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Internal noise enhanced detection of hormonal signal through intracellular calcium oscillations

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Abstract

A variety of cell types respond to extracellular hormonal signals by repetitive intracellular calcium spikes. Here, by constructing a mesoscopic stochastic model for intracellular calcium oscillations in hepatocytes, we have investigated the influence of internal noise on the detection of sub-threshold hormonal signals using chemical Langevin equation (CLE) and Poisson approximation. It is found that stochastic calcium spikes appear when the internal noise is considered, and the regularity of the spike train undergoes a maximum with the variation of the internal noise level, indicating the occurrence of *internal noise stochastic resonance* (INSR). Since the magnitude of the internal noise is changed via the variation of the system size, the INSR also represents itself a kind of *system size resonance*.

1. Introduction

The constructive roles of noise in nonlinear systems have gained much attention in the last two decades. It was demonstrated that there exists a 'resonant' noise intensity at which the response of the system to an external periodic force is maximally ordered, which is well-known as stochastic resonance (SR). Since it was put forward in the 1980s [1], it has been studied in a variety of systems from physics [2], chemistry [3] to biology [4–10]. An important application of SR in biological systems is its ability to enhance the detection of weak signals, which has been studied experimentally and theoretically in many systems, e.g., the mechanoreceptive system in crayfish [4], human tactile sensation [5–7], human brain system [8], neuron system [9], hair bundle system [10], and so on. It was shown that there existed an optimal level of noise which results in the maximum enhancement, whereas further increase or decrease of the noise intensity only degrades the detectability or information contents.

Nevertheless, most studies so far account for ad hoc external noise. The system's dynamics is often described by a macroscopic deterministic equation, and noise items are added to the equation either directly or via the perturbation of parameters. One may control the intensity and the properties of the external noise at our own will, without caring about the system's own dynamics. However, for chemical reactions taking place in small scale systems, one must pay much attention to the internal noise which results from the random fluctuations of the stochastic reaction events. It is generally accepted that the strength of the internal noise scales as $1/\sqrt{\Omega}$, where Ω is the system size. Therefore, for macroscopic systems where Ω is infinite, the internal noise can be ignored. But for cellular or sub-cellular reaction systems where the number of reaction molecules is often

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low [11–14], 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 [15,16] have demonstrated that optimal intracellular calcium signaling appears at a certain size or distribution of the ion channel clusters. Ion channel clusters of optimal sizes can enhance the encoding of a sub-threshold stimulus [17,18]. In recent studies, using the Brusselator model [19] and a circadian clock system [20], we have also shown that stochastic oscillations occurred when the internal noise is considered in the region close to the deterministic oscillatory dynamics and an optimal system size exists, characterized by a clear maximum in the signal-to-noise ratio (SNR) as a function of system size.

Endocrine system is one of the most major systems in the exchange of biological information. In the endocrine system, information is specifically transmitted via the blood stream. The specificity of signaling arises from the biochemical structure of the hormones and their respective receptors. The cellular response upon extracellular hormonal stimulation is mediated by a number of different intracellular second messenger pathways. The Ca^{2+}-phosphatidylinositol (PI) signaling pathway plays a major role in transmembrane signaling in a large number of cell types [21]. In this pathway, a variety of cell types can detect the extracellular hormonal signal through repetitive intracellular calcium spikes, and then encode information to specifically regulate distinct cellular functions, such as the activation of protein kinases [22], the activation of genes [23], and so on. In the last decades, the response of hepatocytes to hormonal stimulus by intracellular calcium spikes has been numerically studied experimentally [24] and theoretically [25–27]. However, to our knowledge, the influence of internal noise on the detection of hormonal signals has not been studied yet.

In the present Letter, we have constructed a mesoscopic stochastic model for intracellular calcium oscillations in hepatocytes to investigate the influence of internal noise on the detection of sub-threshold hormonal signals using chemical Langevin equation (CLE) and stochastic simulations via poissonian dynamics. By numerically simulations, we find that, when the extracellular hormonal signal is sub-threshold to fire calcium spikes, stochastic calcium spikes appear when the internal noise is considered, and the regularity of the spike train undergoes a maximum with the variation of the internal noise level, indicating the occurrence of *internal noise stochastic resonance* (INSR). Since the magnitude of the internal noise is changed via the variation of the system size, the INSR also represents itself a kind of *system size resonance*. Therefore, instead of trying to resist the internal molecular noise, living cells may have learned to exploit it to enhance the ability to detect weak hormonal signals. It is also interesting to note that the optimal size is close to the volume of cytosolic compartment of the real living cells.

2. Model description

The model discussed in the present Letter is based on the receptor-controlled model for intracellular calcium oscillations in hepatocytes proposed by Cuthbertson and Chay [25,28]. If the internal noise is ignored, the model can be summarized by the following equations [25]:

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

in which, $[G_\alpha - \mathrm{GTP}]$, [DAG], $[\mathrm{Ca}^{2+}]_i$, [PLC*], $[G_\alpha - \mathrm{GDP}]$, $[\mathrm{IP}_3]$ and [PLC] are the concentrations of $G_\alpha - \mathrm{GTP}$ (G-protein α-subunit bound to GTP), DAG (diacylglycerol), Ca_i^{2+} (intracellular calcium), PLC* (activated form of Phospholipase), $G_\alpha - \mathrm{GDP}$ (G-protein α-subunit bound to GDP), IP_3 (inositol (1,4,5)-triphosphate) and PLC (Phospholipase), respectively. $[G_\alpha - \mathrm{GDP}]$ is related to $[G_\alpha - \mathrm{GTP}]$ by the relation

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

and [PLC] is related to [PLC*] by

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

where G_0 is the total concentration of the g-proteins and P_0 is the total concentration of PLC. k_g is assumed to be proportional to the agonist concentration, i.e., the concentration of the extracellular hormones. The three kinetic parameters k_p, h_p and k_d are assumed to take the following forms:

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

where $k_n = k_p$, h_p or k_d. See [25] for the more detailed descriptions of the model and parameter values.

However, for a typical living cell system, such a deterministic description is no longer valid due to the existence of considerable internal noise. To investigate the influence of internal noise, generally, one can describe

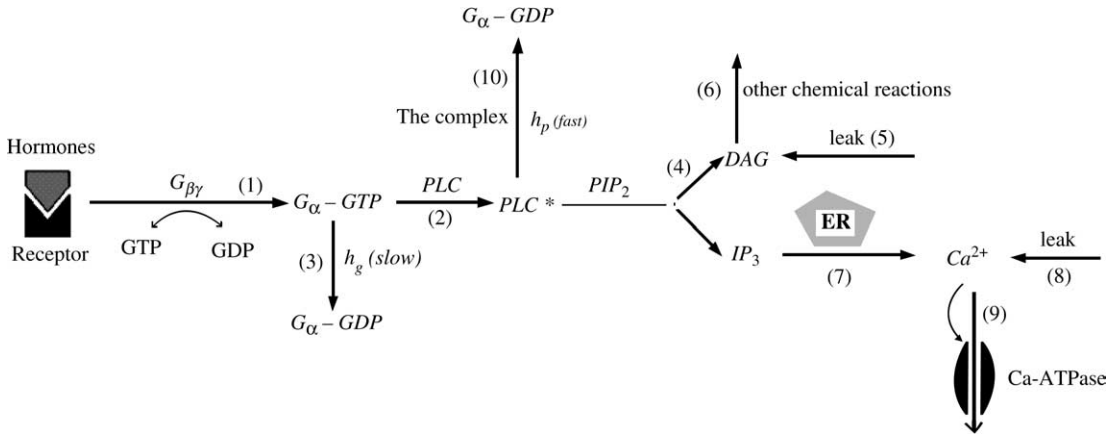

Fig. 1. Simple description about how the intracellular calcium oscillations generate when certain hormones bind to their receptors in the plasma membrane of non-excitable cells. Here, PLC for phospholipase C, IP_3 for Inositol (1,4,5)-trisphosphate, DAG for diacylglycerol, and ER for the endoplasmic reticulum.

the reaction system as a birth-death stochastic process governed by a chemical master equation. But there is no procedure to solve this master equation analytically. One of the widely used simulation algorithm is exact stochastic simulation method proposed by Gillespie [29], which stochastically determines what is the next reaction step and when it will happen according to the transition rate of each reaction process. In accordance with Gillespie's method, we introduce the number of intracellular calcium ions in the cytosol as Z and correspondingly the population number X of $G_\alpha - \mathrm{GTP}$, Y of DAG and W of PLC*, respectively, such that the concentrations of the reactants are obtained as $[G_\alpha - \mathrm{GTP}] = \frac{X}{\Omega}$, $[\mathrm{DAG}] = \frac{Y}{\Omega}$, $[\mathrm{Ca}^{2+}]_i = \frac{Z}{\Omega}$, $[\mathrm{PLC}^*] = \frac{W}{\Omega}$ (note that Ω is the volume of cytosolic compartment of the cell). Then, using the similar procedure as in [30], the reactions in the cell can be grouped into ten elementary processes for the current model. See Fig. 1 for a simple description of the processes, and Table 1 for the corresponding transition rates. Note that the transition rates are proportional to the system size Ω.

Although the direct stochastic simulation method is exact, it is too time-consuming when the system size is large. To overcome this problem, an alternative method to study the internal noise was proposed by Gillespie, which reads chemical Langevin equation (CLE) [31]. It was proved that the CLE is a rather good approximation if a 'macro-infinitesimal' time scale exists in the system, and in our previous studies [19,20], we have shown that it is convenient to use CLE to study the influence of internal noise in a systematic way, at least in a qualitatively manner. Not long ago, another method was also put forward, which is 'the Poisson approximation' [32]. Such approximation was shown to be a more adequate tool to handle systems with large and small populations indistinctly, and for smaller system sizes, the Poisson method is more appropriate. So, when the system size is not large enough, the Poisson approximation is necessary to validate the accuracy of the obtained results from CLE. According to Gillespie, the CLE for the current model reads:

Table 1
Stochastic transition processes and corresponding rates

Transition processes		Description	Transition rates
(1)	$X \to X+1$	The increase of $[G_\alpha - \mathrm{GTP}]$ due to the conversion of $[G_\alpha - \mathrm{GDP}]$ to $[G_\alpha - \mathrm{GTP}]$	$a_1 = \Omega \cdot k_g\,[G_\alpha - \mathrm{GDP}]$
(2)	$X \to X-4\ W \to W+1$	PLC* is formed when 4 mol of $[G_\alpha - \mathrm{GTP}]$ is combined with PLC	$a_2 = \Omega \cdot k_p\,[G_\alpha - \mathrm{GTP}]^4[\mathrm{PLC}]$
(3)	$X \to X-1$	A loss of $[G_\alpha - \mathrm{GTP}]$ due to the hydrolysis to $[G_\alpha - \mathrm{GDP}]$	$a_3 = \Omega \cdot h_g\,[G_\alpha - \mathrm{GTP}]$
(4)	$Y \to Y+1$	The production of DAG from PIP_2 by the action of PLC*	$a_4 = \Omega \cdot k_d\,[\mathrm{PLC}^*]$
(5)	$Y \to Y+1$	A 'leak' process which keeps DAG at the basal level	$a_5 = \Omega \cdot l_d$
(6)	$Y \to Y-1$	The loss of DAG due to other chemical reactions	$a_6 = \Omega \cdot h_d\,[\mathrm{DAG}]$
(7)	$Z \to Z+1$	The increase of $[\mathrm{Ca}^{2+}]_i$ due to the release of Ca^{2+} from the endoplasmic reticulum (ER) triggered by IP_3	$a_7 = \Omega \cdot \rho k_c \frac{[\mathrm{IP}_3]^3}{K_S^3+[\mathrm{IP}_3]^3}$
(8)	$Z \to Z+1$	A 'leak' process which keeps the cell at the basal level of Ca^{2+} in the absence of external stimuli	$a_8 = \Omega \cdot \rho l_c$
(9)	$Z \to Z-1$	The loss of $[\mathrm{Ca}^{2+}]_i$ due to the Ca^{2+}-ATPase pumps	$a_9 = \Omega \cdot \rho h_c\,[\mathrm{Ca}^{2+}]_i$
(10)	$W \to W-1$	The loss of PLC* due to the hydrolysis of the complex back to $[G_\alpha - \mathrm{GDP}]$	$a_{10} = \Omega \cdot h_p\,[\mathrm{PLC}^*]$

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

where $\xi_{i=1,\ldots,10}(t)$ are Gaussian white noises with $\langle\xi_i(t)\rangle = 0$ and $\langle\xi_i(t)\xi_j(t')\rangle = \delta_{ij}\delta(t-t')$. Because the reaction rates a_i are proportional to Ω, the internal noise item in the CLE scales as $1/\sqrt{\Omega}$.

In the following parts, we will mainly use Eq. (5) as our stochastic model for numerical simulation to study the influence of internal noise on the detection of subthreshold hormonal signals. The Poisson approximation is also used to show consistency if necessary.

3. Simulation and results

It has been demonstrated that, under in vivo conditions, most hormones are secreted in a burst-like or pulsatile manner [33], i.e., the concentration of extracellular hormonal signal k_g is a function of time t. Recently, a few studies have been performed under pulsatile hormonal stimulus, for example, the discovery of locking rhythms between the extracellular hormonal stimulus and intracellular calcium response [25]; external noise enhanced hormonal signal transduction [26], coding efficiency and information rates in transmembrane signaling [27], etc. Therefore, we will focus on the influence of internal noise on the detection of pulsatile hormonal stimulus.

As in [25], we use a square wave pulse to represent the time-varying extracellular hormonal signal. Eq. (5) was solved by Eular method with a time step $\mathrm{d}t = 0.01$ s. The system is stimulated periodically by the hormonal pulse, which has a base of bs, a height of hs and a duration of dr. the interval between subsequent pulses is SS. Here, the signal we used has a typical value in [24], $bs = 0.005\ \mathrm{s}^{-1}$, $hs = 0.013\ \mathrm{s}^{-1}$, $dr = 10$ s and $SS = 40$ s, i.e.,

$$k_g(t) = \begin{cases} hs = 0.013 & \text{for } (40j \leqslant t < 40j + 10), \\ bs = 0.005 & \text{for } (40j + 10 \leqslant t < 40j + 40), \\ (j = 0, 1, 2, 3, \ldots, N), \end{cases}$$

as represented in Fig. 2a. This hormonal signal is subthreshold to fire intracellular calcium spikes alone (the threshold to fire calcium spikes is $hs = 0.015\ \mathrm{s}^{-1}$; note that the threshold depends on the values of bs, dr and SS) such that the cell is at a stable state (Fig. 2b). However, when appropriate internal noise is considered, continuous calcium spikes appear, such that the cell system can detect the weak hormonal signal, and then encode information to specifically regulate distinct cellular functions. Part of the calcium spike train corresponding to the system size $\Omega = 100\ \mu\mathrm{m}^3$ is plotted in Fig. 2c.

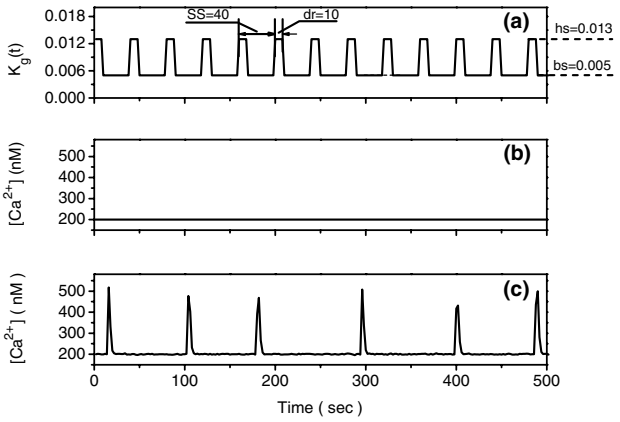

Fig. 2. (a) Pulsatile hormonal stimulus k_g as a function of time t. (b) Corresponding intracellular calcium response to the stimulus obtained via Eqs. (1)–(4). (c) Corresponding intracellular calcium response to the stimulus obtained via Eq. (5) for $\Omega = 100\ \mu\mathrm{m}^3$.

Now, we consider how the intracellular calcium spikes depend on the level of internal noise. Assuming that the system size is large, i.e., the internal noise is too weak, and there would be very few occasional calcium spikes. On the contrary, if the system size is small, although the spike firing becomes more frequently, the internal noise is large and smears the regularity of the calcium spike train. Consequently, for an intermediate system size, i.e., internal noise level, the calcium spike train is the most regular (Fig. 3).

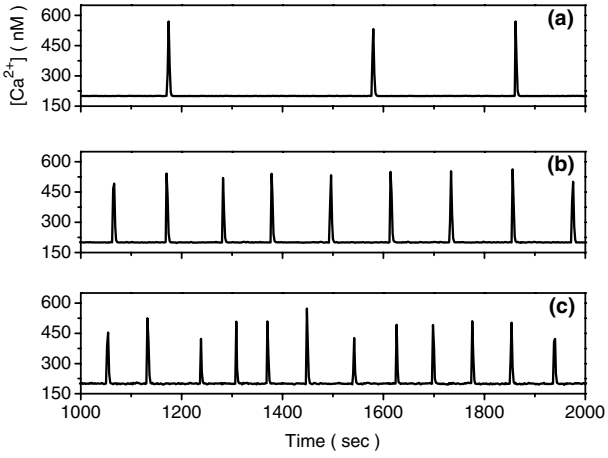

Fig. 3. The time series of intracellular calcium concentration for different system size Ω: (a) $\Omega = 4000\ \mu\mathrm{m}^3$, (b) $\Omega = 200\ \mu\mathrm{m}^3$, (c) $\Omega = 50\ \mu\mathrm{m}^3$.

To measure the relative regularity of the calcium spike train quantitatively, we introduce a coefficient of variation (R), which is defined as the mean value of the spike interval T normalized to the mean root, namely, $R = \frac{\langle T\rangle}{\sqrt{\langle T^2\rangle - \langle T\rangle^2}}$ [34]. 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 threshold we define here is 400 nM). The measure R 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 R means more closeness of the spike train to a periodic one, where R is obviously ∞.

The dependence of R on system size is plotted in Fig. 4. A clear maximum is present for system size $\Omega \sim 200\ \mu m^3$, which demonstrates the existence of a resonance effect. We have also performed stochastic simulations using poissonian dynamics. Good agreement among the CLE method and the Poisson approximation is apparent, which implies that the CLE method is convenient to study the effect of internal noise and the robustness of the present results. 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). We call this phenomenon *internal noise stochastic resonance* (INSR). Since the magnitude of the internal noise is changed via the variation of the system size, the INSR also represents itself a kind of *system size resonance*. It is also interesting to note that this size is close to the volume of cytosolic compartment of the real living cells [30].

Using the CLE, we have also studied how the INSR curve depends on the amplitude of the pulsatile hormonal signal (i.e. *hs*), which is shown in Fig. 5. We find that when the hormonal signal becomes weaker, both the maximum coefficient of variation R and the optimal system size become smaller.

Such INSR phenomenon might be relevant to hormonal signal detecting processes in two ways. *On one hand*, due to the existence of unavoidable internal noise, stochastic calcium spikes appear, indicating that a much wider range of hormonal signals can be detected through intracellular calcium oscillations. *On the other hand*, instead of trying to resist the internal molecular noise, living cell systems may have learned to exploit it to enhance the calcium oscillation performance, so as to enhance intensively the ability to detect weak hormonal signals via the mechanism of INSR. It is also interesting to note that the optimal size is close to the volume of cytosolic compartment of the real living cells. What is more, previous studies have shown that the calcium signaling sensitivity [15] and capability [16] in many cells show the maximum if the channel cluster size is optimal, and the spontaneous action potential in neurons shows the best time precision when the density of axon ion channels reaches an optimal level [35]. Such behaviors imply that INSR might be a widely used mechanism for living organisms to adapt and function.

Other works should be done about this topic, for example, when the pulsatile hormonal signal varies with different base of *bs*, duration of *dr* or interval between subsequent pulses of *SS*, what changes will take place about internal noise enhanced hormonal signal detecting processes? We will discuss in the future.

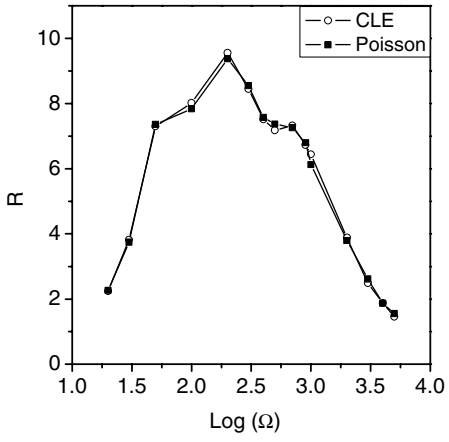

Fig. 4. Coefficient of variation R as a function of system size Ω: ○, CLE results; ■, Poisson approximation. Parameters are $bs = 0.005\ s^{-1}$, $hs = 0.013\ s^{-1}$, $dr = 10$ s, $SS = 40$ s. The solid lines are drawn to guide the eye.

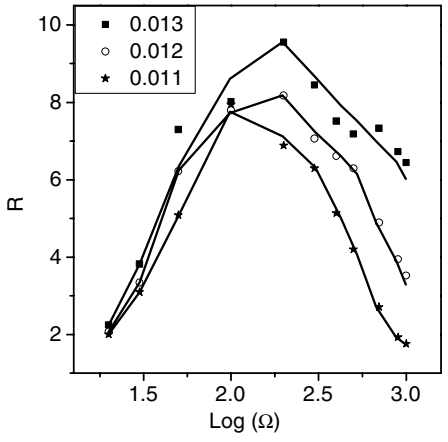

Fig. 5. The dependence of R on system size Ω with different amplitudes of hormonal stimulus. Parameters are $bs = 0.005\ s^{-1}$, $dr = 10$ s, $SS = 40$ s, $hs = 0.013\ s^{-1}$ (■); $0.012\ s^{-1}$ (○); $0.011\ s^{-1}$ (★). The solid lines are shown to guide the eye.

4. Conclusion

To summarize, we have constructed a mesoscopic stochastic model for intracellular calcium oscillations in hepatocytes to study the influence of internal noise on the detection of sub-threshold hormonal signal mainly using chemical Langevin equation (CLE). It is found that stochastic calcium spikes appear when the internal noise is considered, and the regularity of calcium spike train undergoes a maximum with the variation of internal noise level, indicating the occurrence of *internal noise stochastic resonance* (INSR). Therefore, instead of trying to resist the internal molecular noise, living cells may have learned to exploit it to detect a much wider range of extracellular hormonal signals through intracellular calcium oscillations and enhance intensively the ability to detect weak hormonal signals via the mechanism of INSR, and then encode information to specifically regulate distinct cellular functions. It is interesting to note that the optimal size is close to the volume of cytosolic compartment of the real living cells. Since the internal noise in living cell systems can not be ignored and the systems may often encounter sub-threshold stimuli, our findings might have interesting implications for signal detecting processes in living systems.

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