ELSEVIER

Biophysical Chemistry 129 (2007) 23–28

Biophysical Chemistry

http://www.elsevier.com/locate/biophyschem

Coupling and internal noise sustain synchronized oscillation in calcium system

Qianshu Li [a,b,*], Ying Wang [a]

[a] The Institute for Chemical Physics, Beijing Institute of Technology, Beijing, 100081, PR China
[b] School of Chemistry and Environment, South China Normal University, Guangzhou, 510006, PR China

Received 9 February 2007; received in revised form 1 May 2007; accepted 1 May 2007
Available online 8 May 2007

Abstract

In this work, the effects of coupling on two calcium subsystems were investigated, the cooperation between coupling and internal noise was also considered. When two non-identical subsystems are in steady state, coupling can induce oscillations, and distinctly enlarge the oscillatory region in bifurcation diagram. Besides, coupling can make the two non-identical oscillators synchronized. With the increment of the coupling strength, the cross-correlation time of the two oscillators firstly increases and then decreases to be constant, showing the synchronization without tuning coupling strength. When internal noise is considered, similar phenomena can also be obtained under the cooperation between coupling and internal noise.

Keywords: Synchronization; Chemical Langevin method; Coupling strength; Internal noise

1. Introduction

A variety of important biological functions are controlled by oscillatory behavior of intracellular calcium [1,2]. The mechanism of an oscillatory Ca^{2+} signal makes cells control and distinguish different Ca^{2+}-regulated intracellular events, and the temporal increase in Ca^{2+} also enables cells to avoid the cytotoxic effects that prolonged increases of the intracellular Ca^{2+} concentration otherwise would exert on cells [3].

It has been shown recently that many types of different signals could be transmitted from cell to cell by oscillation rather than by stationary states in calcium system [4]. Ca^{2+} waves can be propagated in hepatocyte multiplets [5,6], and when stimulated by hormone, coupled hepatocytes can oscillate with the same period, or nearly the same period [7,8]. Such phenomenon of Ca^{2+} entrainment has also been observed in other cell types, such as tracheal ciliated cells [9,10], pancreatic acinar cells [11], and in the blowfly salivary gland [12]. Ca^{2+} signals can spread between cells through two pathways: (a) gap junctions [13–15] and (b) paracrine signaling [16,17]. Individual hepatocytes have very different intrinsic frequencies but become phase-locked when coupled by gap junctions [18]. However, to the best of our knowledge, most of the previous works cared more about wave propagation or synchronization on coupled subsystems when more than one subsystem are in the oscillatory state, so it's necessary to consider the situation when all the coupled subsystems are at quiescence.

The role of internal noise in biological systems has also drawn great interests in recent years: excitability increased by channel noise [19], the emergence of frequency and phase synchronization induced by conductance noise in populations of weakly coupled neurons [20].When internal noise is considered, stochastic calcium oscillations appear in a parameter region where the deterministic model only yields steady state [21]. The influence of internal noise originates from the fluctuations inside the system on coupled calcium subsystems has been investigated [22,23], with one of the subsystems in oscillation state. However, relatively little work has been carried out so far on the influence of internal noise on coupled calcium subsystems when all the subsystems are in steady states.

* Corresponding author. The Institute for Chemical Physics, Beijing Institute of Technology, Beijing, 100081, PR China. Tel./fax: +86 10 6891 2665.
E-mail address: qsli@bit.edu.cn (Q. Li).

0301-4622/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.bpc.2007.05.001

In the present work, the effects of coupling and internal noise are investigated on two calcium subsystems, with both of them initially lying in the steady state region. Firstly, we coupled two calcium subsystems by using the deterministic model [24], and found that the oscillatory region in bifurcation diagram was enlarged greatly. Furthermore, synchronized oscillations was induced between the two oscillators, and the synchronization without tuning coupling strength occurs. Secondly, the internal noise was taken into account by using Chemical Langevin model. Interestingly, it is shown that the oscillatory region in bifurcation diagram was further increased as a result of the cooperation of internal noise and coupling.

2. Model description

The minimal model discussed in this work, proposed by Dupont et al. [24], is for a gap-junction-dependent mode of intercellular communication. The intercellular communication includes two aspects, the intracellular Ca^{2+} dynamics and the coupling between Ca^{2+} subsystems. A coupled system of the minimal model is considered here and it can be described by the following equations:

$$\begin{aligned}\frac{dz_i}{dt} &= v_0 + v_1\beta_1 - v_2 + v_3 + k_f y_i - kz_i + \gamma(z_j - z_i),\\ \frac{dy_i}{dt} &= v_2 - v_3 - k_f y_i,\end{aligned} \tag{1}$$

where

$$v_2 = V_{M2}\frac{z^n}{K_2^n + z^n}, \quad v_3 = V_{M3}\frac{y^m}{K_R^m + y^m}\cdot\frac{z^p}{K_A^p + z^p}. \tag{2}$$

The index pairs $i, j = 1, 2$ and $2, 1$. γ is the coupling strength and is proportional to the gap junctional permeability. z and y denote the concentration of free Ca^{2+} in the cytosol and in the IP_3-insensitive pool, respectively; v_0 refers to the influx of Ca^{2+} from the extracellular medium; $v_1\beta$ modulates the release of Ca^{2+} from an IP_3-sensitive store into the cytosol. Especially, β measures the saturation of the receptor and is selected as the control parameter, which rises with the level of the stimulus and varies from 0 to 1. More details of the model can be seen in Ref. [24]. The parameter values are: $v_0 = 1\ \mu M\cdot s^{-1}$, $k = 6\ s^{-1}$, $k_f = 1\ s^{-1}$, $v_1 = 7.3\ \mu M\cdot s^{-1}$, $V_{M2} = 65\ \mu M\cdot s^{-1}$, $V_{M3} = 500\ \mu M\cdot s^{-1}$, $K_2 = 1\ \mu M$, $K_R = 2\ \mu M$, $K_A = 0.9\ \mu M$, $m = n = 2$, and $p = 4$.

A deterministic model can only describe the averaged behavior of a system based on large populations. However, due to the finiteness of system size of a cell, the deterministic model cannot account for fluctuations of the behavior in a cell. Stochastic models have been developed based on detailed knowledge of biochemical reactions, molecular numbers, and kinetic rates [25]. Internal noise resulted from the small volume of the system is considered in these stochastic models. The reaction system in this work can be described by a chemical master equation [26], but it's difficult to solve the equation analytically. The chemical Langevin (CL) method [27] has proved to be an efficient simulation algorithm [21,28,29], here the CL equation for the current model reads [21]

Table 1
Stochastic transition processes and corresponding rates [21]

Transition processes	Description	Transition rates
(1) $Z\to Z+1$	A constant input of Ca^{2+} from the extracellular medium to the cytosol	$a_1 = \Omega v_0$
(2) $Z\to Z+1$	Transport of a Ca^{2+} flow from an IP_3-sensitive store (A) into the cytosol	$a_2 = \Omega v_1\beta$
(3) $Z\to Z-1$ $Y\to Y+1$	The pump of Ca^{2+} from the cytosol into the IP_3-sensitive store	$a_3 = \Omega v_2 = \Omega V_{M2} z^n/K_2^n + z^n$
(4) $Z\to Z+1$ $Y\to Y-1$	The release of Ca^{2+} from the IP_3-sensitive store into the cytosol in a process activated by cytosolic Ca^{2+}	$a_4 = \Omega v_3 = \Omega V_{M3} y^m/K_R^m + y^m z^p/K_A^p + z^p$
(5) $Z\to Z+1$ $Y\to Y-1$	Leaky transport of Ca^{2+} from the IP_3-sensitive pool to the cytosol	$a_5 = \Omega k_f y$
(6) $Z\to Z-1$	Transport of cytosolic Ca^{2+} into the extracellular medium	$a_6 = \Omega k z$

$$\begin{aligned}\frac{dz_i}{dt} &= (a_1 + a_2 - a_3 + a_4 + a_5 - a_6) + \frac{1}{\sqrt{\Omega}}\\ &\quad\Big(\sqrt{a_1}\xi_1(t) + \sqrt{a_2}\xi_2(t) - \sqrt{a_3}\xi_3(t) + \sqrt{a_4}\xi_4(t)\\ &\quad + \sqrt{a_5}\xi_5(t) - \sqrt{a_6}\xi_6(t)\Big) + \gamma(z_j - z_i),\\ \frac{dy_i}{dt} &= (a_3 - a_4 - a_5) + \frac{1}{\sqrt{\Omega}}\\ &\quad\Big(\sqrt{a_3}\xi_3(t) - \sqrt{a_4}\xi_4(t) - \sqrt{a_5}\xi_5(t)\Big),\end{aligned} \tag{3}$$

where $\xi_{i=1,\ldots,6}(t)$ are Gaussian white noises with $\langle\xi_i(t)\rangle = 0$ and $\langle\xi_i(t)\xi_j(t')\rangle = \delta_{ij}\delta(t-t')$; Ω is the total cell volume; $z = \frac{Z}{\Omega}, y = \frac{Y}{\Omega}$, Z and Y are the numbers of Ca^{2+} in the cytosol and IP_3-insensitive pool. The additional terms describe internal noise. The meanings of $a_1,\cdots,a_6$ can be seen in Table 1, and the strength of the internal noise terms is scaled as $1/\sqrt{\Omega}$. From the form of CL equation described above, one can easily see that the internal noise is related to the system size. In addition, for identical, symmetrically coupled subsystems, we consider the same level of internal noise.

3. Results and discussion

To probe the influences of coupling and internal noise, it is necessary to investigate the deterministic dynamical behavior of a single system by solving Eq. (1) at $\gamma = 0$. Numerical calculation is performed with the forward Euler method and lasts 5000 s with a time step of 0.001 s. The maximum and minimum values of z are shown in Fig. 1 (dashed lines). With the variation of the control parameter β, the calcium system undergoes two Hopf bifurcation points at $\beta = 0.105$ (left bifurcation point (LBP)) and $\beta = 0.438$ (right bifurcation point (RBP)), respectively. The parameter space is divided into three regions: the low steady state (LSS) region (with lower concentration of calcium), the oscillation state (OS) region, and the high steady state (HSS) region (with higher concentration of calcium).