Structural-diversity-enhanced cellular ability to detect subthreshold extracellular signals

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(Received 31 December 2006; published 16 April 2007)

We study the influence of the structural diversity of cells on subthreshold agonist signals in coupled hepatocytes systems. The variance of the cellular structural parameter σ is employed to characterize the structural diversity. It is found that structural diversity enhances the cellular ability to detect extracellular weak signals through intracellular Ca^{2+} oscillations and the regularity of Ca^{2+} spikes undergoes a maximum with a variation of σ, indicating the occurrence of structural-diversity-induced coherence resonance. Furthermore, the effects of the level of subthreshold stimulus and junctional coupling strength on the behavior of Ca^{2+} dynamics are also considered. Analysis indicates that these phenomena have inherent relevance to both the bifurcation feature of a single cell and intercellular interaction through junctional coupling. Our findings may exhibit that structural diversity plays a constructive role in biological systems.

DOI: 10.1103/PhysRevE.75.041910 PACS number(s): 87.17.Aa, 05.40.−a, 05.45.Xt

I. INTRODUCTION

The magnification of external forcing acted upon a nonlinear system under the presence of the right amount of noise has attracted much attention in the last two decades. This is well-known as stochastic resonance (SR) [1,2]. In the absence of external forcing, the resonantlike phenomenon of coherent motion can be induced by noise only. This is called coherence resonance (CR) [2–4]. An important application of SR or CR in biological systems is its ability to enhance the detection of weak signals. This has been studied experimentally and theoretically [5–12]. More recent works have shifted to spatially extended systems composed of many coupled identical units. However, the assumption of identical units is not very realistic for many natural systems, especially in biology, the units composing the ensemble presenting a disparity in the values of some characteristic parameters. This problem has received some recent attention [13–16]. For instance, Lindner *et al.* have shown that an optimal magnitude of disorder, induced by the disparity of the pendulum length in an array of coupled pendulums, can bring order to spatiotemporal chaos by converting chaotic motion into periodic oscillations [13]. Tessone *et al.* have found that the disparity of the system's parameter could induce a resonant collective behavior in an ensemble of coupled bistable or excitable systems [14]. Analogous problems have also studied in cellular Ca^{2+} signaling systems [17,18]. In Refs. [17,18], synchronization and phase locking in a pair of coupled heterogeneous cells have been studied. When intercellular coupling is absent or very small, the cells oscillate at their own intrinsic frequencies and, in general, there is no fixed phase relation between the cells. When the degree of coupling increases, the phases of the two cells can become locked and the cells become synchronous through increasing the degree of coupling further.

Calcium ions are one of the most important messengers in the cytosol of living cells. Intracellular Ca^{2+} oscillations play a significant role in signal transduction from receptors at the cell membrane to enzymes and genes controlling the complex biochemical network of the cell [19–21]. The release of calcium ions from internal stores, most notably the endoplasmic reticulum (ER), through inositol (1,4,5)-trisphosphate receptors (IP_3Rs) activated by inositol (1,4,5)-trisphosphate (IP_3), plays the central role for calcium signals in many cell types. Agonist binding to G-protein coupled receptors in the cell membrane results in production of the second messenger IP_3, which diffuses from the cell membrane to the nearby ER and binds to an IP_3R which can open and release Ca^{2+} from the ER which in turn can open more IP_3 channels [calcium-induced calcium release (CICR)] and thus cause a fast release of Ca^{2+} from internal stores. This Ca^{2+} signal is terminated when the intracellular concentration becomes large and the Ca^{2+} pumps remove Ca^{2+} from the intracellular space into the ER and out of the cell. Thus, repetitive Ca^{2+} oscillations are produced if the concentration of IP_3 is larger than a threshold value. In a word, many types of cells respond to extracellular agonist signals by repetitive intracellular calcium spikes.

Intracellular calcium dynamics has been widely studied through different theoretical models [22,23]. Especially, internal noise has been considered because it is unavoidable in finite size biochemical systems [24–30]. These studies show that the internal noise—e.g., stochastic opening or closing of ion channels—can enhance the cellular capability to detect subthreshold IP_3 signals through intracellular Ca^{2+} oscillations. However, even if in the same cell type, there exists a slight difference in cellular structure, and thus cytosolic calcium oscillations may differ in each cell in distinct parts of the tissue. Therefore, it is an intriguing problem as to how the cellular structural difference would influence the signaling process in a real coupled-cell system, whether such a difference can be effectively used to modulate information processing *in vivo*. Specifically, for the purpose of the present work, we are wondering whether, in coupled systems, the capability of detection the weak external stimulation can be probably improved by selecting proper structural diversity.

In this paper, to study the problems mentioned above, we study the influence of structural diversity on subthreshold

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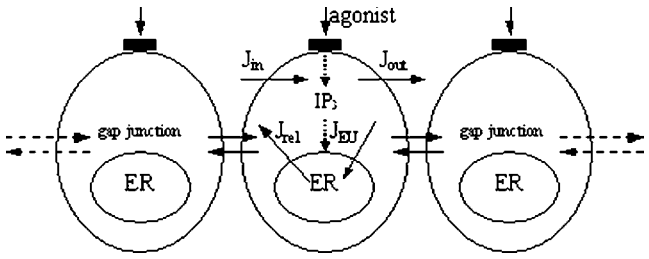

FIG. 1. The schematic representation of intracellular and intercellular calcium dynamic mechanism. Parameter values are $\nu_0=0.2\ \mu\mathrm{M\ s^{-1}}$, $\nu_c=4.0\ \mu\mathrm{M\ s^{-1}}$, $\nu_3=9.0\ \mu\mathrm{M\ s^{-1}}$, $\nu_4=3.6\ \mu\mathrm{M\ s^{-1}}$, $k_0=4.0\ \mu\mathrm{M}$, $k_1=40.0\ \mathrm{s^{-1}}$, $k_2=0.02\ \mathrm{s^{-1}}$, $k_3=0.12\ \mu\mathrm{M}$, $k_4=0.12\ \mu\mathrm{M}$, $d_1=0.3\ \mu\mathrm{M}$, $d_2=0.4\ \mu\mathrm{M}$, $d_3=0.2\ \mu\mathrm{M}$, $d_p=0.2\ \mu\mathrm{M}$, $d_a=0.4\ \mu\mathrm{M}$, $\rho=0.02\ \mu\mathrm{M}$, and $\beta=0.1$.

agonist signals in coupled hepatocytes. Structural diversity originates from the disparity of the structural parameter that is the ratio of the area of ER membranes to the one of plasma membrane. We show that structural diversity could enhance the detection of subthreshold agonist signals. The dependence of the regularity of Ca^{2+} spikes on σ exhibits a resonant quality by numerical calculations.

II. MODEL DESCRIPTION

In the present work, we adopt the mathematical model devoted in the vast literature that describes intracellular calcium oscillations in hepatocytes [17]. According to this model, the intracellular Ca^{2+} dynamics in a single cell involves the four processes—i.e., the calcium release flux from ER and reuptake through ER calcium ATPase denoted by J_{rel} and J_{EU} and the calcium influx and efflux across the plasma membrane denoted by J_{in} and J_{out}. For the multicellular systems, calcium ions can exchange between adjacent cells through the gap junctions. A schematic representation of the mechanism for the model is exhibited in Fig. 1.

Let us consider x_i and z_i as the calcium concentration in the cytosol of the ith cell and the free calcium concentration of the whole cell in the ith cell, respectively. Therefore, the ith cell is described by the set of equations

$$\frac{dx_i}{dt} = \rho[(J_{in} - J_{out}) + \alpha_i(J_{rel} - J_{EU})] + C(x_{i+1} + x_{i-1} - 2x_i),$$

$$\frac{dz_i}{dt} = \rho(J_{in} - J_{out}) + C(x_{i+1} + x_{i-1} - 2x_i), \tag{1}$$

where the expressions of the four processes are as follows:

$$J_{rel} = k_r(x,P)\beta^{-1}[z - (1+\beta)x],$$

$$J_{EU} = \nu_3 x^2/(K_3^2 + x^2),$$

$$J_{in} = \nu_0 + \nu_c P/(K_0 + P),$$

$$J_{out} = \nu_4 x^2/(K_4^2 + x^2). \tag{2}$$

The IP_3R release function $k_r(x,P)$ describes the gating kinetics of IP_3 receptor R and is given by

$$k_r(x,P) = k_1\left[\frac{d_2(d_1+P)Px}{(d_p+P)(d_a+x)[d_2(d_1+P)+x(d_3+P)]}\right]^3 + k_2. \tag{3}$$

In Eqs. (1)–(3) ($i=1,\ldots,N$), P is the concentration of IP_3 in the cell, which denotes the level of the agonist stimulation. C is the junctional coupling strength. α_i is the ratio of the area of ER membranes to the one of the plasma membrane in the ith cell, and in this paper it is considered the structural parameter. A detailed description of the model (see Ref. [17]) and parameter values can be found in the caption of Fig. 1. In order to introduce the structural diversity, we assume that structural parameter α_i satisfies $\langle\alpha\rangle=\alpha_0$ and $\langle\alpha_i\alpha_j\rangle=\sigma^2\delta_{ij}$, where σ is the measurement of structural diversity. Obviously, the structural parameters of all cells are deemed to the same if $\sigma=0$ and there exists a difference in the cellular structure while $\sigma>0$.

III. RESULT AND DISCUSSION

Following the initial literature [17], we take $\alpha_0=2.0$. It deserves to be mentioned that the value of α_i is always positive in this paper. In a single cell, when $\alpha=\alpha_0=2.0$, the system undergoes a supercritical Hopf bifurcation at $P=P_0\approx 1.45\ \mu\mathrm{M}$. For the purpose of studying the response of the system to subthreshold agonist stimulus, we take $P<P_0$. In order to qualify the response of the system to structural-diversity-induced motion, distributions of the pulse duration $T_k^i=\tau_{k+1}^i-\tau_k^i$ are examined. A measurement of the sharpness of the distribution is, for example,

$$R = \langle T_k^i\rangle/\sqrt{\langle (T_k^i)^2\rangle - (\langle T_k^i\rangle)^2},$$

$$\langle (T_k^i)^n\rangle = \sum_{i=1}^{N}\sum_{k=1}^{K_i}(T_k^i)^n \Big/ \sum_{i=1}^{N} K_i, \tag{4}$$

where τ_k^i is the time of the kth spike in the ith cell, which is determined by the threshold value of $x_i(t)$ at $x_i=0.3\ \mu\mathrm{M}$. K_i is the number of spikes in the ith cell. R can be viewed as the signal-to-noise ratio, which provides an indication of the coherence of spike events. Biologically, this quantity is widely adopted because it is related to the timing precision of the information processing. A larger R implies more regularity of the Ca^{2+} spikes. In our numerical calculation, R is considered to be zero if all cells are in the steady state and the value of R is obtained through an average of 40 runs. In what follows, periodic-boundary conditions are adopted.

To begin, we fix the number of cells, $N=500$, and junctional coupling strength $C=0.05$. The curves of R as a function of σ at different levels of the agonist stimulation P are plotted in Fig. 2. On the one hand, under the condition of a certain value of P, when σ is zero or very small, all the cells are in a steady state—i.e., $R=0$. With an increment of σ, R reaches a maximum and decreases when further increasing σ. Thus, there exists an optimal $\sigma=\sigma_{opt}$ for the maximal $R=R_{\max}$, indicating the occurrence of structural-diversity-induced coherence resonance. On the other hand, σ_{opt} decreases with an increment of P.

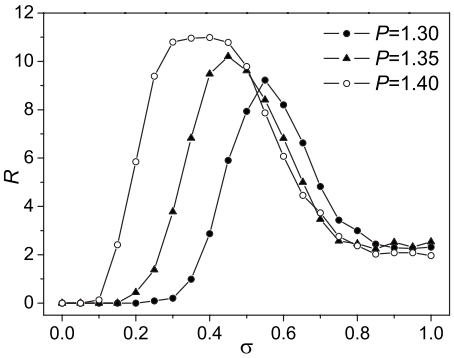

FIG. 2. The curves of R as a function of σ for different P. Some system parameters are $N=500$, $C=0.05$, and $\alpha_0=2.0$.

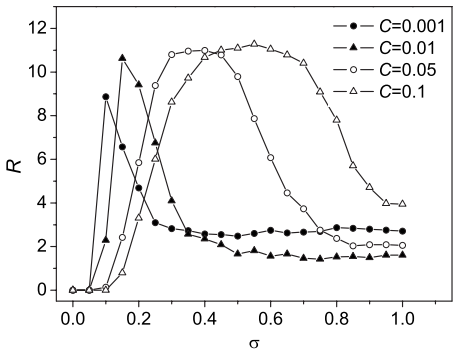

FIG. 3. The curves of R as a function of σ for different C. P is fixed at 1.4.

From the biological point of view, these phenomena imply the significance of the diversity of cellular structure in the detection of external weak signals. In detail, an optimal structural diversity exists at which the response of the systems to certain levels of extracellular subthreshold stimulation is maximally ordered. When the level of subthreshold stimulation is changed, cellular systems may have the ability to make the best response to the change of stimulation by a corresponding adjustment of the structural diversity.

How does one understand the occurrence of structural-diversity-induced coherence resonance? Maybe, it has inherent relevance both to the bifurcation feature of a single cell and the intercellular interaction through junctional coupling. First, for a single cell without calcium ion flux through the gap junction, there exists a supercritical Hopf bifurcation point corresponding to $\alpha=\alpha_h$; i.e., the system locates in a steady state when $\alpha<\alpha_h$ and an oscillatory state when $\alpha>\alpha_h$. Second, for coupled multicellular systems, when σ is zero or very small, all cells are in a steady state, and thus $R=0$ obviously. As σ increases, more cells locate in the steady state, but other cells locate in the oscillatory state all the same. Due to junctional coupling, cells locating in the oscillatory state could drag steady-state cells to the oscillatory state. If σ increases further, some cells locate in the steady state but far from the bifurcation point. Therefore, oscillatory cells do not have the capability to drag them to the oscillatory state. Thus, an optimal σ should exist for the best behavior of the systems. In Fig. 2, one can observe that σ_{opt} decreases with an increment of P. This is because α_h has different values for different P, such as $\alpha_h\approx 2.6$ for $P=1.3$, $\alpha_h\approx 2.4$ for $P=1.35$, and $\alpha_h\approx 2.2$ for $P=1.4$, respectively. At a certain σ, there are more cells located in the oscillatory state for larger P. Thus, a lower external stimulation—i.e., for smaller P—requires larger σ_{opt}. This indicates that the living system may effectively detect the extracellular weaker signals by increasing the structural diversity or vice versa.

We now consider the effects of junctional coupling strength C on structural-diversity-induced coherence resonance. In Fig. 3, the curves of R as a function of σ for different C are exhibited. One can notice that, on the one hand, the optimal σ_{opt} increases with an increment of C. On the other hand, the resonant peak becomes broader with an increment of C. Since a larger junctional coupling enables one to drag cells much far then from the oscillatory region to the oscillatory state, a larger σ_{opt} and a broader region of σ for the regular dynamical behavior are easily understood. Moreover, this shows that it is beneficial to detect subthreshold extracellular signals by increasing the coupling strength C. Because coupling can enhance obviously the coherence of the systems' collective dynamics in an array of coupled systems, the observed phenomenon mentioned above might be related to the so-called array-enhanced coherence resonance [31,32].

IV. CONCLUSION

In conclusion, based on the model of one-dimensional bidirectional coupled hepatocytes systems subjected to subthreshold signals, we show that the regularity of Ca^{2+} spikes undergoes a maximum with variation of σ, indicating the occurrence of structural-diversity-induced coherence resonance. Furthermore, in order to obtain the best performance in response to the change of the level of subthreshold extracellular stimulation, cellular systems may make the corresponding self-adjustment by a different variance of the structural parameter. These results imply that structural diversity plays a constructive role in the detection of subthreshold extracellular signals. Analysis indicates that these results have essential connections with both the bifurcation feature of a single cell and the intercellular interaction. Generally speaking, cellular structures are very little different even in same type cell and the systems may often encounter subthreshold stimuli. Therefore, our findings may have interesting implications for signal-detecting processes in living systems.

ACKNOWLEDGMENTS

This work is supported by the Educational Commission of Anhui Province of China (Grant No. KJ2007A079). The authors gratefully acknowledge the support of the Research Fund of Anhui Normal University (2006xzx09).

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