A constructive role of internal noise on coherence resonance induced by external noise in a calcium oscillation system

Guang Yu, Ming Yi, Ya Jia *, Jun Tang

Department of Physics and Institute of Biophysics, Huazhong Normal University, Wuhan 430079, China

Accepted 6 December 2007

Communicated by Prof. Grigolini

Abstract

A stochastic cytosolic calcium oscillation model simultaneously driven by external noise and internal noise has been investigated by using the chemical Langevin equation method. When the extracellular stimulation is subthreshold, it is found that the internal-noise coherence resonance can be suppressed by the external noise, while the external-noise coherence resonance can be enhanced by modulating the internal-noise intensity. Besides a qualitative analysis with a competitive mechanism is given for the results, a further explanation is also provided theoretically by using the small noise approximation and bifurcation analysis.

© 2007 Elsevier Ltd. All rights reserved.

1. Introduction

Noise plays a constructive role in many nonlinear systems and its effect has been widely studied in the last two decades. One of the important effects is noise-induced enhancement of temporal regularity which is there exists a resonant noise intensity at which the response of the system is maximally ordered. This phenomenon, known as stochastic resonance (SR), has been investigated in a large variety of physical [1,2], chemical [3,4], and biological systems [5–7]. In early studies of SR, it was considered that the occurrence of SR needs three necessary conditions: a nonlinear system, a external periodic signal and environment noise. However, with the development of SR studies, it has been shown that without an external periodic signal coherence of noise-induced oscillations is maximized for an optimal level of noise intensity. This phenomenon was termed as coherence resonance (CR) [8–10] or autonomous SR.

In a biochemical reaction system, it is known that the external noise and internal noise are both unavoidable [11–13]. The external noise originates from the random variation of one or more of the externally set control parameters, such as the rate constants associated with a given set of reactions. Many previous works have demonstrated that the coherence resonance phenomenon can be induced by external noise [8,14,15], which is called external-noise coherence resonance (ENCR). While internal noise comes from the random fluctuations of the stochastic chemical reaction events in finite-size biochemical systems [16]. It is generally accepted that the strength of the internal noise is inversely proportional to
the square root of the number of particles, an indicator of the system size $V$ [17]. In finite-size biochemical systems, it
has been found that internal noise can induce stochastic oscillations when the system is subthreshold or suprathreshold,
the stochastic oscillations show the best performance at an optimal system size [18–20], and this phenomenon is called
internal-noise coherence resonance (INCR).

It is well known that intracellular Ca$^{2+}$ is one of the most important second messengers in the cytosol of living cells.
The oscillations of intracellular Ca$^{2+}$ play an important role in the control of many cellular processes, for example, the
birth, life, and death of cells, muscle contraction, gene expression, etc., [21–23]. So studies about the effects of external/
internal fluctuation on Ca$^{2+}$ oscillations are important to reveal the essence of cellular living processes. Recently, Zhong
et al. [24] and Li and Wang [25] have studied ENCR in a Ca$^{2+}$ oscillations model proposed by Houart et al. [26]. They
found that ENCR can occur when the extracellular stimulation is subthreshold and random. In 2005, Li et al. [19] have
investigated INCR for intracellular calcium oscillations in a cell system. They found that INCR can occur when the
extracellular stimulation is subthreshold (or suprathreshold) and the internal noise is considered. The largest amount
of work regarding fluctuations has been focused on the consideration of systems with just one noise (either internal
noise or external one). However, for cellular or subcellular biochemical reaction systems, internal and external noise
should be considered simultaneously. To our knowledge, only a few studies have been done so far. Recently, our group
in [27] have studied a circadian oscillator driven by the external noise and internal noise, and found that the internal
noise plays a destructive role on ENCR.

In the present paper, by constructing a mesoscopic stochastic model for intracellular calcium oscillations in a cell
system, the combined effect of both the external noise and internal noise on the calcium oscillations system is studied
using the chemical Langevin equation method. When the extracellular stimulation is subthreshold, it is found that the
INCR can be suppressed by the external noise, while the ENCR can be enhanced by modulating the internal-noise
intensity in the calcium oscillations system. This paper is organized as follows: In Section 2, the deterministic model
is first introduced, then the stochastic model driven by both the internal and external noise is derived. In Section 3,
the combined effect of both the noises on the system is studied numerically. Then a qualitative analysis with a compet-
itive mechanism and a theoretical explanation by using the small noise approximation and bifurcation analysis are
given for the present results, respectively. We end with conclusions in Section 4.

2. Mathematical model

2.1. The deterministic model

To study the effects of intrinsic and extrinsic noise for intracellular calcium oscillations, a minimal calcium determin-
istic model proposed by Berridge and coworkers [28] is used here:

$$\frac{dz}{dt} = v_0 + v_1 \beta - v_2 + v_3 + k_f y - k_z,$$
$$\frac{dy}{dt} = v_2 - v_3 - k_f y,$$

with

$$v_2 = V_{M_2} \frac{z^n}{K_2^n + z^n},$$
$$v_3 = V_{M_3} \frac{y^{n_0}}{K_R^{n_0} + y^{n_0}},$$

where $z$ and $y$ are two variables in the model and represent the concentration of cytosolic Ca$^{2+}$, the concentration of
Ca$^{2+}$ in the IP$_3$-insensitive pool, respectively. $\beta$ is the external control parameter that denotes the degree of extracellular
simulation and varies from 0 to 1. The values of other parameters are $v_0 = 1.0$ μM s$^{-1}$, $v_1 = 7.3$ μM s$^{-1}$, $k = 10$ s$^{-1}$,
$k_f = 1$ s$^{-1}$, $V_{M_2} = 65$ μM s$^{-1}$, $V_{M_3} = 500$ μM s$^{-1}$, $K_2 = 1$ μM, $K_R = 2$ μM, $K_A = 0.9$ μM, $m = 2.0$, $n = 2.0$, $p = 4.0$.
The detailed description of the model can be found in [28,29]. With the above parameter values, the system has two
supercritical Hopf bifurcation points: $\beta_1 = 0.289$ and $\beta_2 = 0.779$, respectively. And the regular intracellular Ca$^{2+}$
oscillations can occur when $\beta_1 \leq \beta \leq \beta_2$. To study CR in this model system, the value of the external control parameter $\beta$ is
set to the subthreshold $\beta_0 = 0.287$. In the absence of noise part, the system is in the stable steady state at $\beta_0$. All results
of this paper are calculated with the above parameter values if not otherwise stated.
2.2. The stochastic model driven by both the internal and external noise

In order to derive a stochastic model driven by both the noises, the internal noise is first introduced by virtue of the chemical Langevin equations. Then the external noise is further introduced into the chemical Langevin equations through a external control parameter.

For intracellular calcium oscillations in a cell system, the system size is finite, so the effect of internal noise is significant. To study the role of internal noise, a mesoscopic stochastic model should be used instead of the deterministic ones. Generally, one should describe such a reaction system as a birth–death stochastic process governed by a chemical master equation. However, there is no practical procedure to solve the chemical master equation. An alternative method to study the internal noise is the Chemical Langevin equation (CLE) proposed by Gillespie in 2000 [30]. The recent works of Hou and co-workers [19,31] have shown that it is applicable to use the CLE to study the effect of the internal noise in small biochemical reaction systems qualitatively.

Following Gillespie’s method, we introduce the number of cytosolic Ca$^{2+}$ as $Z$ and the number of Ca$^{2+}$ in the insensitive pool as $V$. Then, the $z = Z/V, y = Y/V$, where $V$ is the volume of the cytosolic compartment of the cell. The stochastic processes involving the change of $Z$ or $Y$ are listed in Table 1. Note that there are six reaction channels $R_j (j = 1, \ldots, 6)$ as shown in Table 1 for two species $S_i (i = 1, 2)$ and the transition rates $a_{j=1, \ldots, 6}$ are proportional to the system size $V$. The propensity function (i.e., the transition rate) $a_j$ for $R_j$ and the state change vector $v_j$, whose $i$th component $v_{ji}$ is the change in the number of $S_i$ molecules produced by one $R_j$ reaction ($j = 1, \ldots, 6; i = 1, 2$), together completely specify the reaction channel $R_j$. For $S_1$ (i.e., the cytosolic Ca$^{2+}$), the values of $v_{ji}$ are $v_{i1} = 1$, $v_{i2} = 1$, $v_{i3} = -1$, $v_{i4} = 1$, $v_{i5} = 1$, $v_{i6} = -1$; for $S_2$ (i.e., Ca$^{2+}$ in the IP$_3$-insensitive pool), the values of $v_{ji}$ are $v_{12} = 1$, $v_{22} = -1$, $v_{23} = -1$, $v_{24} = 1$, $v_{25} = 1$, $v_{26} = -1$. Let the system’s state at the current time $t$ be $(Z(t), Y(t))$ and a random variable $K_j (Z(t), Y(t), \tau)$ for any $\tau > 0$, be the number of $R_j$ reactions that occur in the subsequent time interval $[t, t + \tau]$. Since each of those reactions will increase the $S_i$ population by $v_{ji}$, the number of $S_i$ molecules in the system at time $t + \tau$ will be

$$Z(t + \tau) = Z(t) + K_1(Z(t), Y(t), \tau) + K_2(Z(t), Y(t), \tau) - K_3(Z(t), Y(t), \tau) + K_4(Z(t), Y(t), \tau)$$

$$Y(t + \tau) = Y(t) + K_5(Z(t), Y(t), \tau) - K_6(Z(t), Y(t), \tau),$$

(5)

(6)

An excellent approximation to $K_j (Z(t), Y(t), \tau)$ can be obtained if the following two conditions are imposed [30]: (i) $\tau$ is small enough so that $K_j$ varies little during the period $[t, t + \tau]$. Each $K_j (Z(t), Y(t), \tau)$ will be a statistically independent Poisson random variable, $\mathcal{P}_j (a_j (Z(t), Y(t), \tau), \tau)$:

$$K_j (Z(t), Y(t), \tau) = \mathcal{P}_j (a_j (Z(t), Y(t), \tau), \tau).$$

(7)

(ii) $\tau$ is large enough so that the expected number of occurrences of each reaction channel $R_j$ in $[t, t + \tau]$ be much larger than 1, which allows us to approximate each statistically independent Poisson random variable $\mathcal{P}_j (a_j (Z(t), Y(t), \tau), \tau)$ by a normal random variable $\mathcal{N}_j (m_j, \sigma_j^2)$ with the same mean $m_j$ and variance $\sigma_j^2$:

$$\mathcal{P}_j (a_j (Z(t), Y(t), \tau), \tau) = \mathcal{N}_j (a_j (Z(t), Y(t), \tau), a_j (Z(t), Y(t), \tau) \tau).$$

(8)

The linear combination theorem for normal random variables,

$$\mathcal{N}_j (m_j, \sigma_j^2) = m_j + \sigma_j \mathcal{N}_j (0, 1),$$

(9)

where $\mathcal{N}_j (0, 1)$ is the unit normal random variable. Thus, Eqs. (5) and (6) have the canonical form of standard Langevin equations for multivariate continuous Markov processes. By using the two conditions and the relationship between

<table>
<thead>
<tr>
<th>Reaction channel</th>
<th>Description</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) $Z \rightarrow Z + 1$</td>
<td>Constant plasma membrane influx</td>
<td>$a_1 = \frac{V_0}{V}$</td>
</tr>
<tr>
<td>(2) $Z \rightarrow Z + 1$</td>
<td>Stimulus-induced plasma membrane influx</td>
<td>$a_2 = \frac{V_1}{V}$</td>
</tr>
<tr>
<td>(3) $Z \rightarrow Z - 1, Y \rightarrow Y + 1$</td>
<td>ER release</td>
<td>$a_3 = \frac{V_2}{V}$</td>
</tr>
<tr>
<td>(4) $Z \rightarrow Z + 1, Y \rightarrow Y - 1$</td>
<td>ER uptake</td>
<td>$a_4 = \frac{V_3}{V}$</td>
</tr>
<tr>
<td>(5) $Z \rightarrow Z + 1, Y \rightarrow Y - 1$</td>
<td>Leak flux</td>
<td>$a_5 = \frac{V_4}{V}$</td>
</tr>
<tr>
<td>(6) $Z \rightarrow Z - 1$</td>
<td>Plasma membrane efflux</td>
<td>$a_6 = \frac{V_5}{V}$</td>
</tr>
</tbody>
</table>
the concentration and the molecular number of each species are satisfied, the chemical Langevin equations corresponding to the macroscopic differential equations (1) and (2) can be obtained from Eqs. (5) and (6):

\[
\frac{dx}{dt} = \frac{1}{V} (a_1 + a_2 - a_3 + a_4 + a_5 - a_6) + \frac{1}{V} [\sqrt{a_1} \xi_1(t) + \sqrt{a_2} \xi_2(t) - \sqrt{a_3} \xi_3(t) + \sqrt{a_4} \xi_4(t) + \sqrt{a_5} \xi_5(t) - \sqrt{a_6} \xi_6(t)],
\]

\[
\frac{dy}{dt} = \frac{1}{V} (a_3 - a_4 - a_5) + \frac{1}{V} [\sqrt{a_3} \xi_3(t) - \sqrt{a_4} \xi_4(t) - \sqrt{a_5} \xi_5(t)].
\]

Then, CLEs (10) and (11) can be read:

\[
\frac{dx}{dt} = (v_0 + v_1 \beta - v_2 + v_3 + k_f y - kz) + \frac{1}{V} \left[ \sqrt{v_0} \xi_1(t) + \sqrt{v_1} \beta \xi_2(t) - \sqrt{v_2} \xi_3(t) + \sqrt{v_3} \xi_4(t) + \sqrt{k_f y} \xi_5(t) - \sqrt{kd} \xi_6(t) \right],
\]

\[
\frac{dy}{dt} = (v_2 - v_3 - k_f y) + \frac{1}{V} \left[ \sqrt{v_2} \xi_3(t) - \sqrt{v_3} \xi_4(t) - \sqrt{k_f y} \xi_5(t) \right],
\]

where \( \xi_{k-1,...,6}(t) \) are independent Gaussian white noises, with zero mean and unit variance, \( \langle \xi_k(t) \rangle = 0 \), \( \langle \xi_k(t) \xi_{k'}(t') \rangle = \delta_{k,k'}(t-t') \). So Eqs. (12) and (13) are stochastic dynamic equations when only the internal noise is considered into the system. However, for cellular systems, the external and internal noises are both unavoidable and should be considered simultaneously. Thus, in the following work the external noise also should be involved in the stochastic dynamic equations (12) and (13) in order to investigate their combined effects.

To study the role of external noise, we can consider that the extracellular stimulation is a subthreshold value added to a noise term \( \eta(t) \). Thus the external noise is introduced into the system through the external control parameter \( \beta \)

\[
\beta = \beta_0 (1 + \eta(t)),
\]

where \( \eta(t) \) is the Gaussian noise with zero mean value, \( \langle \eta(t) \rangle = 0 \), and autocorrelation function \( \langle \eta(t) \eta(t') \rangle = 2D \delta(t-t') \), where \( D \) denotes the noise intensity. Substituting Eq. (14) into Eq. (12), the external noise is introduced into both \( v_1 \beta \) term and \( \frac{1}{V} \sqrt{v_1} \beta \xi_2(t) \) term of Eq. (12). It can be seen that the value of \( \frac{1}{V} \sqrt{v_1} \beta \xi_2(t) \) term is much more smaller than that of \( v_1 \beta \) term, especially in the case of large system size \( V \gg 1 \). For simplicity, here the external noise is only introduced through the \( v_1 \beta \) term and the \( \beta \) in the \( \frac{1}{V} \sqrt{v_1} \beta \xi_2(t) \) term is taken by the constant \( \beta_0 \). Therefore, the CLE (12) becomes:

\[
\frac{dx}{dt} = v_0 + v_1 \beta_0 [1 + \eta(t)] - v_2 + v_3 + k_f y - kz
\]

\[
+ \frac{1}{V} \left[ \sqrt{v_0} \xi_1(t) + \sqrt{v_1} \beta_0 \xi_2(t) - \sqrt{v_2} \xi_3(t) + \sqrt{v_3} \xi_4(t) + \sqrt{k_f y} \xi_5(t) - \sqrt{kd} \xi_6(t) \right].
\]

Then Eqs. (13) and (15) describe the calcium oscillation system driven by both the internal noise and the external noise under the approximation that the coupling between them is ignored. And it is found that the evolution of \( z \) in Eq. (15) includes three parts: (i) the determinate part \( (v_0 + v_1 \beta_0 - v_2 + v_3 + k_f y - kz) \); (ii) the external noise part \( (v_1 \beta_0 \eta(t)) \); (iii) the internal noise part \( \left( \frac{1}{V} \left[ \sqrt{v_0} \xi_1(t) + \sqrt{v_1} \beta_0 \xi_2(t) - \sqrt{v_2} \xi_3(t) + \sqrt{v_3} \xi_4(t) + \sqrt{k_f y} \xi_5(t) - \sqrt{kd} \xi_6(t) \right] \right) \), while the evolution of \( y \) in Eq. (13) includes two parts: (i) the determinate part \( (v_2 - v_3 - k_f y) \); (ii) the internal noise part \( \left( \frac{1}{V} \left[ \sqrt{v_2} \xi_3(t) - \sqrt{v_3} \xi_4(t) - \sqrt{k_f y} \xi_5(t) \right] \right) \).

2.3. Research method for the stochastic model

In the absence of noise part, the system is in the stable steady state at \( \beta_0 = 0.287 \). In the presence of noise part, Eqs. (13) and (15) are integrated by using a simple forward Euler algorithm with a fixed time step of 0.001 s. It is found that noise can induce calcium spikes, and the regularity of the spikes is different at different noise intensity. To measure the regularity of the spikes, we introduce the reciprocal coefficient of variance (RCV), namely:

\[
R = \frac{\langle T \rangle}{\sqrt{\langle T^2 \rangle - \langle T \rangle^2}},
\]

where \( T \) denotes the inter-spike intervals [32]. In fact, \( R \) represents the degree of CR and is similar to the signal-to-noise (SNR) (see Refs. [33,20] for detailed description of the calculation of SNR).
3. Result and discussion

3.1. Suppression of INCR by external noise and enhancement of ENCR by internal noise

In order to give a simple and clear analysis about the interplay between the external noise and the internal noise of the system near the bifurcation point, we have investigated how the coherence resonance phenomenon induce by one noise is affected the other one.

Firstly, we have investigated how the internal-noise coherence resonance (INCR) is affected by the external noise. The dependence of $R$ on the system size $V$ for the different external-noise intensity $D$ is shown in Fig. 1. It is found that the INCR occurs only for $D < 10^{-2.5}$. In this region of $D$, the INCR curve becomes lower and the right border of the curve slowly run up as the external noise increases. We choose the maximum $R$ (i.e. $R_{\text{MAX}}$) value from each INCR curve and show the dependence of $R_{\text{MAX}}$ on $D$ in Fig. 2. It is shown that the $R_{\text{MAX}}$ decreases with increasing the external-noise intensity. When $D > 10^{-2.5}$, the INCR phenomenon disappears and the curve gradually becomes a plateau. It is because that the external noise dominates the stochastic behavior as $D$ increases. And the system is insensitive to $V$ at such a large value of $D$, so the curve becomes a plateau. When $D$ increases further, the plateau becomes lower. Therefore, it is found that the external noise plays a destructive role in the whole process. The INCR can be suppressed by the external noise. Further more, it is observed that the position of the $R_{\text{MAX}}$ of INCR does not change evidently with the external-noise intensity. The position of each peak of INCR curves keeps nearly constant at $V/C_0 = 10^{3}$. It is interesting that the value of the optimal cell size $V/C_0 = 10^{3}$ is of the same order of real living cells in vivo and is comparable to the obtained in [27,31]. The biological organism may adapt to adjust the optimal size according to the external noise.

Secondly, we have studied how the external-noise coherence resonance (ENCR) is affected by the internal noise. Fig. 3 shows the dependence of $R$ on the external-noise intensity for different choices of system size. When the system size is very small ($V = 10^{1.0}$), meaning the internal-noise intensity is very strong which results in that the system is insensitive to $D$. Thus, the curve forms a plateau. With the increase of the system size, the left border of the curve slowly runs up. Oppositely, when $V > 10^{3}$, as the increase of $V$ the left border of the curve slowly falls which result in that a peak appears in the curve, indicating the occurrence of the ENCR. When $V$ increases further, the ENCR curve becomes lower. If we choose the maximum $R$ value from each ENCR curve and show the dependence of $R_{\text{MAX}}$ on $D$ (which denotes the density of the internal noise [17]), it is shown that $R_{\text{MAX}}$ increases with the increase of the internal-noise intensity in Fig. 4. So the internal noise plays a constructive role in the region ($V > 10^{1.0}$). The ENCR can be enhanced by modulation of the internal-noise intensity. And it also can be observed that the position of the $R_{\text{MAX}}$ of ENCR does not change evidently with the system size. The position of each peak of ENCR curves keeps nearly constant at $D/C_0 = 10^{-1.3}$. We also can get a global view from Fig. 5, where the $R$ as a function of $\log_{10}V$ and $\log_{10}D$ is plotted. In Fig. 5, we can clearly get the above mentioned results.

3.2. Qualitative and theoretic explanations for the present results

Above results show that INCR can be suppressed by external noise, while ENCR can be enhanced by modulating the internal-noise intensity. And the results are just opposite to the results obtained in our previous work [27]. In order
Fig. 2. The dependence of $R_{\text{MAX}}$ on $D$.

Fig. 3. $R$ as a function of $D$ for different system sizes $V$.

Fig. 4. The dependence of $R_{\text{MAX}}$ on $V^{-1/2}$.
to understand the reason, we should analyze the underlying mechanisms of noise control in the stochastic dynamics of coherence resonance. Below, the detailed explanation for the present results and for the difference from our previous work in circadian oscillation system are provided.

(i) A qualitative analysis is given firstly. These phenomenons can be understood from the different mechanisms of the coherence resonance phenomenon induced by internal noise and external noise, respectively. It is known that different noise sources may affect the system’s stochastic dynamics in different ways \([34,35]\). Here, the external noise term is added directly to the deterministic equation multiplicatively, while the internal noise introduced in the chemical reactions is related to the parameter values and the system size, as well as the state variables that evolve with time. Therefore, the mechanisms of the coherence resonance phenomenon induced by internal and external noise, respectively, may be different. When the external-noise intensity \(D = 0\), Eq. (15) becomes Eq. (12), which means that the system is only driven by the internal noise. In Fig. 6, we have plotted the dependence of \(R\) on \(V\). It is shown that \(R\) goes through a maximum \(R_{\text{MAX}} = 5.447\) at an optimal cell size of \(V = 10^{3.0}\), indicating the occurrence of INCR. While when the system size is very large \((V \to \infty)\), the both internal noise parts in Eqs. (13) and (15) are very small and can be neglected, which means that the system is only driven by the external

![Fig. 5. \(R\) plot for different \(\log_{10} V\) and different \(\log_{10} D\).](image)

![Fig. 6. The dependence of \(R\) on the system size \(V\) when \(D = 0\).](image)
noise. In Fig. 7 the dependence of $R$ on $D$ is plotted. It is found that $R$ goes through a maximum $R_{\text{MAX}} = 4.664$ at an optimal noise intensity of $D \approx 10^{-3}$, indicating the occurrence of ENCR. So it can be found that the optimizing performance of stochastic oscillations by the internal noise ($R_{\text{MAX}} = 5.447$) is larger than that by the external noise ($R_{\text{MAX}} = 4.664$). When the ENCR occurs, the added internal noise can enhance the performance of stochastic oscillations by introducing extra dynamics. The extra dynamics may play a crucial role as an energy source, which makes $R_{\text{MAX}}$ increase with the increase of the internal-noise intensity $V^2/C_0$ (see Fig. 4). On the contrary, when the INCR occurs, external noise may play a negative role. Thus the $R_{\text{MAX}}$ decreases with the increase of the external-noise intensity $D$ (see Fig. 2). However, in circadian oscillation system [27], it can be found that the optimizing performance of stochastic oscillations by internal noise ($\text{SNR}_{\text{MAX}} \approx 700$) is much smaller than that by the external noise ($\text{SNR}_{\text{MAX}} \approx 50$), so an opposite result is obtained in the circadian oscillator. Therefore, it implies that there may be a competitive mechanism between internal noise and external noise.

(ii) A theoretic analysis is provided secondly. When study the double-noise system driven simultaneously by multiplicative noise and additive noise, the effective deterministic model can be used proposed by Garcia-Ojalvo et al. [35,36]. When one noise is added into the original deterministic model multiplicatively, the stochastic effect of the multiplicative noise can be estimated by computing its average value, which can be considered as a first order approximation in a small-noise expansion of multiplicative noise. Such treatment leads to the effective deterministic model. Therefore, the systematic contribution of the multiplicative noise is evaluated by separating the systematic contribution from the stochastic one. It is advantageous to use the effective deterministic model to investigate the double-noise system. The multiplicative noise term can be treated as a deterministic term, the additive noise is still regard as a stochastic term. For the case of a stochastic differential equation:

$$\dot{x}(t) = f(x(t)) + g(x(t))\eta(t),$$ (17)

where $\eta(t)$ is the Gaussian white noise with zero mean and $\delta$-correlation in time, i.e. $\langle \eta(t)\eta(t') \rangle = \sigma^2 \delta(t-t'), \sigma^2$ represents the multiplicative noise intensity. Following Garcia-Ojalvo’ method, we can convert it to an effective deterministic equation:

$$\dot{x}(t) = f(x(t)) + \frac{1}{2} \sigma^2 \frac{\partial f(x(t))}{\partial x(t)} g(x(t)),$$ (18)

For the calcium oscillation model, the internal noise is a multiplicative noise, while the external noise is a additive noise. According to Garcia-Ojalvo’ method, we will convert the multiplicative internal noise into the original deterministic model and perform the small-noise expansion for internal noise. Eqs. (12) and (13) represent that the system only subjects to the multiplicative internal noise. Following this method, we can convert them to the effective deterministic equations:
\[
\frac{dz}{dt} = (v_0 + v_1 \beta - v_2 + v_3 + k_f y - k_z) + \frac{1}{2V} \left[ \sqrt{v_0} \frac{d\sqrt{v_0}}{dz} \sigma_1^2 + \sqrt{v_1} \frac{d\sqrt{v_1} \beta}{dz} \sigma_2^2 + \sqrt{v_2} \frac{d\sqrt{v_2}}{dz} \sigma_3^2 \right. \\
+ \sqrt{v_3} \frac{d\sqrt{v_3}}{dz} \sigma_4^2 + \sqrt{k_f y} \frac{d\sqrt{k_f y}}{dz} \sigma_5^2 + \sqrt{k_z} \frac{d\sqrt{k_z}}{dz} \sigma_6^2 \left. \right], \\
\frac{dy}{dt} = (v_2 - v_3 - k_f y) + \frac{1}{2V} \left[ \frac{d\sqrt{v_2}}{dy} \sigma_3^2 + \frac{d\sqrt{v_3}}{dy} \sigma_5^2 + \sqrt{k_f y} \frac{d\sqrt{k_f y}}{dy} \sigma_5^2 \right], 
\]

where \( \sigma_{i=1...6} \) represent the noise intensity. Because when ENCR occurs, our numerical simulation result shows the internal noise plays a constructive role when \( V > 10^{10} \). We choose \( V = 10^{1.5} \) as an illustration.

So the six internal noise terms become their corresponding deterministic terms, and the original stochastic equations (12) and (13) are converted into the effective deterministic equations (19) and (20), which will result in the change of the Hopf bifurcation point of the original deterministic model. Therefore, it will affect the CR phenomenon induced by the additive external noise. Fig. 8 shows the bifurcation diagram of the original deterministic model and the effective deter-
ministic one. It is found that the Hopf bifurcation point is changed from HB_0 to HB_1 when multiplicative noise terms are treated as the deterministic terms. Thus, the distance of the control parameter \( \beta_0 \) from the Hopf bifurcation point becomes shorter, which means the chance of the system driven into the oscillation region becomes larger when the system subjects to the additive external noise. Therefore, it results in the enhancement of ENCR by internal noise as the chance of the system driven into the oscillation region becomes larger.

For the circadian oscillation model [27], we also do the same treatment and get the bifurcation diagram of Fig. 9. From Fig. 9, it is found that the Hopf bifurcation point is changed from HB_0 to HB_1 when the multiplicative internal noise terms are treated as the effective deterministic terms. Thus, the distance of the control parameter \( k_{dp}^0 \) from the Hopf bifurcation point becomes longer, which means the chance of the system driven into the oscillation region becomes smaller when the system subjects to the external noise. Therefore, it results in the suppression of ENCR by internal noise.

After the internal noise terms are converted into the effective deterministic terms, for the calcium oscillation model, the distance of the control parameter from the Hopf bifurcation point becomes shorter which results in ENCR is enhanced by the internal noise. While for the circadian oscillation model [27], the distance of the control parameter from the Hopf bifurcation point becomes longer which results in INCR is suppressed by the internal noise, so an opposite result is obtained.

4. Conclusion

In conclusion, by constructing a mesoscopic stochastic model for intracellular calcium oscillations in a cell system, we have investigated the CR phenomenon induced by both the external noise and the internal noise. It is shown that the CR can occur at appropriate noise intensity and the position of the \( R_{\text{MAX}} \) of one noise-induced-coherence resonance does not change evidently with the other noise intensity. Most of important, it is found that the INCR can be suppressed by the external noise, while the ENCR can be enhanced by modulating the internal-noise intensity in this calcium oscillations system. Besides a qualitative analysis with a competitive mechanism is given for above result, we also give a further explanation by using the effective deterministic mode and bifurcation analysis.

It is well known that calcium oscillations play a very important role in regulating many cellular processes. Studying the effects of intrinsic and extrinsic noise on intracellular calcium oscillations is significant to reveal the essence of cellular processes. We hope our finding is helpful for studying the interaction of the internal and external noises in the calcium oscillation system when involved in the mechanisms for coherence resonance, although it is not still clear whether biological systems use the above regulatory mechanism to play functional roles in cellular process. It should be pointed out that at the current stage we are not yet clear whether this phenomenon is universal for all the calcium oscillation systems, or if it is system dependent. Actually, we have also performed similar investigations in another calcium oscillation system in hepatocyte proposed by Höfer [37] and similar results have also been obtained, but it is hard to reach a general conclusion from these two examples. However, based on our theoretical studies above, we think that this phenomenon may depend on the bifurcation features of the original and effective deterministic models.

Acknowledgement

This work was supported by the National Natural Science Foundation of China under Grant No. 10575041.

References
