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System Size Resonance Associated with Canard Phenomenon in a Biological Cell System

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The influence of internal noise on the calcium oscillations is studied. It is found that stochastic calcium oscillations occur when the internal noise is considered, while the corresponding deterministic dynamics only yields a steady state. Also, the performance of such oscillations shows two maxima with the variation of the system size, indicating the occurrence of system size resonance. This behavior is found to be intimately connected with the canard phenomenon. Interestingly, it is also found that one of the optimal system sizes matches well with the real cell size, and such a match is robust to the variation of the control parameters.

Key words: Internal noise, Calcium oscillations, System size resonance, Canard phenomenon

I. INTRODUCTION

It is well known that intracellular calcium (Ca^{2+}) is one of the most important second messengers in the cytosol of living cells [1-2]. Cytosolic calcium oscillations play a vital role as a communication mechanism between distinct parts of the cell and between adjacent cells in the tissue. Many processes [2-4], like intracellular and extracellular signaling processes, muscle contraction, cell fertilization, gene expression, and so on, are all controlled by the oscillatory regime of the cytosolic calcium concentration. Calcium is called "a life and death signal" [5] because of its paramount importance for the control of all these processes. So far, most studies about calcium oscillations in cell systems account for ad hoc external noise [6,7], and the system's dynamics is often described by a macroscopic deterministic equation. However, for cellular or sub-cellular reaction system, the number of reaction molecules is often low [8-10], and one must pay much attention to the internal noise which results from the random fluctuations of the stochastic reaction events.

Only recently, the constructive role of internal noise has gained attention in calcium oscillation systems. For example, Shuai and Jung demonstrated that optimal intracellular calcium signaling appears at a certain size or distribution of the ion channel clusters [11,12]. In a previous study [13], we have also shown that stochastic calcium oscillations occur when the internal noise is considered, and the regularity of such oscillations shows a maximum with the variation of the system size. It is generally accepted that the internal noise level is inversely proportional to the square-root of the system size, so an optimal system size implies an optimal level of internal noise. This constructive role of internal noise recalls the well-known phenomenon of stochastic resonance (SR). We call this phenomenon internal noise stochastic resonance or system size resonance. Similar results have also been reported in Refs.[14-19].

On the other hand, "canard phenomenon", a complex temporal behavior resulting from excitability and multiple time scales in a dynamical system, has been observed in many biological [20-23], physical [24-26], and chemical systems [27-30]. It describes a dramatic change of frequency and amplitude of period orbit within an exponentially narrow parameter region. As a certain control parameter increases beyond the Hopf bifurcation point, the amplitude and period of the limit cycle first increases slowly, with these small amplitude oscillations being termed as canard trajectory; then in an exponentially small neighborhood of some critical point, the so-called canard point, the limit cycle explodes, becoming a relaxation oscillator with much larger amplitude and period. It is worthy to note that canard phenomenon is also observed in calcium signaling processes [21-23]. However, to our knowledge, the effects of noise in such systems were not well investigated.

In the present work, by constructing a mesoscopic stochastic model for intracellular calcium oscillations in a cell system, we have investigated how the internal noise would influence the calcium oscillations using chemical Langevin equations. It is found that stochastic calcium oscillations occur when the internal noise is considered, while the corresponding deterministic dynamics only yields a steady state, and the performance of such oscillations shows two maxima with the variation of the system size, indicating the occurrence of system

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size resonance. This behavior is found to be intimately connected with the canard phenomenon, the sudden explosion, as the control parameter passes through a value known as the canard point, of a limit cycle born at a supercritical Hopf bifurcation. Interestingly, we also find that one of the optimal system sizes matches well with the real cell size, and such a match is robust to the variation of the control parameters.

II. MODEL DESCRIPTION

The model used in the present work is based on the minimal model for intracellular calcium oscillations with the mechanism of "calcium induced calcium release (CICR)" [31]. Although there are many different models of intracellular calcium oscillations, we choose the simplest to qualitatively illustrate how the calcium oscillations depend on the internal noise. If the internal noise is ignored, the model can be described by the following equations [31]:

$$\frac{\mathrm{d}z}{\mathrm{d}t} = v_0 + v_1\beta - v_2 + v_3 + k_f y - kz \quad (1)$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = v_2 - v_3 - k_f y \quad (2)$$

$$v_2 = V_{\mathrm{M2}}\frac{z^n}{{K_2}^n + z^n} \quad (3)$$

$$v_3 = V_{\mathrm{M3}}\frac{y^m}{{K_{\mathrm{R}}}^m + y^m}\cdot\frac{z^p}{{K_{\mathrm{A}}}^p + z^p} \quad (4)$$

There are two dynamics variables: the concentration of free Ca^{2+} in the cytosol and in the IP_3-insensitive pool, denoted by z and y, respectively. This model has been studied extensively by Goldbeter and Dupont *et al.* [31,32], where one can find detailed descriptions of the parameters.

For a typical living cell system however, the number of reaction molecules is often low, so the influence of internal noise must be considered. Therefore, a mesoscopic stochastic model rather than the deterministic equations should be used. Generally, one can describe such a reaction system as a birth-death stochastic process governed by a chemical master equation [33], which describes the time evolution of the probability of having a given number of molecules of the two species. For the current model, the stochastic processes are listed in Table I, in which we have introduced the number of calcium ions in the cytosol as Z and correspondingly the number of calcium ions in the IP_3-insensitive pool as Y. And a simple description of the processes is illustrated in Fig.1, in which the concentrations of the two species are obtained as z=Z/Ω, y=Y/Ω (Ω is the total cell volume).

For these processes, one can readily write down the chemical master equation for the system. However, there is no practical procedure to solve this equation analytically. A widely-used method to handle the master equation is the exact stochastic simulation method introduced by Gillespie [34], but it is too time consuming, especially for large system sizes. Recently, Gillespie found that, under certain circumstance, it is reasonable to approximate the master equation by a chemical Langevin equation (CLE) [35]. In our previous studies [13,17-19], we have also shown that it is applicable to use the CLE to qualitatively study the effect of the internal noise. According to the stochastic processes and the transition rates shown in Table I, the CLE for the current model reads:

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{1}{\Omega}(a_1 + a_2 - a_3 + a_4 + a_5 - a_6) +$$

TABLE I Stochastic processes.

Processes		Description
(1)	$Z \to Z+1$	A constant input of Ca^{2+} from the extracellular medium to the cytosol
(2)	$Z \to Z+1$	Transport of a Ca^{2+} flow from an IP_3-sensitive store (A) into the cytosol
(3)	$Z \to Z-1$	The pump of Ca^{2+} from the cytosol into
	$Y \to Y+1$	the IP_3-insensitive store
(4)	$Z \to Z+1$	The release of Ca^{2+} from the IP_3-
	$Y \to Y-1$	insensitive store into the cytosol in a process activated by cytosolic Ca^{2+}
(5)	$Z \to Z+1$	Leaky transport of Ca^{2+} from the IP_3-
	$Y \to Y-1$	insensitive pool to the cytosol
(6)	$Z \to Z-1$	Transport of cytosolic Ca^{2+} into the extracellula medium

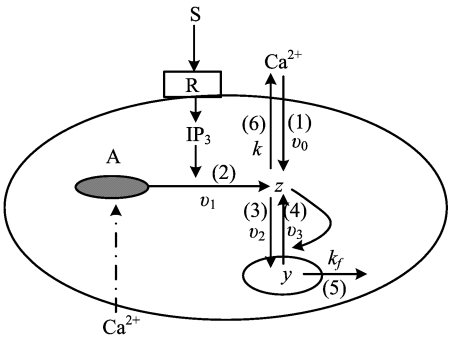

FIG. 1 Schematic representation of the mechanism for the minimal model of signal-induced calcium oscillations. The external signal (S) acts on a membrane receptor (R), and triggers the production of IP_3 which then modulates the release of Ca^{2+} from an IP_3-sensitive store (A) into the cytosol. Each level of IP_3 controls a constant flow of Ca^{2+} into the cytosol, denoted by $v_1\beta$; Cytosolic Ca^{2+} (z) is pumped into an IP_3-insensitive store, determined by v_2; Ca^{2+} in this store (y) is transported into the cytosol in a process activated by cytosolic Ca^{2+}, denoted by v_3; Parameters v_0, k and k_f relate respectively to the influx of extracellular Ca^{2+} into the cytosol, to the efflux of cytosolic Ca^{2+} from the cell and to a passive leak of y into z. The dashed arrow refers to replenishment of the IP_3-sensitive Ca^{2+} store (See Ref.[31] for further details).

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$$\frac{1}{\Omega}\big[\sqrt{a_1}\xi_1(t)+\sqrt{a_2}\xi_2(t)-\sqrt{a_3}\xi_3(t)+\sqrt{a_4}\xi_4(t)+\sqrt{a_5}\xi_5(t)-\sqrt{a_6}\xi_6(t)\big] \quad (5)$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{1}{\Omega}(a_3-a_4-a_5)+\frac{1}{\Omega}\big[\sqrt{a_3}\xi_3(t)-\sqrt{a_4}\xi_4(t)-\sqrt{a_5}\xi_5(t)\big] \quad (6)$$

$$a_1 = \Omega v_0 \quad (7)$$

$$a_2 = \Omega v_1\beta \quad (8)$$

$$a_3 = \Omega v_2 = \Omega V_{\mathrm{M2}}\frac{z^n}{{K_2}^n+z^n} \quad (9)$$

$$a_4 = \Omega v_3 = \Omega V_{\mathrm{M3}}\frac{y^m}{{K_\mathrm{R}}^m+y^m}\cdot\frac{z^n}{{K_\mathrm{A}}^p+z^p} \quad (10)$$

$$a_5 = \Omega k_f y \quad (11)$$

$$a_6 = \Omega k z \quad (12)$$

where $\xi_{i=1-6}(t)$ are Gaussian white noises with $\langle\xi_i(t)\rangle$=0 and $\langle\xi_i(t)\xi_j(t')\rangle$=$\delta_{ij}\delta(t-t')$, and v_0=1 μm/s, v_1=7.3 μm/s, V_{M2}=65 μm/s, V_{M3}=500 μm/s, k_f =1 s^{-1}, k=10 s^{-1}, K_2=1 μm, K_R=2 μm, K_A=0.9 μm, m=2, n=2, and p=4. Because the reaction rates a_i are proportional to Ω, the internal noise item in the chemical Langevin equation scales as $1/\sqrt{\Omega}$. In the following parts, we will mainly use Eq.(5) and Eq.(6) as our stochastic model for numerical simulation to study how the internal noise would influence the intracellular calcium oscillations.

III. RESULTS AND DISCUSSIONS

We choose β as the control parameter, which measures the saturation of the IP_3 receptor and rises with the level of the stimulus. We perform numerical calculation of Eqs.(1)-(4) with a time step 1 ms. Simulation results show that, with the variation of the control parameter β, the deterministic equation undergoes a supercritical Hopf bifurcation (HB) at $\beta_1\approx0.2887$, which transits very fast transition from a small amplitude oscillation to a large amplitude oscillation at $\beta_2\approx0.2895$, where "canard explosion" happens. See Fig.2(a) for the bifurcation diagram in the vicinity of the HB point and Fig.2(b) for the dependence of the trajectories on the parameter β and the appearance of the canard orbits. It is shown that there exist a supercritical Hopf bifurcation point at $\beta_1\approx0.2887$ and a canard point at $\beta_2\approx0.2895$, and these two points divide the parameter space into three distinct regions. The HB point and the canard point divide the bifurcation diagram into three regions: region-1 for $\beta<\beta_1$, where only steady state can be observed; region-2 for $\beta_1<\beta<\beta_2$, where small amplitude oscillations appear; and region-3 for $\beta>\beta_2$, where large amplitude oscillations occur.

We have firstly studied the influence of internal noise in region-1 with the control parameter β=0.287 which is sub-threshold for the deterministic calcium oscillations, however, when the internal noise is considered, the results altered. For very large system size, e.g., Ω=10^8 $\mu\mathrm{m}^3$, the internal noise is very small and only slight fluctuations of calcium concentration around the deterministic steady state exist (Fig.3(a)). When the system size decreases to a smaller value, e.g., Ω=10^6 $\mu\mathrm{m}^3$, random fluctuations around the steady state change to stochastic oscillation with small amplitude (Fig.3(b)). With further decreasing of the system size, we find that occasional calcium spikes appear on the background of the small stochastic oscillations (Fig.3(c)). For a certain smaller system size, e.g., Ω=10^3 $\mu\mathrm{m}^3$, the number of calcium spikes increases and the spike train becomes regular (Fig.3(d)). If the system size is too small, although the spikes appear more frequently, the internal noise is large and smears the regularity of the spike train (Fig.3(e)). Consequently, with the variation of the system size Ω, small amplitude oscillations firstly appear and then are replaced by stochastic spikes. Then the spikes become the most regular at an optimal system size, and finally are overwhelmed into the internal noise background.

To measure the relative regularity of the stochastic

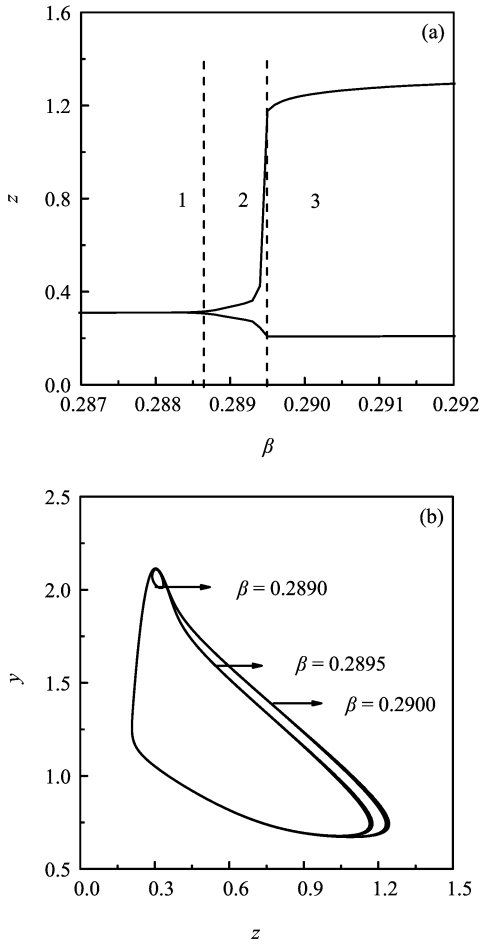

FIG. 2 (a) Schematic bifurcation diagram for the deterministic dynamics. (b) The dependence of the trajectories on the parameter β and the appearance of canard phenomenon without considering the internal noise.

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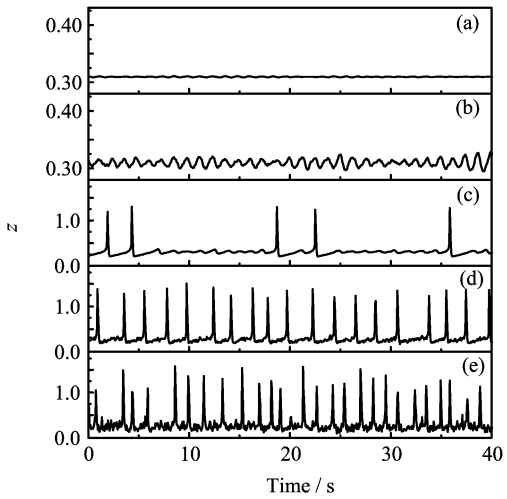

FIG. 3 The stochastic oscillations for five different system sizes with the control parameter β=0.287. (a) Ω=10^8 μm^3, (b) Ω=10^6 μm^3, (c) Ω=10^5 μm^3, (d) Ω=10^3 μm^3, (e) Ω=10^2 μm^3.

calcium oscillations quantitatively, we have used the effective SNR, defined as the relative height of the peak in the power spectrum divided by its half-height width [19]. The dependence of effective SNR on system size Ω for β=0.287 is plotted in Fig.4(a). The data are obtained by the chemical Langevin equations. Two maxima are present for system size $\Omega\approx10^3$ μm^3 and $\Omega\approx10^6$ μm^3. We call such a phenomenon "system size resonance". From the chemical Langevin equation, we know that the internal noise item is proportional to $1/\sqrt{\Omega}$ if all other parameters are fixed. Therefore, an optimal system size implies an optimal level of internal noise, so we also called it "internal noise coherence resonance".

To understand if such a phenomenon depends on β, we have gone through the parameters from region-1 to region-3, and the results are shown in Fig.4(b). We show that, there are two maxima for parameters in region-1 (β=0.279), located at $\Omega\approx10^3$ μm^3 and $\Omega\approx10^5$ μm^3 respectively; there is only one maximum for parameters in region-2 (β=0.289), located at $\Omega\approx10^3$ μm^3; but there is no maximum for parameters in region-3 (β=0.299) in which the SNR value decreases monotonically with the increases of internal noise level, that is, the existence of internal noise in this region is destructive.

The above discussions suggest that the phenomenon of "system size resonance" is intimately connected with the canard phenomenon, as shown in Fig.2. When the control parameter is located in region-1, where the system is sub-threshold for the calcium oscillation but excitable, small internal noise intends to draw the system into region-2, where small amplitude oscillations occur, while large internal noise will arouse large amplitude oscillations and drive the system into region-3. So the first maximum-$\Omega\approx10^3$ μm^3 corresponds to large amplitude

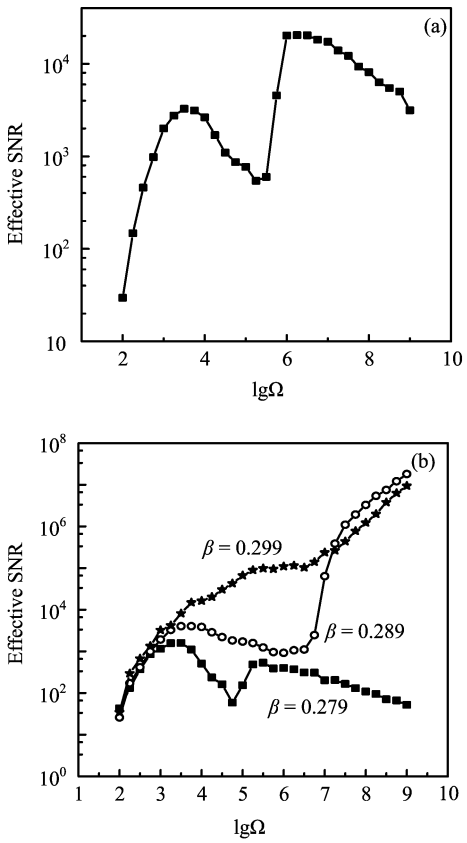

FIG. 4 (a) The dependence of effective SNR of the stochastic calcium oscillations on Ω with β=0.287. (b) The dependence of effective SNR of the stochastic calcium oscillations on Ω with at β=0.279, 0.289, and 0.299, respectively, which are located in three different regions.

stochastic oscillations and the second one-$\Omega\approx10^5$ μm^3 corresponds to small amplitude stochastic oscillations.

It should be pointed out that when the control parameter is located in region-2, the system shows deterministic oscillations when internal noise is ignored. In previous studies, it was demonstrated that in such a region, the inclusion of internal noise will only play a destructive role, but there also exists an optimal system size, which is implicit from the occurrence of resonance effect. We think that the existence of the canard phenomenon from this region to region-3 is the reason for such a phenomenon.

To get more insight into the mechanism of the system size resonance, we also studied how this phenomenon depends on the value of the control parameter β. This is shown in Fig.5. Results show that, with the variance of the control parameters, the height and the position of the first peak remains nearly unchanged corresponding to $\Omega\approx10^3$ μm^3; while the position of the second peak shifts obviously and the height decreases rapidly when the control parameter becomes farther away from the HB point. It is interesting to note that the size of $\Omega\approx10^3$ μm^3 is of the same order with real living cells *in vivo*.

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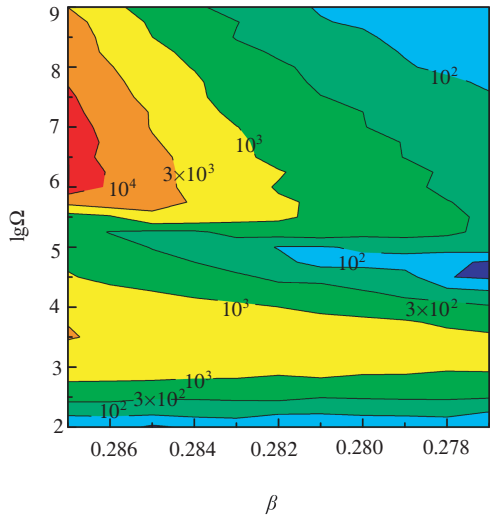

FIG. 5 The contour plot of effective SNR of the stochastic calcium oscillations on Ω with different β.

Then can we imagine that the cell system has learned to tune its kinetics parameters to work at an optimal state?

IV. CONCLUSION

Using a mesoscopic stochastic model for intracellular calcium oscillations in a single biological cell, we investigated the influence of internal noise using the chemical Langevin equation. It is found that stochastic calcium oscillations occur when the internal noise is considered, while the corresponding deterministic dynamics only yields a steady state. The performance of such oscillations shows two maxima with the variation of the system size, indicating the occurrence of system size resonance. We find that the occurrence of double maxima is associated with the canard phenomenon. Since the frequency and amplitude of the noise-induced oscillation show distinct characteristics at the two maxima, the resonance phenomenon indicates some kind of select effect of internal noise. It is interesting to note that the optimal size for the relaxation oscillation, say $\Omega \approx 10^3$ μm^3, matches well with the real cell size and such a match is robust to the variation of the control parameters. This robustness might have quite interesting implications for calcium signaling processes *in vivo*.

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