or dead. In acute ischaemic cardiac tissue, the contraction twitch and the stiffness are reduced [24,25], which can be modeled in a RDM model by a decrease in active contractile force scaling p and decrease in stiffness c , or increase in c for late infarction. Based on results shown in Fig. 2, we can expect that during acute ischaemia (lower c and p), the leading mechanisms of arrhythmia onset are III and IV with the occurrence of premature beats. And indeed, a previous whole-heart modeling study on acute ischaemic cardiac tissue predicted formation of premature beats and formation of spirals due to mechanism III [21], where mechanical inhomogeneity was modeled by equally downscaling stiffness and active tension in acute ischaemic tissue up to 25%. For the late infarction state, where stiffness is increased (low p , high c), our model predicts occurrence of premature beats and spiral formation mainly via mechanism I. Another possibility may be related to a neurogenic cardiac regulation. A local release of catecholamines (e.g., resulting from local sympathetic nervous activity) could increase active tension (increase in p) in a region. In that case our model predicts that the most likely mechanism for spiral formation is mechanism I without the occurrence of premature beats. Note that the parametric region in which spiral waves emerge is small here.

Discussion.—In this Letter we identified 5 mechanisms of spiral wave initiation in a heterogeneous RDM system. The leading mechanisms of spiral wave formation in (p, c) turned out to be I “nonclassical vulnerability” and III “accommodation” (67% in total), whereas “classical vulnerability” II accounted for only 2%. In this study, we stimulated a single initial wave and further waves were caused by MEF. We expect that further mechanisms might be found with the RDM approach, if, for example, a high frequency stimulation protocol would be applied.

Relating mechanisms I–IV'' to parameters p, c is a complex problem as it requires a study of the interplay of the deformation field with other emergent properties such as curvature of wave fronts and vulnerability phenomena. The main aim of this Letter was to describe the observed patterns and classify them for a particular mechanical setup. More work is necessary to obtain a better understanding of complex relations between observed regimes and model parameters. It could be interesting to generalize the analytical approach of Alvarez-Lacalle and Echebarria [26] for a nonhomogenous 2D case or to use other methods, for instance singular perturbation theory, to analytically study the effect of MEF on spiral wave formation.

The results of our study might be tested in 2D electro-mechanical experimental systems, such as myocardial tissue slices [27] and cell cultures [28]. Heterogeneity can be induced by various means. For example, ischaemia can be mimicked by covering a cell culture with a glass coverslip [29].

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