Two system-size-resonance behaviors for calcium signaling: For optimal cell size and for optimal network size

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(Received 11 January 2006; revised manuscript received 3 July 2006; published 1 September 2006)

We have studied the collective calcium signaling behavior of an array of coupled N cells, taking into account the internal noises resulting from the small cell size V. The system's performance was characterized by the reciprocal coefficient of variance (RCV) of the calcium spike train. Two system-size resonances were observed, namely, the RCV value shows a clear peak when both N and V are optimal. Therefore, an optimal number of cells of optimal size work the best as a whole.

DOI: 10.1103/PhysRevE.74.031901 PACS number(s): 05.40.−a, 05.45.−a, 05.45.Xt

The study of noise-induced constructive effects in nonlinear dynamical systems has drawn great research interest in the last two decades. It was demonstrated that there exists a "resonant" noise intensity at which the response of the system to a periodic force is maximally ordered, which is well known as stochastic resonance (SR) [1], or the order of the noise-driven system itself can have a maximum in the absence of periodic forcing, which is called coherent resonance (CR) [2,3]. Very recently, the frontier of this interest has shifted to a new and quite interesting SR-like phenomenon, system-size resonance [4–13]. So far, mainly two types of "size-resonance" behavior have been reported. On one hand, it was demonstrated that the collective behavior of an array of coupled N noisy dynamical elements may be the most ordered when the system size (here it is the number of elements N) has an optimal value [4–6]. In such a case, the noise is *ad hoc* external and the system size N plays a role in changing the effective noise strength subjected to the mean field. For example, system-size stochastic resonance was found in an ensemble of coupled noisy bistable elements subjected to a small periodic force [4], and system-size coherent resonance was demonstrated in a one-dimensional lattice of diffusively coupled excitable neurons in the absence of an external signal [5]. On the other hand, for chemical oscillating reactions taking place in small systems, stochastic oscillations can be observed and there is an optimal system size at which such stochastic oscillations show the best performance [7–13]. In such small systems, the molecule numbers of the reactants are often low and the internal noise resulting from the stochastic reaction events must be considered (it is generally accepted that the strength of the internal noise scales as $1/\sqrt{V}$, where V is proportional to the system size). There have been a few quite interesting findings of this type. It was reported that ion-channel clusters of optimal sizes can enhance the encoding of a sub threshold stimulus [7,8], and optimal intracellular calcium signaling appears at a certain size or distribution of the ion-channel clusters [9–11]. In recent studies, using the Brusselator and a circadian clock model, we have shown that the internal noise can induce stochastic oscillations in a regime close to the deterministic oscillatory dynamics, and an optimal system size exists for such stochastic oscillations, characterized by a clear maximum in the effective signal-to-noise ratio (SNR) as a function of system size V [12]. To outline, a chain of N-coupled noisy dynamic elements may show system-size N resonance, and a mesoscopic chemical oscillator of size V can show system-size V resonance. Note that the first one only accounts for external noise so far, and the second one results from the internal noise in small chemical-reaction systems.

In the present paper, we report an interesting phenomenon, namely, two system-size resonances for coupled mesoscopic chemical oscillators. Such a phenomenon demonstrates the coexistence of both N resonance and V resonance in a system. We have studied the collective dynamics of an array of N-coupled hypatocyte cells, each of size V, by using chemical Langevin equations (CLE). Internal noise is expected to induce calcium spikes, of which the regularity is evaluated by the reciprocal coefficient of variance (RCV), defined as the mean value of the spike interval τ normalized to its standard deviation, namely, $R=\tau/\sqrt{\langle\tau^2\rangle-\langle\tau\rangle^2}$. Two size resonances are found, i.e., R can reach a maximum at an optimal cell size V when the network size N is fixed, and it also shows a maximum for an optimal N if V is fixed. In short, an *optimal number of cells of optimal size function the best for their collective dynamics*.

Calcium often acts as a second messenger in living cells so as to regulate multiple cellular functions, and there is a vast literature devoted to the mathematical modeling of intracellular and intercellular calcium oscillations and waves observed in the experiments [14]. The model to be considered below was proposed to describe the intercellular calcium oscillations in hypatocytes [15,16]. According to this simplified model, the calcium signaling dynamics in a single cell involves the interplay of calcium fluxes from and into the endoplasmic reticulum and across the plasma membrane.

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TABLE I. Stochastic processes for calcium signaling in coupled hepatocytes. [Note: $k_r(x,p)=k_1[d_2(d_1+P)Px/(d_p+p)(d_a+x)[d_2(d_1+P)+x(d_3+P)]]^3+k_2$ is the IP_3 receptor release function. Parameter values are $\alpha=2.0$, $\beta=0.1$, $\rho=0.02\ \mu M^{-1}$, $\nu_0=0.2\ \mu M\ s^{-1}$, $\nu_c=4.0\ \mu M\ s^{-1}$, $\nu_3=9.0\ \mu M\ s^{-1}$, $\nu_4=3.6\ \mu M\ s^{-1}$, $k_0=4.0\ \mu M$, $k_3=0.12\ \mu M$, $k_4=0.12\ \mu M$, $d_1=0.3\ \mu M$, $d_2=0.4\ \mu M$, $d_3=0.2\ \mu M$, $d_p=0.2\ \mu M$, $d_a=0.4\ \mu M$, $k_1=40.0\ s^{-1}$, $k_2=0.02\ s^{-1}$. ER refers to endoplasmic reticulum (see Ref. [15] for more details)].

Stochastic processes	Rate	Consequence
(1) Plasma membrane influx	$a_1=V\rho_i\left(\nu_0+\nu_c\frac{P}{k_0+P}\right)$	$\Delta X_i^{(1)}=\Delta Z_i^{(1)}=1$
(2) Plasma membrane efflux	$a_2=V\rho_i\nu_4x_i^2/(k_4^2+x_i^2)$	$\Delta X_i^{(2)}=\Delta Z_i^{(2)}=-1$
(3) ER release	$a_3=V\alpha_i k_r(x_i,P)\lvert\frac{z_i-x_i}{\beta_i}-x_i\rvert$	$\Delta X_i^{(3)}=\mathrm{sgn}\left(\frac{z_i-x_i}{\beta_i}-x_i\right)$
(4) ER uptake	$a_4=V\alpha_i\nu_3x_i^2/(k_3^2+x_i^2)$	$\Delta X_i^{(4)}=-1$
(5) Diffusion to cell $i-1$	$a_5=V\gamma\lvert x_{i-1}-x_i\rvert$	$\Delta X_i^{(5)}=\Delta Z_i^{(5)}=\mathrm{sgn}(x_{i-1}-x_i)$
(6) Diffusion to cell $i+1$	$a_6=V\gamma\lvert x_{i+1}-x_i\rvert$	$\Delta X_i^{(6)}=\Delta Z_i^{(6)}=\mathrm{sgn}(x_{i+1}-x_i)$

Since the typical size of a cell is about $10^3\ \mu M^3$ and the numbers of reactant molecules involved in calcium signaling are often low, internal noise is expected to be considerable. The observation of localized stochastic Ca^{2+} puffs or sparks and variations in the amplitudes and widths of the calcium oscillations in experiments, also support this issue [17]. As stated by M. Falcke, fluctuations "render intracellular Ca^{2+} dynamics a truly stochastic medium" [18,19]. In this respect, the reaction steps are all stochastic, including the exchange of calcium ions between adjacent cells through the gap junctions. Denoting the population numbers of free calcium in the cytosol of cell i by X_i and that in the whole cell by Z_i, the stochastic processes involving the change of X_i or Z_i are listed in Table I, where V is the volume of the cytosolic compartment of the cell, and $x_i=X_i/V$, $z_i=Z_i/V$ denote the concentrations of the reactants. P is the concentration of inositol trisphosphate (IP_3) in the cell, which denotes the level of the agonist simulation and is chosen to be the control parameter. γ is the junctional coupling strength and the diffusion process will lead to the same changes of X_i and Z_i.

To study the role of internal noise, a mesoscopic stochastic model should be used instead of the deterministic ones. Basically, one should describe the reactions as a birth-death stochastic process governed by a chemical master equation, which describes the time evolution of the probability of having a given number of X_i and Z_i [20], with i ranging from 1 to N. There is no general procedure to solve this master equation analytically, but it provides the starting point for numerical simulations, including the widely-used exact stochastic simulation algorithm (SSA) proposed by Gillespie in 1977 [21], and some other improved methods. Here in the present paper, we will use the CLE, which was put forward also by Gillespie very recently [22] as our stochastic model. Although the rigorous validity of the CLE requires the existence of a macroinfinitesimal time scale, which may not always be the case, our previous studies have shown that CLE is a good choice to study the effect of the internal noise [12,13], given that the total number of reactant molecules is not too low. The benefit is that the CLE is much faster for numerical simulation than the SSA method, and it clearly shows how the internal noises relate to the reaction dynamics and the system size. We would like to emphasize here that the main results of the present paper can be well reproduced, at least qualitatively, by other approximate accelerated simulation methods such as the Poissonian method [23] and the τ-leap method [24].

Please note that the reaction steps and rates listed in Table I have been handled in an effective way. The reaction steps are not "elementary," and quasi-steady-state approximation has been applied. For the ER release and diffusion steps, for instance, the elementary steps would be a random jump of calcium ions through the ER or cell membrane with rates proportional to the number of calcium ions in the starting side, no matter whether the concentration gradient is positive or negative. In some coarse-grained time scale, however, the net diffusion would be ion fluxes from a high concentration side to a low side, and the net diffusion rates would be proportional to the concentration gradient as listed in Table I. In this time scale, the reactions inside a single cell are assumed to be homogeneous, such that the diffusion rates are also proportional to the cell size. The cases are similar for other processes. This "coarse-grained" procedure does not change the deterministic dynamics shown in the CLE (1) below, but the internal noise items will be different. However, since the CLE is an approximation of the stochastic dynamics in a "macroinfinitesimal time scale," one may expect that the "coarse-grained" procedure here is applicable, at least in a quantitative manner. It is interesting to study the effect of internal noise without coarse graining, while how to take into account the fluctuations in different time and space scales for intercellular calcium dynamics is an open question.

Based on the processes in Table I, the CLE for the coupled cell system, to write in a compact form, read

$$\frac{dx_i}{dt}=\frac{1}{V}\sum_{k=1}^{6}\Delta X_i^{(k)}[a_k+\sqrt{a_k}\xi_k(t)], \tag{1a}$$

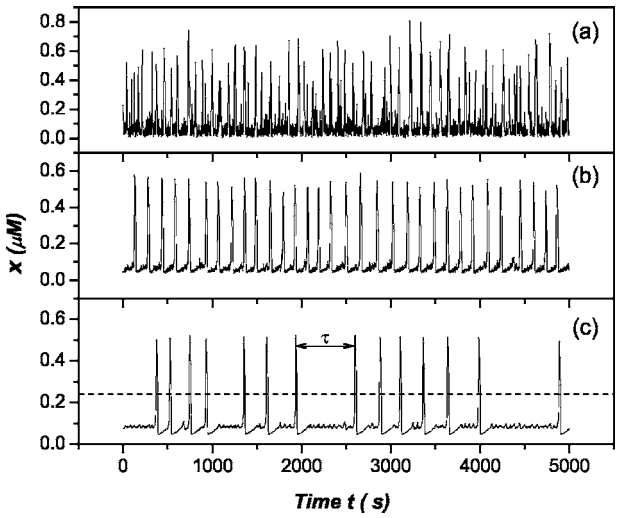

FIG. 1. Stochastic oscillations at different cell sizes for $N=1$. From top to bottom, $\log(V)$ is equal to 2, 3.5, and 5, respectively. A best regularity of the pulses can be observed for $\log(V)=3.5$. The dashed line in (c) shows the threshold to define the pulses, and τ refers to the time interval between consecutive pulses.

$$\frac{dz_i}{dt} = \frac{1}{V}\sum_{k=1}^{6} \Delta Z_i^{(k)}[a_k + \sqrt{a_k}\xi_k(t)], \tag{1b}$$

where $(i=1,\ldots,N)$, $\xi_{k=1,\ldots,6}(t)$ are independent Gaussian white noises with zero mean and unit variance, $\langle \xi_k(t)\rangle = 0$, $\langle \xi_k(t)\xi_k'(t')\rangle = \delta_{kk'}(t-t')$. It is clear that these internal noise items are proportional to $1/\sqrt{V}$ since all a_k are proportional to V. A simple Euler method with special treatment of the noise terms is used for numerical calculation; the time step is 0.02 s. A zero-flux boundary condition is adopted, and all the cell size V and control parameter P are assumed to be the same. The average cytosolic calcium concentration $x(t)=\frac{1}{N}\Sigma_{i=1}^{N} x_i(t)$ is calculated to characterize the collective dynamics of the system.

To begin, we first study the behavior of a single cell ($N=1$). With the parameter values listed in Table I, the system undergoes a supercritical Hopf bifurcation at $P=P_c\simeq 1.45$ μM. It was reported that inside the deterministic oscillation region, the dependence of the stochastic oscillatory dynamics on the system size is trivial, i.e., the correlation time of the oscillation decreases monotonically when the system size decreases [25]. In the subthreshold region, however, the system's dynamics shows nontrivial dependence on the cell size. In the present work, we choose $P=1.35$ μM, which is slightly below the Hopf bifurcation. If V is very large, the CLE [Eq. (1) with $N=1$] approximately recovers the deterministic dynamics and no calcium oscillation exists. However, for a small value of V, the internal noise items make sense and stochastic calcium pulses can be observed, with variations in the amplitude and width. If the size is too small, internal noise will dominate and the pulse train loses regularity. Therefore, there exists an optimal cell size for the intracellular calcium signaling, namely, *cell size*

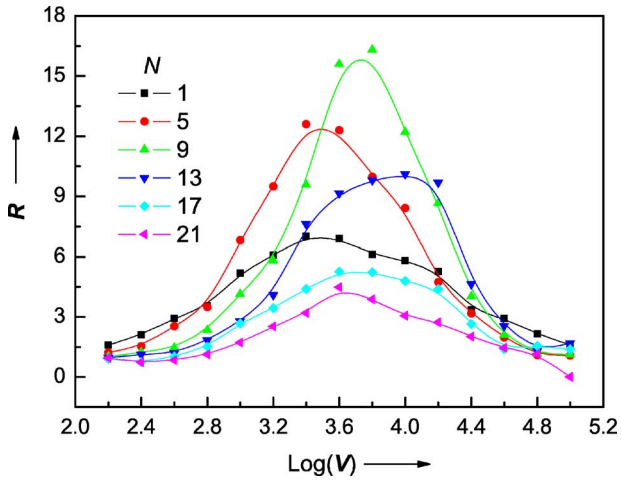

FIG. 2. (Color online) The dependence of the pulse regularity R on the cell size for a different chain size. It can be seen that an optimal cell size exists for the collective behavior of the system.

V resonance occurs. In Fig. 1, the temporal evolutions of $x(t)$ for three different V are shown. It is clear that the calcium pulses are rather regular for $V=10^{3.5}$, which is obviously much more regular than those for $V=10^2$ and $V=10^5$. The RCV value R shows a clear maximum for $V\sim 10^{3.5}$ as displayed in Fig. 2 (squares). Here a pulse is defined when $x(t)$ exceeds a certain threshold value x_0 from below (we take it arbitrarily as $x_0=0.25$ here, and the value of R is not sensitive to the choice of x_0). One notes that R could be of biological significance because it is related to the time precision of the information processing. A larger R means an increased closeness of the pulse train to a periodic one where R is obviously infinity.

Such a resonance behavior is also found for $N>1$. In Fig. 2, we have also plotted the dependence of R on V for a different network size N. The coupling coefficient is $\gamma=0.2$ except for Fig. 4. All the curves have an apparent maximum at an optimal cell size V. The location of the op-

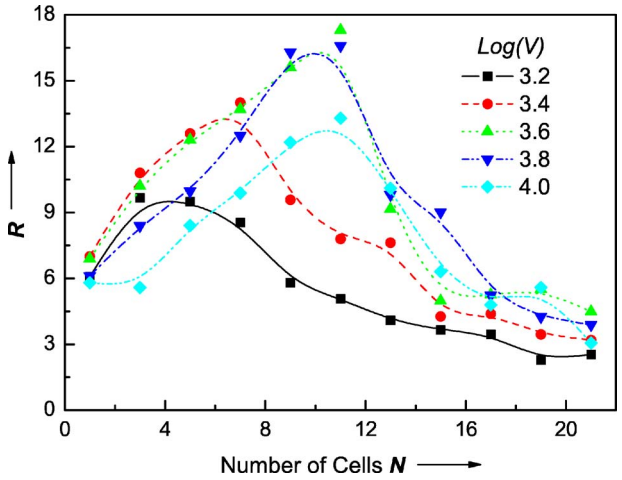

FIG. 3. (Color online) The dependence of R on the array size N for different cell sizes. We observe a second kind of system-size resonance, i.e., at an optimal N, the regularity of the calcium pulses reaches the maximum.

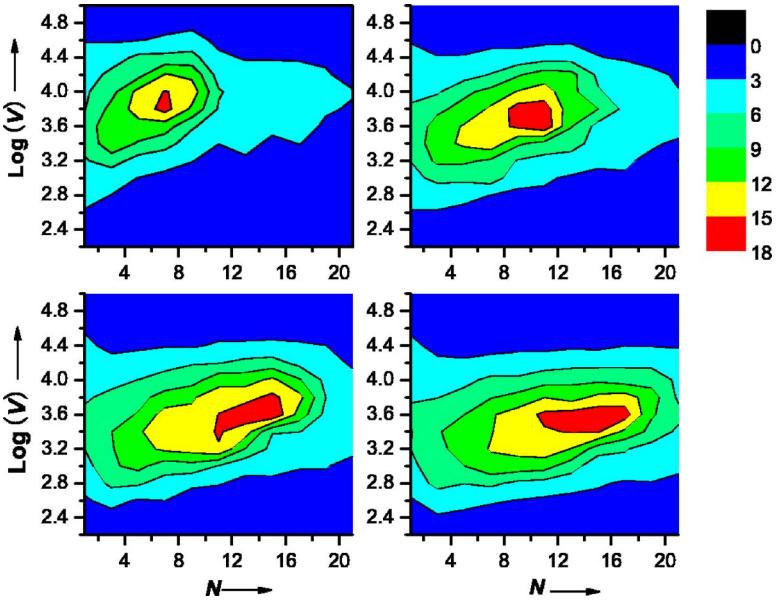

FIG. 4. (Color online) Contour plot of R in the N-V plane for $\gamma=0.05$, 0.1, 0.15, and 0.2, respectively. An optimal island clearly exists, where the value of R is much larger than that of a single cell.

timal cell size $V\sim 10^{3.5}$ does not change significantly with N. Note that for $N=9$, the maximal R is much larger than that for $N=1$, showing a kind of array-enhanced system-size resonance.

The existence of a cell-size resonance for calcium signaling might have interesting implications. On one hand, the existence of stochastic oscillations indicates that intracellular (intercellular) calcium oscillations can be sustained in a greater parameter range than those predicted by the deterministic model, i.e., it shows strong robustness to external stimulations, which should be beneficial for their proper functioning. On the other hand, it is interesting to note that the value of the optimal cell size $V\sim 10^{3.5}$ is of the same order of real living cells *in vivo*, which implies that the kinetic coefficients of the mechanism might have evolved to be optimal for the size of a cell. Finally, such a phenomenon cannot be reproduced by a deterministic model at all, indicating that models of calcium signaling should take careful account of the internal noise.

Taking another look at Fig. 2, one notes that when N increases, the maximal R value increases at first and then decreases, indicating an optimal value of N also. In Fig. 3, the dependences of R on N for five different V are depicted. As expected, each curve undergoes a clear maximum, demonstrating the occurrence of *network-size N resonance*. Unlike in Fig. 2, the optimal value of N shifts apparently for a different cell size. The time series of $x(t)$ (not shown here) shows apparent regularity for an intermediate N.

One may recall the system-size-coherence resonance reported in coupled excitable neurons [5]. For the N-resonance behavior observed here, however, the system is not subjected to any external noise, but the system's dynamics *must* be described by mesoscopic stochastic models due to the considerable internal noises. Both behaviors may share the same mechanism, i.e., the coupling between dynamical elements changes the effective noise intensity, either internal or external, subjected to the mean field. To some extent, however, the phenomenon we find here is a "real" behavior of coupled cells.

The above results already indicate the existence of two system-size resonances in the present system. Namely, for coupled hypatocyte cells, the collective calcium signaling is the most regular when both the network size N and the cell size V have optimal values. We have drawn the contour plot of R in the N-V plane for $\gamma=0.2$ in Fig. 4 (the last panel), where an optimal "island" of N-V values appears in the middle of the plot for $N\sim 10$ and $V\sim 10^{3.5}$. In real systems, the coupling strength γ is also an important parameter, and the collective behavior of the coupled system may strongly depend on it. For the hepatocytes, a reasonable range of γ values of physical significance is between 0.07 and 0.2 [15]. The results for $\gamma=0.05, 0.1, 0.15$ are also shown in Fig. 4. One sees that the existence of an optimal island is robust to the coupling strength, though quantitatively the island moves a little bit to larger N when the coupling becomes stronger.

At the current stage, we are not yet clear whether this phenomenon is universal for coupled mesoscopic chemical oscillators tuned near Hopf bifurcation, or if it is system dependent. Actually, we have also performed similar studies in coupled Hodkin-Huxley neuron models and similar results have also been obtained [26], but it is hard to reach a general conclusion from these two examples. Intuitively, we think that this phenomenon may depend on the system's deterministic bifurcation features near the Hopf bifurcation. However, this is not an easy question to answer and deserves more detailed work in the future.

To conclude, we have performed a model study on the calcium-signaling behavior of a one-dimensional network of identical hepatocyte cells coupled through gap junctions. The cells are tuned in a regime, which is subthreshold for the deterministic oscillatory dynamics. In such a regime, stochastic calcium spikes are observed, which are induced by the internal noises. The stochastic calcium spike train becomes the most regular when the network size N and

the cell size V have optimal values, i.e., two types of system-size resonances occur. Consequently, an optimal number of cells with an optimal cell size work the best for their collective dynamics. Our findings may find interesting applications for intercellular calcium signaling processes *in vivo* on one hand, and also may induce further perspectives on the study of internal noise as well as system-size resonance in the future.

ACKNOWLEDGMENTS

This work is supported by the National Science Foundation of China (Grant No. 20433050), the Foundation for the Author of National Excellent Doctoral Dissertation of the People's Republic of China (FANEDD), the Program for New Century Excellent Talents in University (NCET), and the Fok Ying Dong Education Foundation.

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