Chapter 11
Agonist Fluctuation Maintained Calcium Signaling in a Mesoscopic System

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ABSTRACT
Signals in transduction cascades are widely exposed to stochastic influences. In this work, we investigate the effects of agonist release noises on calcium signaling. Besides the usually considered “amplitude noise”, the case of “frequency noise” is also discussed. Simulation results show that the transduction cascades may amplify these noises when its intensity is bigger than certain critical value. The amplified noise show constructive effect to maintain the calcium signaling in critical signal-free cases. Moreover, the signal is more sensitive to the “frequency noise” than to the “amplitude noise”. This suggests frequency fluctuations in signaling cascades may have greater influence than the amplitude ones, which is an important finding for signal transduction in complex pathways. Since biological systems are inherently stochastic, this work demonstrates how the calcium system takes advantage of the environmental fluctuations to maintain signaling, and therefore provide effective, sensitive signal communication.

INTRODUCTION
Signal transduction in living systems is inevitably disturbed by stochastic factors, such as the internal molecular noise, 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

(Ullah & Jung, 2006; Falcke, 2004; Li et al., 2005; Dupont et al., 2008; Perc et al., 2008). Ullah & Jung (2006) found that signaling model that taking the stochastic channel behavior into consideration can accurately describe the statistically properties of the elementary calcium release events; Falcke (2004) reviewed the stochastic clustering character of ion channel and found that there is an optimal cluster size that best sustain the signaling; Li et al. (2005) investigated the role of internal molecular noise in intracellular calcium oscillations. In most
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of former investigations, the stochastic character is directly involved in the signaling process. Exccellular signals influence calcium signaling in the form of agonist (hormone or neurotransmitter) stimulus. It triggers the signaling by binding to the receptor on the cell surface. Calcium agonist stimulus is actually another kind of signal, such as hormone or neurotransmitter signal. Environmental random perturbations or internal fluctuations may lead to stochastic changes in their release process. Related investigations have revealed that noise or external force can result in frequency (as well as the amplitude) fluctuations in oscillatory signals (Skupin et al., 2008; Ji et al., 2008; Li & He, 2005). It has been reported that the agonist stimulus plays a crucial role in calcium signaling process (Woods et al., 1986; Kawanishi et al., 1989). Under in vivo conditions, agonists are emitted as abrupt quantal “packets” in continuous pulsatile fashion, which varies not only in amplitude, but also in frequency and duration. In this work, we investigated the influence of random factors in the agonist release processes (“agonist release noise”) on calcium signaling. Those that can pronouncedly influence the amplitude or frequency of the agonist signal are termed as “amplitude noise” and “frequency noise”, respectively.

BACKGROUND

Agonist influences the Ca\(^{2+}\) signaling through many pathways such as Ca\(^{2+}\)-phosphatidylinositol (PI) pathway, NMDA receptor mediated synapses, dendritic calcium action potentials, and Ca\(^{2+}\) liberated by Ca\(^{2+}\) phenomena linked or not to the role of ryanodine receptors of the intracellular endoplasmic reticulum. Here, we employ the receptor-controlled model for intracellular Ca\(^{2+}\) signaling in hepatocytes proposed by Cuthbertson et al. (1991). In this model, the calcium signal (oscillation) is triggered by the binding of agonists (hormone or neurotransmitter) to their receptors, which is the basic signaling mechanism for most of the calcium signaling systems. The influence of agonist is expressed by its concentration. The system dynamics can be described by the following equations:

\[
\begin{align*}
\frac{d[G_a-GTP]}{dt} &= k_1[G_a - GDP] - 4k_b[G_a - GTP]^4[PLC] - b_2[G_a - GTP] \\
\frac{d[DA^G]}{dt} &= k_1[PLC] - b_3[DA^G] + t_l \\
\frac{d[Ca^{2+}]}{dt} &= \rho \left( k_p \frac{[IP_3]_p}{K_{IP_3}^p + [IP_3]_p} - k_h[Ca^{2+}]_p + t_l \right) \\
\frac{d[PLC]}{dt} &= k_2[G_a - GTP]^4[PLC] - b_4[PLC]^4
\end{align*}
\]

(1)

For simplicity, it is assumed that [DA^G] and [IP_3] increase with the same rate, i.e., [DA^G] = [IP_3]. [GA^G-GDP] and [PLC] are determined by the relations:

\[
\begin{align*}
[G_a - GDP] &= G_0 - [G_a - GTP] - 4[PLC]^4 \\
[PLC] &= P_0 - [PLC]^4
\end{align*}
\]

in which \(G_0\) and \(P_0\) are the total concentration of G-proteins and PLC, respectively. Parameter \(k_p\) is proportional to the agonist concentration. \(l_a\) and \(l_c\) are “leak” terms of the signaling dynamics, which keeps the cell at its basal level of [DA^G] and [Ca\(^{2+}\)], respectively, in the absence of external stimuli. \(k_p\), \(h_p\), and \(k_d\) are supposed to take the form:

\[
k_n = k_n \frac{[DA^G]^2}{K_{IP_3}^p + [DA^G]^2}
\]

where \(k_n = k_p h_p\) or \(k_d\).

Detailed information about the model can be found in Ref (Cuthbertson et al., 1991).

In mesoscopic systems where the number of reactant molecules is small, internal molecular noise resulting from the stochastic nature of the discrete chemical reaction events becomes important (Hou & Xin, 2004). It is reported that this kind of internal noise can constructively induce oscillation in parameter space where only the steady-state can be observed in the corresponding macroscopic system (internal noise induced signal). In addition, the signal-to-noise ratio (SNR) of the noise-induced oscillation peaks as the noise intensity increases, indicating the occurrence of internal noise coherent resonance (INCR) (Shuai & June, 2002; Schmid et al., 2004; Hou et al.,...