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Stimulus perturbation induced signal: A case study in mesoscopic intracellular calcium system

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ABSTRACT

Noise abounds in different signal transduction pathways. Even though the noise effects are extensively studied, the indirect influence of noise on other transduction section is seldom reported. In this work, the calcium signal induced and optimized by agonist release noise is reported. Simulation results prove that the signal is more sensitive to the "frequency noise" than to the often discussed "amplitude noise". This is an important finding for signal transduction in complex pathways, which suggests that frequency fluctuations in the signaling cascade may have greater influence than the amplitude ones.

1. Introduction

Calcium is an important life signal that is generated through a complex transduction process. It has been reported that the agonist (hormone or neurotransmitter) stimulus is crucial in this process. It can not only trigger the signals, but also significantly change their amplitudes or frequencies [1,2]. Under *in vivo* conditions, the agonists are actually emitted as abrupt quantal "packets" in continuous pulsatile fashion [3–5], which varies not only in amplitude, but also in frequency and duration. This kind of "square-wave" stimulus has already been employed in the study of many other biological systems, such as neuron dynamics [6], circadian oscillation [7], mitotic synchronization [8], chemoreceptor [9–11] and tactile sensation [12]. It is also similar to the strong and fast pulse in the bang-bang control strategy [13–16], in which appropriate temporal arrangement of the pulse can effectively control the system dynamics.

Signal transduction in living systems are inevitably disturbed by stochastic factors [17–21], such as the internal molecular noise, the random openings and closings of voltage-gated membrane channels, thermal fluctuations of membrane potential etc. Many investigations have been done to explore the effects of stochastic factors on calcium signals [22–30], for example, stochastic channel behavior [22–24], system internal stochastic influence [25], external noise perturbation [26–28] and medium inhomogeneity [29] etc. But most of them are direct noise effect. Actually, the agonist release processes are also disturbed by stochastic factors, and they may make the agonist signal fluctuate in not only the amplitude, but also the frequency or other characters. Related investigations have revealed that appropriate noise or external force can result in the frequency (as well as the amplitude) fluctuation of living system signals [31–35]. The random factors that influence the agonist release processes are called "agonist release noise" here. Those that can pronouncedly influence the amplitude or frequency of the agonist signal are termed as "amplitude noise" and "frequency noise", respectively. How does the calcium signaling respond to the indirect agonist release noise? What if it is "frequency noise" rather than "amplitude noise"? These are still interesting topics. In this work, we discuss the indirect noise effect on calcium signaling when the agonist stimulus amplitude, or frequency (period) is disturbed.

2. Model and methods

Agonist influences the Ca^{2+} signaling through the Ca^{2+}-phosphatidylinositol (PI) pathway (Fig. 1). In this transduction process, the binding of the agonist to their receptors can trigger the formation of IP_3 and then release Ca^{2+} from internal stores through the activation of G-proteins. Meanwhile, with the help of the feedback mechanisms *via* Ca^{2+}-ATPases, continuous calcium signal (spiking) can be spontaneously sustained. Here, we employ the receptor-controlled model for

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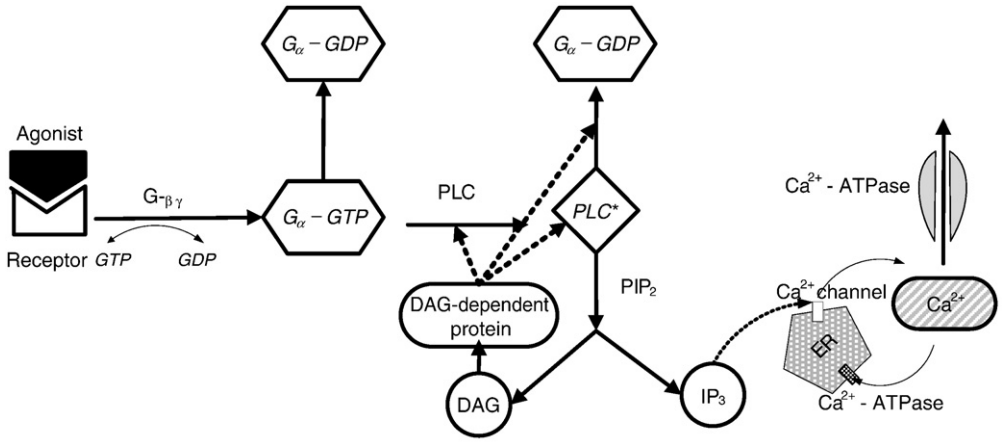

Fig. 1. Simple description of intracellular calcium signal generation at the stimulus of external agonists.

intracellular Ca^{2+} signals proposed by Cuthbertson and Chay [36,37]. Its dynamics can be described by the following equation group:

$$\begin{aligned}
\frac{d[G_\alpha - GTP]}{dt} &= k_g[G_\alpha - GDP] - 4k_p[G_\alpha - GTP]^4[PLC] - h_g[G_\alpha - GTP] \\
\frac{d[DAG]}{dt} &= k_d[PLC^*] - h_d[DAG] + l_d \\
\frac{d[Ca^{2+}]}{dt} &= \rho\left\{k_c\frac{[IP_3]^3}{K_S^3 + [IP_3]^3} - h_c[Ca^{2+}]_i + l_c\right\} \\
\frac{d[PlC^*]}{dt} &= k_p[G_\alpha - GTP]^4[PLC] - h_p[PLC^*]
\end{aligned} \tag{1}$$

where $[Ca^{2+}]_i$ is the intracellular Ca^{2+} concentration, $[IP_3]$, $[DAG]$, $[PLC]$, $[PLC^*]$, $[G_\alpha$–$GTP]$, $[G_\alpha$–$GDP]$ are the concentrations of inositol 1,4,5-trisphosphate, 1,2-diacylglycerol, phospholipase C, the activated form of phospholipase C, G_α–GTP (the α-subunit of G-protein bound to GTP), G_α–GDP (the α-subunit of G-protein bound to GDP), respectively. For simplicity, it is assumed that $[DAG]$ and $[IP_3]$ increase with the same rate, i.e., $[DAG] = [IP_3]$. $[G_\alpha$–$GDP]$ and $[PLC]$ are determined by the relations:

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

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

in which G_0 and P_0 are the total concentration of the G-proteins and PLC, respectively. Parameter k_g is proportional to the agonist concentration. l_d and l_c are "leak" terms of the signaling dynamics, which keeps the cell at its basal level of $[DAG]$ and $[Ca^{2+}]_i$, respectively, in the absence of external stimuli. k_p, h_p and k_d are supposed to take the form:

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

where $k_n = k_p$, h_p, or k_d. For detailed information about the model, see Ref. [36].

For calcium signaling, the internal noise produced by the fluctuations in the opening of the IP_3R channel proteins plays an important role [24]. It makes the deterministic models no longer strictly valid, and mesoscopic models such as chemical master equations should be used. Hou and his coworkers [38] prove that the chemical Langevin equation (CLE) [39] provides good simulation results for mesoscopic systems, and it qualitatively agrees well with other simulation algorithms of chemical master equation, such as the exact stochastic simulation (ESS) or τ-leap method. Therefore, CLE for the present model is employed. It can be described as following:

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

in which a_i $(i = 1,\ldots 10)$ are the transition rates per volume: $a_1 = k_g$ $[G_\alpha$–$GDP]$; $a_2 = k_p$ $[G_\alpha$–$GDP]^4$ $[PLC]$; $a_3 = h_g$ $[G_\alpha$–$GTP]$; $a_4 = k_d$ $[PLC^*]$; $a_5 = h_d$ $[DAG]$; $a_6 = l_d$; $a_7 = \rho k_c$ $[IP_3]^3 / \{K_S^3 + [IP_3]^3\}$, $a_8 = \rho h_c$ $[Ca^{2+}]_i$, $a_9 = \rho l_c$, $a_{10} = h_p$ $[PLC^*]\xi_i(t)$ $(i = 1,\ldots 10)$ are Gaussian white noises with $\langle\xi_i(t)\xi_i(t')\rangle = \delta_{ij}\delta(t-t')$ and $\langle\xi_i(t)\rangle = 0$. V is the system size.

Here, the agonist is assumed to be released in square wave fashion (Fig. 2). Therefore, its concentration is a time-dependent parameter instead of a constant one. Now, it can be characterized by three parameters: amplitude *amp*; duration *kep* and period *per*. To satisfy the "continuous supply" requirement, there is also another parameter "*base*" that represents the stimulus strength when the "packages" are not released. Since it represents very weak agonist stimulation in the unreleased state, we assume it won't be affected by noise, and fix it as 0.005 s^{-1} throughout this work.

The agonist release noise are introduced by incorporating white noise ingredient in the release parameters as: $\beta(t) = \beta_0(1 + \gamma(t))$. β describes the agonist release parameter (*amp* or *per*). β_0 is a constant reference value. $\gamma(t)$ is Gaussian white noise with the intensity D. During the simulation, a random array that follows the Gaussian

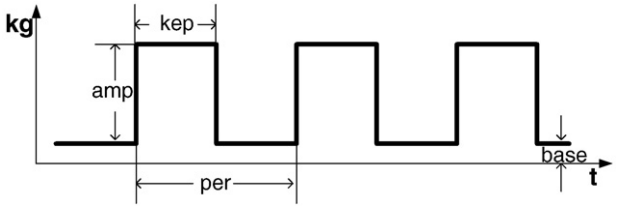

Fig. 2. The "square-wave" form agonist stimulus diagram. The agonist concentration k_g can be described by the amplitude "*amp*"; duration "*kep*" and period "*per*", "*base*" is the basal level of agonist when it is not released.

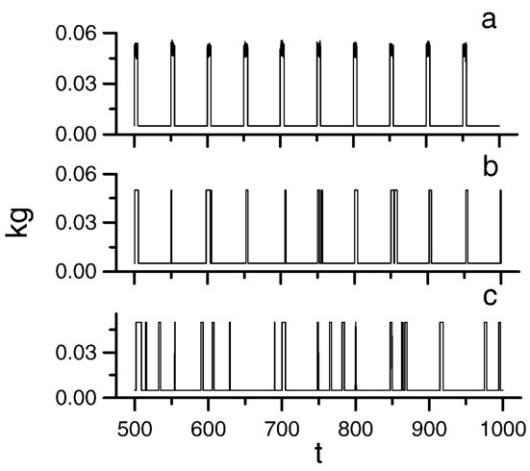

Fig. 3. The disturbed agonist stimulation. a. Agonist signal is perturbed by "amplitude noise" ($D=10^{-5}$); b. Agonist signal is perturbed by "frequency noise"($D=10^{-7}$); c. Agonist signal is perturbed by "frequency noise" ($D=10^{-5}$).

distribution is generated so that at every integration step, there's a random β to determine the stimulus strength by:

$$k_g(t)=\begin{cases} amp & t\in[n\cdot per, n\cdot per+kep] \\ base & t\in(n\cdot per+kep,(n+1)\cdot per)\end{cases}(n=0,1,2\ldots) \quad (6)$$

Here, *amp*, *kep* or *per* can be a time dependent value when they are disturbed. Our investigations show that *kep* plays similar role as *amp*, i.e., to control the received agonist amount. Therefore, only two kinds of noise are discussed here. One is the "amplitude noise" that *amp* fluctuates, the other is the "frequency noise" in which *per* is disturbed. The perturbed stimulus sequence under these two kinds of noise are depicted in Fig. 3.

Dynamic parameters used for the simulation are[36]: $h_g=0.0\ s^{-1}$, $k_d'=700\ s^{-1}$, $h_d=100\ s^{-1}$, $l_d=250$ nM s^{-1}, $\rho k_c=9.0\times 104$ nM s^{-1}, $\rho h_c=1.0\ s^{-1}$, $\rho l_c=200$ nM s^{-1}, $k_p'=2\times10^{-7}$ $nM^{-4}\ s^{-1}$, $h_p'=0.5\ s^{-1}$, $K_s=300$ nM, $K_D=25$ nM, $G_0=200$ nM, and $P_0=10$ nM. Considering the physiological constraints, *amp* is kept less than 0.50 s^{-1} and *kep* no longer than 20 s in all simulations. It is proved that the calcium spikes show no apparent difference when *per* is bigger than 100 s [36]. Therefore, we fix *per* (or per_0) at 50 s unless otherwise mentioned. Eq. (5) is integrated utilizing Euler algorithm for SDE (stochastic differential equation) with fixed step of 0.01 s. All the quantitative characterization data are the average of 50 independent runs.

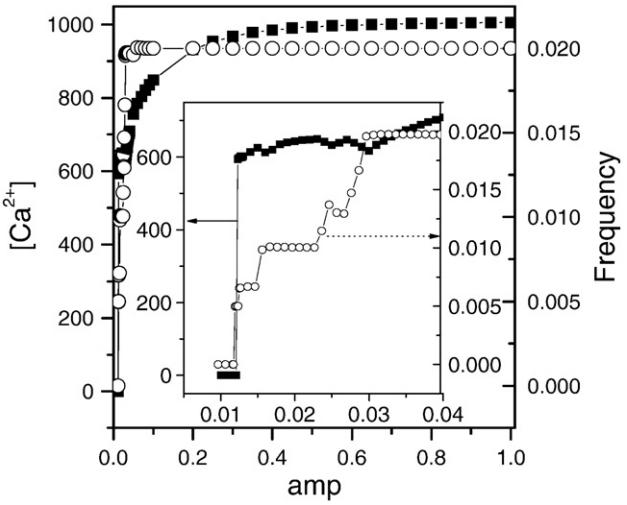

Fig. 4. Calcium signaling bifurcation diagram of the deterministic system with unperturbed square wave stimulus ($per=50$, $kep=15$).The filled squares and the empty circles are the amplitude and the frequency of the signal, respectively.

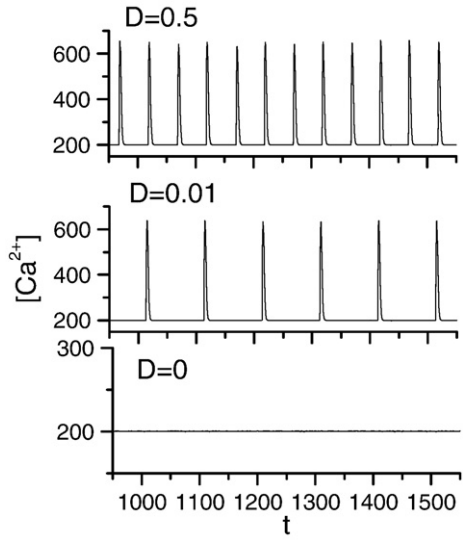

Fig. 5. The calcium signal induced by "amplitude noise" with different intensities as noted in each line ($V=5\times10^3$).

3. Results and discussion

We firstly investigate the signaling bifurcation character of the deterministic system under unperturbed square wave stimulus. Fig. 4 shows the change of signal amplitude and frequency with *amp* when *kep* is fixed at 15 s.

In this case, the deterministic system predicts Hopf bifurcation at $amp=0.0123$. The signal undergoes a period of gradual frequency increase after it appears. When *per* and *kep* are chosen as other values, similar bifurcation characters can be observed, which are not shown here. In this work, we choose reference *amp* values close to but before the bifurcation point for each given set of agonist release parameters (*per* and *kep*). That is, the system is signal free under the unperturbed square wave stimulus. For detailed discussion, we use the results under the release parameter setting $amp=0.01 s^{-1}$, $per=50$ s and $kep=15$ s for instance.

The following parts discuss the response of the calcium signaling to the agonist release noise in the mesoscopic system. Simulation results prove that calcium signal can be induced by either the "amplitude noise" or the "frequency noise". Low frequency signals can be induced at weak intensities, then stronger noise can further enhance the signal by increasing their frequency. Fig. 5 illustrates the spiking sequence

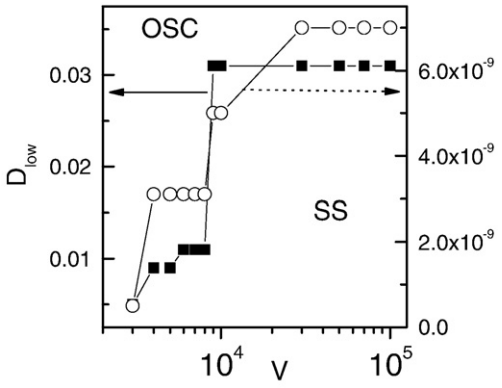

Fig. 6. The phase diagram for the appearance of calcium signal induced by agonist release noise. The filled squares stand for the "amplitude noise" situation; the empty circles represent the "frequency noise" case.

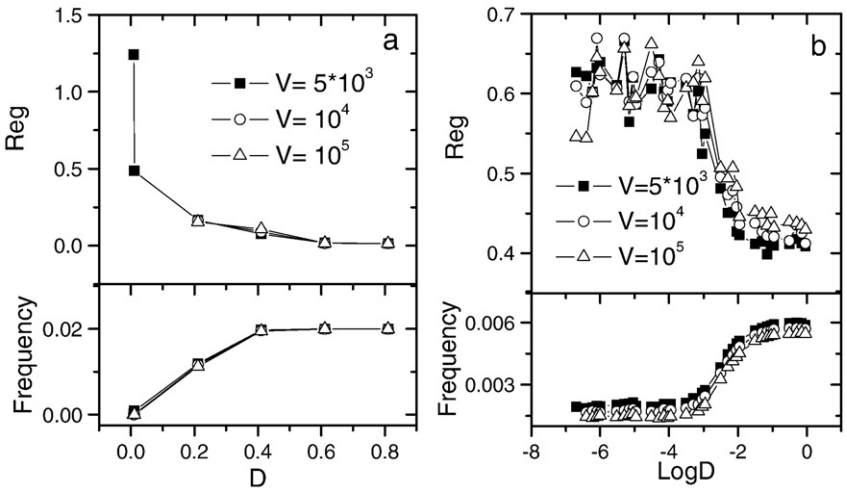

Fig. 7. The dependence of regularity and frequency of the noise induced signal with noise intensity. a. "amplitude noise"; b. "frequency noise".

induced by the "amplitude noise". Similar signals can also be induced by the "frequency noise", which are not shown. This indicates that the indirect perturbations in agonist release can also induce the calcium signal, and the fluctuations in both the stimulus strength and frequency are effective. However, quantitative investigations show that the "frequency noise" can induce signal at much weaker intensity.

It is known that the intensity of the internal noise in mesoscopic systems can be represented by the system size V, and the smaller system means the stronger internal noise. To systemically explore the agonist release noise induced calcium signal, we study the dependency of lowest noise intensity necessary to induce the signal (D_{low}) on V. Fig. 6 shows the noise induced signal phase diagram for both the "amplitude noise" and "frequency noise". Note that in the agonist noise free system, calcium signals can not be sustained if V is bigger than 10^3. Obviously, in the "frequency noise" case, only a tiny fluctuation can induce the signal, which is about seven orders of magnitude weaker than that of the "amplitude noise". That is to say, the "frequency noise" is more efficient in inducing the calcium signal. This may relate to the frequency-encoded character of calcium signal, and it suggests that calcium signal is also sensitive to the frequency fluctuations of its agonist signals. Since frequency fluctuations are proved to appear at the influence of noise [31–35] the results discovered here may suggest that frequency fluctuation may be more influential for further information transduction.

In Fig. 6 we can find that when $V<10^4$, D_{low} increases with V, but after that it is kept constant. This indicates the internal noise only helps to induce calcium signal in small systems, but not in the big ones. Nevertheless, the D_{low} of the "frequency noise" in the phase diagram is generally six to seven orders of magnitude weaker than that of the "amplitude noise", independent of the V value. This suggests the sensitivity of the signaling to the frequency noise is an intrinsic character of the calcium system.

To quantitatively characterize the noise induced signals, their spiking regularity *Reg*, which is defined as following, is calculated.

$$Reg = \frac{\sqrt{\langle T^2\rangle - \langle T\rangle^2}}{\langle T\rangle} \tag{7}$$

T in the definition denotes the time interval between two neighbored peaks in the calcium spiking evolution sequence. Obviously, smaller *Reg* represents more regular signal. Note that a spike is identified when the calcium concentration crosses a certain threshold value from below, and it turns out that the threshold value can change in a wide range without altering the resulting spiking dynamics. To avoid the perturbation from the unstable signal in the transient period, the first 50 s evolution data are eliminated, and at least 100 spikes in the evolution are used for calculation.

Fig. 7 displays the influence of the two kinds of noise on the regularity and frequency of the noise induced signal. It is clear that similar tendency is obtained. With the increase of D, the signal regularity can be optimized while its frequency is enhanced. The "amplitude noise" can help the signal reaching a "regular" state ($Reg=0$). When the "frequency noise" is weak, only low frequency signals with worse regularity can be sustained. Similar to the "amplitude noise" case, the signal regularity can be optimized with the increase of D. But now, the *Reg* is stabilized only at some lower value. Generally, the value of V dose not qualitatively influences these changing tendencies.

Further investigations prove that if the agonist release parameters are chosen as other values, as long as the system is near the critical state that is close to but before the Hopf bifurcation point, similar results can be obtained. The D_{low} of "frequency noise" is always several orders of magnitude weaker than that of the "amplitude noise", and the increase of noise intensity can both optimize the regularity of the induced signals and enhance their frequency. If the "stimulate–respond" process is viewed as a simple "diffuse arrive and then respond" one, the "frequency noise" means a second stimulus may come along before the response to the former one has fully dissipated. In this case, the pulse may pile-up and has a highly nonlinear effect on dynamics, as shown here. But the "amplitude noise" only linearly affects the single respond extent when it is in an effective limit. Therefore, similar phenomenon may be anticipated in other exocytosis or nerve firing processes where the signaling is induced by excellular (or exorganelle) input, as long as it has diffusion or first-order dissipation of a critical species. In fact, early investigation about synaptic noise on neuron spiking has already suggested this effect [40].

4. Summary

In this work, two kinds of agonist release noises are discussed with respect to their influence on calcium signaling. Simulation results prove that both of the "amplitude noise" and the "frequency noise" can induce calcium signal and improve both the frequency and the regularity of the signal, but the former always needs to be much stronger than the latter. This indicates that the calcium signaling is more sensitive to frequency fluctuations of the stimulation than the usually discussed amplitude noises. This is of significance for living signal transduction, and since stochastic fluctuations are unavoidable in transduction pathways and many signals are frequency encoded, our findings suggest the frequency fluctuations among signaling cascades may trigger more pronounced responses than the amplitude ones.

Acknowledgements

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