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Spatiotemporal multiple coherence resonances and calcium waves in a coupled hepatocyte system*

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Spatiotemporal multiple coherence resonances for calcium activities induced by weak Gaussian white noise in coupled hepatocytes are studied. It is shown that bi-resonances in hepatocytes are induced by the interplay and competition between noise and coupling of cells, in other words, the cell in network can be excited either by noise or by its neighbour via gap junction which can transfer calcium ions between cells. Furthermore, the intercellular annular calcium waves induced by noise are observed, in which the wave length decreases with noise intensity augmenting but increases monotonically with coupling strength increasing. And for a fixed noise level, there is an optimal coupling strength that makes the coherence resonance reach maximum.

Keywords: multiple resonance, coherence, intercellular calcium wave, noise
PACC: 0340K, 0545, 0547

1. Introduction

Recently, the effects of noise were studied universally in living systems such as genes, neurons, heart and other cells.[1−3] It was discovered experimentally and theoretically that noise could bring about temporal and spatially ordered structures in organisms.[4,5] This phenomenon is generally called noise-induced resonance that involves stochastic resonance and coherence resonance according to whether there is an external signal.[6,7] While in some research work, coherence resonances were found at different noise levels in excitable systems, such as bi-coherence resonance or tri-coherence resonance, each of which comprises multiple resonances.[8,9] Generally, coherence resonance is engendered when the frequency of noise-induced oscillation escaping from a steady state matches the inherent frequency of the original system, usually before the determinate Hopf bifurcation.[10,11] Multiple resonances may be produced by many ingredients, such as multiple frequencies of the random system which essentially make temporal ordering structure abundant, or the mutual excitation controlled by noise and coupling between cells or others.[9] The analysis of multiple resonances in organism has attracted much attention, especially in neuron and calcium dynamic systems, and interesting results are obtained.[12,13]

It is well known that calcium ion (Ca^{2+}) plays an important role in organism as a second messenger that participates in many cellular processes such as airway epithelium secretion, muscle contraction, and life reproduction.[14] When the cell is stimulated, Ca^{2+} is released by inositol trisphosphate receptors (IP_3Rs) or ryanodine receptors (RyRs) from internal stores, mainly the endoplasmic reticulum (ER) or sarcoplasmic reticulum (SR). This can expedite the opening of IP_3R to release more Ca^{2+}, thereby forming whole Ca^{2+} signals such as oscillations or waves to transfer information. And its further research announced that the elevation of the concentration of calcium ions ($[Ca^{2+}]$) or the inositol trisphosphate ($[IP_3]$) in cytoplasm could propagate from one cell to another by gap junction between cells, which mediated the intercellular communication. For example, intercellular Ca^{2+} signals were observed in pancreatic acinar cells, astrocytes network in the nervous system and especially in intact livers, in which intercellular periodic Ca^{2+} waves were found.[15−17] Because the intrinsic stochastic behaviour arises from ion channels randomly opening and closing in cells due to thermal and other fluctuations, noise controls the dynamics of Ca^{2+} current which may induce spatiotempo-

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ral order behaviour producing resonance.[18] An appropriate coupling strength of gap junction can enhance the power of resonance among cells and ensure intercellular periodic waves developing in multicellular organisms.[19] Thus it is worthwhile to study the stochastic spatiotemporal dynamics of calcium induced by noise.

In the present paper, we mainly analyse the spatiotemporal calcium dynamic behaviour of a stochastic nonlinear system in square coupled excitable hepatocytes. The corresponding deterministic model constructed by Höfer illuminates that the coupled hepatocytes can be locked in phase although the inherent oscillation frequencies for individual cells are highly different.[20] Because biological organisms are always in a noisy environment, it is necessary to further consider the resonance behaviour of coupled hypatocytes with noise, which has not been considered in Ref.[20], as well as the characteristics of calcium waves induced by noise. By gap junction between cells, the noise-induced variation of $[Ca^{2+}]$ in one cell can transport to its neighbouring cells to generate resonances, and so intercellular annular calcium waves are present, of which the wave length decreases with the noise level increasing. It is found here that due to the mutual effect of coupling and noise, bi-resonances of calcium oscillation may appear in this excitable system. Furthermore, the effect of coupling strength is analysed, and there is an optimal coupling strength making the resonance maximum.

The remainder of the present paper is constructed as follows. The mathematical model of calcium activities in coupled hepatocytes is introduced in Section 2. Presented in Section 3 are the multiple resonances of calcium oscillations. Intercellular calcium waves in the system are shown in Section 4. In Section 5 the characters of noise-induced spatiotemporal dynamics are analysed to illustrate the emergence of multiple resonances. Finally, the conclusion drawn from the present study is given in Section 6.

2. Stochastic calcium model in hepatocytes

A model constructed by Höfer in Ref.[20] originally is used to simulate calcium oscillations in hepatocyte elicited by hormones and investigate the important role of junctional calcium fluxes between two cells on synchronization of calcium oscillations. The equations of $[Ca^{2+}]$ are conceived in the balance of calcium fluxes which flow into or out of ER and across the plasma membrane and possibly also other compartments such as mitochondria. In the present paper, Gaussian white noise is used to investigate the spatiotemporal dynamic characters of coupled excitable hepatocytes, which are located in an $N \times N$ square lattice (N=128 here) and each cell is only connected to its nearest neighbour by gap junction. The stochastic model in this paper is depicted by

$$\begin{aligned}\frac{\mathrm{d}x_{i,j}}{\mathrm{d}t} =&\rho(J_{\mathrm{in}} - J_{\mathrm{out}} + \alpha(J_{rel} - J_{\mathrm{serca}}))\\ &+ D(x_{i-1,j} + x_{i+1,j} + x_{i,j-1}\\ &+ x_{i,j+1} - 4x_{i,j}) + \xi_{i,j},\\ \frac{\mathrm{d}z_{i,j}}{\mathrm{d}t} =&\rho\{J_{\mathrm{in}} - J_{\mathrm{out}} + D(x_{i-1,j} + x_{i+1,j}\\ &+ x_{i,j-1} + x_{i,j+1} - 4x_{i,j}) + \xi_{i,j}. \qquad (1)\end{aligned}$$

Here, $x_{i,j}$ and $z_{i,j}$ denote the cytoplasm $[Ca^{2+}]$ and the whole $[Ca^{2+}]$ in the (i,j)-th $(i,j \le N)$ cell, respectively. J_{in} and J_{out} describe the calcium currents flowing into cytoplasm from liquid outside membrane and that pumped out of cell, respectively. J_{rel} represents the calcium flux released from ER into cytoplasm which is mediated by IP_3R, and J_{serca} refers to the current pumped out from cytoplasm back into ER. The expressions of these fluxes are given by

$$\begin{aligned}J_{\mathrm{in}} =& v_0 + v_c\frac{P}{K_0 + P},\\ J_{\mathrm{out}} =& v_4\frac{x_{i,j}^2}{K_4^2 + x_{i,j}^2},\\ J_{\mathrm{rel}} =& \left(k_1\frac{\left(d_2\dfrac{d_1+P}{d_3+P}Px_{ij}\right)^3}{(d_P+P)^3\,(d_a+x_{ij})^3\left(d_2\dfrac{d_1+P}{d_3+P}+x_{ij}\right)^3} + k_2\right)\beta^{-1}(z_{i,j} - (1+\beta)x_{i,j}),\\ J_{\mathrm{serca}} =& v_3\frac{x_{i,j}^2}{K_3^2 + x_{i,j}^2},\end{aligned}$$

where the parameter P denotes $[IP_3]$, which controls the operation of IP_3R and the flowing of Ca^{2+} current. α, β and ρ are structural characteristics of the hepatocyte.

The stochastic effect is introduced by Gaussian white noise $\xi_{i,j}$ in the (i,j)-th hepatocyte, which satisfies $<\xi_{i,j}(t)>=0$ and $<\xi_{i,j}\xi_{m,n}(t')>=\sigma^2\delta(t-t')\delta_{i,m}\delta_{i,n}$. D is the coupling strength between neighbours. Periodic boundary condition is adopted here and the initial values of the system are randomly in [0, 1]. Without noise, hepatocytes are excitable but cannot oscillate before the deterministic Hopf bifurcation value P reaches 1.45. Thereinafter we take P=1.40 below, at which the multi-cellular system stays in a steady state without noise. Other parameter values used here are listed in Table 1.

Table 1. Parameter values.

parameter	value	parameter	value	parameter	value	parameter	value
k_1	40.0	k_2	$0.02\,\mathrm{s}^{-1}$	K_3	$0.12\,\mu$M	K_4	$0.12\,\mu$M
v_0	$0.2\,\mu\mathrm{M}\cdot\mathrm{s}^{-1}$	v_3	$9.0\,\mu\mathrm{M}\cdot\mathrm{s}^{-1}$	v_4	$3.6\,\mu\mathrm{M}\cdot\mathrm{s}^{-1}$	v_c	$4.0\,\mu\mathrm{M}\cdot\mathrm{s}^{-1}$
d_1	$0.3\,\mu$M	d_2	$0.4\,\mu$M	d_3	$0.2\,\mu$M	d_a	$0.4\,\mu$M
d_p	$0.2\,\mu$M	ρ	$0.02\,\mu\mathrm{m}^{-1}$	β	0.1	α	2

In this paper, calcium diffusion between cells is assumed to be regular, namely, calcium current in one cell flows only into its nearest neighbours by gap junction and the coupling strength D dominates the speed of calcium spreading in hepatocytes. The stochastic differential equations are computed in this paper by using the forward Euler algorithm with a fixed time step of 0.01s，in which the computation accuracy is tested by using smaller discretization intervals.

3. Coherence resonance of calcium oscillations

An appropriate noise can make $[Ca^{2+}]$ in excitable hepatocytes excurse into an oscillatory region from the steady state at P=1.40, inducing periodic oscillations in this cell. For example, the time-dependent variation of the cytoplasm $[Ca^{2+}]$ in the central cell for different noise intensities with the coupling strength D=0.07 is shown in Fig.1.

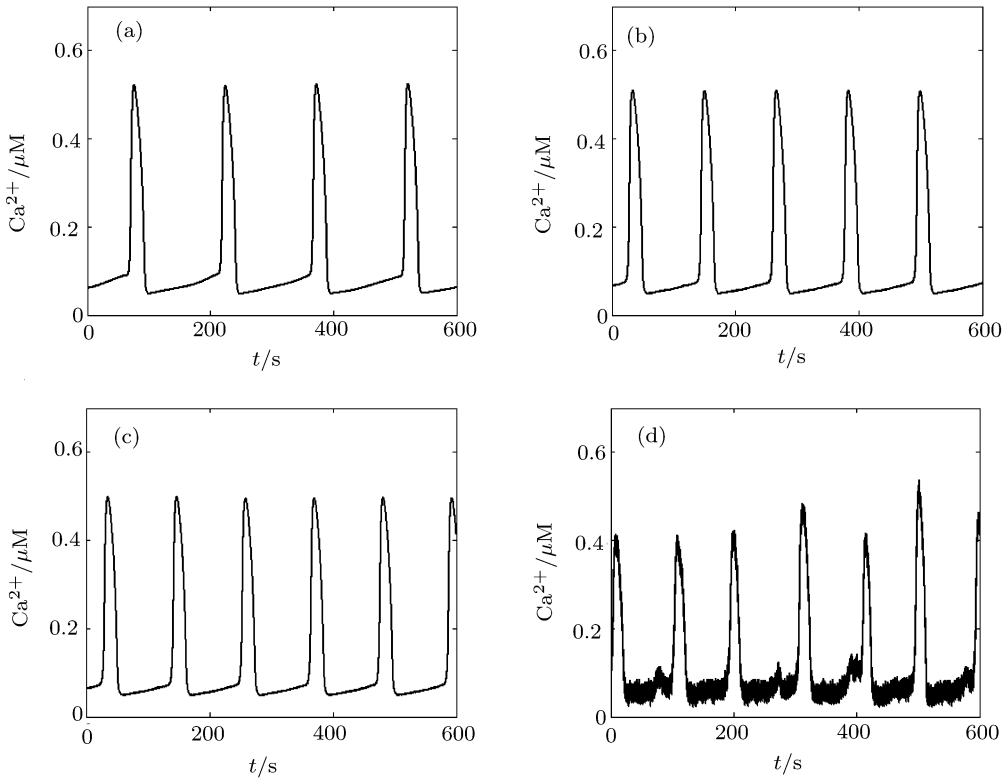


Fig.1. Oscillations of $[Ca^{2+}]$ in cytoplasm for the central cell in coupled hepatocyte system (1) with the coupling strength D=0.07, where σ =0.0008 (a), 0.0023 (b), 0.0027 (c), and 0.045 (d).

Actually, the oscillations of the cytoplasm $[Ca^{2+}]$ in other cells in this network are similar to those of the central cell. When noise is very small, there exist at most very small $[Ca^{2+}]$ oscillations below $0.1\,\mu$M, which cannot bring about any obvious oscillation character in the network (the relevant figure is not shown here). For intermediate noise, the cytoplasm $[Ca^{2+}]$ oscillates regularly with the frequency increasing, with noise levels augmented but the amplitude remaining constant (see Figs.1(a)–1(c)). While for a larger noise, the amplitude and the time series of oscillations are affected by noise to present scrambling (see Fig.1(d)).

$[Ca^{2+}]$ increases rapidly, and it can exceed some threshold values (such as 0.15 μM in Fig.1); we call $[Ca^{2+}]$ eruption happening in a cell when $[Ca^{2+}]$ is greater than 0.15 μM in cytoplasm. Thus, to depict the dynamic characters of the stochastic coupled system, the calcium eruption rate function $\pi(t) = m(t)/N^2$ is defined here to describe the proportion of erupting cells in hepatocytes at given time t, where m is the number of erupting cells. When the noise intensity σ is moderate, the value of $\pi(t)$ varies periodically, in which the frequency is increasing but its amplitude does not vary monotonically with σ increasing (see Figs.2(a)–2(c)). It is also observed that the amplitudes of $\pi(t)$ in Figs.2(a) and 2(c) are larger than those in Fig. 2(b). While for a larger noise, the value of $\pi(t)$ does not regularly vary, which means that the periodicity of $[Ca^{2+}]$ is destroyed (see Fig.2 (d)). The variation of $\pi(t)$ exhibits some characters of coherence resonance induced by noise in the system, and its detailed analysis is given in Section 5.

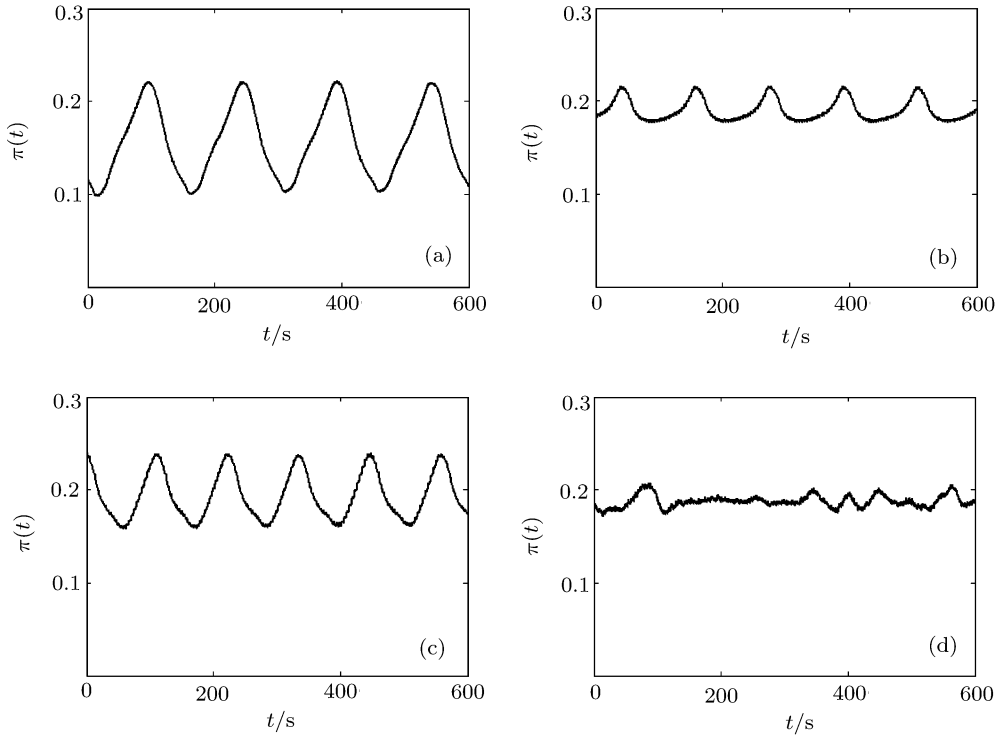


Fig.2. Curves for calcium eruption rate function $\pi(t)$ for noise intensity σ =0.0008 (a), 0.0023 (b), 0.0027 (c) and 0.045 (d), with D=0.07.

4. Intercellular calcium waves

An appropriate noise brings about the $[Ca^{2+}]$ enhancement in cytoplasm, which is transferred from one cell into the next cell by gap-junction such that calcium resonance among hepatocytes may be associated with some spatiotemporal behaviours, such as intercellular Ca^{2+} waves. The spatial profiles of $[Ca^{2+}]$ in $N \times N$ (N=128) coupled hepatocytes for different noise intensities with the coupling strength D=0.07 are presented in Fig.3，in which $[Ca^{2+}]$ in bright cells (about $0.5\,\mu$M) is much higher than that in dark cells (about $0.08\,\mu$M). It is evident that too small a noise cannot activate any spatial dynamic behaviour in the studied media (see Fig.3(a)). As the noise increases to some moderate extent, spatial annular intercellular Ca^{2+} waves emerge in the system, which propagate homogeneously among cells (see Figs.3(b)–3(e)). It is

noticed that the calcium wave length in the network decreases and so the wave number increases with noise increasing. The spatial patterns of calcium waves shown in Figs.3(b)–3(e) are given only for a fixed time. Taking account of the periodicity of $[Ca^{2+}]$ oscillation of hepatocytes (see Figs.2(a)–2(c)), the annular calcium waves are also periodic in time, expanding from the wave sources until collision occurs between them. For a large enough noise value, the spatially ordered patterns are destroyed again and the spatial dynamics is random as shown in Fig.3(f). Therefore, the fact that the spatially ordered patterns of calcium waves can be induced only by moderate noise should be referred to as spatiotemporal coherence resonance.

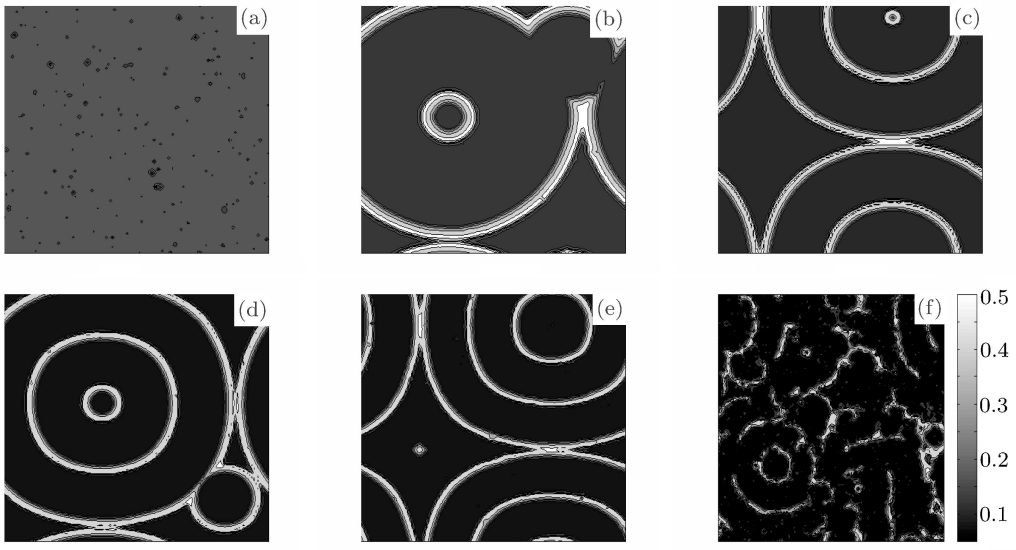
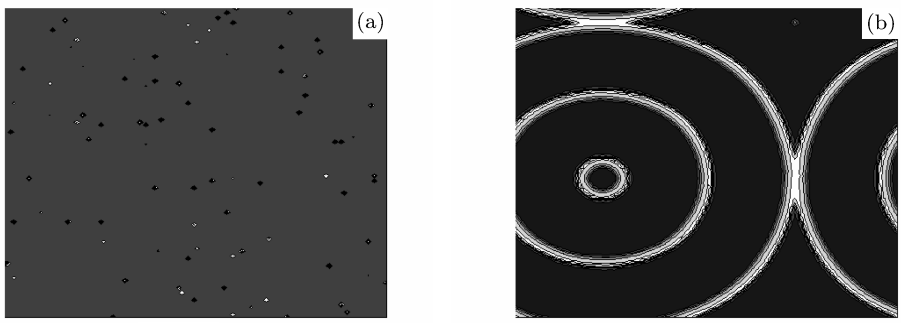


Fig.3. Spatial patterns in stochastic coupled hepatocyte system for noise level σ=0.0005 (a), 0.0008 (b), 0.0023 (c), 0.0027 (d), 0.006 (e) and 0.045 (f), with D=0.07.

The coupling between cells also plays an important role in the process of the generation of regular calcium waves. For example, intercellular calcium waves induced by noise with different values of D and σ=0.001 are shown in Fig.4. When hepatocytes are independent without coupling, there only exist some calcium eruptions stochastically because the cell membrane blocks the transportation of Ca^{2+} (see Fig.4(a)). When Ca^{2+} can transfer between cells efficiently, local $[Ca^{2+}]$ excitabilities as initiators propagate around to produce ordered intercellular circular calcium waves (see Figs.4(b)–4(d)). It is noticed from the figures that the wave becomes sparse and the wave number decreases with coupling strength increasing. The reason is that small coupling abates the diffusion speed of calcium wave, thus the density of wave stripes is enhanced. Consequently, the spatiotemporal coherence resonance of system (1) is achieved at intermediate coupling, and finally vanishes after D=0.13, with calcium waves disappearing due to quick diffusion.



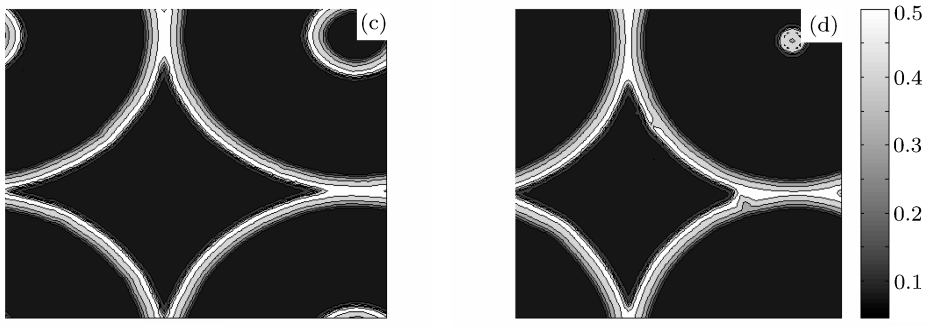


Fig.4. Intercellular calcium waves induced by coupling strength D =0 (a), 0.04 (b), 0.07 (c) and 0.10 (d), with σ=0.001.

It is also observed from Fig.4 that the wave crest width for a greater coupling strength is wider and its variation with coupling strength can be well fitted by the law $w = \tau(D - 0.08)\ (D - 0.13)\ +8.1$ (see Fig.5), where w is the wave crest width and $\tau \propto n_{\rm e}$=const, with $n_{\rm e}$ being the excursion time which depicts the interval between spikes in Fig.1.

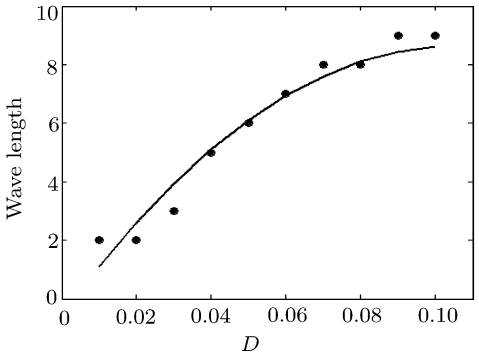


Fig.5. Wave crest widths for various coupling strengths, where solid circle '•' denotes the evaluated wave width and the fitting curve is governed by $w = \tau(D-0.08)\ (D-0.13)$ +8.1 for τ=833.

5. Analysis of multiple coherence resonances

The power spectra of the calcium eruption rate $\pi\ (t)$ defined in Section 3 for different noise levels are given in Fig.6, where there are two peaks in each spectrum curve for a given value of σ. It is seen that the basic frequency of $\pi(t)$ increases from 0.0067 to 0.0088 as the value of σ increases from 0.0008 to 0.0027. The variation of the peak height of power spectrum is not monotonic with noise level, for example, the peaks for σ=0.0008 and 0.0027 are higher than two others, but the breadth of the peak for σ=0.0027 is obviously larger than that for σ=0.0008, implying the former is more random than the latter. This can also be considered as the evidence of the phenomenon of coherence bi-resonance induced by noise.

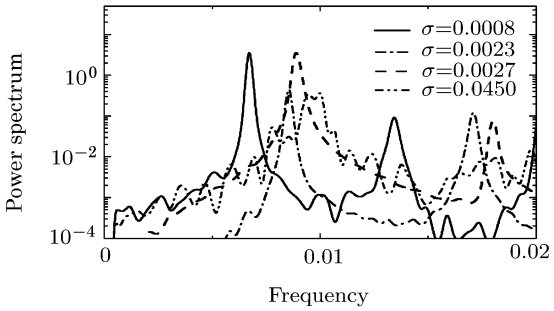


Fig.6. Power spectral density of $\pi(t)$ corresponding to different noise intensities in Fig.2, where D =0.07.

In order to quantify coherence resonance in the Höfer stochastic system (1), based on the frequency feature of the calcium eruption rate $\pi(t)$ in hepatocytes, a measure function β is introduced here as follows:

$$\beta = H\frac{\omega_{\rm p}}{\Delta\omega}, \tag{2}$$

where $\omega_{\rm p}$ is the frequency of the main peak in the spectrum of $\pi(t)$, H represents the peak height at $\omega_{\rm p}$, and $\Delta\omega$ is the half-width of the main peak, reflecting the temporal randomness of $\pi(t)$.[21] The higher (and/or the narrower) the peak in the power spectrum is, the more regular spatiotemporal order the system possesses. Actually, the quantity β represents the degree of resonance and can be associated with the signal-to-noise ratio (SNR) of $\pi(t)$.

The variations of the resonance degree β with noise intensity for different coupling strengths are shown in Fig.7(a), in which a larger value of β means a greater coherence resonance. When the noise increases above the threshold value, the system rapidly enters into the first coherence resonance (see peak 1

in Fig.7(a)). It is also observed that the first coherence resonance occurs in a narrow range of noise level, and the resonance degree β represented by the peak height is enhanced rapidly as coupling strength increases. Then when the noise intensity increases further, the value of β augments again to achieve the second coherence resonance (see peak 2 in Fig.7(a)). It is noticed that the height of peak 2 is about half that of peak 1. These results clearly reveal the phenomenon of coherence bi-resonance induced by noise in the Höfer stochastic system (1) of coupled hepatocytes. In contrast, it is seen from Fig.7(b) that there is only one resonance peak induced by noise for a single uncoupled hepatocyte (that is, D=0). Therefore, the coherence bi-resonance phenomenon induced by noise is due to the existence of coupling in the network.

The noise level that makes the network reach coherence resonance is much smaller than that for a single uncoupled cell. For instance, it is found that the resonance peak is located at σ=0.008 for a single hepatocyte (see Fig.7(b)), while the first resonance peak appears at σ=0.0008 and the second one at σ=0.0027 for the network with D=0.07. Moreover, the oscillation of cells in the network at σ=0.0008 (see Fig.1(a)) is more regular than that of an uncoupled single cell (see Fig.7(c)), in which there exist small amplitude fluctuations. These results manifest that the coherence resonance of network coupled with cells can be achieved more easily by weak noise than that of an uncoupled single cell. This is because a cell in the network may be excited not only by noise but also by coupling with neighbours. Hence, the emergence of bi-resonance in the stochastic system (1) is the common result of the interplay and competition between $[Ca^{2+}]$ oscillation induced by noise and Ca^{2+} propagation caused by coupling.

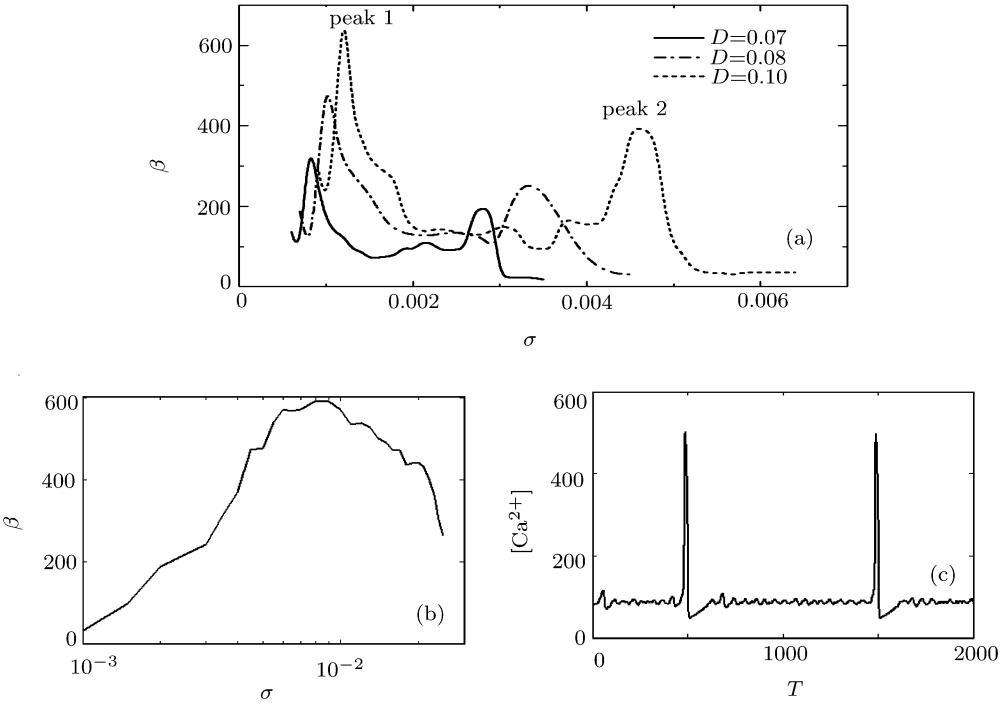


Fig.7. (a) Bi-resonances induced by noise for coupling strength D=0.07 (solid line), 0.08 (dash-dotted line) and 0.1 (short dashed line), (b) the time-dependent variation of β of a single uncoupled hepatocyte, and (c) $[Ca^{2+}]$ oscillation in a single uncoupled cell for σ=0.0008.

It is also noticed from Fig.7(a) that for a larger coupling strength, a stronger noise is required to achieve calcium resonances. For example, peak 1 is attained at σ=0.0009 for D=0.07 while σ=0.0012 for D=0.1; as for peak 2, it is reached at σ=0.0028 for D=0.07 while σ=0.0046 for D=0.1. This phenomenon may be explained by the fact that a large coupling inside gap junction leads Ca^{2+} to rapidly diffuse among cells, which induces the local excitable calcium propagation further. At the same time, a large coupling leads to the quick decay of local calcium excitations so that a higher rate of local excitation is required for propagating through the whole region. Therefore, the system with a larger coupling needs stronger noise to

exhibit coherence resonance.

The variation of the peak heights with coupling strength is shown in Fig.8(a). The height of peak 1 is enhanced remarkably with coupling increasing. At the same time, the height of peak 2 also increases with coupling increasing, but the ascending trend slows down especially for $D > 0.09$. This can demonstrate that the coupling has a stronger effect on the resonance of the first peak than that of the second one.

The values of resonance degree β for different coupling strengths for σ=0.001 are shown in Fig.8(b), which demonstrates that there is an optimal value of D at 0.08 making the coherence maximum. This result is in accord with that in Fig.4 for a fixed noise level and can be interpreted by the fact that appropriately large coupling transfers more Ca^{2+} to the neighbouring cells so that more cells are excited toward erupting and forming coherence resonance. While too strong a coupling may lead to too quick a diffusion of Ca^{2+} between cells and the $[Ca^{2+}]$ oscillation to vanish, so there is no clear spatial pattern in the network.

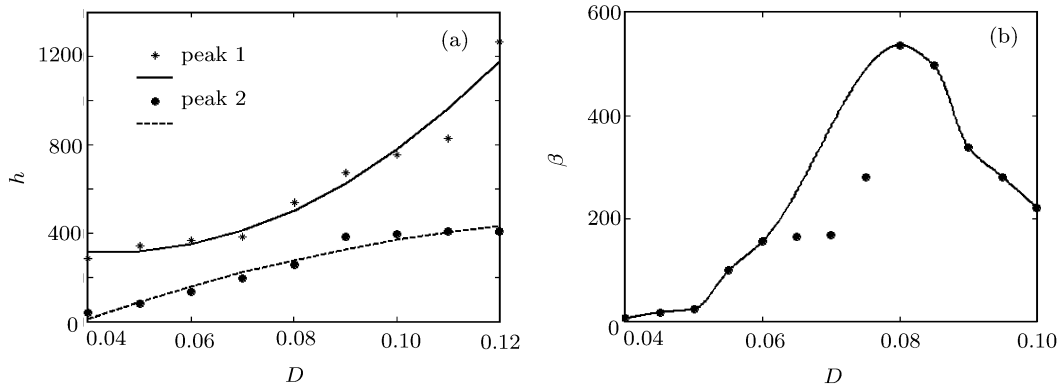


Fig.8. (a) Heights of peak 1 ('*') and peak 2 ('•') for different coupling strengths, and (b) values of β for various coupling strengths with σ=0.001.

6. Conclusion

In the present work, the noise-induced spatiotemporal dynamical property of calcium activities is analysed for the stochastic Höfer model in coupled hepatocytes. By numerical simulation, it is found that coherence bi-resonance occurs in this excitable system, where the first coherence resonance peak is higher than the second one. This result of coherence resonance may be produced by the interplay between coupling of cells and noise so that a cell in this network is excited not only by noise but also by its neighbouring cells. The first peak is affected mainly by coupling of cells, whereas the second peak seems to be controlled chiefly by noise. Furthermore, the spatiotemporal behaviour, the coherence, is enhanced by coupling first and then descended, so there is an optimal coupling strength that can lead the resonance to reach a maximum value.

It is discovered in experiment that calcium signals can be transferred into the liver to form intercellular Ca^{2+} waves, which is believed to provide a means to coordinate the function of metabolic zones of the liver lobule and the liver function.[22] However, because stochastic factors can be transformed to form a determinate behaviour in temporal and spatial dynamics, the stochastic and coherence resonance phenomenon in excitable media is an important paradigm with many applications in biology and physiology systems. In this paper, the spatiotemporal multiple coherence resonances of $[Ca^{2+}]$ in hepatocytes is studied and ordered intercellular waves are observed. Owing to the important role of calcium in transmitting the information to down-stream Ca^{2+}-sensitive metabolic processes, it is worthwhile making further exploration on the complex calcium activities and their mechanisms in biological models.

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