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The influence of internal noise on the detection of hormonal signal with the existence of external noise in a cell system

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A B S T R A C T

In recent years, the constructive role of internal noise in mesoscopic system has attracted much attention. Because the external noise is also unavoidable, it is more practical to study the influence of internal noise with the existence of external noise in these systems. By constructing a mesoscopic stochastic model of a cell system, we discussed the influence of internal noise on the detection of hormonal signal with the existence of external noise. Results have found that internal noise can play a constructive role when external noise intensity is at some regions ($D < 1.0$ and $D > 1.16$), so that the cell system can effectively detect the weak hormonal signal through intracellular calcium spikes. This phenomenon is different from the results found previously, where it was found that internal noise always played a destructive role except for at very small external noise intensity.

1. Introduction

It is well known that external noise and internal noise are both unavoidable in mesoscopic biological and chemical systems [1–2]. External noise originates from the random fluctuation of the external surroundings, for example, the fluctuation of the CO partial pressure in the catalytic oxidation system of CO [3], the fluctuation of the concentration of extracellular hormones in the cell system [4], and so on. Internal noise comes from the random fluctuations of the stochastic chemical reaction events in a finite-size system [5–8], for example, the fluctuation of the size or distribution of the ion channel clusters [9–13], the random fluctuations of the stochastic reaction events in cell system [14,15], NO reduction system [16], CO oxidation system [17], and so on. Previous studies have found that stochastic oscillations in lots of systems show the best performance at optimal external or internal noise intensity, this phenomenon has been called stochastic resonance (SR) [18,19], internal signal stochastic resonance (ISSR) [20–23] and internal noise stochastic resonance (INSR) [14,15,24–27]. The impact of noise on cell systems has been studied a lot in the recent past. For example, it was shown that noise could enhance robustness of intracellular Ca^{2+} oscillations [28], periodic calcium waves [29] and chaos [30] could emerge due to internal noise, the fact that noise can play a constructive role has been shown in Ref. [31], pacemaker could enhance noise-induced synchrony in cellular arrays [32], and so on. In recent years, the constructive role of noise has also been paid much attention [33–39].

The biological information between distant cells or organs is transmitted by two major systems: nervous system and endocrine system. In the nervous system, information is encoded in the temporal pattern of discrete action potentials [40]. In the endocrine system, information is transmitted via the blood stream. The specificity of signaling arises from the biochemical structure of the hormones and their respective receptors [4]. The cell can detect the extracellular hormonal signal

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through repetitive intracellular calcium spikes via the mechanism shown in Fig. 1 in Ref. [4], and then specifically regulate many distinct cellular functions from the system to the molecular level [41–43].

In previous studies, the response of the cell to hormonal stimulus has been discussed [4,44–46]. For example, Laer et al. [4] found that external noise can enhance hormonal signal's transduction; Prank et al. [44] found that the fluctuating hormonal signals can be encoded by calcium spike trains, and so on. In our previous study [14], we studied the influence of only internal noise on the detection of hormonal signal. Results have shown that the cell system may exploit internal noise to detect a much wider range of extracellular hormonal signals through intracellular calcium oscillations. Because the external noise is also unavoidable in cell system, it is more practical to study the influence of internal noise on the detection of hormonal signal with the existence of external noise. In this article, by constructing a mesoscopic stochastic model of a cell system, we study the influence of internal noise on the detection of hormonal signal with the existence of external noise.

2. Model description

The mesoscopic stochastic model we used here is identical with the stochastic model in Ref. [14], except for the modulation of external noise on the concentration of the extracellular hormones. For completeness, we briefly describe the model below.

The original model is developed by Cuthbertson and Chay [46,47] to describe intracellular calcium oscillations in hepatocytes. If the internal noise is ignored, the dynamics of the model can be described by four-variable equations [46]:

$$\begin{aligned}\frac{d[G_\alpha-\mathrm{GTP}]}{dt}&=k_g[G_\alpha-\mathrm{GDP}]-4k_p[G_\alpha-\mathrm{GTP}]^4[\mathrm{PLC}]-h_g[G_\alpha-\mathrm{GTP}]\\ \frac{d[\mathrm{DAG}]}{dt}&=k_d[\mathrm{PLC}*]-h_d[\mathrm{DAG}]+l_d\\ \frac{d\left[\mathrm{Ca}^{2+}\right]_i}{dt}&=\rho\left\{k_c\frac{[\mathrm{IP}_3]^3}{K_S^3+[\mathrm{IP}_3]^3}-h_c\left[\mathrm{Ca}^{2+}\right]_i+l_c\right\}\\ \frac{d[\mathrm{PLC}*]}{dt}&=k_p[G_\alpha-\mathrm{GTP}]^4[\mathrm{PLC}]-h_p[\mathrm{PLC}*]\end{aligned}\tag{1}$$

where

$$[G_\alpha-\mathrm{GDP}]=G_0-[G_\alpha-\mathrm{GTP}]-4[\mathrm{PLC}*]\tag{2}$$

$$[\mathrm{PLC}]=P_0-[\mathrm{PLC}*]\tag{3}$$

$$k_n=k_n'\frac{[\mathrm{DAG}]^2}{K_D^2+[\mathrm{DAG}]^2}\tag{4}$$

where $k_n = k_p$,h_p or k_d.$[G_\alpha - \mathrm{GTP}]$, [DAG], $[\mathrm{Ca}^{2+}]_i$, [PLC*] are the concentrations of G-protein α-subunit bound to GTP, diacylglycerol, intracellular calcium, activated form of Phospholipase, respectively. k_g is assumed to be proportional to the agonist concentration, i.e. the concentration of the extracellular hormones. The meanings and values of other parameters have been explained in detail in Ref. [46], and hence will not be introduced here again. See Fig. 1 in Ref. [4] for a simple description of the mechanism.

Considering the influence of internal noise, the mesoscopic stochastic model can be described by a chemical Langevin equation (CLE) as:

$$\begin{aligned}\frac{d[G_\alpha-\mathrm{GTP}]}{dt}&=\frac{1}{V}\left[(a_1-4a_2-a_3)+\sqrt{a_1}\xi_1(t)-4\sqrt{a_2}\xi_2(t)-\sqrt{a_3}\xi_3(t)\right]\\ \frac{d[\mathrm{DAG}]}{dt}&=\frac{1}{V}\left[(a_4+a_5-a_6)+\sqrt{a_4}\xi_4(t)+\sqrt{a_5}\xi_5(t)-\sqrt{a_6}\xi_6(t)\right]\\ \frac{d\left[\mathrm{Ca}^{2+}\right]_i}{dt}&=\frac{1}{V}\left[(a_7+a_8-a_9)+\sqrt{a_7}\xi_7(t)+\sqrt{a_8}\xi_8(t)-\sqrt{a_9}\xi_9(t)\right]\\ \frac{d[\mathrm{PLC}*]}{dt}&=\frac{1}{V}\left[(a_2-a_{10})+\sqrt{a_2}\xi_2(t)-\sqrt{a_{10}}\xi_{10}(t)\right]\end{aligned}\tag{5}$$

where $\xi_{i=1...10}(t)$ are Gaussian white noises with $\langle\xi_i(t)\rangle=0$ and $\langle\xi_i(t)\xi_j(t')\rangle=\delta_{ij}\delta(t-t')$. $a_{i=1......10}$ are the transition rates of ten stochastic transition processes. V denotes the system size. See Table 1 for the detailed descriptions of the stochastic processes. Because the reaction rates a_i are proportional to V, the internal noise item in the CLE scales as $1/\sqrt{V}$.

To investigate the influence of external noise, we consider k_g (the concentration of the extracellular hormones) is perturbed by external noise:

$$k_g=k_{g,0}[1+D\xi(t)]\tag{6}$$

where $\xi(t)$ is the Gaussian white noises with $\langle\xi(t)\rangle=0$ and $\langle\xi(t)\xi(t')\rangle=\delta_{ij}(t-t')$. D denotes the intensity of external noise.