How to Tell a Target from a Spiral: The Two Probe Problem

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Targets and spirals are ubiquitous wave patterns found in excitable media. Here, we show how to distinguish a target from a spiral using only two probes to measure activity and deliver stimuli. The different spatiotemporal symmetry properties of targets and spirals are revealed applying stimuli interchangeably at both probes. Our technique has diagnostic implications for cardiology since targets and spirals are associated with different mechanisms of cardiac arrhythmia. [S0031-9007(99)09448-X]

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Targets and spirals are distinct wave patterns that have been observed in a variety of physical, chemical, and biological systems [1,2]. A target pattern is produced by concentric waves traveling away from a rhythmic source, whereas a spiral wave is generated by a rotating source. Despite their different mechanisms, both wave patterns lead to indistinguishable rhythms when measured at a single point in space. This ambiguity sparked the early debate over the mechanism of the periodic radio waves measured from pulsars [3], and has implications for the mechanisms of several biological rhythms, some of which are life threatening [2,4].

Our interest in distinguishing spirals from targets is motivated by a problem in cardiac electrophysiology: targets and spirals underlie serious arrhythmias in the heart [4,5] and cardiologists need to diagnose the mechanism to launch the appropriate therapy. However, cardiac targets and spirals are not readily distinguishable since it is presently impossible to measure a high-resolution activation map in an intact human heart. Rather, a small number of probes can be placed on the heart's inner surface in order to measure local electrical activity and deliver stimuli [5]. Here, we pose the following problem: what is the minimum number of probes required to distinguish a target from a spiral?

For an excitable medium like the heart, a localized stimulus can cause a global spatiotemporal change in the wave pattern. For example, a time shift is caused by a sufficiently large stimulus delivered at the right time and location [2,5–8]. The time shift of the rhythm is called phase resetting, or simply resetting (Fig. 1). Here, we show that targets and spirals can be distinguished by interchanging the stimulus location between two probes and measuring the resetting response at both probes.

The phase ϕ of a rhythm measured at position $\mathbf{r}$ is defined as the time since the previous activation normalized for the period of the rhythm T_0:

$$\phi(\mathbf{r}, t) = \frac{t - \tau(\mathbf{r})}{T_0} \pmod 1 , \qquad (1)$$

where $\tau(\mathbf{r})$ is the time at which the activation variable crosses some threshold, and ϕ advances from 0 to 1 with the period of the rhythm. The phase field $\phi(\mathbf{r}, t)$ completely describes the spatiotemporal activation pattern. The phase difference at locations $\mathbf{r_1}$ and $\mathbf{r_2}$ is determined by the time delay between the activation of probes at the different locations:

$$\phi(\mathbf{r}_1, t) - \phi(\mathbf{r}_2, t) = -\frac{\Delta t_{12}}{T_0} , \qquad (2)$$

where $\Delta t_{12} = \tau(\mathbf{r}_1) - \tau(\mathbf{r}_2)$ is the time difference between the activation of probes p_1 and p_2.

Target and spiral phase fields have different symmetry properties. Let the operator $\hat{R}_\varphi$ denote a rotation of the plane about the origin by an angle φ and let $\hat{T}_t$ denote a

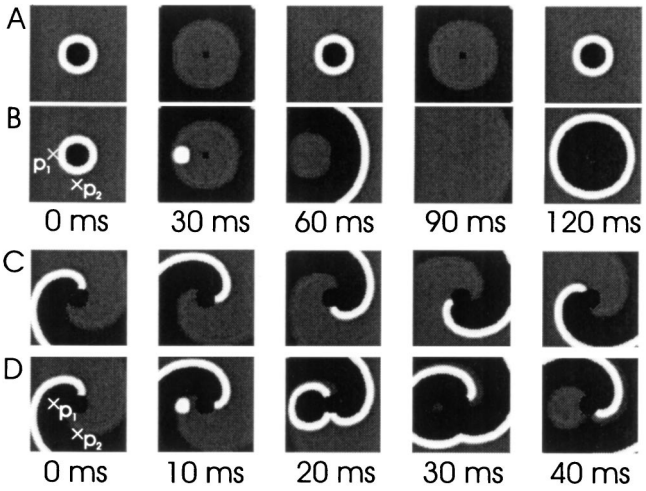

FIG. 1. Resetting of a target pattern and a spiral wave. (A) A target pattern with period $T_0 = 59.7$ ms generated by a pacemaker at the center of the square. (B) The stimulus delivered at p_1 at phase $\phi_1 = 0.4$ results in a wave that causes the pacemaker to fire prematurely and thereby resets the rhythm. (C) A spiral wave propagating around a circular obstacle with a period $T_0 = 47.7$ ms. (D) The stimulus delivered at p_1 at $\phi = 0.4$ generates a wave that collides with the obstacle and breaks into two waves circulating in opposite directions. The wave traveling in the same direction as the original wave continues on to reset the rhythm. The original wave collides with the oppositely traveling wave and both are annihilated.

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time translation by an amount t. The symmetry properties of the two phase fields are expressed by their invariance under the following transformations:

$$\begin{aligned} &\text{Target:} \quad \hat{R}_\varphi \phi(\mathbf{r},t) = \phi(\mathbf{r},t), \quad \forall \varphi\,, \\ &\text{Spiral:} \quad \hat{T}_{t^*}\hat{R}_\varphi \phi(\mathbf{r},t) = \phi(\mathbf{r},t), \quad t^* = \frac{\varphi T_0}{2\pi}\,. \end{aligned} \tag{3}$$

Thus, the target pattern is invariant under a rotation about an arbitrary angle, whereas the spiral pattern is invariant under a rotation combined with a particular time translation.

The above symmetry properties imply the following analytic forms for the phase fields. For the target,

$$\phi(r,\theta,t) = \frac{t}{T_0} - \frac{r}{cT_0} \pmod 1\,, \tag{4}$$

where c is the propagation velocity [9] and (r,θ) are the radial and angular coordinates of a polar coordinate system with the origin at the center of the pacemaker region. The spiral phase field is given by

$$\phi(r,\theta,t) = \frac{t}{T_0} + \psi(r) + \frac{\theta}{2\pi} \pmod 1\,, \tag{5}$$

where $\theta = -2\pi\psi(r)$ describes the shape of the spiral wave front rotating clockwise around a circular obstacle at the origin [10,11].

Measuring the resetting by stimulation at two probes reveals the different symmetry properties of the target and spiral waves. Figure 1 illustrates resetting of a target pattern (Figs. 1A,1B) and a spiral wave rotating around a circular obstacle (Figs. 1C,1D) in a modified FitzHugh-Nagumo model of excitable media [12]. We measured the activity at two probes labeled p_1 and p_2 and delivered the stimuli to probe p_1.

The notation is illustrated in Fig. 2A. The local phase ϕ_i of the stimulus is measured at both probes. The effect of the stimulus is determined by measuring the successive activation times since the activation prior to the stimulus $T_1^{(i)}, T_2^{(i)}, \cdots, T_j^{(i)}$ where the index i indicates the probe and the index j indicates the number of activations since the stimulus was delivered (Fig. 2A) [7]. The local activation times $T_j^{(i)}$ depend on both the phase and the location of the stimulus.

Figure 2B shows the normalized resetting curves for the spiral and target patterns using stimuli delivered and measured at probe p_1. The local phase measurements at probe p_2 are given by Eq. (2). Furthermore, the resetting curves measured at p_1 and p_2 are related by

$$T_j^{(1)}(\phi_1) = T_j^{(2)}\left(\phi_2 - \frac{\Delta t_{12}}{T_0}\right), \tag{6}$$

for j large enough so that the transient effects of the stimulus have dissipated. Equation (6) represents the general result that resetting curves due to stimuli delivered at a single location, but measured at two different probes, are related by a horizontal shift equal to the phase lag of activation between the two probes during the underlying rhythm.

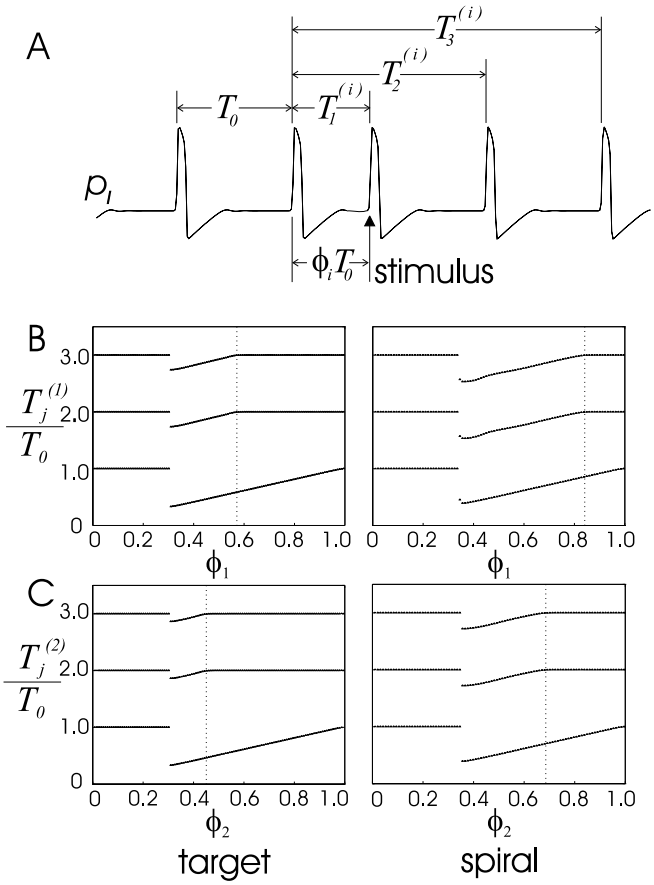

FIG. 2. Resetting curves. (A) Definition of measurements at probe p_i. (B) The resetting curves as measured at the stimulus probe p_1 for a target (left) and a spiral (right). The phase ϕ_1^* at the junction between the interference and resetting zones is marked by the dotted vertical line. (C) Resetting curves for stimuli delivered at p_2. ϕ_2^* (dotted vertical line) is shifted to the left compared to ϕ_1^* in (B) because p_2 is farther from the source of the rhythm. The magnitude of the shift is predicted by Eq. (7) in the case of the target but not for the spiral.

The resetting curves obtained at the stimulus probe are strikingly similar for both targets and spirals (Fig. 2B). The similarity is easily explained. Early stimuli fall in the refractory zone and therefore have no effect on the rhythm. Such stimuli give the flat part on the left of the resetting curve. On the other hand, a late stimulus results in a new wave that is annihilated before interacting with the pacemaker or the tip of the spiral. Thus, late stimuli fall in an "interference zone" and also have no effect on the rhythm. Only stimuli at intermediate phases reset the rhythm and result in the diagonal part of the resetting curve.

Therefore, the resetting curve measured at the stimulation probe is divided into three zones: the refractory zone at small phases, the resetting zone at intermediate phases, and the interference zone at late phases. The stimulus phase ϕ^* separates the resetting and interference zones [13].

The position of ϕ^* is determined by the distance between the stimulation probe and the source of the rhythm. Since a resetting stimulus must generate a wave that interacts with the source, the stimulus must be delivered early enough so that the wave has time to travel and interact with the pacemaker or the tip of the spiral. A wave generated by a late stimulus will be annihilated by the original target or spiral wave before interacting with the source. Therefore, as the distance of the stimulus from the source increases, the junction phase ϕ^* shifts earlier in the cycle.

Figure 2C shows the resetting curves measured at the stimulation probe p_2. Comparing with the resetting curves from stimuli delivered at p_1 (Fig. 2B), we find that $\phi_2^* < \phi_1^*$ for both the target and the spiral, implying that p_2 is farther from the source than p_1.

Because of the rotational symmetry of the target pattern, the junction phase at a stimulus probe p_i is given by $\phi_i^* = 1 - \frac{2r_i}{cT_0}$. From Eqs. (2) and (4) the time delay between activation of the probes depends on their relative distance from the source: $\Delta t_{12} = (r_1 - r_2)/c$. Therefore, for a target pattern the time delay between the activation of two probes predicts the shift of the junction phase ϕ^* resulting from interchanging the stimulation site between the probes:

$$\phi_1^* - \phi_2^* = -\frac{2\Delta t_{12}}{T_0}, \tag{7}$$

where ϕ_i^* is the junction phase measured at the stimulus site i. The factor of 2 arises from Eq. (6) since the phase measurements are made at their respective stimulation sites. Since the spiral pattern lacks rotational symmetry, probe activation delays alone cannot predict the change in the interference zones caused by interchanging the location of the stimulus. Therefore, targets and spirals can be distinguished on this basis.

To illustrate this symmetry property, we applied prediction (7) in our simulations of the FitzHugh-Nagumo model. From Fig. 2B, we find that $\phi_1^* = 0.57$ and 0.84 for the target and spiral patterns, respectively. Similarly, Fig. 2C shows that $\phi_2^* = 0.45$ for the target and $\phi_2^* = 0.68$ for the spiral. The activation time delays were $\Delta t_{12} = -3.5$ ms for the target and $\Delta t_{12} = 8.0$ ms for the spiral. Thus, as expected, (7) is satisfied for the target pattern but not for the spiral for this arrangement of probes.

Whereas a target pattern satisfies (7) for any two probes positions, a spiral pattern will satisfy (7) only in the special case where the probes are placed along a curve whose shape depends on the shape of the spiral [14]. Measurement uncertainties may also lead to (7) being satisfied for a spiral. Thus, failure to satisfy (7) rules out a target pattern, but more than two probes should be used to confirm a target.

Although our analysis is based on the rotational symmetry properties of target patterns in homogeneous media, Eq. (7) is also satisfied for target patterns with broken rotational symmetry arising from anisotropic wave propagation. Provided that the time for a wave to propagate from the pacemaker to the stimulus probe is equal to the time for the stimulus wave to propagate to the pacemaker, the broken rotational symmetry is compensated by the anisotropic propagation of waves generated by stimuli. Thus, Eq. (7) can be used to identify distorted target patterns.

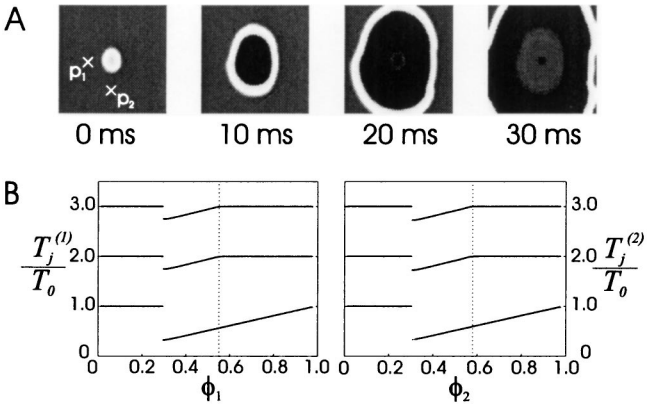

FIG. 3. (A) A distorted target pattern with $T_0 = 61.6$ ms caused by heterogeneous anisotropic diffusion. (B) The resetting curve measured at the stimulation site p_1 (left panel) shows that the junction phase $\phi_1^* = 0.55$, whereas the resetting curve measured from stimulation site p_2 (right panel) shows that the junction phase is $\phi_2^* = 0.58$. Equation (7) is also satisfied for the distorted target.

For example, Fig. 3A shows a highly distorted target pattern with a period of $T_0 = 61.6$ ms that was produced by inhomogeneous anisotropic diffusion [15]. We measured the activity at p_1 and p_2 and found that $\Delta t_{12} = 0.8$ ms. The curves in Fig. 3B show the resetting response for stimuli delivered at p_1 (left panel) and p_2 (right panel). We find that $\phi_1^* = 0.55$ and $\phi_2^* = 0.58$, thereby confirming that Eq. (7) is satisfied for the distorted target pattern.

Since inhomogeneity and anisotropy do not affect our ability to identify a distorted target pattern, our techniques will work in excitable media with complex wave propagation. Furthermore, our technique also applies to target patterns in three dimensions since they are also described by the radially symmetric phase field (4).

Targets and spirals correspond to different mechanisms of cardiac arrhythmia with different therapies [4,5,16]. Therefore, distinguishing between them is of crucial clinical importance. Our two-probe diagnostic technique uses resetting stimuli to identify the geometry of the propagating waves. Since resetting stimuli are routinely used for other diagnostic purposes [5,8], cardiologists should be able to use our method to distinguish targets from spirals in clinical settings.

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[9] Because of curvature effects, the propagation velocity c generally depends on the distance r from the pacemaker. For simplicity, we have taken c to be a constant. Nevertheless, our results apply provided that the time for a wave to propagate from the pacemaker to the stimulus probe is equal to the time for the stimulus wave to propagate to the pacemaker.

[10] A spiral wave circulating around a circular obstacle is a model for a common class of cardiac arrhythmia called anatomical reentry. Reentry that does not involve an obstacle is called functional reentry and was not studied in the present paper.

[11] A counterclockwise rotation is described by changing the sign of the $\theta/2\pi$ term in the spiral phase field. See J. D. Murray, *Mathematical Biology* (Springer-Verlag, Berlin, 1993), 2nd ed., p. 348.

[12] We implemented the following modified FitzHugh-Nagumo model:

$$\frac{\partial v}{\partial t} = \frac{1}{\epsilon}\left(v - \frac{1}{3}v^3 - w\right) + D\nabla^2 v + I_{\mathrm{loc}} + I_{\mathrm{stim}}(t),$$

$$\frac{\partial w}{\partial t} = \epsilon(v + \beta - \gamma w)g(v),$$

where v is the excitation variable, w is the recovery variable, $\beta = 0.7$, $\gamma = 0.5$, and $\epsilon = 0.3$. The diffusion coefficient $D = 1\ \mathrm{cm^2\,s^{-1}}$. I_{loc} is a constant current applied to a localized region at the center of the sheet in order to either make it oscillate, mimicking a pacemaker, or depress excitability thereby creating an obstacle around which a spiral wave can propagate. $I_{\mathrm{stim}}(t)$ is a pulsatile stimulation current used for resetting. The sigmoidal function $g(v)$ controls the rate of the pacemaker: $g(v) = (w_H - w_L)/(1 + e^{-kv}) + w_L$, where $k = 4.0$, $w_H = 0.6$, and $w_L = 0.13$ in the pacemaker region and 0.4 everywhere else. For the spiral wave $k = 4.0$, $w_H = 0.6$, and $w_L = 0.4$. The equations were solved using an Euler integration scheme on an 80×80 grid with zero-flux boundary conditions, a spatial discretization of 0.4 mm and a time step of 0.05 ms.

[13] For reentrant waves, the resetting curves have a discontinuity between the refractory and resetting zones [7].

[14] If probe p_1 is at position (r_1, θ_1), our theory predicts that (7) will be satisfied when p_2 is placed on the curve $f(r) + 3\psi(r) + \theta/\pi = f(r_1) + 3\psi(r_1) + \theta_1/\pi$. f is an increasing function such that $f(r_0) = 0$ where r_0 is the radius of the obstacle. If the propagation velocity does not depend on the curvature of the wave front, then $f(r) = (r - r_0)/cT_0$. Otherwise, f can be measured by performing resetting at varying probe positions: $f(r) = 1 - \phi^*(r) - \Delta t(r)/T_0$, where $\phi^*(r)$ is the measured junction phase at (r, θ) and $\Delta t(r)$ is the time delay between probes at (r, θ) and (r_0, θ).

[15] We randomly chose four large squares of average size 30×30 grid points with each square being assigned random diffusion coefficients, averaging $1\ \mathrm{cm^2\,s^{-1}}$ in one direction and $1.5\ \mathrm{cm^2\,s^{-1}}$ in the perpendicular direction. Elsewhere, the diffusion coefficients were assigned the average values.

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