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Formation of fast spirals on heterogeneities of an excitable medium

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We study the process of formation of spiral waves in a heterogeneous excitable medium under external stimulation, using numerical and analytical methods. We show that in an excitable medium with several heterogeneities with respect to refractory period, fast rotating spiral waves can be generated. These fast spirals are formed as a result of a phenomenon of period decrease, which is the generation by a heterogeneity of waves with a period shorter than the period of the external stimulation.

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Spiral waves are known to exist in spatially distributed physical, chemical, and biological systems belonging to the class of excitable media. The initiation of spirals in cardiac tissue leads to different kinds of cardiac arrhythmias [1–3], and mechanisms of spiral wave initiation are of great interest.

Over the years, many mechanisms of spiral wave initiation were proposed. One of the first mechanisms was so-called S1S2 stimulation. In this mechanism, the spiral wave originates from a wavebreak induced by a stimulus (S2) applied to the refractory tail of the previous wave (S1) [4–6]. Spiral waves can also be induced at anatomical obstacles or lines of lateral separation of cells [8,9]. Spiral wave turbulence can occur as a result of dynamically induced heterogeneity due to the restitution properties of cardiac tissue [7]. However, the most accepted mechanism of spiral wave formation is due to heterogeneity of an excitable medium with respect to the refractory period [10–12,19], depicted in Fig. 1. Assume that within the medium with refractory period R_{med}, there is a region H with a prolonged period of refractoriness R_{het}. If we apply two stimuli with a coupling interval T_{stim} such that

$$R_{\text{het}} > T_{\text{stim}} > R_{\text{med}}, \tag{1}$$

the second wave will break at H and as a result two counter-rotating spirals will be initiated (see Fig. 1).

It was shown that these spiral waves can either annihilate or drift into the heterogeneity [13]. As a result, the period of spiral will be longer than R_{het}: ($T_{\text{spiral}} \geqslant R_{\text{het}}$), and in accordance with (1),

$$T_{\text{spiral}} \geqslant R_{\text{het}} > T_{\text{stim}}. \tag{2}$$

Therefore, the spiral will have a longer period than the period of initial stimulation, and this mechanism cannot explain initiation of fast spiral waves at low frequency of external simulation (for example at normal heart rate).

Of course, in more complex models that, for instance, incorporate action potential duration (APD) restitution, the period of spiral wave rotation can decrease during rotation, which might lead to the initiation of fast spiral waves. However, there are practically important cases in which APD restitution properties of tissue are not pronounced (for example during ischemia [14]). Moreover, it would be important to know of other processes different from restitution that can contribute to the formation of fast spiral waves.

In this paper, we present a mechanism that can generate a spiral wave in a heterogeneous excitable medium, with a period shorter than the period of external pacing. The mechanism does not require any APD restitution properties of the medium and is based on distributed multiple heterogeneities with respect to refractory period. We confirm our mechanism by numerical simulations and propose a simple phenomenological model for its explanation.

MATHEMATICAL MODEL AND METHOD OF COMPUTATION

We use the following two-variable FitzHugh-Nagumo (FHN) model [15]:

$$\partial e/\partial t = \nabla^2 e - f(e) - g,$$

$$\partial g/\partial t = \varepsilon(e,g)(3 * e - g), \tag{3}$$

$$\varepsilon(e,g) = \begin{cases} \varepsilon_1; & e < e_1, g > g_1 \\ \varepsilon_4; & e < e_1, g \leqslant g_1 \\ \varepsilon_2; & e_1 \leqslant e \leqslant e_2 \\ \varepsilon_3; & e > e_2 \end{cases},$$

$$f(e) = \begin{cases} 20 * e; & e < e_1 \\ -3 * e + 0.06; & e_1 \leqslant e \leqslant e_2, \\ 15 * (e-1); & e > e_2, \end{cases}$$

where $e_1 = 0.002\,61$, $e_2 = 0.837$, and $g_1 = 1.8$. Function $f(e)$ is a nonlinear N-shape function that specifies fast processes such as the initiation of the action potential. The dynamics of the recovery variable g in Eqs. (3) is determined by the function $\varepsilon(e,g)$. In $\varepsilon(e,g)$, ε_2^{-1} corresponds to the wave front and

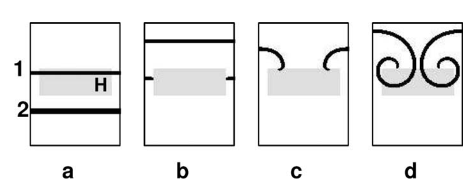

FIG. 1. Schematic representation of formation of a spiral in a heterogeneous excitable medium with two stimuli applied at the bottom of the medium.

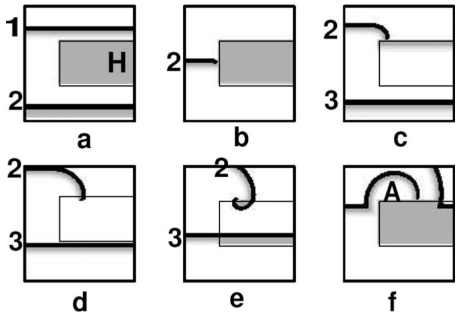

FIG. 2. The process of wave break at a heterogeneity. Computations using model (3). In a grid of 100×100 elements, the parameter values were $\varepsilon_2^{-1}=10.0$, $\varepsilon_3^{-1}=0.5$, and $\varepsilon_4^{-1}=1.75$. In the normal medium, $\varepsilon_1^{-1}=1.0$; in the heterogeneity [shaded box in (a)], $\varepsilon_1^{-1}=110$. Three stimuli were applied at the bottom of the medium with $T_{\mathrm{stim}}=22.5$. Pictures at (a) $t=25.5$, (b) $t=38.5$, (c) $t=51.5$, (d) $t=60.5$, (e) $t=64.0$, and (f) $t=76.5$, where black represents the excited state ($e>0.6$) and gray represents the refractory state.

wave back. The parameter ε_1^{-1} specifies the recovery time constant for relatively large values of g and small values of e. This region corresponds approximately to the refractory period. Similarly, ε_4^{-1} specifies the time constant for the recovery of the tissue after the refractory period (small values of e and g). Nullclines for system (3) without the diffusion term are shown in Ref. [16]. We modeled the heterogeneities by increasing ε_1^{-1} with respect to its value in the normal medium. For numerical computations, we used the explicit Euler method with Neumann boundary conditions. The medium consisted of 100×100 elements up to 400×400 elements, with time integration step from 0.012 to 0.05 dimensionless time units (t.u.) and space step from 0.25 to 0.9 dimensionless space units (s.u.).

RESULTS

The phenomenon of period decrease

Figure 2 shows the process of wave break at a heterogeneity, computed using the FHN model (3). The medium with the heterogeneous region, H, is periodically stimulated from the bottom. In Fig. 2(a), we see that the first wave passed through the heterogeneity, H (shaded box). The second wave cannot penetrate H as it is still not recovered, and breaks at it [Fig. 2(b)]. Subsequently, the tip of the wave break follows the upper boundary of H [Fig. 2(c)], penetrates H [Fig. 2(d)], and reenters the normal medium [Fig. 2(e)]. After that, the wave tip propagates along the boundary of the heterogeneity [Fig. 2(f)] and disappears at the right boundary of the medium. Thus, in this case we obtained formation of a transient spiral wave that had a finite lifetime and was annihilated after the first rotation. Interesting here is that there is an area [indicated by "A" in Fig. 2(f)] where the elements are excited by the spiral wave before the third stimulus wave appears.

In Fig. 3(a), we show the interval between the second and the third wave of excitation ($T_{W2\text{-}W3}$) of all elements outside H. The area where the period between the second and the third excitation is shorter than the external stimulation period (22.5 t.u.) is shaded by gray and black. For example, in a

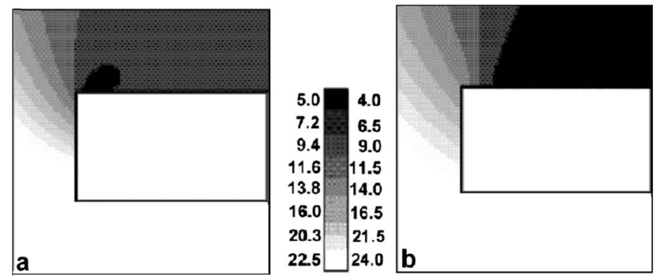

FIG. 3. The periods between the second and the third excitation ($T_{W2\text{-}W3}$) of all elements outside heterogeneity H for (a) the simulation in the FHN model (parameters are as in Fig. 2), and (b) the phenomenological model with parameters $R_{\mathrm{med}}=4.0$, $R_{\mathrm{het}}=32.0$, $T_{\mathrm{stim}}=24.0$, and $v=1.0$. Gray and black mark the areas where $T_{W2\text{-}W3}<T_{\mathrm{stim}}$. In the white area, $T_{W2-W3}=T_{\mathrm{stim}}$.

region shown by the black area in Fig. 3, the period between the second and the third excitation is between 5.0 and 7.2 t.u., which is close to the refractory period of the medium ($R_{\mathrm{med}}=4.0$ t.u.). We also see that in most of the regions above and to the right of the heterogeneity, the periods of excitation are much shorter than the external stimulation period of 22.5 t.u. Thus, even a single rotation of a spiral wave here results in the generation of waves with a short coupling interval, which we refer to as the phenomenon of period decrease induced by the heterogeneity.

Phenomenological model of period decrease

The observed phenomenon can be explained in terms of a simple phenomenological model.

Let us consider an excitable medium with a refractory period R_{med} with a heterogeneous region, H, where the refractory period is R_{het}. For our phenomenological model, we will assume that the velocity of wave propagation v is constant. This assumption is appropriate for waves propagating at low frequency, as for most of the models of cardiac tissue the conduction velocity approaches some saturated value at a low frequency of excitation (e.g., see Fig. 3 of [17], and Fig. 2 of [12]). Let us calculate now the time of arrival of the second wave $t_2(P)$ at any point $P=(P_x,P_y)$ outside H (Fig. 4). The planar part of this wave excites the points to the left of H [i.e., for $P_y<A_y$ or $P_x<A_x$; see Fig. 4(a)] and gives the following arrival times:

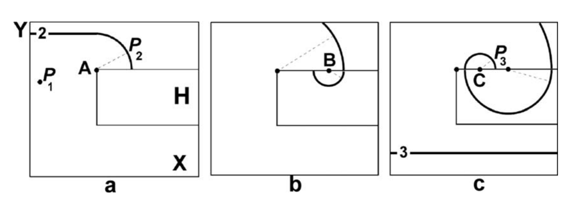

FIG. 4. Schematic representation of the process of wave break at a heterogeneity H: (a) shows the second wave (indicated by "2"), consisting of a planar wave and a circular wave with center A; (b) shows the wave after penetration into the heterogeneity at point B; and (c) shows the wave after its reentry into the normal medium at point C. The third stimulus wave here is depicted by "3."

$$t_2(P) = \frac{P_y}{v}. \quad (4)$$

Here we assume that $t_2=0$ corresponds to the initiation time of the second stimulus at the bottom boundary ($P_y=0$), P_y is the y coordinate of P, and v is the velocity of wave propagation.

The circular part of the wave excites the points to the right and above H (i.e., for $P_y > A_y$ *and* $P_x > A_x$; see Fig. 4(a)],

$$t_2(P) = \frac{A_y}{v} + \frac{\sqrt{(P_x - A_x)^2 + (P_y - A_y)^2}}{v}. \quad (5)$$

To calculate the time of arrival of the third wave, we first have to find the x coordinates of two points: point B, where the second wave penetrates into H [Fig. 4(b)], and point C, where this wave reenters the medium outside H [Fig. 4(c)]. These two points serve as the sources of two circular waves, one traveling downward (B), the other traveling upward (C).

The x coordinate, B_x, can be calculated as

$$B_x = A_x + v(R_{\text{het}} - T_{\text{stim}}), \quad (6)$$

where $R_{\text{het}} - T_{\text{stim}}$ is the recovery time from the previous excitation. After penetrating into H, the wave tip travels backward along the border and reenters the normal excitable medium as soon as it reaches the recovered elements. Because the recovery time is R_{med}, the wave reenters the normal medium at a point C, with C_x given by

$$C_x = B_x - v\frac{R_{\text{med}}}{2}. \quad (7)$$

To find the arrival time of the third wave, note that any point outside the heterogeneity H can be excited by the planar wave of the third stimulus ($3S$), or by either of these circular waves originating at points B or C ($3B, 3C$), and the arrival time of the third wave, $t_3(P)$, can be calculated as

$$t_3(P) = \min(t_{3S}, t_{3B}, t_{3C}) \quad (8)$$

with

$$t_{3S}(P) = T_{\text{stim}} + P_y/v,$$

$$t_{3B}(P) = t_2(B) + \sqrt{(P_x - B_x)^2 + (P_y - B_y)^2}/v,$$

$$t_{3C}(P) = t_2(C) + \sqrt{(P_x - C_x)^2 + (P_y - C_y)^2}/v, \quad (9)$$

where the arrival time of the second wave to point B is $t_2(B) = \frac{A_y}{v} + R_{\text{het}}\text{-}T_{\text{stim}}$, and the arrival time of the second wave to point C is $t_2(C) = t_2(B) + \frac{R_{\text{med}}}{2}$.

Using this model, we calculated the interval between the times of arrival of the second and the third wave $T_{W2\text{-}W3}$ in the same way as we did for the FHN model [see Fig. 3(b)]. Comparing Fig. 3(b) with Fig. 3(a), we see that our calculation gives qualitatively similar results. Both figures show a substantial area where the excitation period is shorter than the period of external stimulation. We also see qualitatively similar shapes of the gray regions corresponding to periods of excitation that are substantially longer than the refractory period. However, there are differences in shape for the black region corresponding to the short excitation periods. Such differences between numerical and analytical results might be due to the fact that our assumption of constant velocity holds only for the low frequency of wave propagation.

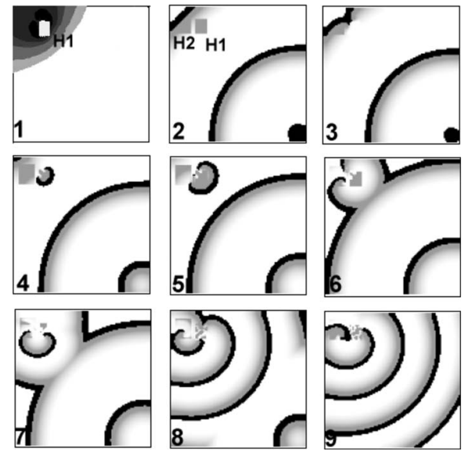

FIG. 5. Frame (1) shows the interval between the second and the third excitation of all elements outside H_1 (representation the same as in Fig. 3). Frames (2)–(9) show the evolution of waves initiated by the pacemaker located at the lower right corner of the medium. In a grid of 400×400 elements, the parameter values were $\varepsilon_2^{-1} = 5.0$, $\varepsilon_3^{-1} = 0.5$, and $\varepsilon_4^{-1} = 2.75$. In the normal medium, $\varepsilon_1^{-1} = 3.5$; in the first heterogeneity (H_1), $\varepsilon_1^{-1} = 104.0$; and in the second heterogeneity (H_2), $\varepsilon_1^{-1} = 29.0$. Period of stimulation $T_{\text{stim}} = 23.25$ t.u. Frames taken at (2) $t=52.5$, (3) $t=75.0$, (4) $t=80.0$, (5) $t=82.5$, (6) $t=87.5$, (7) $t=107.5$, (8) $t=150.0$, and (9) $t=200.0$. Data representation here is the same as in Fig. 3.

Formation of fast spirals

Now, let us show how it is possible to generate spirals with a period shorter than the period of external stimulation, using the phenomenon of period decrease (Fig. 5). First, let us consider simulation for an excitable medium with one heterogeneity H_1 shown in Fig. 5, frame (1) and a pacemaker located in the bottom-right corner. The stimulation period was chosen such that it resulted in the initiation of wave breaks and transient spirals on the heterogeneity H_1. In the same way as we did in Fig. 3(a), we determined the coupling intervals between the second and third excitation waves generated at this heterogeneity ($T_{W2\text{-}W3}$) and found that there are regions with short periods of (re)excitation due to period decrease [Fig. 5, frame (1)]. After that, we placed the second heterogeneity H_2 in the "black" region on the left side of H_1 and we chose the refractory period of H_2 to be slightly longer than the coupling interval between waves 2 and 3 in that area. In a medium with such properties, it was possible to generate fast spirals, as depicted in Fig. 5, frames (2)–(9). We see that after the wave breaks at H_1, two spirals are created in the medium [Fig. 5, frames (2)–(4)]. They break at H_2 due to the short $T_{W2\text{-}W3}$ in that region [Fig. 5, frame (5)]. After some transient process, a stationary spiral wave located within H_2 is formed (the left spiral in Fig. 5), which rotates at high frequency and periodically excites the medium [see periodic wavetrain in Fig. 5, frame (9)]. The period of this spiral ($T_{spiral} \approx 10$ t.u.) is lower than the period of external stimulation ($T_{stim}=23.25$ t.u.), therefore it increasingly dominates the medium [Figs. 5, frames (6)–(8)] until it finally totally suppresses the pacemaker [Fig. 5, frame (9)].

From this, we conclude that in order to produce a fast spiral via the phenomenon of period decrease, a medium should contain two heterogeneities with refractory periods R_{het1} and R_{het2} such that $R_{het1} > T_{stim} > R_{het2} > R_{med}$ and the second heterogeneity H_2 should be placed inside the region where the coupling interval between waves generated by the primary spiral is shorter than T_{stim}. As follows from our phenomenological consideration, the regions with the shortest coupling intervals are located close to the point where wave 2 reenters normal tissue from the heterogeneity H_1. The exact location of this region depends on several factors, such as the size and shape of H_1, its position with respect to the pacemaker position, and the relation of R_{het1} and T_{stim}.

DISCUSSION

In this paper, we have described a mechanism that can account for the formation of fast spiral waves in an excitable medium under low-frequency external forcing. This mechanism is based on the phenomenon of period decrease and requires the existence of two heterogeneous regions that are in close proximity. Experimental studies show that an infarcted zone consists of patches with different properties [3]. These patches can serve as several heterogeneities and may provide a substrate for arrhythmogenesis via our mechanism.

A limitation of our study is that the model of excitable medium we used does not show pronounced APD restitution properties. We choose this approach because the aim of this research was to study the basic mechanisms of formation of fast spirals in a heterogeneous excitable medium, without extra complicating factors. The effects of APD restitution will be additional to the effects studied in this paper and are expected to shorten the period of spiral waves in addition to the phenomenon of period decrease found in this paper. Also, differences in APD restitution curves in normal tissue and at the heterogeneity may result in different mechanisms of spiral wave generation and breakup in heterogeneous media [12,18,19].

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