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Selective effects of external noise on Ca^{2+} signal in mesoscopic scale biochemical cell systems

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Abstract

We have investigated how the external noise would influence the intracellular calcium signaling processes due to the existence of internal noise in small systems. Using chemical Langevin equations, we demonstrate numerically that the behavior of 'system size bi-resonance' induced by internal noise will change with the external noise intensity in different regions, indicating the occurrence of selective effects of external noise. Meanwhile, cell system may also automatically select an optimal cell size to obtain the best performance in the presence of external noise. These results may imply that such selective-effect phenomenon should have some inherent relevance with the distinct deterministic bifurcation features of the system.

Keywords: Selective effects; Ca^{2+} signal; Internal noise; External noise; Stochastic bi-resonance

1. Introduction

In the last two decades, the constructive effects induced by noise in nonlinear systems have been widely studied theoretically and experimentally in different fields of science, one of the most interesting phenomena is stochastic resonance (SR)[1]. Recently, a new type of SR-like phenomenon, system size resonance [2–4], has gained growing attention. So far, mainly two types of 'noise-induced' effects have been reported. On the one hand, for the first kind of SR, i.e., the traditional concept of SR-like behavior, it was demonstrated that there exists a 'resonant' noise intensity at which the response of the system is maximally ordered [5–7]. On the other hand, it has been demonstrated that in small-scale systems, such as in chemical oscillation systems or in living cell systems, stochastic oscillations can be observed and there exists an optimal system size such that the stochastic oscillations show the best performances [8,9]. One notes that the first type effect is mainly a result of external noise, while the second type is a result of the interplay between the internal noise and the systems' nonlinear dynamics.

It is well known in a real biochemical cell system, oscillations of cytosolic Ca^{2+} play a vital role in providing the intracellular signaling. Many important cellular processes and biological function, such as muscle contraction, and gene expression etc. are regulated by Ca^{2+} signals [10]. To our knowledge, both external and internal fluctuation for an actual mesoscopic scale biochemical cell systems are unavoidable [11,12]. It is widely agreed that the oscillatory behaviors of intracellular Ca^{2+} may be modulated by these environmental fluctuations which come from outside and inside of cell system [9,13]. In our group, we have observed that there exists stochastic bi-resonance (SBR), whichever kind of noises is considered [9,14] Therefore, it is naturally the next step to study the effects affected simultaneously by internal and external noise. Specifically, for the purpose of the present work, we are wondering whether the SBR behavior induced by internal noise also exists when disturbed simultaneously by another one? And if so, how it is affected by the noise intensity? And which kind of noises plays the dominant role?

Consequently, in this paper, effects induced by internal and external noises in a cell system of rat hepatocyte are studied. By calculating numerically Signal-to-Noise (SNR)[15], one can observe that the diagram can be divided into four typical regions with the variation of internal noise for different external noise intensity. In each region, SBR induced by internal noise has the different characteristic, indicating the occurrence of selective effects of external noises. Meanwhile, cell system may also automatically select an optimal cell size to obtain the best SNR in the

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presence of external noise. These results show that selective-effect phenomenon is quite relevant to the deterministic bifurcation features of the system, and their relationship is also discussed.

2. Model

In this paper, we use the stochastic version of the deterministic model for intracellular Ca^{2+} signal, proposed by Höfer and Gracheva [16–18]. The deterministic model for time evolution of concentration of the cytosolic Ca^{2+} (denoted by x) and total Ca^{2+} in the cell (denoted by z) are as following:

$$\frac{dx}{dt} = \rho\left(v_0 + v_c\frac{P}{k_0+P} - v_4\frac{x^2}{k_4^2+x^2} + \frac{\alpha k_r(x,P)}{\beta}(z-(1+\beta)x) - \alpha v_3\frac{x^2}{k_3^2+x^2}\right)$$

$$\frac{dz}{dt} = \rho\left(v_0 + v_c\frac{P}{k_0+P} - v_4\frac{x^2}{k_4^2+x^2}\right) \quad (1)$$

Where P is the inositol 1,4,5-trisphosphate (IP_3) concentration in the cell, the IP_3 receptors (IP_3R) release function $k_r(x,P)$ describes the gating kinetics of IP_3 receptor R and is given by

$$k_r(x,P) = k_1\left[\frac{d_2(d_1+P)Px}{(d_p+P)(d_a+x)(d_2(d_1+P)+x(d_3+P))}\right]^3 + k_2 \quad (2)$$

The detailed description of the model see Refs [16–18] and parameter values can be found in the caption in Fig. 1. With the variation of the control parameter P, the deterministic Eq. (1) undergoes *Hopf* Bifurcation at $P=1.45$ and at $P=8.892$. The bifurcation diagram (see Fig. 1) is divided into four regions: A, B, C and D. A and D are steady state regions, B is small oscillation region and C is relaxation oscillation region.

First, for a real living cell whose size is small, such a deterministic model is no longer strictly valid due to the existence of considerable noise. Instead, a mesoscopic stochastic model must be used. Now two kinds of noises, internal and external noise, are considered. Generally, one can describe a stochastic process in such a reaction system by a chemical master equation, 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 proposed by Gillespie [19], 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 X and correspondingly the number of total calcium ions in the cell as Z, such that the concentrations of the reactants are obtained as $x=X/V$, $z=Z/V$, where V is the total cell volume. Then, using the similar method as in Ref. [16], the reactions in the cell can be grouped into four elementary processes for the current model. See Eq. (3) for the corresponding transition rates. Note that the transition rates are proportional to the system size. 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 [20], 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 system size 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 [21], which is the chemical 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. It is generally accepted that the strength of the internal noise scales as $1/\sqrt{V}$, where V is proportional to the system size.

Second, the external noise comes from the environmental fluctuations [17,22], which results in stochastic influence in the interplay of Ca^{2+} fluxes from and into the endoplasmic reticulum and across the plasma membrane. Due to the concentration of IP_3 fluctuations are not needed to produce Ca^{2+} oscillations, it is assumed that P rapidly reaches a steady state value [23]. Finally, we introduced the following expressions for the rates in accordance with Gillespie's method [21,24].

$$a_1 = V\rho\left(v_0 + v_c\frac{P}{k_0+P} + \frac{\alpha k_r(x,P)}{\beta}z\right)$$

$$a_2 = V\rho\left(v_4\frac{x^2}{k_4^2+x^2} + \frac{\alpha k_r(x,P)}{\beta}(1+\beta)x + \alpha v_3\frac{x^2}{k_3^2+x2}\right)$$

$$a_3 = V\rho\left(v_0 + v_c\frac{P}{k_0+P}\right)$$

$$a_4 = V\rho v_4\frac{x^2}{k_4^2+x^2} \quad (3)$$

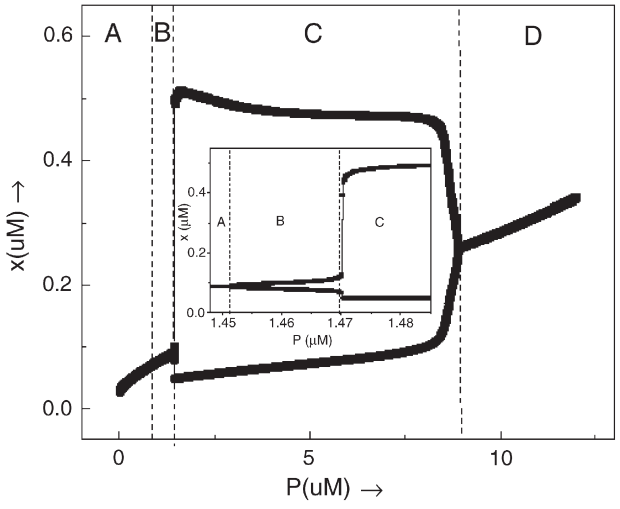

Fig. 1. Bifurcation diagram for the deterministic model. It is shown that the parameter space of $P=IP_3$ concentration is divided into four distinct regions: A, B, C and D. Inset is a detail magnification of region B. Parameter values are $v_0=0.2\ \mu Ms^{-1}$, $v_c=4.0\ \mu Ms^{-1}$, $v_3=9.0\ \mu Ms^{-1}$, $v_4=3.6\ \mu Ms^{-1}$, $k_0=4.0\ \mu M$, $k_3=0.12\ \mu M$, $k_4=0.12\ \mu M$, $d_1=0.3\ \mu M$, $d_2=0.4\ \mu M$, $d_3=0.2\ \mu M$, $d_p=0.2\ \mu M$, $d_a=0.4\ \mu M$, $k_1=40.0\ s^{-1}$, $k_2=0.02\ s^{-1}$, $\rho=0.02\ \mu M$, $\alpha=2.0$, $\beta=0.1$.

Hence, we add the noises terms to the deterministic differential Eq. (1) i.e.

$$\frac{dx}{dt} = \frac{1}{V}(a_1 - a_2) + \frac{1}{\sqrt{V}}\left[\sqrt{a_1}\xi_1(t) - \sqrt{a_2}\xi_2(t)\right] + \Gamma_1(t)$$

$$\frac{dz}{dt} = \frac{1}{V}(a_3 - a_4) + \frac{1}{\sqrt{V}}\left[\sqrt{a_3}\xi_3(t) - \sqrt{a_4}\xi_4(t)\right] + \Gamma_2(t) \quad (4)$$

Internal and external noise are described by the second term and the third term in Eq. (4), respectively. V is the volume of the cytosolic compartment of the cell, $a_{1,2}$ are the reaction rates of cytosolic Ca^{2+} ions and denote the increasing and decreasing process respectively, while $a_{3,4}$ represent the same process for the total Ca^{2+} in a cell. Since all the reaction rates $a_{1,2,3,4}$ are proportional to the system size V, the internal noise term in Eq. (4) scales as $1/\sqrt{V}$. $\xi_{1,2,3,4}(t)$are Gaussian white noises with $\langle \xi_i(t)\xi_j(t')\rangle = \delta_{ij}\delta(t-t')$ and $\langle \xi_i(t) = 0\rangle$.In the present paper, in order to mainly study the pure effect of noises, much more attention is paid to how the external noise would influence the calcium oscillations of such an internal noisy system. We will keep all other parameters fixed and change the cell size and the external noise intensity only. i.e., the external noise term $\Gamma_k(t)$ is simply treated as additive and mutually uncorrelated Gaussian distributed with zero mean, and white both in space and time, $\langle \Gamma_k(t) = 0\rangle$ and $\langle \Gamma_k(t)\Gamma_{k'}(t')\rangle = 2D\delta_{kk'}\delta(t-t')$, with different random seeds for $k=1$ and 2 respectively, where D is the external noise intensity. Furthermore, the "numerical recipes" is used for the generation of independent random numbers for $k=1$ and 2 respectively, with the Box–Muller algorithm providing the Gaussian distributed random numbers [25].

In the following parts, by constructing a mesoscopic stochastic model for such a cell system, we fix the control parameter $P=1.3$ μM, which is below but close to the left *Hopf* Bifurcation point, i.e. the system can be located in the steady state region A according to the deterministic Eq. (1). It is necessary to study the corresponding deterministic kinetics as a comparison. We perform numerical calculation of Eqs. (1) and (2) by Euler method with a time step 0.05 s. Bifurcation graphs are shown in Fig. 1. However, Eqs. (3) (4) were integrated by using stochastic simulation methods and chemical Langevin method. We have analyzed the Fourier power spectrum of the time series of x through averaging 20 runs. The SNR can be calculated as defined in Ref [15], $\mathrm{SNR} = h\omega_0/\Delta\omega$, where ω_0 is the principal peak frequency of the spectrum, h is the maximum peak height, and $\Delta\omega$ is the width of the peak at half maximum height.

3. Result and discussion

According to the expression of SNR mentioned above, four typical curves of SNR as a function of the $\mathrm{Log}_{10}V$ for different external noise intensities are plotted in Fig. 2, respectively. We find that the behavior of 'system size bi-resonance' induced by internal noise will change with the external noise intensity. It implies the selective effect of noise appears, and these results are displayed in Fig. 2. Without the external noise (i.e. $D=0$), the curve exhibits two maxima with the variation of the cell size, indicating the occurrence of SBR helped by internal noise [9]. When small external noise is added ($D=10^{-4}$), the contour of two-peak still existed due to effect of external noise is feeble. But when $D=10^{-3}$, we find the first peak still exists, while the second peak disappears. Interestingly, when external noise intensity $D=10^{-2}$, we find that two peaks disappear, i.e., the increment of external noise can elevate the second peak but

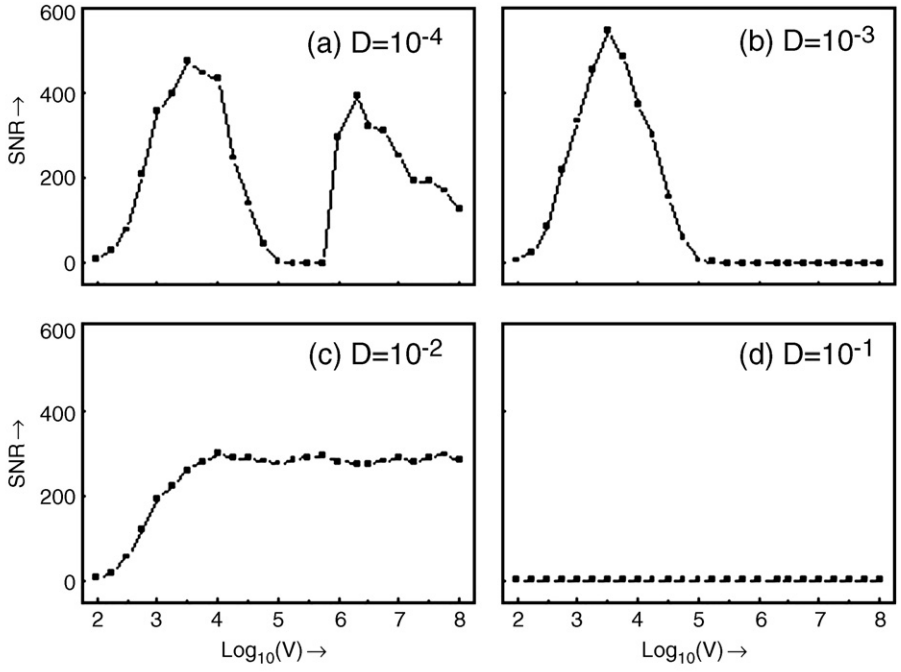

Fig. 2. SNR as a function of $\mathrm{Log}_{10}V$ for different external noise intensities D. $P=1.3$, other parameter values see caption of Fig. 1 (a) $D=10^{-4}$, (b) $D=10^{-3}$, (d) $D=10^{-2}$, (d) $D=10^{-1}$.

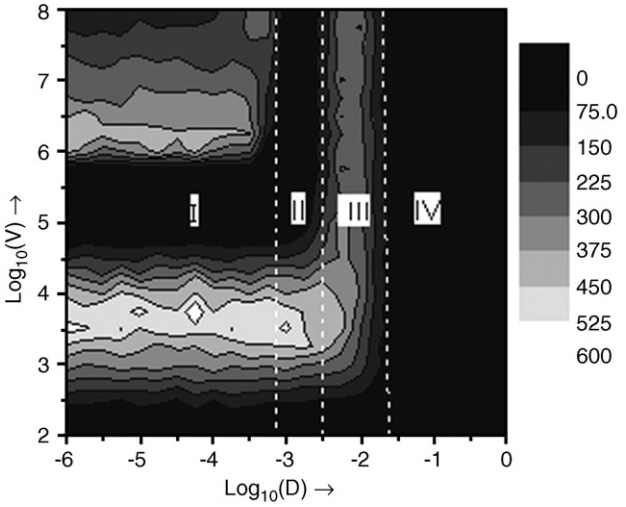

Fig. 3. SNR plot for different $\mathrm{Log}_{10}V$ and different $\mathrm{Log}_{10}D$. It is shown that the parameter space of external noise intensity D is divided into four distinct regions: I, II, III and IV.

depress the first one. Thus it is obviously observed that there exists a plateau under this condition. The SNR does not change evidently with the internal noise, which indicating that the system's response to internal fluctuation is rather robust. Finally, for further larger $D=0.1$, the SNR is very low all the time.

To get a global view, we plot the SNR as function of $\mathrm{Log}_{10}V$ and $\mathrm{Log}_{10}D$ in Fig. 3. One notes that the dependence of SBR on the cell size (internal noise) has different features with the variation of external noise, thus the diagram can be divided into four regions: region I, II, III and IV, respectively. In region I, SBR can still appear due to very low external noise. Thus, the character of this region resembles the result that without external noise. Detailed discussion can see Ref [9]. It is obvious that, internal noise plays the dominant role and cell system may also automatically select two optimal cell sizes to obtain the best SNR (SBR is obtained in such region). In the larger noise region IV, the value of SNR is completely suppressed implying the external noise is so large that it plays the destructive role.

Unlike in regions I and IV, the dynamic behaviors in regions II and III are interesting. One can see in region II, when the external noise is near 10^{-3}, only the fist peak appears near at $\mathrm{Log}_{10}V=3.5$, but the second peak disappears. It shows that the effect of small internal noise (corresponding to the larger cell size) is counteracted by that of the external noise, while the effect induced by larger internal noise still exists. Thus we only observe a single-peak resonance, instead of two-peak resonance. (see the curve of $D=10^{-3}$ in Fig. 2). However, in region III, the considerable large value of SNR is always maintained even if the cell size is very large, i.e., under such external noise condition, the cell system maintains a good performance for a larger parameter space of system size, so stranger robustness to response cell size fluctuation is shown. Of cause, the temporal behavior of system in these two regions can be used to explain the different effect of noises. On the one hand, in Fig. 4, two typical time series of Ca^{2+} oscillations are plotted for $\mathrm{Log}_{10}V=3.5$ and 6, respectively. One notes that in region II, Ca^{2+} oscillations only appear in small cell size (Fig. 4a, b), while in region III Ca^{2+} oscillations can appear even though cell size is very large (Fig. 4c, d). On the other hand, in region III one can also find that Ca^{2+} oscillations are very regular. In order

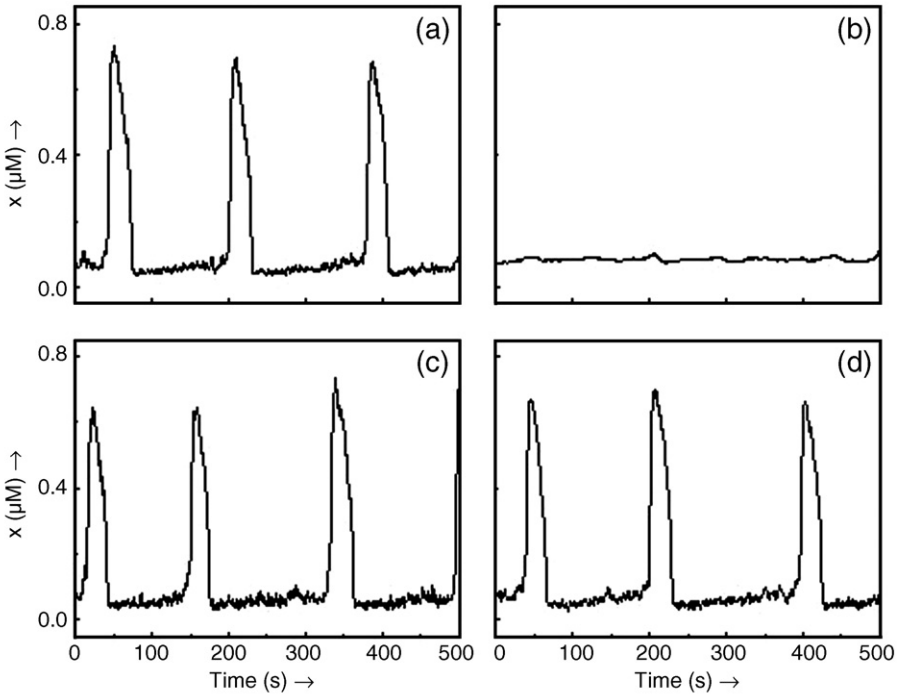

Fig. 4. Temporal behavior of Ca^{2+} oscillations for different cell size V and different external noise intensity D. (a) $\mathrm{Log}_{10}V=3.5$, $\mathrm{Log}_{10}D=-3$ (b) $\mathrm{Log}_{10}V=6$, $\mathrm{Log}_{10}D=-3$ (c) $\mathrm{Log}_{10}V=3.5$, $\mathrm{Log}_{10}D=-2$ (d) $\mathrm{Log}_{10}V=6$, $\mathrm{Log}_{10}D=-2$.

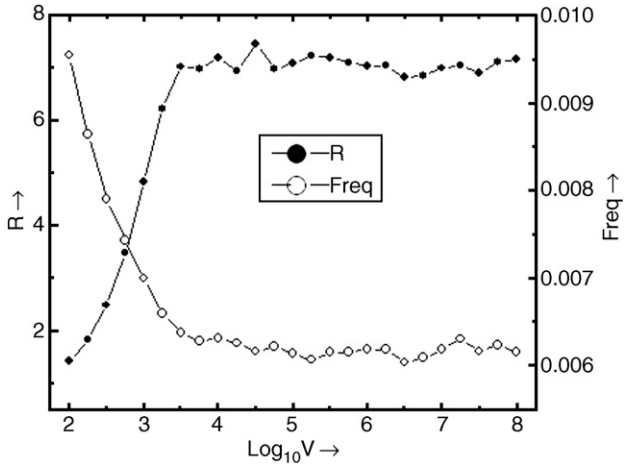

Fig. 5. R and frequency of Ca^{2+} oscillations as a function of $Log_{10}V$. D=0.01 is fixed, other values see caption of Fig. 1.

to quantitatively describe the regular degree of Ca^{2+} spikes, R is defined as follow:

$$R = \frac{1}{N}\sum_{k=1}^{N} \frac{<T_k>}{\sqrt{<T_k^2> - <T_k>^2}} \quad (5)$$

Where T_k is the kth period of Ca^{2+} spikes, the averages <…> are with respect to the number of the Ca^{2+} spikes, N is the number of Ca^{2+} spikes. Bigger value of R implies better regular degree of Ca^{2+} spikes. We select N=100, and plot R as well as frequency of Ca^{2+} spikes as a function of cell size in Fig. 5. If $Log_{10}V$<3.5, the R increases and frequency decreases monotonously as the increment of cell size. If $Log_{10}V \geq 3.5$, the R and frequency keep almost constant value. In other words, the R and frequency of Ca^{2+} oscillations are less susceptible to the fluctuation of cell size and thus some level external noise enhances the robustness of Ca^{2+} oscillations [26].

How does the external noise influence the SBR induced by internal noise, and what is the mechanism of the selective-effect behavior? From Figs. 1 and 3, one will see that such a bifurcation character in Fig. 1 maybe the very reason of selective-effect behavior shown in Fig. 3. When the external noise is not added or the noise intensity is very low, the system will work in region I. In such case, internal noise induced by the fluctuation of cell size, plays a leading role and drives the system into B or C region, thus the SBR appears; As external noise increases to II region, it may equal to the small internal noise (cell size in very large) whose effect will be counteracted, thus only the first peak can exist; If external noise increases to region III, the system is driven into C region, and it's dynamic behavior is controlled almost by external noise. Notice that the response ability of the system is less affected by the fluctuation of system size (internal noise). It shows stronger robustness of the best performance to external stimulus. Finally, when D is further increased to IV region, external noise will play a destructive role and completely suppress the Ca^{2+} oscillations. From discussion above, we think that the distinct deterministic bifurcation features of the system should have some inherent relevance with such a selective-effect phenomenon.

4. Conclusion

The mechanism of noise in Ca^{2+} oscillations is still an open question. To my knowledge, the influence of internal and external noise together on cell system has few studies before. In this paper, three points may be addressed. On one hand, in the presence of different level external noise intensities, the stochastic model exhibits different characteristics. It shows cell system has selective effect of external noise. Thus we may reasonably consider cell have self-adapted ability to environmental fluctuation. On the other hand, in region III, we find that the existence of some level external noise can help to sustain the regularity of Ca^{2+} oscillations in a larger range of cell size. In particular, the frequency of Ca^{2+} oscillations is almost unchanged in this region. From the biological point of view, some level of external noise is helpful to Ca^{2+} signal frequency encoding due to the frequency of Ca^{2+} oscillations that is less susceptible to the fluctuation of cell size [27,28]. In this sense, some level external noise may strengthen robustness of Ca^{2+} oscillations [26]. At last, there may be competitive mechanism between internal and external noise. The temporal behavior of Ca^{2+} oscillations may be dominated by one type noise through competition. We hope our findings could find some interesting applications for Ca^{2+} signaling in real systems, and can also open more perspectives in the study of internal noise in biological systems. The complex mechanism of noise in Ca^{2+} oscillations will be further studied in our future work.

Acknowledgments

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