Internal noise stochastic resonance for intracellular calcium oscillations in a cell system

Hongying Li, Zhonghuai Hou,* and Houwen Xin
Department of Chemical Physics, University of Science and Technology of China, Hefei, Anhui, 230026, People's Republic of China
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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 of such a system using stochastic simulation methods and chemical Langevin method. It is found that stochastic calcium oscillations appear when the internal noise is considered, while the deterministic model only yields steady state. The performance of such oscillations undergoes a maximum with the variation of the internal noise level, indicating the occurrence of internal noise stochastic resonance. Interestingly, we find that the optimal system size matches well with the real cell size when the control parameter is tuned near the left Hopf bifurcation point, and such a match is robust to the variation of the control parameters.

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I. INTRODUCTION

The constructive effects of noise in nonlinear systems have gained much attention in the last two decades. It was demonstrated that there exists a resonant noise intensity, at which the response of a system to a periodic force is maximally ordered, which is well known as stochastic resonance (SR). Since it was put forward in the 1980s [1], SR has been studied in a variety of systems from physics [2], chemistry [3] to biology [4]. Recently, much attention has been paid to an interesting SR-like phenomenon, internal noise stochastic resonance (INSR), or system size resonance. For chemical oscillating reactions taking place in small scale systems, where the molecule numbers of the reactants are often low and the *internal* noise resulting from the stochastic reaction events must be considered, stochastic oscillations can be observed in a region subthreshold to deterministic oscillatory dynamics, and there is an optimal system size at which such stochastic oscillations show the best performance [5–13]. For example, Shuai and Jung demonstrated that optimal intracellular calcium signaling appears at a certain size or distribution of the ion channel clusters [5,6]. Ion channel clusters of optimal sizes can enhance the encoding of a subthreshold stimulus [7–9]. In recent studies, we have also found such a phenomenon in the Brusselator model [10], circadian clock system [11], surface catalytic reaction system [12], and neuron system [13].

It is well known that intracellular calcium (Ca^{2+}) is one of the most important second messengers in the cytosol of living cells [14,15]. Cytosolic calcium oscillations play a vital role as a communication mechanism between distinct parts of the cell or between adjacent cells in the tissue. Many processes [15–17], 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" [18] because of its paramount importance for the control of all these processes. So far, most studies about calcium oscillations account for ad hoc external noise [19–21], and the system's dynamics is often described by a macroscopic deterministic equation. However, as stated in above, for cellular or subcellular reaction system, the number of reaction molecules is often low [22–25] and one must pay much attention to the internal noise which results from the random fluctuations of the stochastic reaction events.

In the present paper, 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 of such a system using stochastic simulation methods and chemical Langevin method. We find that stochastic calcium oscillations appear when the internal noise is considered, in a parameter region where the deterministic model only yields steady state. The performance of such oscillations undergoes a maximum with the variation of the internal noise level, indicating the occurrence of *internal noise stochastic resonance* (INSR). Interestingly, we find that the optimal system size matches well with real cell size when the control parameter is tuned near a Hopf bifurcation point, and such a match is robust to the variation of the control parameters.

II. MODEL DESCRIPTION

The model discussed in the present paper is based on the minimal model for intracellular calcium oscillations with the mechanism of calcium induced calcium release (CICR) [26]. Although there are many different models of intracellular calcium oscillations, this minimal model has been frequently studied even in the recent years [27,28]. Here, we choose such a minimal model to simply illustrate how the internal noise would influence the calcium oscillations. If the internal noise is ignored, the system can be described by the following dynamical equations [26]:

$$\frac{dz}{dt} = \nu_0 + \nu_1\beta - \nu_2 + \nu_3 + k_f y - kz,$$

*Corresponding author. Electronic address: hzhlj@ustc.edu.cn

$$\frac{dy}{dt} = \nu_2 - \nu_3 - k_f y, \tag{1}$$

where

$$\nu_2 = V_{M2}\frac{z^n}{K_2^n + z^n}, \quad \nu_3 = V_{M3}\frac{y^m}{K_R^m + y^m}\frac{z^p}{K_A^p + z^p}. \tag{2}$$

In these equations, z and y denote the concentration of free Ca^{2+} in the cytosol and in the IP_3-insensitive pool, respectively; ν_0 refers to a constant influx of Ca^{2+} from the extracellular medium; $\nu_1\beta$ denotes the IP_3-modulated influx from the IP_3-sensitive store. The rates ν_2 and ν_3 refer to the pumping of Ca^{2+} into the IP_3-insensitive store and the release of Ca^{2+} from this store into the cytosol in a process activated by cytosolic Ca^{2+}; V_{M2} and V_{M3} denote the maximum values of these rates. k_f is a rate constant measuring the passive, linear leak of y into z; k relates to the assumed linear transport of cytosolic Ca^{2+} into the extracellular medium. Parameters K_2, K_R, and K_A are threshold constants for pumping, release, and activation; n, m, and p denote the Hill coefficients characterizing these processes. Especially, the parameter β measures the saturation of the IP_3 receptor and is selected as the control parameter, which rises with the level of the stimulus and varies from 0 to 1. The detailed description of the model and parameter values can be found in Ref. [26].

For a typical living cell system however, such a deterministic description is no longer valid due to the existence of considerable internal noise. Rather, a mesoscopic stochastic model should be used. Generally, one can describe such a reaction system as a birth-death stochastic process governed by a chemical master equation [29], but there is no practical procedure to solve this equation analytically. One of the widely used simulation algorithms is the exact stochastic simulation (ESS) method introduced by Gillespie in 1977 [30], which stochastically determines what is the next reaction step and when it will happen according to the transition probability of each reaction event. In accordance with Gillespie's method, we introduce 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, such that the concentrations of the reactants are obtained as $z=Z/\Omega$, $y=Y/\Omega$, where Ω is the total cell volume. Then, using the similar procedure as in Ref. [31], the reactions in the cell can be grouped into six elementary processes for the current model. See Fig. 1 for a simple description of the processes, and Table I for the corresponding transition rates. Note that the transition rates are proportional to the system size Ω.

Although the ESS method has been widely used to study the effects of internal noise in many systems, it is too time consuming when the system size is large. To overcome this problem, Gillespie developed the τ-leap method [32], and it has been proved that the τ-leap method is a rather good approximation of the ESS method for large system sizes. Therefore, it is convenient for us to use the ESS method for small systems and employ the τ-leap method for large ones during our stochastic simulation if a large range of system size must be accounted for.

A further alternative method to study the internal noise was also proposed by Gillespie [33], which is the chemical

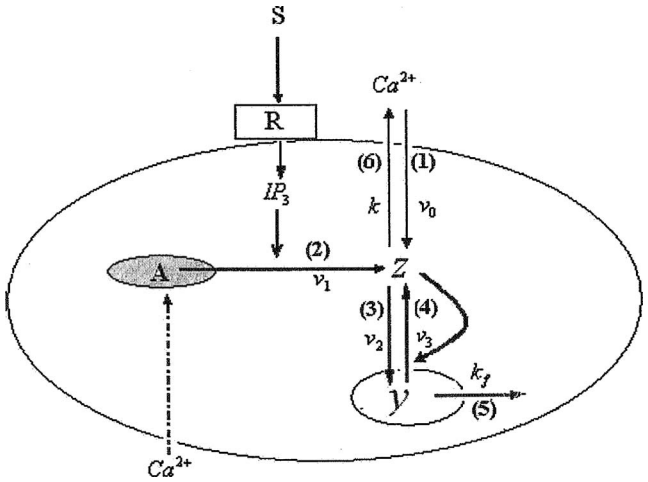

FIG. 1. Schematic representation of the mechanism for the minimal model of signal-induced calcium oscillations. The external signal (S) acts on a membrane receptor (R), and triggers the production of IP_3 which then modulates the release of Ca^{2+} from an IP_3-sensitive store (A) into the cytosol. Each level of IP_3 controls a constant flow of Ca^{2+} into the cytosol, denoted by $\nu_1\beta$; cytosolic Ca^{2+} (z) is pumped into an IP_3-insensitive store, determined by ν_2; Ca^{2+} in this store (y) is transported into the cytosol in a process activated by cytosolic Ca^{2+}, denoted by ν_3; parameters ν_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. [26] for further details).

Langevin (CL) method. It was proved that the CL method is a rather good approximation if a "macroinfinitesimal" time scale exists in the system. Compared to the ESS and τ-leap methods, the CL equation gives us clear information about how the internal noise depends on the system size as well as the reaction dynamics. According to Gillespie, the chemical Langevin equation for the current model reads

$$\frac{dz}{dt} = (a_1 + a_2 - a_3 + a_4 + a_5 - a_6) + \frac{1}{\sqrt{\Omega}}[\sqrt{a_1}\xi_1(t) + \sqrt{a_2}\xi_2(t) - \sqrt{a_3}\xi_3(t) + \sqrt{a_4}\xi_4(t) + \sqrt{a_5}\xi_5(t) - \sqrt{a_6}\xi_6(t)],$$

$$\frac{dy}{dt} = (a_3 - a_4 - a_5) + \frac{1}{\sqrt{\Omega}}[\sqrt{a_3}\xi_3(t) - \sqrt{a_4}\xi_4(t) - \sqrt{a_5}\xi_5(t)], \tag{3}$$

where $\xi_{i=1,\ldots,6}(t)$ are Gaussian white noises with $\langle\xi_i(t)\rangle=0$ and $\langle\xi_i(t)\xi_j(t')\rangle=\delta_{ij}\delta(t-t')$. 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. (3) as our stochastic model for numerical simulation to study how the internal noise would influence the intracellular calcium oscillations. The ESS method and the τ-leap method are also used to show consistency if necessary.

One should note that the methods used in the present work to account for internal noise is different from those of Shuai and Jung [5,6]. In their work, the internal noise comes

TABLE I. Stochastic transition processes and corresponding rates.[a]

Transition processes		Description	Transition rates
(1)	$Z \to Z+1$	A constant input of Ca^{2+} from the extracellular medium to the cytosol	$a_1=\Omega\nu_0$
(2)	$Z \to Z+1$	Transport of a Ca^{2+} flow from an IP_3-sensitive store (A) into the cytosol	$a_2=\Omega\nu_1\beta$
(3)	$Z \to Z-1$ $Y \to Y+1$	The pump of Ca^{2+} from the cytosol into the IP_3-insensitive store	$a_3=\Omega\nu_2$ $=\Omega V_{M2}z^n/K_2^n+z^n$
(4)	$Z \to Z+1$ $Y \to Y-1$	The release of Ca^{2+} from the IP_3-insensitive store into the cytosol in a process activated by cytosolic Ca^{2+}	$a_4=\Omega\nu_3$ $=\Omega V_{M3}y^m/K_R^m+y^m z^p/K_A^p+z^p$
(5)	$Z \to Z+1$ $Y \to Y-1$	Leaky transport of Ca^{2+} from the IP_3-insensitive pool to the cytosol	$a_5=\Omega k_f y$
(6)	$Z \to Z-1$	Transport of cytosolic Ca^{2+} into the extracellular medium	$a_6=\Omega kz$

[a]Parameter values used in the paper, $\nu_0=1\ \mu\mathrm{M\ s^{-1}}$, $\nu_1=7.3\ \mu\mathrm{M\ s^{-1}}$, $V_{M2}=65\ \mu\mathrm{M\ s^{-1}}$, $V_{M3}=500\ \mu\mathrm{M\ s^{-1}}$, $k_f=1\ \mathrm{s^{-1}}$, $k=10\ \mathrm{s^{-1}}$, $K_2=1\ \mu\mathrm{M}$, $K_R=2\ \mu\mathrm{M}$, $K_A=0.9\ \mu\mathrm{M}$, $m=2$, $n=2$, $p=4$.

from the stochastic gating dynamics of calcium channels inside a *channel cluster*, which involves a fast time scale and small space scale. They focused on the effects of channel noise and used deterministic dynamics for the exchange of calcium. In our work, however, the internal noise comes from the stochastic reaction events *in the whole cell*. Treating the reactions involving the exchange of calcium as stochastic steps as listed in Table I, one can write down a master equation which is the basis for the stochastic simulation and the chemical Langevin equation. These reactions happen in a much slower time scale than the open-close events of the channel gates as suggested by Hofer [34]. Therefore, although the channel noise still exists, it can be averaged out by quasi-steady-state approximation as demonstrated very recently by Rao and Arkin [35]. Substituting the steady-state value of the gating variables into the reaction rates of the channel flux, one finally obtains an expression like a_4 in Table I. One should note that the minimal model used in the present work is in a rather simplified form, but basically the discussions above remain valid.

III. RESULTS AND DISCUSSION

To investigate the influence of internal noise, it is necessary to study the corresponding deterministic kinetics as a comparison. We perform numerical calculation of Eqs. (1) and (2) by Eular method with a time step 0.001 s. Simulation results show that, with the variation of the control parameter β, the system undergoes two Hopf bifurcations (HB) at $\beta \approx 0.291$ and $\beta \approx 0.775$. The maximum and minimum values of the variable z are plotted in Fig. 2. The two HB points divide the parameter space into three regions, the low steady state to the left hand side (LSS region), the oscillation state in the middle (OS region), and the high steady state to the right hand side (HSS region).

We have first studied the influence of internal noise in the OS region with the control parameter $\beta=0.60$. Simulation results show that the calcium oscillation performance measured by effective signal-to-noise ratio (SNR) (see Ref. [11] for detailed description of the calculation of effective SNR) decreases monotonically with the increases of internal noise level (see Fig. 3). That is, internal noise plays a destructive role in this region. However, this result fails when the system is tuned near the HB point but outside the oscillation region. One should note that it is always near the critical points where internal noise can play constructive roles. Therefore,

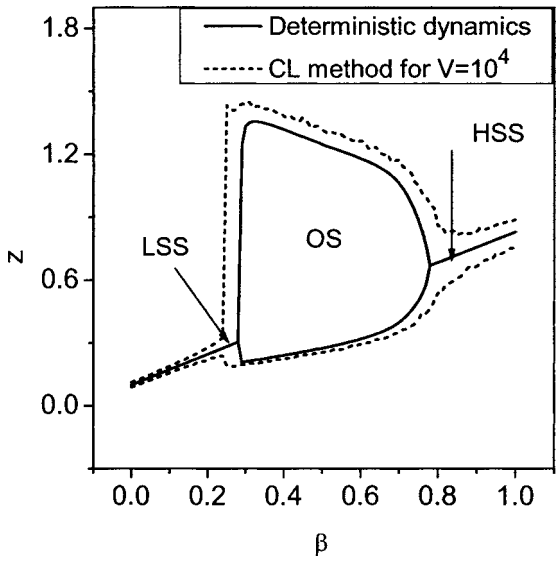

FIG. 2. Schematic bifurcation diagram for the deterministic dynamics (solid line). The Hopf bifurcation points are $\beta \approx 0.291$ and $\beta \approx 0.775$. For comparison, the range of stochastic oscillation for $\Omega=10^4$ obtained from the chemical Langevin equation is also plotted (short dashed line).

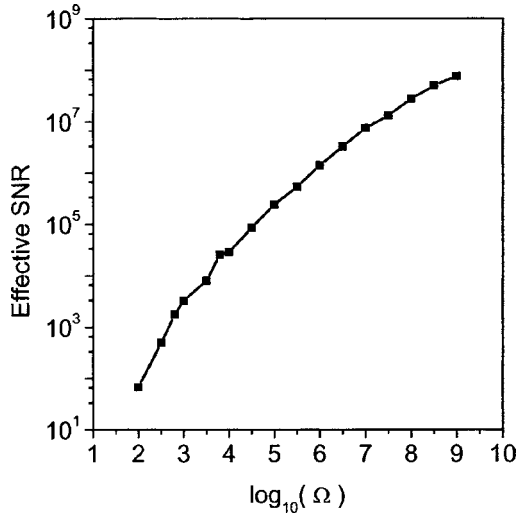

FIG. 3. Dependence of effective SNR on the system size with the control parameter $\beta=0.60$.

in the following parts, much more attention is paid to these regions.

We tune the control parameter $\beta=0.78$, which is near the right HB point but in the HSS region. So that, when the system size is very large, the internal noise can be ignored and the system is at a stable state. However, if the system size is small, we must take into account the internal noise. Simulations via the ESS method, the τ-leap method and the CL method all show stochastic calcium oscillations. That is, when the internal noise is considered, a wider range of OS region exists. To compare with the deterministic kinetics, we have also shown the range of OS region of z for $\Omega=10^4$ μm^3 in Fig. 2. Obviously, the HB point defined by the deterministic dynamics disappears. We can say that the calcium oscillations become to be quite robust to the variation of the control parameter in virtue of internal noise.

Now we consider the influence of different internal noise level on the stochastic calcium oscillations. In Fig. 4, the power spectrums for the stochastic oscillations of z are plotted for three different system sizes, corresponding to three different internal noise levels. A Welch window function is

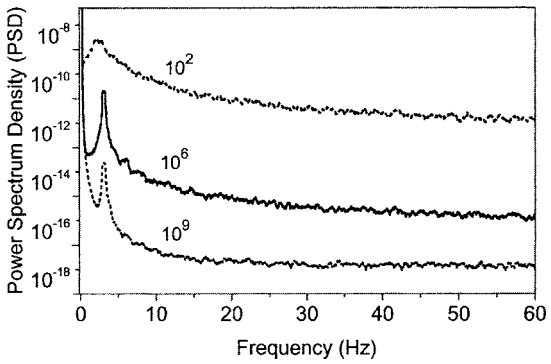

FIG. 4. The smoothed power spectrums for three different system sizes $\Omega=10^2$, $\Omega=10^6$, and $\Omega=10^9$, respectively. The control parameter is $\beta=0.78$. The curves are all obtained from the chemical Langevin method.

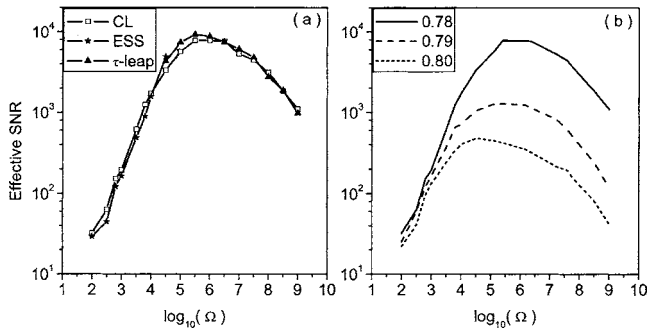

FIG. 5. (a) The dependence of effective SNR on the system size Ω with the control parameter $\beta=0.78$. Open square, chemical Langevin method (CL); solid star, exact simulation method (ESS); solid triangle, τ-leap method. (b) The dependence of SNR on system size with different control parameters obtained by the CL method, 0.78 (solid line); 0.79 (dashed line); 0.80 (short dashed line). The data have been smoothed.

used during the estimation of the power spectrum. The time series used to calculate the power spectrum contains 16 384 data points, and the smoothed curves are obtained by nearest averaging over 50 points from the original one. Clear peaks appear in the power spectrum, which implies that the stochastic oscillations are distinct from random noise and it contains periodic information. When the system size decreases from 10^9 μm^3 to 10^2 μm^3, i.e., with the increase of internal noise level, both the signal level and the noise background increase at the peak (see Ref. [11] for the definition of the signal and the noise background).

To measure the relative performance of the stochastic calcium oscillations quantitatively, we also use the effective SNR. The dependence of effective SNR on system size for $\beta=0.78$ is plotted in Fig. 5(a). A clear maximum is present for system size $\Omega\approx10^6$ μm^3. 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. This constructive role of internal noise recalls one well-known phenomenon of stochastic resonance (SR). Therefore, we call this INSR.

The SNR values obtained from the ESS method and the τ-leap method are also shown in Fig. 5(a). Good qualitative agreement among the CL method, the ESS method and the τ-leap method is apparent. This agreement implies that it is convenient to use the CL method to study the qualitative effects of internal noise and the robustness of the present results. Using the CL method, we have also studied how the INSR behavior depends on the value of the control parameter, which is shown in Fig. 5(b). Results show that, when the control parameter becomes farther away from the HB point, both the maximum SNR and the optimal system size become smaller.

Using the methods discussed above, we have also studied the influence of internal noise when the control parameter is tuned near the left HB point but inside the LSS region. Similar results are obtained that INSR occurs and such a behavior depends on the value of the control parameter. When the control parameter becomes farther away from the HB point,

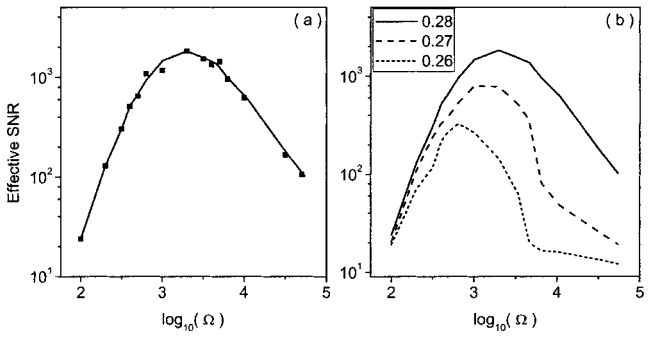

FIG. 6. (a) The dependence of effective SNR on the system size Ω with the control parameter $\beta=0.28$. (b) The dependence of SNR on system size with different control parameters, 0.28 (solid line); 0.27 (dashed line); 0.26 (short dashed line). The results are all obtained by the CL method and the data have been smoothed.

both the maximum SNR and the optimal system size become smaller (see Fig. 6). However, with regard to the position of the peak for different control parameters, we find some distinct features near the left HB compared to the right HB. One can see that when the control parameter is tuned near the right HB, the position of the peak changes obviously (from $\Omega \approx 10^6$ μm^3 to $\Omega \approx 10^4$ μm^3), i.e., the system is sensitive to the internal noise. Near the left one, however, the position of the peak keeps nearly constant at $\Omega \approx 10^3$ μm^3 for a wide range of control parameter values, i.e., the system is robust to the variation of the internal noise intensity. It is also interesting to note that the size of real living cells *in vivo* is around 10^3 μm^3.

How can the INSR phenomenon have implications for living cellular functions is still an open question. For the current stage, our results may be of relevance to calcium signaling in two ways. *On the one hand*, due to the existence of unavoidable internal noise, stochastic calcium oscillations can persist for a much wider parameter range, that is, calcium oscillations can be quite robust to the variation of the control parameter. *On the other hand*, instead of trying to resist the internal molecular noise, living cell systems may have learned to exploit it to enhance the calcium oscillation performance via the mechanism of INSR. It is also interesting to note that the calcium signaling sensitivity [5] and capability [6] in many cells show the maximum if the channel cluster size is optimal, and the spontaneous action potential in neurons shows the best time precision when the density of axon ion channels reaches an optimal level [36]. Such behaviors imply that INSR might be a widely used mechanism for living organisms to adapt and function.

We would like to emphasize here that, as stated by Martin Falcke, "fluctuations render the intracellular calcium dynamics a truly stochastic medium" [37]. Actually, it was already demonstrated that stochastic models can show spatial and temporal structures even with parameters providing a nonoscillatory or nonexcitable deterministic regime in calcium dynamics [15,38], which is also one of the main results of our present work. Besides this, we find that inside this kind of parameter regime, an optimal level of internal noise can mostly favor the formation of intracellular oscillation, indicating some kind of self-tuning mechanism involved in stochastic calcium dynamics.

IV. CONCLUSION

In conclusion, 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 of such a system using stochastic simulation methods and chemical Langevin method. It is found that stochastic calcium oscillations appear when the internal noise is considered, while the deterministic model only yields steady state. The performance of such oscillations undergoes a maximum with the variation of internal noise, indicating the occurrence of INSR. Interestingly, we find that the optimal system size matches well with the real cell size when the control parameter is tuned near the left Hopf bifurcation point, and such a match is robust to the variation of the control parameters. Our findings may imply the constructive role of internal noise on intracellular calcium oscillations in living systems.

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