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Novel effect of interplay of internal and external noise on the dynamics of calcium oscillations

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ABSTRACT

Using a mesoscopic stochastic model, the effect of interplay of external and internal noise on the dynamics of calcium oscillations was studied. When the system was tuned near a Hopf bifurcation point and driven by external noise or internal noise only, the existence of external noise coherence resonance (ENCR) or internal-noise stochastic resonance (INSR) was found, respectively. When both of the noises were considered, it was found that ENCR could be suppressed by internal noise, while INSR could be enhanced by external noise in a certain range of external noise intensity. It was also interesting to note that the optimal system size can be regulated by the external noise when the INSR occurs. The cell system may adapt to adjust the optimal size according to the external noise, indicating some kind of self-tuning mechanism involved in stochastic calcium dynamics.

1. Introduction

In the last two decades, the constructive effects of external noise in nonlinear systems have gained much attention. It was demonstrated that there existed an optimal external noise intensity, at which the response of a system to a periodic signal was maximally ordered, which was well-known as stochastic resonance (SR) [1]. Many previous works have also demonstrated that nonlinear systems in the presence of external noise can also display SR-like behavior, even without an external signal, this phenomenon was being called external noise coherence resonance (ENCR) [2]. SR and ENCR have been widely studied in various systems [3–12].

In recent years, the effects of internal noise resulting from the stochastic reaction events in small scale systems have been paid much attention in biological and chemical systems, such as ion channels [13], circadian clock [14], intracellular calcium signaling [15–17], genetic regulation [18], surface catalytic reaction system [19,20], neuron system [21] and so on. It was found that stochastic oscillations could be observed in a region sub-threshold to deterministic oscillatory dynamics, and there existed an optimal internal noise intensity at which the stochastic oscillations showed the best performance, which was well-known as internal-noise stochastic resonance (INSR), or system size resonance.

So far, most works regarding noise have focused on the influence to systems with just one noise, either internal noise or external noise. However, these two kinds of noise are both unavoidable in small scale systems, so one must take into account the interplay of internal and external noise on a system's dynamics. Only recently, the interplay of external noise and internal noise has been studied in a circadian oscillator system [22], NO reduction system [23,24] and CO oxidation system [25], and so on. But to our knowledge, few works have been carried out so far on the influence of interplay of internal and external noise on the dynamics of calcium oscillations in cell systems.

In this paper, based on the mesoscopic stochastic model of a calcium oscillation system, we have studied the interplay effect of external and internal noise on the dynamics of calcium oscillations.

2. Model and equations

The mesoscopic stochastic model we used here is identical with the stochastic model in Ref. [17], except for the modulation of external noise on the degree of cell stimulation by agonist. For completeness, we will briefly describe the model below.

The original model used here accounting for the intracellular calcium oscillations was proposed by Shen and Larter [26]. The functioning of the model system is based on the mechanisms of inositol 1,4,5-trisphosphate cross-coupling (ICC) and the calcium-induced calcium release (CICR). If the internal noise is ignored, the dynamics can be described by a simple three-variable system of equations:

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$$\begin{aligned}
\frac{d[Ca_{cyt}]}{dt} &= J_{ch} + J_{leak} - J_{pump} + k_{in1}\cdot r + k_{in2} - J_{out},\\
\frac{d[Ca_{er}]}{dt} &= J_{pump} - J_{ch} - J_{leak},\\
\frac{d[IP_3]}{dt} &= J_{+} - J_{-},
\end{aligned} \tag{1}$$

where

$$\begin{aligned}
J_{ch} &= k_{ch}\cdot\left(\frac{[IP_3]^4}{[IP_3]^4+K_1^4}\right)\times\left(\frac{K_4[Ca_{cyt}]}{([Ca_{cyt}]+K_4)([Ca_{cyt}]+K_5)}\right)^3\cdot[Ca_{er}].\\
J_{leak} &= k_{leak}\cdot[Ca_{er}].\\
J_{pump} &= k_{pump}\cdot\frac{[Ca_{cyt}]^2}{[Ca_{cyt}]^2+K_2^2}.\\
J_{out} &= k_{out}\cdot[Ca_{cyt}].\\
J_{+} &= k_{+}\cdot r\cdot\frac{[Ca_{cyt}]}{[Ca_{cyt}]+K_3}\\
J_{-} &= k_{-}\cdot[IP_3].
\end{aligned} \tag{2}$$

$[Ca_{cyt}]$, $[Ca_{er}]$ and $[IP_3]$ represent the concentration of free Ca^{2+} in the cytosol, free Ca^{2+} in the endoplasmic reticulum (ER) and the inositol 1,4,5-trisphosphate in the cytosol, respectively. The parameter r measures the degree of cell stimulation by agonist and is selected as the control parameter. The meanings and values of the other parameters have been explained in detail in Ref. [17]. And hence will not be stated here again. See Fig. 1 for a simple description of the mechanism. The system exhibits two Hopf bifurcation (HB) points at $r_1 = 0.2345$ and $r_2 = 0.6859$, respectively [26,27].

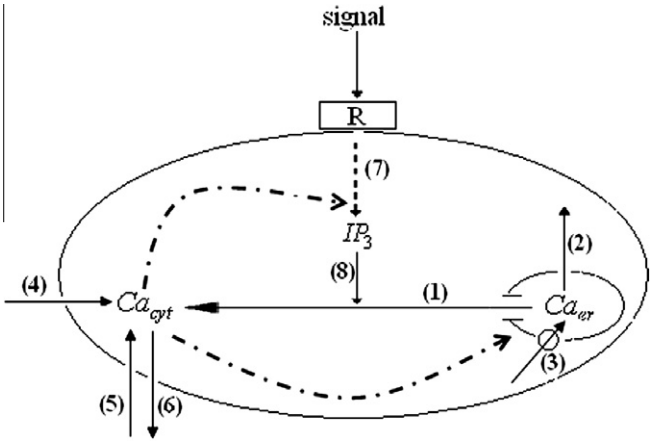

Fig. 1. Schematic representation of the model proposed by Shen and Larter based on the interplay between CICR and ICC.

However, for a typical cell system, the number of reaction molecules is often low [28–30], and we must consider the internal noise which results from the random fluctuations of the stochastic reaction events. The reactions in the cell can be grouped into eight elementary processes. See Fig. 1 for a simple description of the six processes, and Table 1 for the stochastic processes and the corresponding transition rates. In Table 1, X and Y represent the number of calcium ions in the cytosol and in the ER, respectively. So $X = [Ca_{cyt}]\cdot V$, $Y = [Ca_{er}]\cdot V$ and $Z = [IP_3]\cdot V$, where V is the cell volume. Then the Chemical Langevin Equation (CLE) for the current model is as follows:

$$\begin{aligned}
\frac{d[Ca_{cyt}]}{dt} &= \frac{1}{V}[(a_1 + a_2 - a_3 + a_4 + a_5 - a_6) + \sqrt{a_1}\xi_1(t) + \sqrt{a_2}\xi_2(t)\\
&\quad - \sqrt{a_3}\xi_3(t) + \sqrt{a_4}\xi_4(t) + \sqrt{a_5}\xi_5(t) - \sqrt{a_6}\xi_6(t)],\\
\frac{d[Ca_{er}]}{dt} &= \frac{1}{V}\left[(-a_1 - a_2 + a_3) - \sqrt{a_1}\xi_1(t) - \sqrt{a_2}\xi_2(t) + \sqrt{a_3}\xi_3(t)\right],\\
\frac{d[IP_3]}{dt} &= \frac{1}{V}\left[(a_7 - a_8) + \sqrt{a_7}\xi_7(t) - \sqrt{a_8}\xi_8(t)\right],
\end{aligned} \tag{3}$$

Where $\xi_i(t)$ ($i = 1, 2, 3, 4, 5, 6, 7, 8$) are Gaussian white noises with $\langle\xi_i(t)\rangle = 0$ and $\langle\xi_i(t)\xi_j(t')\rangle = \delta_{ij}(t - t')$ .The reaction rates a_i are proportional to V, so the internal noise item in the CLE scales as $1/\sqrt{V}$.

To study the influence of external noise, we consider the degree of cell stimulation by agonist is perturbed by an external noise:

$$r = r_0[1 + D\xi(t)], \tag{4}$$

where $\xi(t)$ is the Gaussian white noise with $\langle\xi(t)\rangle = 0$ and $\langle\xi(t)\xi(t')\rangle = \delta(t - t')$; D denotes the intensity of external noise. The dimension of D is $sec^{1/2}$. We tune $r_0 = 0.22$, which is slightly smaller than the left Hopf bifurcation (HB) value r_1, so that the cell is at a stable state in the absence of noise.

In the following parts, we will use the CLE (3) and Eq. (4) to study the interplay effect of the external noise and internal noise on the dynamics of calcium oscillations.

3. Results and discussion

3.1. Enhancement of INSR by external noise

The effect of only internal noise on the calcium oscillations has been investigated in Ref. [17].We found that when the internal noise was considered, the internal noise induced calcium oscillations occurred, and there existed an optimal system size V at which the regularity of the calcium oscillations was the best. From the CLE, we can see that the internal noise item in the CLE scales as $1/\sqrt{V}$, so an optimal system size implies an optimal internal noise

Table 1
Stochastic transition processes and corresponding rates.

	Transition processes	Description	Transition rates
(1)	$X \to X+1$, $Y \to Y-1$	The release of Ca^{2+} from the ER into the cytosol in a process induced by IP_3	$a_1 = V\cdot J_{ch} = V\cdot k_{ch}\cdot\left(\frac{[IP_3]^4}{[IP_3]^4+K_1^4}\right)\times\left(\frac{K_4[Ca_{cyt}]}{([Ca_{cyt}]+K_4)([Ca_{cyt}]+K_5)}\right)^3\cdot[Ca_{er}]$
(2)	$X \to X+1$, $Y \to Y-1$	Leaky transport of Ca^{2+} from the ER to the cytosol	$a_2 = V\cdot J_{leak} = V\cdot k_{leak}\cdot[Ca_{er}]$
(3)	$X \to X-1$, $Y \to Y+1$	The pump of Ca^{2+} from the cytosol into the ER	$a_3 = V\cdot J_{pump} = V\cdot k_{pump}\cdot\frac{[Ca_{cyt}]^2}{[Ca_{cyt}]^2+K_2^2}$
(4)	$X \to X+1$	The agonist-depended influx into the cytosol	$a_4 = V\cdot k_{in1}\cdot r$
(5)	$X \to X+1$	The Constant Ca^{2+} influx into the cell	$a_5 = V\cdot k_{in2}$
(6)	$X \to X-1$	Transport of cytosolic Ca^{2+} into the extracellular medium	$a_6 = V\cdot J_{out} = V\cdot k_{out}\cdot[Ca_{cyt}]$
(7)	$Z \to Z+1$	The production of IP_3 activated by cytosolic ca^{2+}	$a_7 = V\cdot J_{+} = V\cdot k_{+}\cdot r\cdot\frac{[Ca_{cyt}]}{[Ca_{cyt}]+K_3}$
(8)	$Z \to Z-1$	The degradation of IP_3 which stimulates the release of Ca^{2+} from the ER into the cytosol	$a_8 = V\cdot J_{-} = V\cdot k_{-}\cdot[IP_3]$