Controlling intracellular Ca^{2+} spiral waves by the local agonist in the cell membrane*

Qiu Kang(仇 康)[a], Tang Jun(唐 军)[b]†, Ma Jun(马 军)[c], and Luo Ji-Ming(罗继明)[b]

[a] *Department of Mathematics and Physics, Xuzhou Medical College, Xuzhou* 221004, *China*
[b] *College of Science, China University of Mining and Technology, Xuzhou* 221008, *China*
[c] *Department of Physics, Lanzhou University of Technology, Lanzhou* 730050, *China*

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A modified spatially extended Tang–Othmer Ca^{2+} model is used to study intracellular Ca^{2+} spiral waves numerically. It is found that, as a local stimulation, the local agonist-binding on the cell membrane, which enhances the local concentration of the messenger molecule inositol 1,4,5-trisphosphate(IP_3), can influence the dynamics of the spiral waves. 1) Strong enough stimuli can change the spiral wave from a meandering to a rigidly rotating one. 2) On the other hand, strong enough stimuli can suppress the spiral wave from the system. It provides the theoretical clue for controlling the spiral waves by stimulating the cell membrane.

Keywords: spiral wave, local stimuli, calcium signaling, IP_3
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1. Introduction

Intracellular calcium signaling mechanisms have become a very important issue in recent years.[1] Ca^{2+} ion, which is found as a ubiquitous second messenger in cell signaling, is involved in many cellular functions, such as muscle contraction, sensory perception, bursting oscillations and the injury of brain tissue.[2,3] Ca^{2+} is mostly stored in the endoplasmic reticulum (ER) and mitochondria. Through inositol (1,4,5)-trisphosphate receptors(IP_3Rs) activated by IP_3, Ca^{2+} is released from the stores to cytosol. As Ca^{2+} is released, it activates nearby IP_3Rs and leads to further Ca^{2+} releasing. This is the well-known mechanism of Ca^{2+}-induced Ca^{2+} release(CICR).

Spiral wave is a certain kind of special spatial pattern and has been observed in many excitable physical, biological and chemical systems, such as the Belousov–Zhabotinsky reaction,[4] the catalytic CO oxidation on Pt(110) surface,[5] the cAMP dynamics in Dictyostelium discoideum in the aggregation stage.[6] Spiral wave is very important and interesting because it is supposed to be relevant to cardiac arrhythmias and sudden heart death, which can induce clinical death in only a few minutes.

Spiral wave of Ca^{2+} concentration in the cytosol was first discovered by Lechleiter *et al*[7] in immature oocytes. The propagation of Ca^{2+} spiral wave has been extensively simulated by various dynamical models. In these models, Ca^{2+} exchanges between the cytosol and extracellular surroundings or internal Ca^{2+} stores, diffusion of Ca^{2+} in the cytosol are considered. Based on these models, many experimental results about the period and the velocity of Ca^{2+} spiral waves have been reproduced.

Many methods for controlling spiral waves are presented,[8−11] such as the external field, parameter perturbation, etc. Both experimental results and numerical simulations show that IP_3 concentration ($[IP_3]$) influences Ca^{2+} spiral waves extensively. $[IP_3]$ is an experimentally controllable parameter, which can be stimulated and adjusted by the binding of extracellular agonists such as hormones or neurotransmitters to receptors in the membrane.[12] Tang *et al.*[13] have studied the effect of $[IP_3]$, which is homogenous in the cytosol, on the stability of Ca^{2+}spiral waves. But, in fact, extracellular agonists always bind to local receptors, then local IP_3 concentration in the cytosol is elevated, which in turn diffuses throughout the whole cytosol. In this paper, we will focus on how the local elevation of IP_3 concentration influences Ca^{2+} spiral waves.

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†Corresponding author. E-mail: tjuns1979@yahoo.com.cn
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2. Model

The model used in Ref. [13] was first developed by Tang *et al.*[14] and was modified to describe Ca^{2+} wave in Xenopus oocytes by Falcke *et al.*[15,16] In this model, the exchanges between the cytoplasm and the ER or mitochondria are considered, and fluxes across the cell membrane are neglected. The equations are given by

$$\begin{aligned}\frac{\mathrm{d}c}{\mathrm{d}t} &= v_{\mathrm{r}}(c_{\mathrm{r}}-c)\left[P_{\mathrm{r}}^{\mathrm{leak}}+P_{\mathrm{r}}^{\mathrm{chan}}\frac{c(1-n)}{c+\beta_1(1+K/[\mathrm{IP_3}])}\right]\\ &\quad - v_m\left(V_{\max}^1\frac{c^2}{c^2+K_d^2}-V_{\max}^2\frac{[\mathrm{Na^+}]^2}{[\mathrm{Na^+}]^2+K_{\mathrm{Na}}^2}\frac{m}{K_m+m}\right)\\ &\quad - v_{\mathrm{r}}P_{\mathrm{r}}^{\max}\frac{c^2}{c^2+K_{\mathrm{r}}^2}+D_{Ca^{2+}}\nabla^2 c, \end{aligned} \tag{1}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t}=\varepsilon\left[\frac{c^2(1-n)}{\beta_2(c+\beta_1(1+K/[\mathrm{IP_3}]))}-n\right], \tag{2}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t}=V_{\max}^1\frac{c^2}{c^2+K_d^2}-V_{\max}^2\frac{[\mathrm{Na^+}]^2}{[\mathrm{Na^+}]^2+K_{\mathrm{Na}}^2}\frac{m}{K_m+m}. \tag{3}$$

The Ca^{2+} concentrations in the cytosol, ER, and mitochondria are denoted by c, c_{r} and m, respectively. $[\mathrm{IP_3}]$ is the concentration of cytosolic $\mathrm{IP_3}$ and n is the fraction of inhibited ion channel. The ratio of the effective volume of the ER to the cytosolic volume is $v_{\mathrm{r}}=0.185$, and the effective volume of mitochondria is $v_{\mathrm{m}}=0.1$. C_{M} denotes the total amount of Ca^{2+} in the cell. If there is no Ca^{2+} flux across the cell membrane, the value of $C_{\mathrm{M}}=(c+v_{\mathrm{r}}c_{\mathrm{r}}+v_{\mathrm{m}}m)/(1+v_{\mathrm{r}}+v_{\mathrm{m}})$ will be constant, which is set to 1.56 μM. Thus, c_{r} can be calculated by $c_{\mathrm{r}}=[(1+v_{\mathrm{r}}+v_{\mathrm{m}})C_{\mathrm{M}}-c-v_{\mathrm{m}}m]/v_{\mathrm{r}}$. $K=0.8$ μM denotes the effective dissociation constant for binding of $\mathrm{IP_3}$ to the ion channel.[17] $D_{\mathrm{Ca^{2+}}}=5$ $\mu\mathrm{m}^2/\mathrm{s}$ denotes the diffusive coefficient of Ca^{2+}. The other parameter values are $P_{\mathrm{r}}^{\mathrm{leak}}=0.0097$ s^{-1}, $P_{\mathrm{r}}^{\mathrm{chan}}=3.89$ s^{-1}, $P_{\mathrm{r}}^{\max}=5.31$ μM/s, $\beta_1=0.12$ μM, $\beta_2=0.1$ μM, $\varepsilon=0.15$ s^{-1}, $K_{\mathrm{r}}=0.0296$ μM, $K_d=1.5$ μM, $K_{\mathrm{m}}=1$ μM, $V_{\max}^1=6.0$ μM/s, $V_{\max}^2=3.0$ μM/s, $[\mathrm{Na^+}]=10$ mM, and $K_{\mathrm{Na}}=5$ mM. To understand the meanings of these parameters clearly, see Refs. [14] and [15].

In the above-mentioned model, the concentration of $\mathrm{IP_3}$ is always homogeneous over the cytosol. In this paper, the diffusion of $\mathrm{IP_3}$ will be considered, so an additional equation is added to represent the diffusion of $\mathrm{IP_3}$,

$$\frac{\mathrm{d}[\mathrm{IP_3}]}{\mathrm{d}t}=D_{\mathrm{IP_3}}\nabla^2[\mathrm{IP_3}], \tag{4}$$

where $D_{\mathrm{IP_3}}=35$ $\mu\mathrm{m}^2/\mathrm{s}$ denotes the diffusive coefficient of $\mathrm{IP_3}$.[18]

A square of 200 μm×200 μm is used to model the cell, and the local stimulus is modeled by elevating $[\mathrm{IP_3}]$ to a value I_{E} (the value of I_{E} denotes the strength of the stimulus) in a square of 16×16 $\mu\mathrm{m}^2$ near the boundary of the system. This square will be called 'stimulation area' in this paper. Equations (1)–(4) of our model are integrated by using an Euler forward scheme, with a spatial discretization of 0.8 μm and a time step of 0.0005 s.

3. Results and discussion

First, we will study the effect of local stimulus on meandering spiral wave. For homogeneous $[\mathrm{IP_3}]$ less than 0.15 μM, Ca^{2+} spiral wave in the system is a meandering one.[13] As a typical example, $[\mathrm{IP_3}]$ in the system is set as 0.14 μM homogenously. The meandering spiral wave is developed from an initial condition named 'locally perturbed rest state',[13] and this well-developed spiral wave[see Fig. 1(a)] will be the initial condition of our study. Then, to model the local agonist-binding, $[\mathrm{IP_3}]$ in the stimulation area is raised to a high value of I_{E}.

Figure 1 shows the spiral pattern evolution for $I_{\mathrm{E}}=10.0$ μM. A homogeneous area with high Ca^{2+} concentration appears in the stimulation area, and then disappears. A new stable spiral wave with a larger frequency is developed [see Fig. 1(d)]. The influence of local stimulus on the spiral pattern first occurs in the stimulation area, and then diffuses to the whole

system. The corresponding spiral tip trajectories are recorded in Fig. 2(c), the trajectory of the spiral tip is changed from a meandering one to a rigidly rotating one under the influence of the local stimulus with $I_{\rm E} = 10.0$ μM. We have performed simulations for different $I_{\rm E}$. It is found that for low $I_{\rm E}$, although the meandering radius is decreased, the spiral cannot be changed to a rigidly rotating spiral[see Fig. 2(a)]. Only if $I_{\rm E}$ is larger than a threshold value 2.2 μM, can the spiral wave be changed to a rigidly rotating one. Furthermore, the rotating radius of rigidly rotating spiral decreases with increasing $I_{\rm E}$.

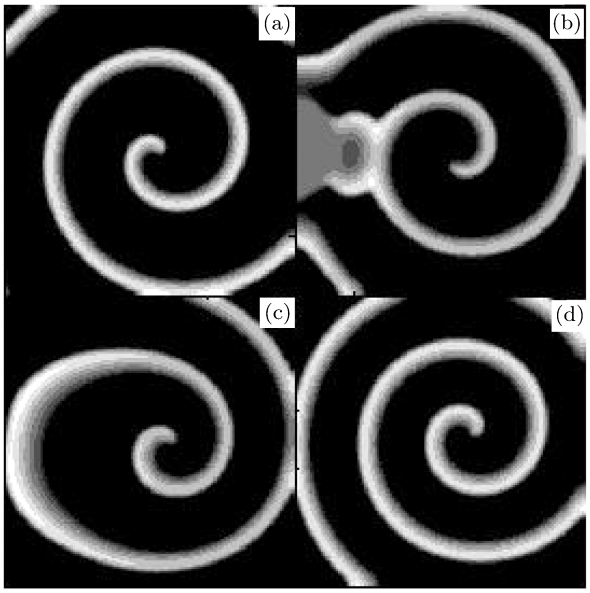


Fig. 1. Time sequence illustrating the process after local stimulus with $I_{\rm E} = 10.0$ μM at time. (a) $t = 0$; (b) $t = 10$; (c) $t = 20$; (d) $t = 100$ s. The black to white gray scale represents the lowest value 0 to the highest value 1 μM. This gray scale will be used in all figures throughout this paper.

To qualitatively analyse the results in Fig. 2, the corresponding contour lines of $[IP_3]$ for $I_{\rm E} = 10.0$ μM are depicted in Fig. 3. It indicates that the IP_3 diffuses from the stimulation area, and after long enough time, $[IP_3]$ of the system becomes homogeneous. If $[IP_3]$ of this homogeneous system is large enough (larger than 0.15 μM), the final spiral pattern is a rigidly rotating spiral wave. Besides, for low $[IP_3]$, the local dynamics of the system has only one stable state with low Ca^{2+} concentration, but for large enough $[IP_3]$, the local dynamics of the system possesses another stable state with high Ca^{2+} concentration. In Fig. 3(b), the $[IP_3]$ close to the stimulation area is large enough to possess high-Ca^{2+} state, so a homogeneous area with high Ca^{2+} concentration appears in the stimulation area [see Fig. 1(b)]. After diffusion for sufficiently long time, the $[IP_3]$ close to the stimulation area is decreased to a much less value, and the homogeneous area with high Ca^{2+} concentration disappears [see Figs. 1(c) and 1(d)]. From a biological point of view, increasing $[IP_3]$ improves the probability of Ca^{2+} release from the ER, which assists the system to maintain a more stable spiral patterns. Although some intermediate pattern, such as the homogeneous pattern with high Ca^{2+} concentration, appear temporarily, the system will develop to a more stable spiral pattern finally.

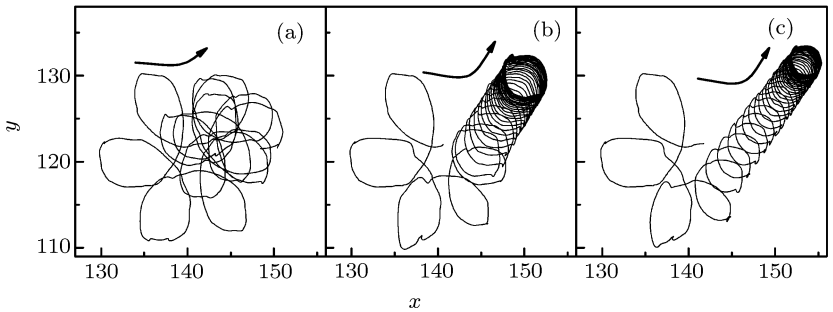


Fig. 2. Tip trajectories of a Ca^{2+} spiral for 3 typical local $[IP_3]$ recorded to illustrate the spiral dynamics as a function of local $[IP_3]$. From (a) to (c): $[IP_3] = 1.5$, 5.0, and 10.0 μM respectively. All X, Y coordinates throughout this paper are in unit of 0.8 μm.

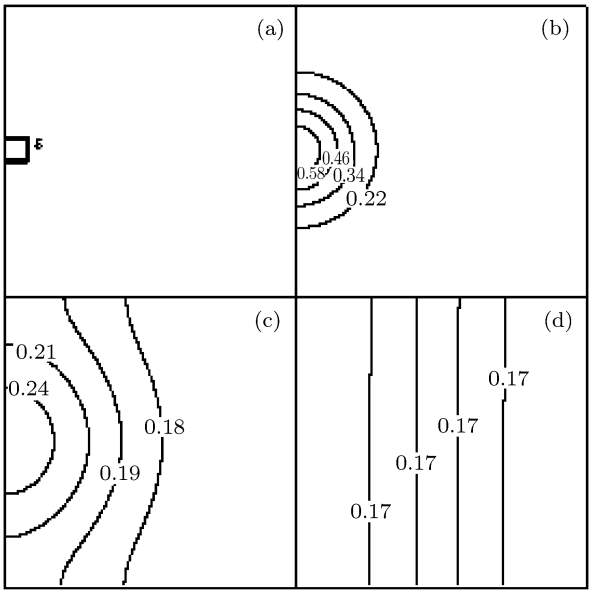


Fig. 3. The contour lines of $[IP_3]$ for $I_E = 10.1$ μM corresponding to the evolution in Fig. 1. From (a) to (d): $t = 0$, 10, 20 and 100 s, respectively.

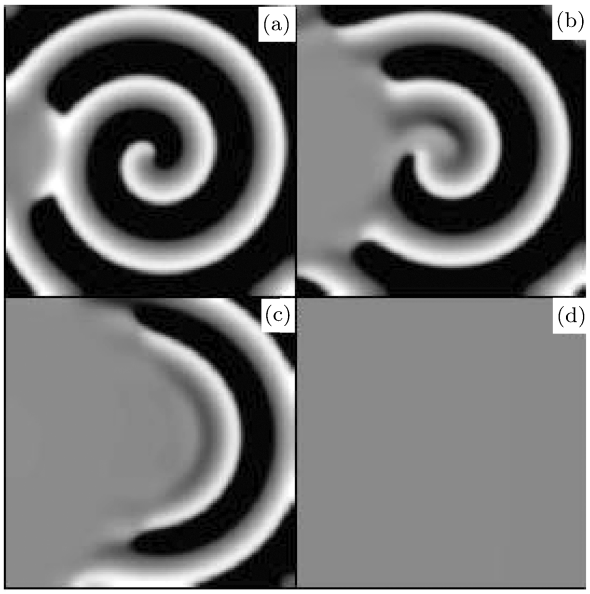


Fig. 4. Time sequence illustrating the process after local stimulus with $I_E = 10.0$ μM at time $t = 0$. (a) $t = 5$, (b) $t = 10$, (c) $t = 20$, and (d) $t = 100$ s.

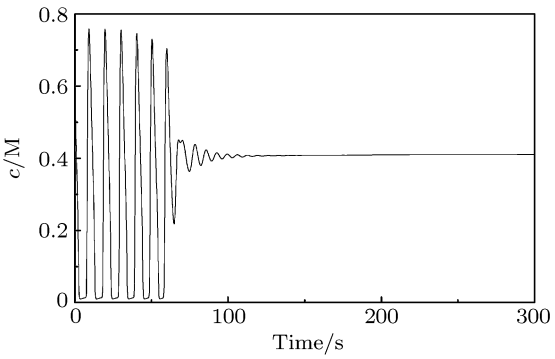


Fig. 5. Time evolution of Ca^{2+} concentration at a point (160 μm, 100 μm).

Secondly, the effect of local stimulus on rigidly rotating spiral wave will be studied. As a typical example, $[IP_3]$ in the system is set to 0.30 μM homogenously. The rigidly rotating spiral wave is still developed from the initial condition named 'locally perturbed rest state',[13] and in what follows, this well-developed rigidly rotating spiral wave will be the initial condition. Then $[IP_3]$ in the stimulation area is increased to a high value I_E.

Figure 4 shows the pattern evolution for $I_E = 10.0$ μM. A homogeneous area with high Ca^{2+} concentration appears in the stimulation area, and then grows up. Finally, the homogeneous pattern with high Ca^{2+} concentration occupies the whole system, i.e., the spiral wave is suppressed. The suppression of the spiral wave can be understood from the local dynamics of the system. For a large enough $[IP_3]$, the system possesses a new stable state with high Ca^{2+} concentration. The homogeneous areas with high Ca^{2+} concentration in Fig. 4 correspond to the new stable state, so, with IP_3 diffusing over the whole system, the homogeneous area gradually occupies the system. To more clearly reveal the disappearance of spiral wave, the Ca^{2+} concentration at the selected point (160 μm, 100 μm) is plotted against time in Fig. 5. First, the selected point is excited regularly. After the selected point has been occupied by the homogeneous area with high Ca^{2+} concentration, that point is in a stable state. It is consistent with the results in Fig. 4.

We have also performed simulations for different I_E. It is found that for little I_E, although the homogeneous area with high Ca^{2+} concentration appears in the stimulation area, it rapidly disappears after the diffusion of IP_3, i.e., the spiral cannot be suppressed. It is interesting that for an intermediate $I_E (2.4 < I_E < 2.8$ μM), the homogeneous area with high Ca^{2+} concentration grows up firstly, but fails to occupy the whole system, the remaining area, which is a somewhat turbulence-like pattern, will in turn compress the homogeneous area. Finally, the turbulence-like pattern occupies the whole media (see Fig. 6). It is because for the intermediate $[IP_3]$, the stable state with high Ca^{2+} concentration is metastable. To reveal more clearly the results, the Ca^{2+} concentration at the selected point (40 μm, 100 μm) is plotted against time in Fig. 7. We can see that the point is excited regularly again after the point is reversely compressed out of the homogeneous area.

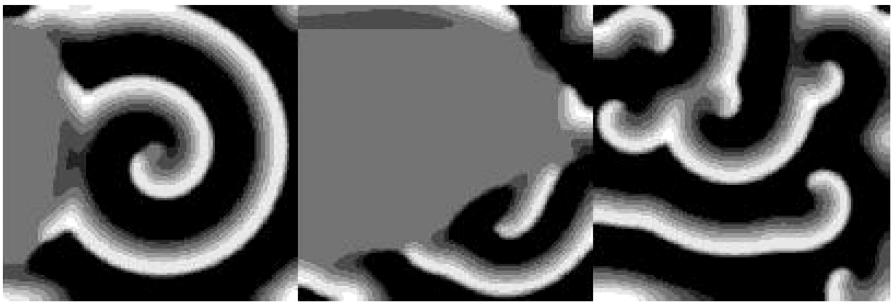


Fig. 6. Time sequence illustrating the process after local stimulus with $I_{\rm E} = 2.6$ μM at time $t = 0$ s. From left to right: $t = 100$, 450, and 1000 s, respectively.

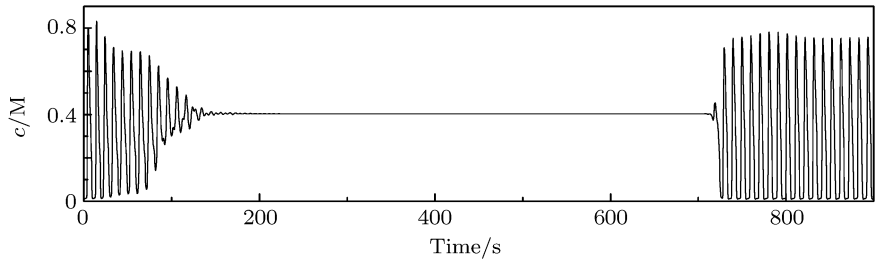


Fig. 7. Time evolution of Ca^{2+} concentration at a point (40 μm, 100 μm).

4. Conclusions

In summary, intracellular Ca^{2+} spiral wave is studied numerically by considering local agonist-binding in the cell membrane. We find that the local stimulus can make the spiral dynamics change from a meandering spiral wave to a rigidly rotating one. On the other hand, local stimuli can suppress the rigidly rotating spiral wave. The results can be qualitatively understood from the local dynamics of the system. The regions of parameters are identified by numerical simulations. We believe that our results are experimentally accessible, because our numerical scheme is related to experiments.

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