The effect of cellular aging on the dynamics of spiral waves*

Deng Min-Yi(邓敏艺), Chen Xi-Qiong(陈茜琼), and Tang Guo-Ning(唐国宁)†

College of Physical Science and Technology, Guangxi Normal University, Guilin 541004, *China*

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Cellular aging can result in deterioration of electrical coupling, the extension of the action potential duration, and lower excitability of the cell. Those factors are introduced into the Greenberg–Hastings cellular automaton model and the effects of the cellular aging on the dynamics of spiral waves are studied. The numerical results show that a 50% reduction of the coupling strength of aging cells has a little influence on spiral waves. If the coupling strength of aging cells equals zero, the ability for the medium to maintain spiral waves will be reduced by approximately 50% when the aging cell ratio increases from 0 to 0.5, where the reduction of cell excitability plays a major role in inducing disappearance of spiral waves. When the relevant parameters are properly chosen, the cellular aging can lead to the meandering of spiral waves, the emergence of the binary spiral waves, and even the disappearance of spiral waves via the stopping rotation or shrinkage of wave. Physical mechanisms of the above phenomena are analyzed briefly.

Keywords: discrete excitable medium, Greenberg–Hastings model, spiral wave, cellular aging

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1. Introduction

Spiral waves exist extensively in excitable and oscillatory systems, such as Belousov–Zhabotinski reactions,[1] the oxidation of carbon monoxide on a Pt (110) surface,[2] the cardiac muscle,[3] etc. It is reported that the appearance of spiral waves in cardiac muscle is associated with arrhythmia and the breakup of a spiral wave is a possible mechanism of ventricular fibrillation, which will cause a rapid death of the heart.[4] Therefore, the investigation of dynamics of spiral waves in cardiac muscle has received much attention in the last decades.[5–9] Many factors influencing the dynamics of spiral waves in reaction–diffusion system have been studied, such as the heterogeneity,[10,11] the external force,[12,13] and the coupling between media,[14,15] etc.

With age, cells alternate their structure and function progressively, and this phenomenon is called cellular aging.[16] During the normal aging, the heart undergoes functional, morphological, and cellular changes. It is reported[17] that the electrical coupling and cell–cell communication deteriorate during aging. The total number of cardiomyocytes in the heart decreases with aging, leading to replacement hypertrophy of the remaining cardiomyocytes. An aging cardiomyocyte displays prolonged contraction (i.e., the prolonged action potential duration),[18] and gradually loses its structural and functional properties. Thus cardiac function is impaired with aging, and cardiac arrhythmias will be more frequent. Stein *et al.*[19] have studied experimentally the effects of excitability and intercellular coupling on conduction velocity restitution. They found that a 50% reduction of excitability impairs conduction velocity restitution significantly, whereas reducing intercellular coupling by 50% did not affect conduction velocity restitution. Liu *et al.*[20] investigated the effects of the aging and systole of the heart on the spiral dynamics using the Greenberg–Hastings Cellular Automaton (GHCA) model.[21] In their work, the heart's aging is imitated by enlarging the neighbor radius and increasing the excitation threshold, and the conclusions about the probability of heart failure, ventricular fibrillation, and death are obtained, and the results accord with the relevant epidemiological survey. However, the effects of the cellular coupling, the number of the aging cell states, and the number of aging cells on the spiral waves have remained unknown, but these can help us find the crucial factor in determining the dynamics of heart with impaired excitability and intercellular coupling.

In this paper, we study the effects of cellular aging on spiral waves using the modified GHCA model. The cells will be divided into two types, one is normal, and the other is aging. The weaker coupling of aging cells is imitated by weaker stimulus sending out from the aging cells. The longer action potential duration and smaller excitability are simulated by a larger number of the cell states and higher excitation threshold, respectively. The above factors are considered in the cellular automata rules and the aging cells are uniformly distributed in a two-dimensional space throughout this paper. We find that the cellular aging can result in changes of the wavelength, meandering or disappearing of spiral waves, and even the superposition of the spiral state and other states. Furthermore, we observe the stopping of rotation of the spirals and find the important factor affecting the dynamics of spiral wave. In the following section, the model, the simulation results, and the explanation will be offered successively. The conclusion is

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†Corresponding author. E-mail: tangguoning@mailbox.gxnu.edu.cn

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presented finally.

2. Model

In the m-state GHCA excitable model,[21] cells are uniformly distributed on a square lattice, and the nearest neighbor distance between cells is taken to be 1. The extended Moore neighborhood is adopted, so, if the radius of the neighbor is R, a cell in the system has $n_R = (2R+1)^2 - 1$ neighbor cells commonly. The state of a cell (i, j) at discrete time t is represented by $\Phi_{i,j}(t) \in (0, 1, 2, \ldots, m-1)$, with $m > 3$. The value of m is the number of states of a cell. The states $\Phi_{i,j}(t) = 0, 1$ denote the rest and excited states, respectively, and $\Phi_{i,j}(t) = 2, 3, \ldots, m-1$ represent the refractory states. The value of $m-1$ corresponds to the action potential duration of a cardiomyocyte. Suppose that a cell sends out a stimulus signal with strength γ if and only if it is in the excited state, where $0 < \gamma \leq 1$. We call γ the coupling strength because cells achieve coupling through the stimulus signal. Considering the nature of the aging cells,[22] the values of $\gamma = 1$ and $0 < \gamma < 1$ represent the stimulus strengths sent from the normal cells and aging cells, respectively. The aging cell ratio ρ is defined as the ratio of the number of aging cells to the number of the total cells. The update rules are as follows:

$$\Phi_{i,j}(t+1) = \begin{cases} (\Phi_{i,j}(t)+1) \bmod m, & \text{if } 1 \leq \Phi_{i,j}(t) \leq m-1, \\ 1, & \text{if } K_{i,j}(t) \geq K_{\text{th}}, \Phi_{i,j}(t) = 0, \\ 0, & \text{if } K_{i,j}(t) < K_{\text{th}}, \Phi_{i,j}(t) = 0, \end{cases}$$

where K_{th} is the excitation threshold, $K_{i,j}(t)$ denotes the total stimulus strength $\sum_{i',j' \in \Omega} \gamma_{i',j'}$, where Ω represents the neighborhood of cell (i, j). If $K_{i,j}(t) \geq K_{\text{th}}$, the cell (i, j) in the rest state would be excited, i.e., it goes from states $\Phi_{i,j}(t) = 0$ to $\Phi_{i,j}(t+1) = 1$. K_{th}, m, R, and t take integer values. The parameters K_{th}, m, and γ control the excitability of cells, the action potential duration, and the coupling between cells, respectively.

The function of the cell is changed due to the aging of the cell. Two types of aging cells are considered as follows:

(i) aging cell A, which has the same property as the normal cell except $0 \leq \gamma < 1$, which means that the stimulus signal coming from these cells is weaker than that from the normal cells;

(ii) aging cell B, which has not only the weaker coupling strength γ, but also $m+1$ states, which reflects that the aging cell of type B has weaker intercellular coupling and longer action potential duration.

In this paper, the two-dimensional excitable medium is divided into $N = 300 \times 300$ discrete cells. The parameter m is fixed at $m = 8$. We vary R in [3,6], K_{th} in [3,30], and ρ in [1/16,1/2]. The non-flux boundary condition is used throughout this paper. Near the medium boundary, the excitation threshold of a cell takes the integer part of $(K_{\text{th}} n'_R / n_R)$, where n'_R is the number of neighbor cells of the cell.

3. Simulation results

First, we generate a spiral wave in a homogenous medium with given parameters. We then introduce the aging cells of type A or type B into the system. The corresponding system is called the system A or system B, respectively. Now we study the effects of the two types of aging cells on the evolution of the spiral wave.

3.1. Evolution of spiral wave in system A

We first consider an extreme case in which the aging cells of type A can be excited but do not send out any stimulus signal, i.e., $\gamma = 0.0$. The effects of the cells A on the spiral wave are studied under the different values of R, ρ, and K_{th}. The simulation results are shown in Fig. 1. In order to show the variation of the spiral wave, we plot the wavelength λ versus the excitation threshold K_{th} and the aging cell ratio ρ in Figs. 2(a) and 2(b), respectively. One can find from Figs. 1 and 2 that with the increase of the excitation threshold K_{th}, the spiral waves undergo the following variations: first, the wavelength equals $m \times R$ (represented by ▲), then the wavelength decreases (represented by ■). But when K_{th} runs up to the first critical value $K'_{\text{th,c}}$, the wavelength stops decreasing and starts to increase slightly (represented by •). After that, the spiral waves begin to meander, and their wavelengths rapidly increase as K_{th} increases (represented by ⋆). When K_{th} reaches or exceeds the secondary critical value $K''_{\text{th,c}}$, the spiral waves disappear, so the value of $K''_{\text{th,c}}$ reflects the ability for a medium to maintain the spiral wave. One can also find from Figs. 1 and 2 that there are four manners of the spiral wave disappearance induced by the aging cells of type A. The first manner is that the spiral wave stops rotating and then evolves as a target wave, and finally the system returns to the rest state because the wave moves out of the system and disappears. This case is represented by □, and the corresponding evolution of the spiral wave is shown in Fig. 3. The second manner is that the spiral wave stops rotation and breaks into a number of small waves due to the low excitability of cells and the anisotropy of wave speeds,[23] and then the small waves shrink while they move to the boundary, and finally the system returns to the rest state because of the disappearance of the small waves. This case is represented by ○, and the corresponding evolution of the patterns is shown in Fig. 4. The third manner is that the spiral wave disappears because the spiral wave cannot spread in the system due to low excitability of cells. This case is represented by Δ. The fourth manner is that the spiral wave meanders out of the system and then the system returns to the rest state. This case is represented by ∇. Further, from Figs. 1 and 2 one can find that when R values equal 3, 4, 5, and 6,

for $\rho = 0$, the values of secondary critical excitation threshold $K''_{\mathrm{th,c}}$ equal 8, 13, 19, and 27, respectively, but for $\rho = 0.5$, $K''_{\mathrm{th,c}}$ values equal 6, 7, 10, and 14, respectively. One can see that the value of $K''_{\mathrm{th,c}}$ decreases by about 50% as the value of ρ increases from 0 to 0.5, which indicates that when the number of the aging cells increases from zero to half the total cells, the capability for the medium to maintain the existence of spiral waves reduces about 50% if the coupling strength of the aging cells is equal to zero. The disappearance of the spiral wave is mainly attributed to the reduction of excitability. Finally, from Figs. 1 and 2 one can find that when the aging ratio ρ increases under the fixed K_{th}, the wavelengths of spiral waves represented by ■ will decrease further (see Fig. 2(b)), or fall into the meandering state, or even vanishe, i.e., the transition between different states emerges.

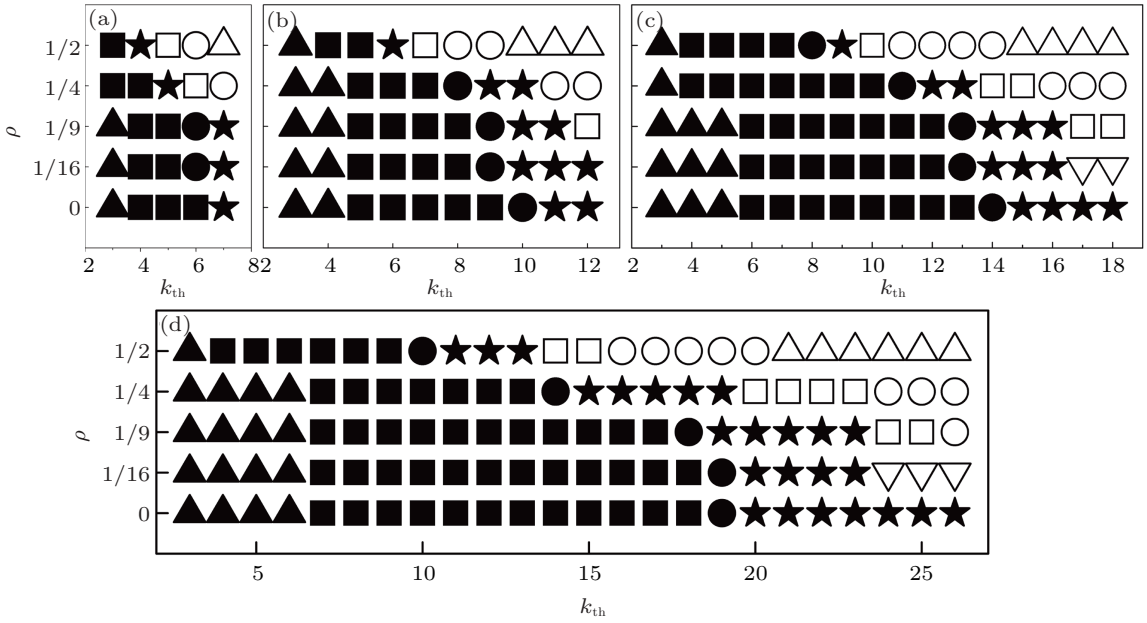


Fig. 1. Phase diagrams with $\gamma = 0.0$ and $R = 3$ (a), 4 (b), 5 (c), and 6 (d). Symbols ▲, ■, and • represent the spiral waves with unchanged wavelength, decreasing wavelength, and the shortest wavelength, respectively. Symbol ⋆ represents the meandering spiral wave. Symbols □, ◯, Δ, and ∇ represent the disappearance of spiral wave though different manners.

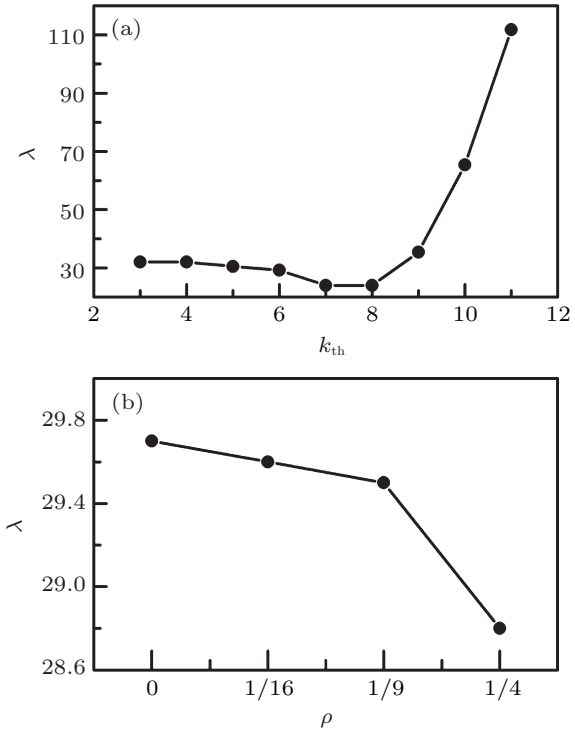


Fig. 2. The wavelengths of spiral waves λ versus (a) the excitation threshold K_{th} with $R = 4$, $\gamma = 0.0$, and $\rho = 1/9$ and (b) the aging cell ratio ρ with $R = 4$, $\gamma = 0.0$, and $K_{\mathrm{th}} = 6$.

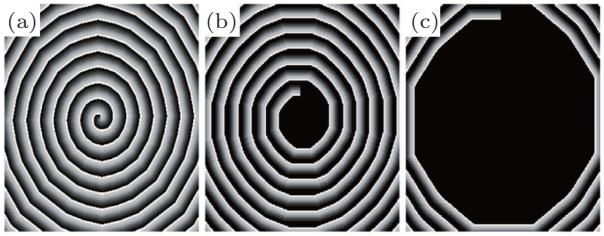


Fig. 3. Patterns at different times under $R = 3$, $K_{\mathrm{th}} = 6$, $\gamma = 0.0$, $\rho = 1/4$, at $t = 0$ (a), 20 (b), and 65 (c).

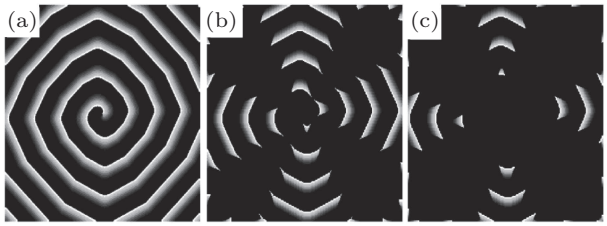


Fig. 4. Patterns at different times under $R = 3$, $K_{\mathrm{th}} = 7$, $\gamma = 0.0$, $\rho = 1/4$, at $t = 0$ (a), 10 (b), and 20 (c).

To obtain the direct observations about the meandering of spiral waves due to the existence of aging cells, the tip trajectories of spiral waves under different parameters are provided in Fig. 5, where the spiral tips are defined as the intersection

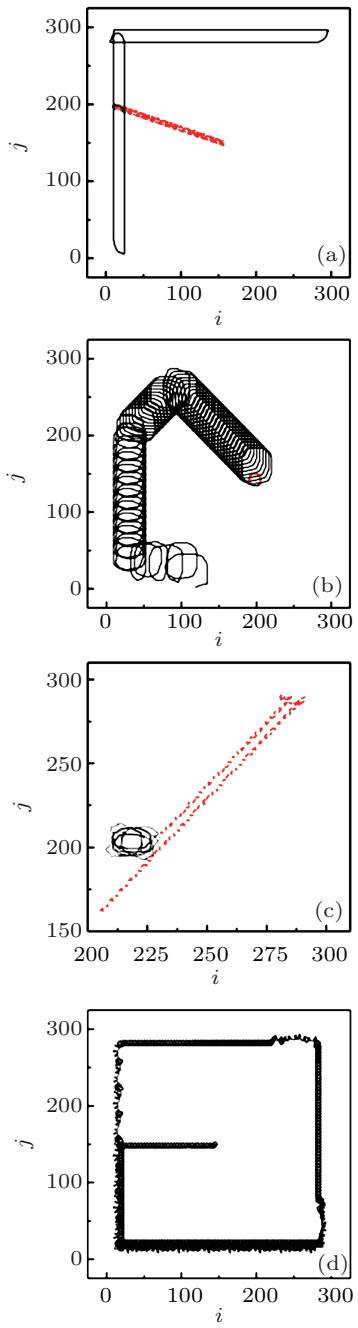


Fig. 5. (color online) Trajectories of spiral wave tips under different parameters, where the black solid and the red dashed lines correspond to spiral waves in the systems with and without aging cells, respectively, at (a) $R = 4$, $\rho = 1/16$, and $K_{\rm th} = 17$; (b) $R = 4$, $\rho = 1/9$, and $K_{\rm th} = 11$; (c) $R = 5$, $\rho = 1/9$, and $K_{\rm th} = 15$; (d) $R = 6$, $\rho = 1/4$, and $K_{\rm th} = 17$.

of two contours $\Phi(t+1) = 3$ and $\Phi(t) = 3$. In Fig. 5(a), the spiral wave meanders to the boundary directly when there are no aging cells in the medium, but the spiral wave meanders along the boundary back and forth due to the existence of aging cells. In Fig. 5(b), the tip trajectory of the original spiral wave is a small circle, but the spiral wave in the medium with aging cells meanders out of the system after some transient movements and then disappears. In Fig. 5(c), the original spiral wave meanders along the diagonal, but the emergence of aging cells causes it to meander in a smaller range, i.e., spiral wave is pinned by aging cells. The spiral wave shown in Fig. 5(d) meanders along the boundary; whereas the original spiral wave is stable (the tip is a red point).

Numerical simulations with other values of γ are conducted. Figure 6 shows the phase diagrams under $R = 4$ and different values of γ. One can obtain similar results to those under other R values. Figure 6 shows that i) for $\rho \leq 1/4$ and $\gamma \leq 0.5$, the reduction of γ has no influence on $K''_{\rm th,c}$, i.e., the reduction in the coupling strength of the aging cells does not influence the self-sustaining nature of spiral waves; ii) for given values of γ and $K_{\rm th}$, the increase of ρ can change the state of the spiral wave, i.e., the transition from one symbol state to other symbol state can occur. When ρ increases form 0 to ρ', the number of the state transitions of the spiral wave in the same excitation threshold range is different for different values of γ. For example, when ρ values increase form 0 to $1/16$, $1/9$, $1/4$, and $1/2$, the numbers of the state transitions of spiral wave are 2, 3, 3, and 4 respectively for $\gamma = 0.9$, and are 2, 3, 3, and 5 respectively for $\gamma = 0.5$. The differences in corresponding number between these two sets of results give the numbers of the state transitions induced by the cellular coupling, which are 0, 0, 0, and 1, respectively. The result shows that the reduced coupling strength by 50% hardly influences the spiral wave. The reduced excitability of cells always plays a key role in the state transition of the spiral wave. Those results imply that the cardiac function hardly remains unchanged under a 50% reduction of cellular coupling. A similar result has been obtained experimentally.[19]

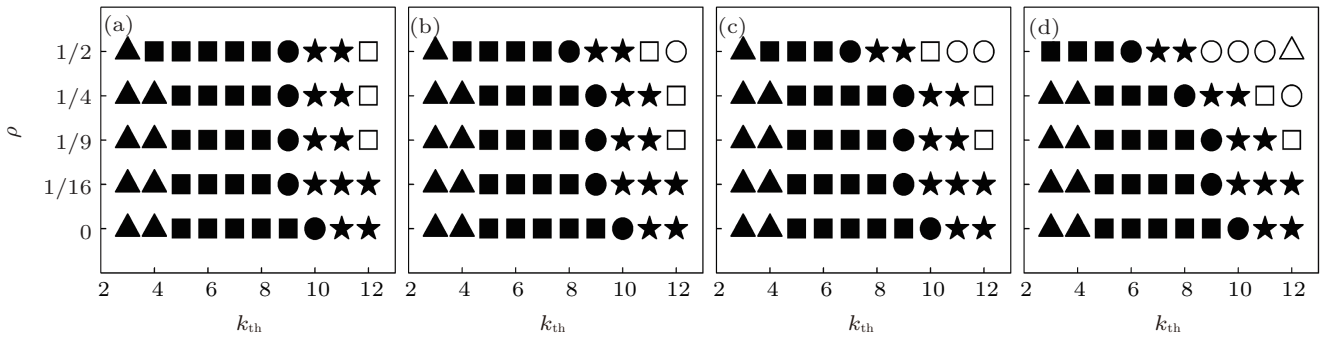


Fig. 6. Phase diagrams with $R = 4$ and $\gamma = 0.9$ (a), 0.7 (b) 0.5 (c), and 0.3 (d). The same symbol represents the same situation as in Fig. 1.

3.2. Evolution of spiral wave in system B

The state number of the normal cells is 8, and the state number of aging cells of type B is 9. Owing to the difference in state number between the two types of cells, the binary spiral wave will emerge, which consists of the two types of spiral waves: one is the normal spiral wave maintained by the normal cells, and the other is the conjugated spiral wave maintained by the aging cells. Since the state of the binary spiral wave is composed only of eight states in the beginning (at the moment when the aging cells are added into the spiral wave), the conjugated spiral wave will encounter the aging cells in the refractory state and fail to propagate, leading to the appearance of conduction block. When the aging cells in the rest state meet the normal cells in the excited state, the normal and aging cells are excited synchronously, and the conjugated spiral wave can continue to propagate. Therefore, when the conjugated spiral wave is not a self-sustained wave due to low excitability, small coupling strength or low aging cell density, the conduction block occurs periodically in the system B. With the different values of ρ and γ, the computer simulations are carried out. We find that the spiral states represented by $\bullet$ and $\star$ in Figs. 1 and 6 are not influenced by the existence of the aging cells of type B. The reason is that the residence time in the rest state for the normal cells exceeds one step so that the two types of cells can be excited synchronously from beginning to end. However, the spiral waves represented by ▲ and ■ in Figs. 1 and 6 are markedly affected by the aging cells of type B because the spiral waves become the binary spiral waves. The normal spiral waves are stable, whereas the conjugated spiral waves become unstable due to the conduction block.

Now we discuss the effect of the conduction block on the conjugated spiral waves. When the values of γ and ρ are small enough, the conjugated spiral wave is not a self-sustained wave and its spiral arm displays wide–narrow variation, which is called the breathing spiral wave. The simulation result exhibiting variation phenomenon is shown in Fig. 7. It is observed from Fig. 7 that the width of the spiral arm decreases after the conduction block has taken place until the normal and aging cells are excited synchronously, which will result in the appearance of gaps in the spiral arm of the binary spiral wave. The spiral arm returns to normal level as time goes on after the synchronous excitation occurs. Since the conduction block appears periodically, the spiral arm of the conjugated spiral wave exhibits wide–narrow variation.

When the values of γ and ρ are large enough, the conjugated spiral wave can become a self-sustaining wave after a transient evolution if the excitability of cells is high enough. In this case, the excitations of the normal and aging cells are generally asynchronous due to the independent evolutions of the two types of spiral waves, which makes the conduction block weaken. The serious conduction block just appears in the places around the vertical and horizontal bisector of the medium. Thus a small double spiral wave or stable target wave forms in the center of the original spiral wave if the relevant parameters are properly chosen, while the local shrinkage of the spiral arm, maintained by the aging cells, comes up periodically. Figure 8 illustrates the formation process of a small double spiral wave and the local shrinkage of the spiral arm. One can see that the original tip vanishes as time goes on. The conduction block and interaction between the normal and conjugated spiral waves generate a small double spiral wave in the center of the spiral. The analogous phenomena shown in Figs. 8(f)–8(h) appear periodically. Furthermore, different size black spots sporadically appear, resulting in the appearance of some pore spaces in the spiral arm of the binary spiral wave.

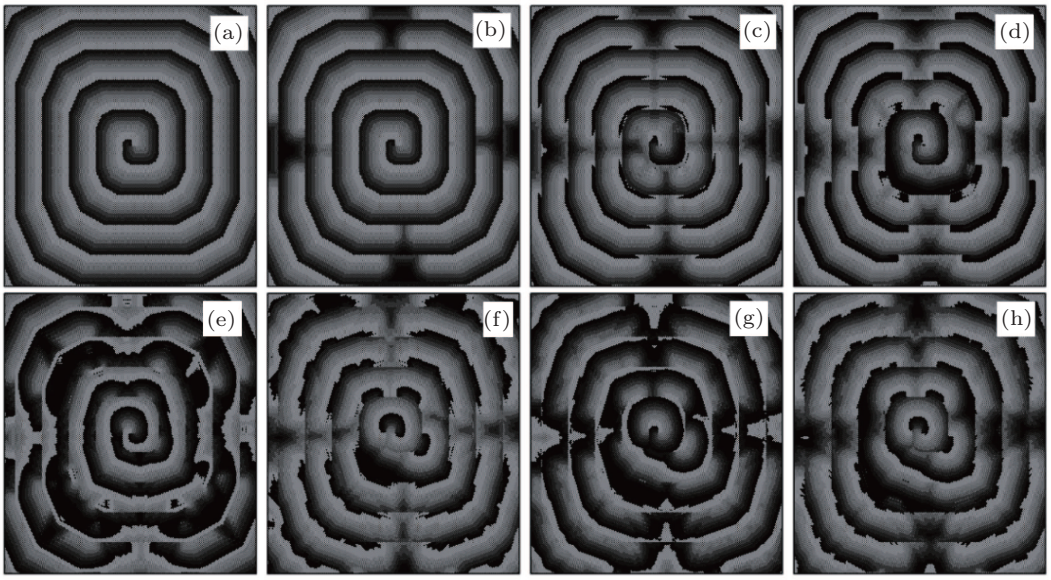


Fig. 7. Spiral wave patterns maintained by aging cells of type B with parameters $R = 4$, $\rho = 1/9$, $K_{\text{th}} = 3$, and $\gamma = 0.5$ applied at $t = 20$ (a), 25 (b), 30 (c), 33 (d), 51 (e), 57 (f), 62 (g), and 66 (h).

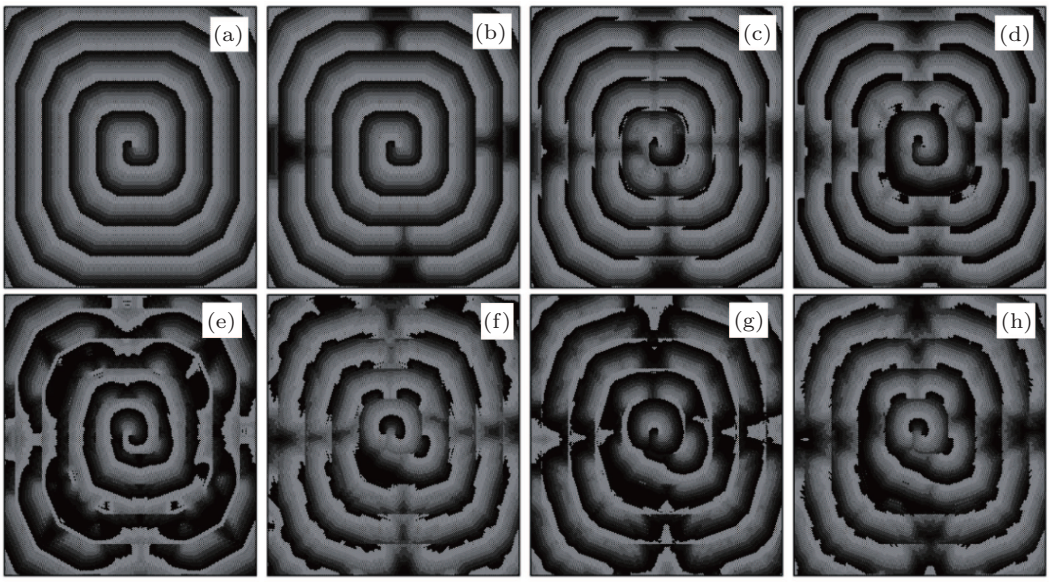


Fig. 8. Spiral wave patterns maintained by aging cells of type B with parameters $R = 4$, $\rho = 1/2$, $K_{\rm th} = 3$, and $\gamma = 0.9$ at $t = 20$ (a), 29 (b), 39 (c), 49 (d), 63 (e), 88 (f), 93 (g), and 96 (h).

4. Conclusion and discussion

The effects of the cellular aging on the spiral wave dynamics are studied in this paper. According to the above simulation results we can draw some conclusions below. (I) When the cellular aging just weakens the coupling strength, the 50% reduction of the coupling strength γ hardly influence the state of spiral wave. Whereas, when the aging cell ratio increases from 0 to $1/2$, the ability for the medium to maintain the spiral wave will reduce about 50% under $\gamma = 0$. The reduction of the excitability of cells plays a major role in the disappearance of the spiral wave. The results are compatible with the experimental results of Stein *et al.*[19] (II) The existence of the aging cells can make the stable spiral wave meander. It either leads to the pinning of the meandering spiral waves, or causes spiral waves to move out of the system and disappear. We discover that the spiral wave can disappear via four different manners, such as stopping rotation. (III) When the cellular aging not only reduces coupling strength but also increases the number of states, the binary spiral wave appears in the system. Since the conduction block prevents some aging cells from exciting, the wave-arm of the binary spiral wave displays gaps and small holes. The asynchronous excitations of the normal and aging cells are observed if the relevant parameters are properly chosen. In the biological context, the asynchronous excitation of cardiomyocytes not only makes the contraction of the heart weaken but also prolongs systole, which is longer than the action potential duration of cardiomyocytes. Our results could contribute to better understanding the extension of contraction duration and importance of excitability of cells in the aging heart.

References

[1] Zaikin A N and Zhabotinsky A M 1970 *Nature* **225** 535
[2] Jakubith S, Rotermund H H, Engel W, von Oertzen A and Ertl G 1990 *Phys. Rev. Lett.* **65** 3013
[3] Glass L 1996 *Physics Today* **49** 40
[4] Fenton F H, Cherry E M, Hastings H M and Evans S J 2002 *Chaos* **12** 852
[5] Pertsov A M, Davidenko J M, Salomonsz R, Baxter W T and Jalife J 1993 *Cir. Res.* **72** 631
[6] Qu Z L, Xie F, Garfinkel A and Weiss J N 2000 *Ann. Biomed. Eng.* **28** 755
[7] Bai Y Q and Zhu X 2010 *Chin. Phys. Lett.* **27** 048201
[8] Qian Y, Mi Y and Huang X 2011 *Int. J. Bifur. Chaos* **21** 1341
[9] Qian Y 2012 *Acta Phys. Sin.* **61** 158202 (in Chinese)
[10] Tang D N and Tang G N 2010 *Acta Phys. Sin.* **59** 2319 (in Chinese)
[11] Qiu K, Tang J, Luo J M and Ma J 2013 *Chin. Phys. Lett.* **30** 118701
[12] Chen J X, Mao J W, Hu B B, Xu J R, He Y F, Li Y and Yuan X P 2009 *Phys. Rev. E* **79** 026209
[13] Liu G Q and Ying H P 2014 *Chin. Phys. B* **23** 050502
[14] Qian Y 2012 *Chin. Phys. B* **21** 088201
[15] Ma J, Tang J, Zhang A H and Ja Y 2009 *Sci. China: Phys. Mech. Astron.* **39** 1754 (in Chinese)
[16] Wang H Y, Hao Y J and Su J 2009 *Chin. J. Gerontology* **10** 1315 (in Chinese)
[17] Bernhard D and Laufer G 2008 *Gerontology* **54** 24
[18] Lakatta E G 2003 *Circulation* **107** 490
[19] Stein M, van Veen T A B, Hauer R N W, de Bakker J M T and van Rijen H V M 2011 *PLoS One* **6** 1
[20] Liu H Y, Yang C Y and Tang G N 2013 *Acta Phys. Sin.* **62** 010505 (in Chinese)
[21] Greenberg J M and Hastings S P 1978 *SIAM J. Appl. Math.* **34** 515
[22] Lakatta E G and Levy D 2003 *Circulation* **107** 490
[23] Guo G F, Wei H M and Tang G N 2012 *Chin. Phys. Lett.* **29** 054203