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ARTICLE

Constructive Role of Internal Noise for the Detection of Weak Signal in Cell System

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Abstract: Taking into account the existence of internal noise in small scale biochemical reaction systems, we studied how the internal noise would influence the detection of weak external signal in the cell system using chemical Langevin equation. The weak signal was too small to, separately, fire calcium spikes for the cell. We found that, near the Hopf bifurcation point, the internal noise could help the calcium oscillation signal cross a threshold value, and at an optimal internal noise level, a resonance occurred among the internal noise, the internal noise-induced calcium oscillations, and the weak signal, so as to enhance intensively the ability of the cell system to detect the weak signal. Since the internal noise was changed *via* the cell size, this phenomenon demonstrated the existence of an optimal cell size for the signal detection. Interestingly, it was found that the optimal size matched well with the real cell size, which was robust to external stimulus, this was of significant biological meaning.

Key Words: Internal noise; Detection of weak signal; Calcium oscillation; Resonance

Noise is usually considered a nuisance, degrading the performance of dynamic systems. But in some nonlinear systems, the presence of noise can enhance the ability of the system to detect weak signals. This phenomenon of noise-enhanced detection of weak signals has been studied experimentally and theoretically in various systems. For example, this phenomenon was reported in the mechanoreceptive system in crayfish[1,2] and dogfish[3], human tactile sensation[4], visual perception[5], cricket sensory system[6], human brain system[7,8], chemical reaction system[9], neuron system[10,11], hair bundle system[12] and so on. The uniform feature in these systems is the concurrence of a threshold, a subthreshold stimulus, and the noise. There exists an optimal level of noise that results in the maximum enhancement, whereas further increases or decreases in the noise intensity only degrade detectability or information contents. The threshold is ubiquitous in nature, especially in some biological systems, and these systems may receive external stimulus all the time. Usually, the stimulus is by itself below the threshold, never crosses it, and is therefore undetectable, whereas when the system is embedded with noise, threshold crossing occurs with great probability so as to intensively enhance the ability of the system to detect weak signals.

However, most of the studies so far only account for external noise. With the recent development of studies in mesoscopic chemical oscillation systems, an even important source of noise, internal noise, has attracted considerable attention, which results from the random fluctuations of the stochastic reaction events in systems. It is generally accepted that the strength of the internal noise scales as $1/\sqrt{\Omega}$, where Ω is the system size. In the macroscopic limit where Ω is infinite, the internal noise can be ignored. However, in small systems, such as cellular and subcellular systems, the number of reaction molecules is very low, so the internal noise must be taken into account. Recently, the important effects of internal noise in chemical oscillation reaction systems have gained growing attention. For example, Shuai and Jung[13,14] demonstrated that optimal intracellular calcium signaling appeared at a certain size or distribution of the ion channel clusters. Ion channel clusters of optimal sizes can enhance the encoding of a subthreshold stimulus[15,16]. In recent studies, Xin′s group also found such a phenomenon in the Brusselator model[17], cir-

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cadian clock system[18], calcium signaling system[19,20], neuron system[21], synthetic gene network[22], catalysis system[23] and so on. There exists an optimal system size (that is internal noise value), at which the stochastic oscillation shows the best performance. They call this phenomenon "internal noise stochastic resonance" or "system size resonance". Therefore, a basic question is: will the internal noise influence the signal detection in small systems?

In the present article, *via* the inositol 1,4,5-trisphosphate-calcium cross-coupling (ICC) cell model, we investigated how the internal noise would influence the detection of weak signal.

1 Model

The model used in the present article describes the dynamics of calcium ions in cytosol, which was first produced by Meyer and Stryer in 1991[24]. If the internal noise is ignored, the time evolution of the species is governed by the following macroscopic kinetics[25]:

$$\frac{\mathrm{d}x}{\mathrm{d}t}=-\frac{\mathrm{d}y}{\mathrm{d}t}=vJ_{\mathrm{channel}}-J_{\mathrm{pump}} \tag{1a}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t}=k_{\mathrm{PLC}}-Du \tag{1b}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t}=F_v(1-v)-E_vx^4v \tag{1c}$$

where x, y, u represent the concentration of three key species: the cytosolic Ca^{2+} (Ca_i), the calcium ions sequestered in an intracellular store (Ca_s), and the inositol 1,4,5-trisphosphate (IP_3), respectively; v denotes the fraction of open channels through which the sequestered calcium is released into cytosol; D, F_v, and E_v are constants that are relative to the variable u and v; the flux J_{channel} is associated with the release of sequestered calcium from an internal store, the fulx J_{pump} corresponds to calcium sequestration, k_{PLC} is the rate of IP_3 production, which are given by

$$J_{\mathrm{channel}}=\left[\frac{Au^4}{(u+K_1)^4}\right]y,\ J_{\mathrm{pump}}=\frac{Bx^2}{x^2+K_2^2},\ k_{\mathrm{PLC}}=C\left[1-\frac{K_3}{(x+K_3)(1+R)}\right] \tag{2}$$

where A, B, C, K_1, K_2, and K_3 are constants. Choosing R, which represents the fraction of activated cell surface receptors, as an adjustable parameter. See Ref.[25] for the detailed descriptions and values of the parameters in Eqs.(1) and (2).

However, for a typical living cell, such a deterministic description is no longer valid due to the existence of considerable internal noise. Instead, a mesoscopic stochastic model must be used. To investigate the effect of internal noise, basically, one can describe the reaction system as a birth-death stochastic process governed by a chemical master equation. But there is no procedure to solve this master. A widely used simulation algorithm has been introduced by Gillespie[26], which stochastically determines what is the next reaction step and when it will happen according to the transition rate of each reaction process. For the current model, the reactions in the cell can be grouped into four elementary processes according to Ref.[27], the processes and their reaction rates are defined in Table 1 (note that the reaction rates are proportional to the system size Ω), where $X=x\Omega$, $U=u\Omega$. X and U are the numbers of the cytosolic Ca^{2+} (Ca_i) and the IP_3 production, respectively.

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

Stochastic process	Reaction rate
$X\rightarrow X+1$	$a_1=\Omega vJ_{\mathrm{channel}}$
$X\rightarrow X-1$	$a_2=\Omega J_{\mathrm{pump}}$
$U\rightarrow U+1$	$a_3=\Omega k_{\mathrm{PLC}}$
$U\rightarrow U-1$	$a_4=\Omega Du$

This simulation method is exact because it exactly accounts for the stochastic nature of the reaction events, but it is rather time-consuming if the system size is large. To solve this problem, Gillespie developed chemical Langevin equation (CLE)[28]. We have also shown that it is applicable to use the CLE to qualitatively study the effect of the internal noise[17−20]. According to Gillespie[28], the CLE for the current model is as follows:

$$\frac{\mathrm{d}x}{\mathrm{d}t}=\frac{1}{\Omega}\left[(a_1-a_2)+\sqrt{a_1}\xi_1(t)-\sqrt{a_2}\xi_2(t)\right] \tag{3a}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t}=\frac{1}{\Omega}\left[(a_3-a_4)+\sqrt{a_3}\xi_3(t)-\sqrt{a_4}\xi_4(t)\right] \tag{3b}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t}=F_v(1-v)-E_vx^4v \tag{3c}$$

where $\xi_i(t)$ (i=1, 2, 3, 4) are Gaussian white noises with $<\xi_i(t)>=0$ and $<\xi_i(t)\xi_i(t')>=\delta_{ij}\delta(t-t')$. Because the reaction rates (a_i) are proportional to Ω, the internal noise item in the CLE scales as $1/\sqrt{\Omega}$.

Now, we consider that the cell system is subjected to a weak periodic signal, which probably comes from an external stimulus. Then, the system′s dynamics can be described as:

$$\frac{\mathrm{d}x}{\mathrm{d}t}=\frac{1}{\Omega}\left[(a_1-a_2)+\sqrt{a_1}\xi_1(t)-\sqrt{a_2}\xi_2(t)\right]+M\sin(2\pi\varpi t) \tag{4a}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t}=\frac{1}{\Omega}\left[(a_3-a_4)+\sqrt{a_3}\xi_3(t)-\sqrt{a_4}\xi_4(t)\right] \tag{4b}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t}=F_v(1-v)-E_vx^4v \tag{4c}$$

where M and ϖ are the amplitude and frequency of the weak signal, respectively. In the following parts, we will use equations (4a−4c) as our stochastic model for numerical simulation to study the effect of the internal noise on the detection of the weak signal.

2 Simulation and results

We tune the control parameter R=0.605, which is very close to the Hopf bifurcation point designated by the macroscopic kinetics, but the deterministic system does not sustain oscillations (see Ref.[25] for more detailed description of the bifur-

cation action). One should note that it is always near this critical point, at which noise can play constructive roles. For the weak periodic signal, we choose M=1.5 and $\omega=\varpi_c$=0.505 Hz, ϖ_c is the frequency of the intrinsic oscillation of the cell. This signal itself is too weak to excite calcium spikes separately (the threshold we choose here is x=1.2 μmol·L^{-1}) and is therefore undetectable. Whereas when the internal noise is considered, threshold crossing occurs with great probability, and at an optimal noise level, a resonance occurs among the noise, the noise-induced oscillation, and the signal so as to intensively enhance the ability of the cell system to detect the weak signal. Fig.1 shows the time series of the variable x for different system sizes. For large system size Ω, corresponding to the low level of internal noise, the system exhibits subthreshold oscillations with small amplitude (Fig.1(a)). Irregular superthreshold spikes appear occasionally when Ω decreases (Fig.1(b)). When Ω decreases further, the superthreshold spikes appear with great probability, and the regularity of the spikes remains well (Fig.1(c)), below which the spikes become irregular again (Fig.1(d)).

To measure the relative regularity of the calcium spike train quantitatively, we introduce a coherence measure (CM), which is defined as the mean value of the spike interval T normalized to the mean root, namely, $\mathrm{CM}=\dfrac{<T>}{\sqrt{<T^2>-<T>^2}}$ [9]. Note that a spike occurs when the intracellular calcium concentration crosses a certain threshold value from below, and it turns out that the threshold value can vary in a wide range without altering the resulting spiking dynamics. The measure CM has been frequently used to quantify the regularity of stochastic spike trains, and it could be of biological significance because it is related to the time precision of information processing. A larger value of CM means more closeness of the spike train to a periodic one, where CM is obviously ∞. The dependence of CM on system size is plotted in Fig.2. A clear maximum is

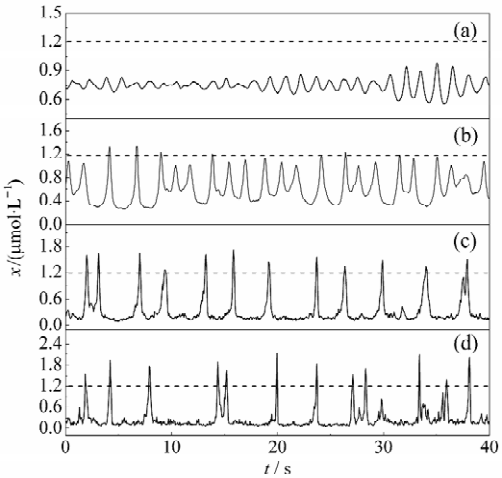

Fig.1 Time series of the variable x for different system sizes (Ω)
Ω/μm^3: (a) 10^6, (b) 10^5, (c) 10^3, (d) 200; The broken line denotes the threshold chosen.

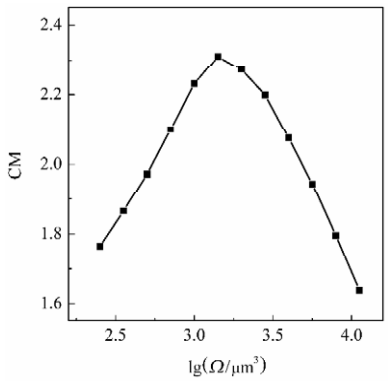

Fig.2 Coherence measure (CM) as a function of system size

present for system size Ω (≈10^3 μm^3), which demonstrates the occurrence of "system size resonance". It is interesting to note that this size is of the same order as the living cells *in vivo*. From the CLE, one notes 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 the well-known phenomenon of stochastic resonance (SR), so it also can be called "internal noise stochastic resonance". The cell system is likely to exploit the internal noise to enhance the ability to detect weak signals with the aid of system size resonance.

In the case of a fixed threshold (here we choose x=1.2 μmol·L^{-1}) and variable system size, the detection of the weak signal in a cell system will be influenced mainly by three factors: the signal frequency, the signal amplitude, and the control parameter. Previous study[15] has shown that, in response to a weak signal, a resonance among the noise, the noise-induced oscillation, and the signal can intensively enhance the ability of the system in detection of the weak signal, especially when the frequency of the signal is around that of the intrinsic oscillation of the system. And, because the frequency of the intrinsic oscillation can be adjusted by the internal or external modulations, the system can effectively detect and process signals with various frequencies. This is of significant biological meaning. In the following parts, we will mainly discuss the effect of the signal amplitude and control parameter on the signal detection.

Fig.3 shows the dependence of CM on system size with various signal amplitudes. We can see that for three given amplitudes of the input weak signal, there all exists an optimal system size, and the position of the optimal size remains nearly unchanged at Ω≈10^3 μm^3.

We have also studied how the signal detection behavior depends on the value of control parameter (R). This is shown in Fig.4. When the distance from the deterministic Hopf bifurcation point increases, first, the maximum CM and the optimal system size become smaller; and then, when the control parameter becomes even larger, although the maximum CM continues to become smaller, the position of the optimal size

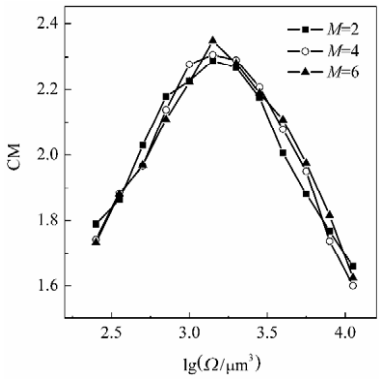

Fig.3 Dependence of coherence measure on system size with different signal amplitudes (M)

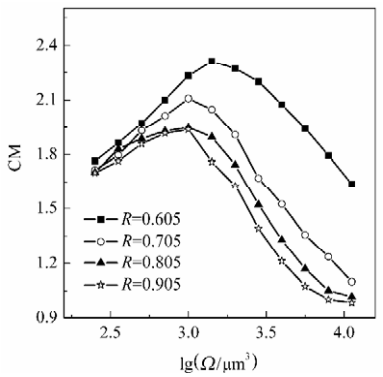

Fig.4 Coherence measure as a function of system size for different control parameters (R)

remains unchanged at $\Omega\approx10^3$ μm^3.

3 Conclusions

To summarize, we have studied the influence of internal noise on the detection of the weak signal. We show that, near the Hopf bifurcation point, instead of trying to resist the internal molecular noise, living cell systems may have learned to exploit the internal noise to intensively enhance the ability to detect weak signals. The performance of calcium oscillation undergoes a maximum with the variety of the system size Ω, indicating the occurrence of "system size resonance". Interestingly, we find that the position of the optimal size remains at $\Omega\approx10^3$ μm^3 for a wide range of signal amplitudes and control parameters, which is of the same order of real living cells *in vivo*. Since the internal noise in living cell systems cannot be ignored and the system may often receive weak signals, our findings may have quite significant implications for living cell systems and may imply the ubiquitous importance of internal noise in functioning processes in living organisms.

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