Unpinning of a spiral wave anchored around a circular obstacle by an external wave train: Common aspects of a chemical reaction and cardiomyocyte tissue

Masanobu Tanaka, Akihiro Isomura,[a] Marcel Hörning, Hiroyuki Kitahata,[b] Konstantin Agladze,[a] and Kenichi Yoshikawa[c]
Department of Physics, Graduate School of Science, Kyoto University and Spatio-temporal Order Project, ICORP JST, Kyoto 606-8502, Japan

(Received 28 January 2009; accepted 22 October 2009; published online 19 November 2009)

It is well known that spiral waves are often stabilized by anchoring to a local heterogeneity ("pinning") and that such pinned waves are rather difficult to eliminate. In the present report, we show that pinned spiral waves can be eliminated through collision with a wave train arriving from the outer region, as confirmed in experiments on the Belousov–Zhabotinsky (BZ) reaction as well as in cardiomyocyte tissue culture. A numerical simulation using the Oregonator, a mathematical model for the BZ reaction, provides the parameter area for successful unpinning. The scenario of unpinning is discussed in terms of the dispersion relation of the wave train by taking into account the curvature effect of the excitation wave. © *2009 American Institute of Physics*.
[doi:10.1063/1.3263167]

Spiral waves are generic structure in excitable systems, which have been actively studied during the past 20 years as a plausible origin on the most dangerous cardiac arrhythmia. The methods of suppression of spiral waves are of great importance and create a basis for curing cardiac rhythm abnormalities leading to fibrillation and sudden death. It was shown recently that antitachycardia pacing (ATP) induces drift of free spiral waves until their annihilation at the boundary of cardiac tissue culture.[1] However, spiral waves are often stabilized by anchoring to a local heterogeneity and such pinned waves are rather difficult to eliminate. In the present article, we show that pinned spiral waves can be eliminated through collision with a wave train arriving from the outer region, which is essentially similar to the application of ATP procedure, and extends ATP capability to the pinned spiral waves. We experimentally confirmed the unpinning process on the spiral waves in Belousov–Zhabotinsky (BZ) reaction as well as in cardiomyocyte tissue culture. A numerical simulation using the Oregonator, a mathematical model for the BZ reaction, provides the parameter area for successful unpinning. The scenario of unpinning is discussed in terms of the dispersion relation of the wave train by taking into account the curvature effect of the excitation wave. The insights obtained in this study are expected to afford a theoretical and mechanistic background for the development of more efficient ATP methods.

I. INTRODUCTION

Excitable systems are widespread in nature. Classical examples are neural networks, cardiac tissue,[2,3] and populations of social amoebae *Dictyostelium discoideum*.[4] In two-dimensional excitable systems, a spiral wave is one of the most characteristic structures and has attracted the attention of many researchers. Spiral waves can be directly observed in several chemical systems: the BZ reaction,[5,6] CO oxidization on a metal surface,[7] and corrosion waves on steel in nitric acid.[8] Spiral waves can also be observed in the heart and they have been shown to be the origin of ventricular tachycardia and fibrillation.[9,10]

To remove spiral waves and to reset the chaotic state of heart tissue to a normal beating motion, a strong electric field delivered by an automated external defibrillator is often used. Similarly, electrical shocks are delivered also by an implantable cardioverter defibrillator. The application of a high voltage/current shock is painful and often results in burning and substantial damage to the cardiac tissue. To avoid this damaging action of cardioversion shocks, new procedures for suppressing spiral waves are based on the delivery of a series of low-voltage stimuli to heart tissue to initiate excitation waves. Although the ATP procedure is successful in about 85% of cases,[11] any improvement could help to save thousands of lives. Recently, it was shown that one of the most probable mechanisms for the ATP is a pacing-induced drift of the spiral wave.[1,12,13] It is well known that a fast organizing center will eventually dominate a slow organizing center. The pacing-induced drift of the spiral wave can be considered in the same way. Although the pacing-induced drift of the spiral wave has been proven for free unpinned spirals, it is not clear whether a similar procedure would work for spiral waves that are pinned to some fixed anatomical heterogeneities or obstacles such as scars or veins.[14–18] A few studies with computer simulations have suggested a pos-

[a]Present address: Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8501, Japan.
[b]Present address: Department of Physics, Graduate School of Science, Chiba University, Chiba 623-8522, Japan.
[c]Author to whom correspondence should be addressed. Electronic mail: yoshikaw@scphys.kyoto-u.ac.jp.

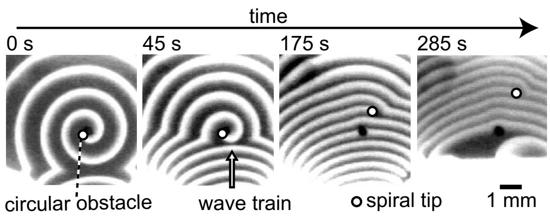

FIG. 1. Experimental results for the unpinning of a pinned spiral wave on a photosensitive BZ medium. Upon the wave train from below, the pinned spiral wave was unpinned and drifted upward. In the fourth figure, the incoming wave train was suppressed by strong light irradiation. The diameter of the circular obstacle was 0.5 mm. The concentrations in the BZ solution are $[NaBrO_3]=0.6$ M, $[H_2SO_4]=0.3$ M, $[CH_2(COOH)_2]=0.2$ M, $[NaBr]=0.05$ M, and $[Ru(bpy)_3Cl_2]=1.7$ mM, which are similar to those in previous studies (Refs. 21 and 22). The white and black regions correspond to oxidized and reduced states, respectively.

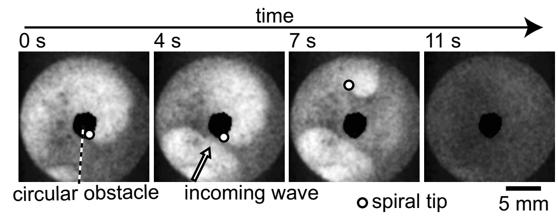

FIG. 2. Experimental results for the unpinning of a pinned spiral wave on cardiomyocyte tissue. Upon the arrival of a wave train from below, the pinned spiral wave was unpinned and drifted upward. At $t=9$ s, initiation of the wave train stopped. The diameter of the circular obstacle was around 3.5 mm. The white region corresponds to the excited state.

sible mechanism of pacing-induced unpinning, but did not provide any clear explanation.[19]

In the present study, we investigate the process of the unpinning of a spiral wave that is pinned around an obstacle in the BZ reaction and in cardiomyocyte tissue with the aid of computer simulations. We also conceptually and analytically clarified the physics that underlies the unpinning phenomenon: dependence on the wave speed versus the period of the wave train (dispersion curve) and the effect of the curvature of the wave front on propagation.

II. EXPERIMENTS

To study the unpinning of a spiral wave, we considered the BZ reaction, which provides excellent experimental reproducibility.[20] We created a pinned wave using the following procedure. Small droplets of oil with a volume of less than several microliters were put on a Millipore filter. When the filter is soaked in the solution for the photosensitive BZ, the oily parts are protected from the solution. Through this procedure, we were able to produce obstacles that measured from 0.5 to 3 mm in diameter, depending on the amount of oil applied. We then generated a wave that rotated around the obstacle. For this purpose, we initiated a plane wave by touching the surface of the filter with a silver wire. When the wave bypassed the obstacle (from both sides), we suppressed the propagating wave on one side of the obstacle by using strong local illumination. Thus, we obtained a wave that rotated around the obstacle under well-controlled conditions with satisfactory reproducibility.

To produce a source of excitation with higher frequency, a microdroplet of 1 M sulfuric acid (2–3 μl) was placed on the Millipore filter at a distance of 20 mm or more from the rotating wave (to ensure that the acid did not influence the pinned wave). The site on the Millipore filter with increased acidity thus served as a high-frequency oscillator, which generated wave trains. Since every wave in the generated wave train propagated slower than the preceding wave, upon reaching the pinned wave the wave train showed a gradually decreasing period between waves. At some point, the pinned wave detached from the obstacle and was forced to drift away. This process is illustrated in Fig. 1.

We also performed an unpinning experiment on a cardiomyocyte tissue culture. For this purpose, we used a culture system of cardiac cells and visualized excitable waves by using a Ca^{2+}-sensitive fluorescent dye, Fluo-4.[1,23] A spiral wave was initiated in tissue culture by a premature stimulus. To create the obstacle to which the rotating wave is pinned, a small piece of the tissue was surgically removed in the vicinity of the core of the spiral wave. The spiral wave attached to such an obstacle was stable enough to propagate for several minutes. Figure 2 shows an example of the experimental observation of the unpinning process in cardiomyocyte tissue. The details in the experiments are described in a different place.[23]

III. NUMERICAL SIMULATION

To obtain deeper insight into the mechanism of unpinning, we carried out a numerical simulation using the Oregonator for the photosensitive BZ reaction,[24,25]

$$\frac{\partial u}{\partial t} = \frac{1}{\epsilon}\left[u(1-u) - (fv+\phi)\frac{u-q}{u+q}\right] + D\nabla^2 u, \tag{1}$$

$$\frac{\partial v}{\partial t} = u - v, \tag{2}$$

where u and v are variables which correspond to the concentrations of the activator and inhibitor, respectively. In the real reaction, u corresponds to the concentration of $HBrO_2$ and v corresponds to that of the oxidized catalyst $Ru(bpy)_3^{3+}$. ϵ, f, and q are parameters which determine the characteristics of the BZ reaction. ϕ corresponds to the light intensity and D is the diffusion constant of the activator. By considering the experimental conditions for our BZ reaction, and for the purpose of simplicity, the diffusion constant of the inhibitor is taken to be zero. In our calculation, the parameters are set as follows: $\epsilon=0.1$, $f=2$, $q=2\times10^{-3}$, $D=1$, and $\phi=1\times10^{-2}$. Under the above conditions, a free spiral wave exhibits rigid rotation with a radius and period of $R_{\text{free}}=1.6$ and $T_{\text{free}}=7.44$. It is noted that the periods of the rotating wave without initiation were 5.2 and 7.6 for $R_0=2.1$ and $R_0=3.3$, respectively. The calculations are performed in cylindrical coordinates, and the mesh sizes are $\Delta t=2\times10^{-5}$, $\Delta r=0.1$, and $\Delta\theta=\pi/400$. A Neumann boundary condition is adopted for both of the boundaries of the obstacle and the periphery. The radius of the outer boundary is 15, although the outer bound-

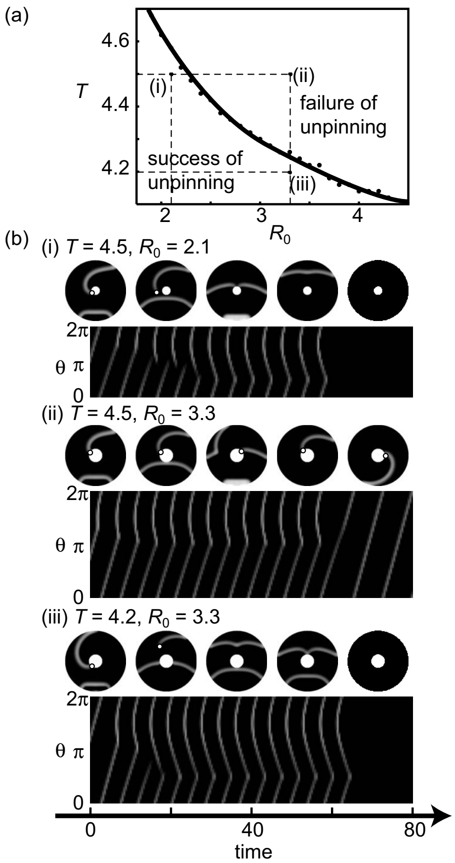

FIG. 3. Numerical results. (a) The relationship of R_0 and T indicates the parameter area of successful unpinning. Black points correspond to the threshold of successful unpinning, and the thick line is an extrapolation of the threshold. (b) Snapshots and spatiotemporal diagrams for the three parameters marked in (a) are shown. Each example is illustrated by five snapshots taken every 20 time units. First and last snapshots correspond to the beginning and end of the spatiotemporal diagram, respectively. The waves are plotted by the activator u and spiral tips are marked by small white dots. The origin of θ corresponds to the horizontal rightward line. The wave train was applied between 0 and 65 time units with the respective period T in the lower periphery. Cases (i) and (iii) show the successful unpinning of the obstacle bounded spiral wave. Case (ii) shows an example of unsuccessful unpinning.

ary does not play an important role in the unpinning of a spiral wave.

The results of the numerical calculation are shown in Fig. 3. As has been reported previously by Fu *et al.*,[19] the spiral wave is more easily unpinned when the period of the wave train T is smaller and when the radius of the circular obstacle R_0 is smaller. It is confirmed that the unpinning phenomena are independent of the radius of the outer boundary and the initial phase of the spiral wave.

Figures 3(b)(i) and 3(b)(iii) show that the wave front of the spiral wave first disappears in the region near the boundary of the obstacle and that the wave tip appears. The continuous wave trains induced the drift of the spiral wave and were finally eliminated [see the last frames in Figs. 3(b)(i) and 3(b)(iii)]. It is noted that high-frequency stimulation was able to sustain the stable wave trains without any wave breaks, since the parameter space we have chosen prohibits wave breaks of wave trains at the range of the periods we have used. It is noted that the periods of the rotating wave without initiation were 5.2 and 7.6 for $R_0=2.1$ and $R_0=3.3$, respectively. We will discuss the mechanism of unpinning by considering the behavior of the chemical wave in this area.

IV. DISCUSSION

First we consider the shape of the spiral wave pinned around a circular obstacle more precisely. With the approximation that the wave velocity is constant, the shape is regarded to be a convolute of a circle.[26–29] In this case, however, we have to think about the effect of the curvature of chemical waves as follows:

$$c = c_0 - DK, \tag{3}$$

where c is the wave velocity affected by the curvature, c_0 is the velocity of a plane wave under the same condition, and K is the curvature of the wave front. Using this relationship, Mikhailov and Zykov[30] discussed the unpinning phenomenon by assuming that a wave has a certain critical curvature K_c at the edge of a circular obstacle. However, by using the framework of Tyson and Keener,[31] we propose an alternative method to explain the unpinning scenario. In that work the velocity of a spiral wave rotating around a circular obstacle with a radius of R_0 can be derived through the following consideration: the shape of the spiral wave is given as $\theta(r)$ in cylindrical coordinates, and ψ is defined as $\psi = r\mathrm{d}\theta/\mathrm{d}r$. The calculation in Ref. 31 leads to

$$\psi = \frac{\alpha\bar{r}}{R_0} + \frac{\beta\bar{r}}{R_0 + \gamma\bar{r}}, \tag{4}$$

where $\bar{r}$ equals $r - R_0$ and α, β, and γ are constants as follows:

$$\alpha = -\frac{1 + 4\bar{c} - \sqrt{1 + 8\bar{c}}}{4(1 + \bar{c})}, \tag{5}$$

$$\beta = \frac{1 - \sqrt{1 + 8\bar{c}}}{4}, \tag{6}$$

$$\gamma = \frac{1 + \sqrt{1 + 8\bar{c}}}{16}, \tag{7}$$

where $\bar{c} = c_0R_0/D$. It is noted that the effect of wave front curvature K_c is encoded in Eq. (4), since ψ represents the shape of the spiral wave.

Here, we adopt Tyson and Keener's derivation. From these results, the wave velocity at the periphery of a circular obstacle with a radius of R_0 is derived as

$$c_{\mathrm{p}}(R_0;c_0) = c_0\frac{1 + (D/4c_0R_0)(1 - \sqrt{1 + (8c_0R_0/D)})}{1 + (D/c_0R_0)}. \tag{8}$$

Next, we considered the dispersion relation of the chemical wave. When chemical waves are initiated at a period of T, the velocity and interval of the wave train can be determined. The velocity of the wave train progressively decreases as the period of initiation decreases. Note that there is a critical period T^* below which every initiation cannot generate a wave. The velocity of a wave train induced by initiation at a critical period is defined as a critical velocity c^*.

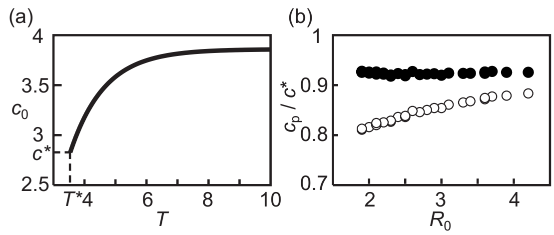

FIG. 4. (a) Dispersion relation obtained by a numerical calculation in a one-dimensional system based on the Oregonator model. The critical velocity c^* and the critical period T^* are $c^*=2.83$ and $T^*=3.52$. Note that a chemical wave with a velocity below c^* cannot exist. (b) Confirmation of the theoretical discussion. Equation (8) is plotted for R_0 vs $c_p(R_0;c_0)/c^*$ and $c_p(R_0+\tilde{R};c_0)/c^*$ in open and closed circles, respectively. Here, $\tilde{R}$ is the modification term, which corresponds to the width of the excitable wave. $\tilde{R}$ is calculated to be 1.57 by minimizing the difference from unity.

The unpinning of a spiral wave clearly depends on the wave velocity at the periphery of a circular obstacle. When the wave velocity at the periphery of an obstacle is below the critical wave velocity, several chemical waves cannot propagate, and they disappear. As a result, unpinning occurs. In contrast, when the wave velocity at the periphery of an obstacle is above the critical wave velocity, every chemical wave can continue to propagate and unpinning does not occur.

To confirm this scenario, we calculated the critical wave velocity by substitution of the critical period for each R_0 shown in Fig. 3 to deduce the dispersion relation shown in Fig. 4(a). The results are shown in Fig. 4(b) with open circles, where $c_p(R_0;c_0(T(R_0)))/c^*$ is plotted against R_0. This value corresponds to the ratio of the critical value $c^*=2.83$ to the velocity at the inner periphery under the critical condition, which is calculated based on Eq. (8) and the results in Figs. 3 and 4(a). If the theoretical discussion is correct, the value should be unity and independent of R_0.

However, Fig. 4(b) shows that the open circles are smaller than unity and slightly dependent on R_0. This discrepancy is attributable to the approximation that the width of the wave front is zero. On the other hand, unpinning of the spiral wave is detected when the ideal wave disappears in the region within a certain area from the circular periphery. This width of the area is comparable to the wave width. Thus, we replaced $R_0(T)$ with $R_0(T)+\tilde{R}$ and obtained the most proper $\tilde{R}$, which minimizes the dependency of $c_p(R_0+\tilde{R};c_0(T(R_0)))/c^*$ on R_0. The most proper value was $\tilde{R}=1.57$, which is comparable to the width of the wave (see Fig. 3). The value $c_p(R_0+\tilde{R};c_0(T(R_0)))/c^*$ is plotted against R_0 when $\tilde{R}=1.57$ with closed circles in Fig. 4(b). The average value is 0.92. Although this value is smaller than unity, the plot is almost independent of R_0, and the modification term $\tilde{R}$ is comparable to the excitable wave width. In order to consider the effect by the diffusion of chemicals from the boundary, we need to use the "diffusion length," which is comparable to the excitable wave width. Thus, this theoretical estimation seems to describe the essential mechanism in a satisfactory manner. The slight difference in the critical velocity could be attributed to the difficulty in accurately determining the critical value in a numerical calculation. On the other hand, the phase difference between the initiation wave and the rotating wave can relate to how soon the spiral wave is unpinned. For further understanding of the mechanism of unpinning, it will be also important to investigate the dependency on the excitable feature which strongly affects the critical velocity and dispersion relation.

V. SUMMARY

We have demonstrated that the unpinning of a spiral wave by a high-frequency wave train is a generic effect that can be observed in two different excitable media: BZ reaction and cardiac tissue. A computer simulation that used the Oregonator model confirmed that pacing induced unpinning for a wide range of parameters and allowed us to determine the critical conditions for the successful application of the procedure, such as the dependence of the necessary pacing period on the size of the obstacle. The analytical estimation is in excellent agreement with the results of computer simulations. The basic understanding obtained in this study may lead to a predictable method for successful unpinning by using such generic properties of the excitable medium as the dispersion relation and curvature-dependent wave propagation. The insights obtained in this study are expected to provide a theoretical and mechanistic background for the development of more efficient ATP methods.

ACKNOWLEDGMENTS

The authors thank Professor Valentin Krinsky (Max Planck Institute, Germany) and Professor Takao Ohta (Kyoto University, Japan) for their helpful discussions.

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