System-Size Biresonance for Intracellular Calcium Signaling

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Introduction

The study of noise-induced constructive effects in nonlinear dynamic systems has attracted considerable attention in the last two decades. It was demonstrated that there is 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] and that 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] Stochastic resonance and coherent resonance have been observed in numerous experiments, and more and more attention has been paid to SR-like phenomena in biological systems, from ion-channel gating and neuron spiking, to life-supporting systems and human balance-control systems.[3] As stated by

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Hänggi,[3] it would indeed seem strange if nature would not have taken advantage of the benefits of ambient noises for nonlinear transmission and/or amplification of feeble information rather than ignoring it.

Very recently, a new and quite interesting SR-like phenomenon, *system-size resonance*, has gained much attention.[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 noisy dynamical elements may be the most ordered when the system size (here the number of elements) has an optimal value.[4–6] In such a case, the noise is *external*, and the system size plays a role in changing the noise strength that is 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 can not be ignored; 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 subthreshold stimulus.[7–8] Shuai and Jung demonstrated that optimal intracellular calcium signaling appears at a certain size or distribution of the ion-channel clusters.[9–11] In recent studies, using the Brusselator model, we have shown that the internal noise can induce stochastic oscillations in the region close to the deterministic oscillatory dynamics, and an optimal system size exists for such stochastic oscillations; this is characterized by a clear maximum in the signal-to-noise ratio (SNR) as a function of system size V.[12] Similar results were also obtained in a circadian-clock system,[13] which may have interesting implications for biological rhythms and signaling processes.

Herein, we have investigated how the cell size would influence the intracellular calcium signaling process. We have used the model for intracellular calcium oscillation in hepatocytes, which was proposed by Höfer.[14] To account for the internal noise, we have used the chemical Langevin equations proposed recently by Gillespie.[15] Unlike previous studies,[9–11] we do not consider the channel noise involving the calcium release from intracellular calcium stores, but those from the stochastic reaction events in the whole cell. In addition, we find that the SNR of the stochastic calcium oscillation, which is absent in the deterministic dynamics, shows double maxima as a function of the cell size, which may be called system-size biresonance. Interestingly, we find that one of the optimal sizes matches rather well with the real cell size, and such a match is rather robust to external stimulus. We show that such a biresonance phenomenon is quite relevant to the deterministic bifurcation features of the system.

Model

Calcium often acts as a second messenger in living cells, to regulate multiple cellular functions. There is a vast amount of literature devoted to the mathematical modeling of the intracellular calcium oscillations and waves observed in the experiments. Most of these models are deterministic and the stochastic effects due to the random channel dynamics or small cell size are neglected. However, the observation of localized stochastic Ca^{2+} puffs or sparks, and variations in the amplitudes and widths of the calcium oscillations suggest that internal noise must be taken into account.[16] Actually, as mentioned above, the stochastic nature of the Ca^{2+} channel dynamics, involved in the release of Ca^{2+} from calcium stores to the cytosol, has already drawn much attention. But to our knowledge, the stochastic effects resulting from the small cell size has not been studied yet.

According to the Höfer model, the calcium signaling dynamics in a single cell involve the interplay of calcium fluxes from and into the endoplasmic reticulum (ER) and across the plasma membrane (not considering the fluxes from and into other possible compartments such as mitochondria). By denoting the population numbers of free calcium ions in the cytosol as X and that in the whole cell by Z, the reactions in the cell can be grouped into four "elementary" processes involving the change of X or Z by 1.[17] These processes and their reaction rates are defined in Table 1, where V is the volume of the cytosolic compartment of the cell, and $x=X/V$, $z=Z/V$ 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.

Table 1. *Stochastic processes and corresponding rates for intracellular Ca^{2+} dynamics.*

Stochastic Processes	Reaction Rates
$X\rightarrow X+1$	$a_1=V_\rho\left[\nu_0+\nu_c\frac{P}{c_{k_0}+P}+\frac{\alpha k_r(x,P)}{\beta}z\right]$, where $k_r(x,P)=k_1\left\{\frac{d_2(d_1+P)Px}{(d_p+P)(d_a+x)[d_2(d_1+P)+x(d_3+P)]}\right\}^3+k_2$
$X\rightarrow X-1$	$a_2=V_\rho\left[\nu_4\frac{x^2}{k_4^2+x^2}+\frac{\alpha k_r(x,P)}{\beta}(1+\beta)x+\alpha\nu_3\frac{x^2}{k_3^2+x^2}\right]$
$Z\rightarrow Z+1$	$a_3=V_\rho\left(\nu+\nu_c\frac{P}{c_{k_0}+P}\right)$
$Z\rightarrow Z-1$	$a_4=V_\rho\nu_c\frac{x^2}{k_4^2+x^2}$

Note: Parameter values are $\alpha=2.0$, $\beta=0.2$, $\rho=0.02\ \mu M^{-1}$, $\nu_0=0.2\mu M s^{-1}$, $\nu_c=4.0\mu M s^{-1}$, $\nu_3=9.0\mu M s^{-1}$, $\nu_4=3.6\mu M s^{-1}$, $k_0=4.0\mu M$, $k_3=0.12\mu M$, $k_4=0.12\mu M$, $d_1=0.3\mu M$, $d_2=0.4\mu M$, $d_3=0.2\mu M$, $d_p=0.2\mu M$, $d_a=0.4\mu M$, $k_1=40.0\ s^{-1}$, $k_2=0.02\ s^{-1}$. See Ref.[17] for more details.

In the case $V\rightarrow\infty$, the internal noise can be ignored and the time evolution of the reactant concentrations can be described by the following deterministic Equations (1):

$$\frac{dx}{dt}=\frac{(a_1-a_2)}{V} \tag{1a}$$

$$\frac{dz}{dt}=\frac{(a_3-a_4)}{V} \tag{1b}$$

With the variation of the control parameter *P*, this deterministic equation undergoes a Hopf bifurcation at $P \approx 1.45$ μM, above which calcium oscillations appear and below which only stable steady state can be observed. Figure 1 displays the bifurcation diagram for Equation (1) in the vicinity of $P = 1.45$ μM, where the solid lines give the maxima and minima of the oscillations (left axis), and the dash line shows the corresponding frequency of the oscillation (right axis). One notes that the diagram can be divided into three regions. In region 1, no deterministic oscillation exists. In region 2, oscillation appears but the amplitude is quite small and increases gradually with the increment of *P*. In region 3, the oscillation is spike-like with large and nearly constant amplitude. Correspondingly, the oscillation frequency first decreases in region 2 and then keeps nearly constant in region 3. Notice there is a sharp inflexion at $P \approx 1.47$μM. One will see that such a bifurcation character maybe the very reason of the system-size biresonance phenomenon, as shown below.

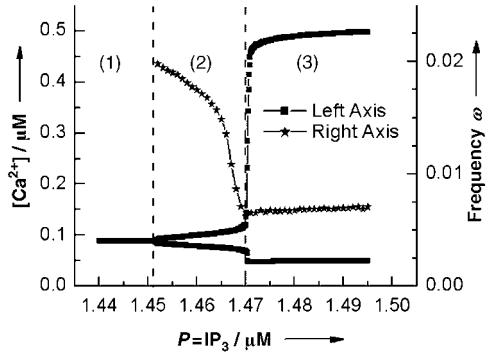

Figure 1. *Bifurcation diagram for the deterministic model.The solid squares denote the maximum and minimum of the deterministic oscillation range (left axis), and the stars correspond to frequency (right axis). It is shown that the parameter space of* $P = IP_3$ *concentration is divided into three distinct regions.*

However, for a typical living cell with $V \approx 10^3 \mu m^3$, such a deterministic description is not strictly valid due to the existence of considerable internal noise. Basically, one should describe the reaction system 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* and *Z*. There is no general procedure to solve this master equation analytically, but it provides the starting point for numerical simulations. Under certain circumstances, it is also reasonable to approximate the reaction processes by a chemical Langevin equation (CLE). In our previous study, we have shown that it is convenient to use the CLE to study the effect of the internal noise caused by the small system size.[12] According to Gillespie, the CLE for the current model reads [Equations (2)]:

$$\frac{dx}{dt} = \frac{1}{V}\left[(a_1 - a_2) + \sqrt{a_1}\xi_1(t) - \sqrt{a_2}\xi_2(t)\right] \quad (2a)$$

$$\frac{dz}{dt} = \frac{1}{V}\left[(a_3 - a_4) + \sqrt{a_3}\xi_3(t) - \sqrt{a_4}\xi_4(t)\right] \quad (2b)$$

where $\xi_{i=1\ldots4}(t)$ are Gaussian white noises with $\langle \xi_i(t) \rangle = 0$ and $\langle \xi_i(t)\xi_j(t') \rangle = \delta_{ij}\delta(t-t')$. Note the reaction rates a_i are proportional to *V*, such that the internal noise items in the CLE scales as $1/\sqrt{V}$. In the following, we will use the CLE to study the effects of the system size *V*.

Results and Discussion

We numerically integrate Equation (2) using the standard procedure for stochastic differential equations with a time step of 0.01 s.[18] In regions 2 and 3, where deterministic oscillations exist, the effect of internal noise is destructive, that is, it makes the deterministic oscillation noisy, leads to phase diffusion, and reduces the correlation time of the oscillation.[19] Therefore, we tune the control parameter *P* in region 1 but close to the Hopf bifurcation (HB) point, where the deterministic system does not sustain oscillation. Often, in such subthreshold cases, noise can play interesting and constructive roles.

For a given subthreshold parameter $P < P_c = 1.45$, the behavior of Equation (2) depends strongly on the system size *V*. If *V* is large enough, the effects of internal noise is negligible and the system show "deterministic" behavior, that is, no oscillation can be observed. When *V* decreases, however, "stochastic" oscillations can be found in this region. Such stochastic oscillations are quite distinct from random noise in that there is a clear peak in its power spectrum. If *V* is too small, internal noise dominates and no pronouncing peak can be found in the power spectrum. Therefore, unlike in regions 2 and 3, the dynamic behavior in region 1 is quite interesting: on one hand, the existence of internal noise can lead to stochastic oscillation which is absent in the deterministic system; on the other hand, there are optimal values of *V* where the stochastic oscillations show the best performance, that is, where system-size resonance occurs.

To quantitatively measure the relative performance of the stochastic oscillations, it is convenient to define an effective signal-to-noise ratio (SNR) as in ref. [13]. Then we can draw the dependence of the SNR on the system size *V* to demonstrate the system-size resonance. When we do this for $P = 1.3$, rather interestingly, we find two clear maxima in the SNR–*V* curve, as shown in Figure 2. Based on the discussion in the last paragraph, this is a kind of system-size biresonance (SSBR).

The stochastic oscillations corresponding to the two peaks are of different nature. In Figure 3, the time behaviors for $V = 10^3$ and 10^6 are shown. For $V = 10^3$, where the first peak locates, the stochastic oscillation is spikelike with a low frequency. But for $V = 10^6$, the stochastic oscillation is of small amplitude and larger frequency. The corresponding power spectrums for these stochastic oscillations are shown in Figure 3c, where the curves are already smoothed by a nearest averaging over 50 points of the original data. The time series used to calculate the power spectrums contains 16384 data points with time interval 1 s. The dependence of the frequencies of the stochastic oscillations, obtained by the principle peak in the power spectrum, is also shown in Figure 2 (right axis). Therefore, it seems that larger internal noise for smaller *V* tends to drive the system into the deterministic region 3 and induce

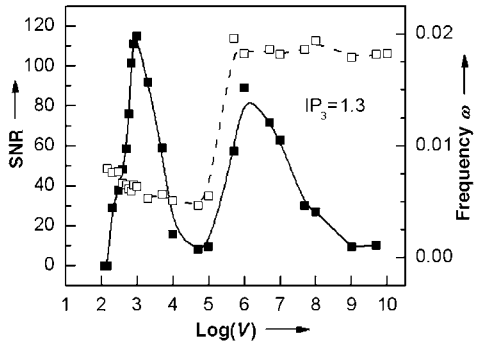

Figure 2. The SNR (left axis) and the corresponding principle frequency (right axis) of the stochastic oscillations for P = 1.3, obtained by numerical simulations of Equation (2). The clear double peaks in the SNR curve indicate the occurrence of system-size biresonance. From the frequency values, we see the stochastic oscillations regarding the two peaks have different natures.

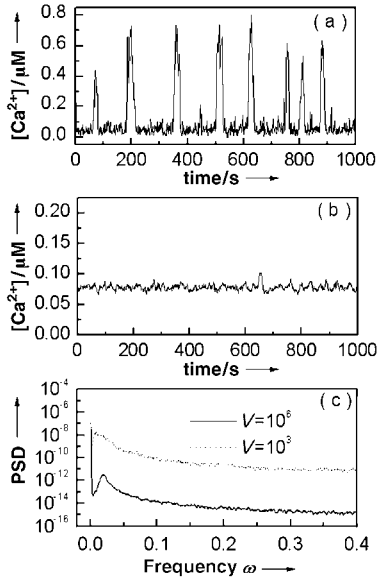

Figure 3. The stochastic oscillations for two typical system size for P = 1.3. a) V = 10^3, stochastic spikes are observed. b) V = 10^6, the system shows small amplitude stochastic oscillation. c) Power spectrum densities (PSD) for the stochastic oscillations shown in (a) and (b). It is observed that there is a clear peak in the PSD for both time series, and the principle frequency is different.

spike-like stochastic oscillations, while smaller internal noise for larger *V* can only induce stochastic oscillations with a small amplitude, like those in region 2. Hence, it is the distinct bifurcation feature of the system that leads to this kind of biresonance phenomenon.

To get more insight into the mechanism of the SSBR, we have also studied how the peak height (Figure 4a) and peak position (Figure 4b) change with the control parameter *P*. With the increase of *P*, the heights of both peaks increase monotonically. We note that before $P \approx 1.32$, the first peak is always higher than the second one. Therefore in a quite wide parameter region, where the deterministic dynamics does not show oscillations, small-sized cells can respond to external stimulus with spike oscillations. On the other hand, as shown in Figure 4b, the position of the second peak increases obviously with *P*, but the first peak remains nearly constant at $V \approx 10^3$. It is interesting to note that this size is of the same order as the living cells in vivo, and the stochastic oscillations corresponding to the first peak is of a spike type, which is the most popular form of intracellular calcium signaling.

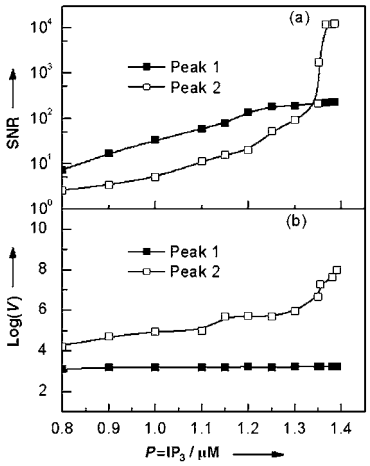

Figure 4. The dependence of the heights (a) and positions (b) for the resonance peaks 1 and 2 on the IP_3 level. For peak 2, both the height and position move to larger values when the control parameter approaches the Hopf bifurcation. For peak 1, the peak position remains nearly constant.

How the SSBR behavior can have implications for living cellular functions is still an open question. At the current stage, three points may be addressed. On one hand, the existence of stochastic oscillations indicates that intracellular calcium oscillations can sustain in a much more parameter range than those predicted by the deterministic model, that is, it shows strong robustness to external stimulations which should be of benefit for their proper functions. On the other hand, due to the fact that the first resonance occurs at nearly constant cell size $V \sim 10^3$, and this size is of the same order of real living cells in vivo, could we imagine that the kinetic coefficients of the mechanism have evolved to be optimal for the size of a cell? Finally, the specific relationship of the biresonance behavior with the deterministic bifurcation features indicate that any model of calcium signaling should take careful account into the internal noise, as well as external noise. We hope that our study can open more perspectives in the future works.

Conclusions

To summarize, we have studied the influence of cell size on intracellular calcium oscillations in hepatocytes using chemical Langevin equations. We show that, in the region where deterministic oscillations do not exist, stochastic oscillations can be induced by the internal noise that results from the small system size. Interestingly, the performance of such stochastic oscillations undergoes two peaks with the variation of the system size *V*, showing the occurrence of system-size biresonance. The stochastic oscillations corresponding to these two peaks have different natures, namely, one is of large amplitude with small frequency and the other small amplitude with large

frequency, which is relevant to the deterministic bifurcation features. More importantly, we find that the position of the first peak, where stochastic spike-oscillations are observed, remains nearly constant at $V \approx 10^3$ for a wide range of external stimulation levels. This robustness might have quite interesting implications for calcium signaling processes in vivo.

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Keywords: calcium · kinetics · oscillating reactions · signaling · stochastic processes

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