Biophysical Chemistry 142 (2009) 40–45

Contents lists available at ScienceDirect

Biophysical Chemistry

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

Explicit calcium bursting stochastic resonance

Ying Wang [a,*], Qianshu Li [b], Ji Luo [c]

[a] School of Chemistry and Pharmaceutical Engineering, Sichuan University of Science and Engineering, Sichuan, 643000, China
[b] Center for Computational Quantum Chemistry, South China Normal University, Guangzhou, 510006, China
[c] Sichuan University of Science and Engineering, Sichuan, 643000, China

ARTICLE INFO

Article history:
Received 7 October 2008
Received in revised form 27 January 2009
Accepted 2 March 2009
Available online 12 March 2009

Keywords:
Chemical Langevin method
Explicit stochastic resonance
Internal noise

ABSTRACT

In the present work the influence of internal noise resulting from small cell volume on bursting calcium oscillations is studied. With the internal noise switched on, the center of the main peak in the PSD (power spectrum density) was modified by internal noise. With increasing of the cell volume, the calculated signal-to-noise ratio (SNR) undergoes a maximum, which is referred in the present work as explicit bursting stochastic resonance. In addition, another quantity, the correlation time is used to measure the coherence of bursting oscillations. We demonstrate that the correlation time of the oscillations also exhibits a maximum at a certain cell volume.

1. Introduction

Bursting activity, which consists of alternating active and silent phases of spiking and quiescence, is a multi-time-scale phenomenon. Since it was firstly reported for the electrical activity of the neuron R15 [1,2], bursting activity has been studied experimentally [3–5] and theoretically [6–10] in the last three decades. For example, bursting has been observed in thalamic neurons [4], AB neurons [5], dopaminergic neurons [6], cerebellar Purkinje cells [11], and pancreatic β-cells [3,12]. Recently, bursting oscillations for intracellular Ca^{2+} signaling has attracted considerable attention. A significant part of signal transduction and controlling the complex behavior of biological systems is performed by the oscillatory changing of free cytosolic calcium concentration in excitable as well as in non-excitable cells [13]. These oscillations regulate many cellular processes ranging from egg fertilization to cell death [14]. Bursting oscillations of free cytosolic calcium have been found experimentally in many types of cells [15–17]. It has been shown that calcium bursting is more effective in maintaining glucose homeostasis than spikes [18,19], which suggests bursting being more helpful for insulin secretion [20].

Internal signal stochastic resonance (ISSR), i.e. noise-induced internal signal amplification [21,22] has been the topic of many investigations in the past both for its inherent interest and for its broad range of applications. With the development of SR studies, another type of ISSR, explicit internal signal stochastic resonance (EISSR) has been reported, where noise is directly added to an oscillatory state which is the intrinsic simple periodic signal of the system [23–26]. While most of the prior work only accounts for experimental external noise, the research attention has been gradually shifted to internal noise stochastic resonance (INSR). Internal noise resulting from the finite system size could induce stochastic oscillations, which show the best performance at a certain system size. However, seemingly little attention has been paid on the intrinsic noise amplification of the complex internal bursting signal.

In the present work, the reduced Kummer model [27] is used to get insight into the influence of internal noise on calcium bursting behavior. An internal noise-induced coherent motion was observed: with the increment of intrinsic noise level the evaluated signal-to-noise ratio (SNR) firstly increases and decreases slightly and then flattens out. The correlation time was also used to measure the coherence of bursting oscillations and the same results were obtained. Similar profiles of SNR and the correlation time demonstrated the occurrence of explicit bursting stochastic resonance.

2. Model description

The reduced Kummer model [27] describing the intracellular calcium oscillations in hepatocytes is used in this research. It is a core model and does not include all the processes that occur in calcium signal transduction but captures the fundamental dynamical characteristics of the complete model [28]. After the binding of an agonist to the extracellular side of a membrane-bound receptor molecule, the G_α subunit at the intracellular side of the receptor-coupled G-protein is activated. The activated G-protein in turn stimulates a phospholipase C (PLC), which leads to the production of IP_3, which diffuses through the cell and binds to receptors at the endoplasmic reticulum. This leads to the liberation of calcium from endoplasmic reticulum and in some cases to the inflow of calcium from extracellular space [28]. The concentration of IP_3 is not considered here as a separate

* Corresponding author. Tel.: +86 813 5594717.
E-mail address: ccbsmm@sina.com (Y. Wang).

0301-4622/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bpc.2009.03.002

variable. For simplicity, IP_3 is assumed to be in a quasistationary state. The reduced model of a single cell is presented as

$$\begin{aligned}\frac{dx}{dt} &= k_1 + k_2 x - \frac{k_3 xy}{x + K_4} - \frac{k_5 xz}{x + K_6},\\ \frac{dy}{dt} &= k_7 x - \frac{k_8 y}{y + K_9},\\ \frac{dz}{dt} &= k_{10} x - \frac{k_{11} z}{z + K_{12}},\end{aligned} \tag{1}$$

where x denotes the concentration of active G_α subunits of the G-protein, y refers to the concentration of active PLC, and z is the concentration of free calcium in the cytosol. More details of the model can be seen in Ref. [27]. Parameter values used here are: $k_1 = 0.212, k_3 = 1.52, K_4 = 0.19$, $k_5 = 4.88$, $K_6 = 1.18$, $k_7 = 1.24$, $k_8 = 32.24$, $K_9 = 29.09$, $k_{10} = 13.58$, $k_{11} = 153.0$, $K_{12} = 0.16$. Herein, k_2 is the concentration of agonist and is selected here as the control parameter.

For a typical living cell, such a deterministic description is not strictly valid due to the existence of considerable internal noise. Generally, one can describe the reaction system as a birth–death stochastic process governed by a chemical master equation [29], which describes the time evolution of the probability of a given number of molecules of reaction species. Although there is no procedure to solve this master equation analytically, it provides the starting point for numerical simulations. The exact stochastic simulation (ESS), introduced by Gillespie [30], implements such a master equation approach to stochastic chemical dynamics, which has been used as the stochastic method to describe the core model [27]. The ESS stochastically determines the reaction that takes place according to the probability of each reaction as well as the time interval to the next reaction. The numbers of molecules of different reacting species as well as the probabilities are updated at each time step. According to the ESS method, the number of active G_α units is introduced as X, the number of active PLC as Y, and the number of calcium ions in the cytosol as Z, such that the concentration of the reactants are $x = \frac{X}{LV}$, $y = \frac{Y}{LV}$ and $z = \frac{Z}{LV}$, where L is the Avogadro's number, V is the total cell volume, which is sometimes referred to as the system size and used to control the number of molecules present in the system, as described in Ref. [31]. The ESS method exactly accounts for the stochastic nature of the reaction events and has been widely used to study the properties and effects of internal noise in a variety of systems, but it is very time consuming and hardly applicable if the system size is large. In addition, it cannot afford us a clear perspective on the origin and magnitude of the internal noise in the system. Provided two dynamical conditions are satisfied, the microphysical premise from which the chemical master equation is derived leads directly to an approximate time-evolution equation of Langevin type. Condition (i): requires the time step dt to be small enough that the change in the state during $[t, t+dt]$ will be so slight that none of the propensity functions changes its value appreciably. Condition (ii): requires dt to be large enough that the expected number of occurrences of each reaction channel in $[t, t+dt]$ be much larger than one. The chemical Langevin (CL) method [32] has proven to be an efficient simulation algorithm [33–35] to account for internal noise. From the form of CLE, one can clearly find how the internal noise involved in the chemical reactions is related to the parameter values, the system size and the state variables that evolve with time. Here, the CL equations for the Kummer model can be described as

$$\begin{aligned}\frac{dX}{dt} &= (a_1 + a_2 - a_3 - a_4) + (\sqrt{a_1}\xi_1 + \sqrt{a_2}\xi_2 - \sqrt{a_3}\xi_3 - \sqrt{a_4}\xi_4),\\ \frac{dY}{dt} &= (a_5 - a_6) + (\sqrt{a_5}\xi_5 - \sqrt{a_6}\xi_6),\\ \frac{dZ}{dt} &= (a_7 - a_8) + (\sqrt{a_7}\xi_7 - \sqrt{a_8}\xi_8)\end{aligned} \tag{2}$$

where

$$a_1 = k_1 \cdot V,\ a_2 = k_2 x \cdot V,\ a_3 = \frac{k_3 xy}{x + K_4} \cdot V,\ a_4 = \frac{k_5 xz}{x + K_6} \cdot V,\ a_5 = k_7 x \cdot V,$$
$$a_6 = \frac{k_8 y}{y + K_9} \cdot V,\ a_7 = k_{10} x \cdot V,\ a_8 = \frac{k_{11} z}{z + K_{12}} \cdot V$$

$a_1 \cdots a_8$ are the transition rates of each reaction channel, as described in Table 1, where several reaction progresses have been eliminated according to the core model. $\xi_{i=1,\ldots,8}(t)$ are Gaussian white noises with $\langle \xi_i(t) \rangle = 0$ and $\langle \xi_i(t)\xi_j(t') \rangle = \delta_{ij}\delta(t-t')$. The additional terms compared to Eq. (1) describe internal noise, which is related to the cell volume V. Thereby V governs the amplitude of internal noise.

According to the relationship between the concentration and the molecule number, the corresponding macroscopic differential equations for the CL equations read

$$\begin{aligned}\frac{dx}{dt} &= \frac{1}{V}[(a_1 + a_2 - a_3 - a_4) + (\sqrt{a_1}\xi_1 + \sqrt{a_2}\xi_2 - \sqrt{a_3}\xi_3 - \sqrt{a_4}\xi_4)],\\ \frac{dy}{dt} &= \frac{1}{V}[(a_5 - a_6) + (\sqrt{a_5}\xi_5 - \sqrt{a_6}\xi_6)],\\ \frac{dz}{dt} &= \frac{1}{V}[(a_7 - a_8) + (\sqrt{a_7}\xi_7 - \sqrt{a_8}\xi_8)]\end{aligned} \tag{3}$$

From the form of Eq. (3) it can be found that the level of internal noise in the studied system is proportional to $1/\sqrt{V}$. If $V \to \infty$, Eq. (3) equal to the deterministic Eq. (1).

Table 1
Stochastic transition processes and corresponding rates.

Transition processes	Description	Transition rates
(1) $X \to X+1$	The spontaneous activation of G_α units	$a_1 = V \cdot k_1$
(2) $X \to X+1$	The accelerated formation of active G_α after binding of agonist to the membrane receptor	$a_2 = V \cdot k_2 x$
(3) $X \to X-1$	The inactivation of G_α units accelerated by active PLC	$a_3 = V \cdot \frac{k_3 xy}{x + K_4}$
(4) $X \to X-1$	Negative feedback of calcium-dependent kinase on G_α units	$a_4 = V \cdot \frac{k_5 xy}{x + K_6}$
(5) $Y \to Y+1$	The activation of PLC depends on the concentration of active G_α units	$a_5 = V \cdot k_7 x$
(6) $Y \to Y-1$	The enzymatic inactivation of PLC	$a_6 = V \cdot \frac{k_8 y}{y + K_9}$
(7) $Z \to Z+1$	The influx of calcium from the extracellular Space	$a_7 = V \cdot k_{10} x$
(8) $Z \to Z-1$	ATP-dependent ion pumps pump Ca^{2+} of cytosol back into the ER	$a_8 = V \cdot \frac{k_{11} z}{z + K_{12}}$

3. Results and discussion

With the variation of the control parameter k_2, the model is able to display spike and burst behaviors as appear in real cells [27]. We are primarily interested in the periodic bursting dynamics, and the control parameter k_2 is thus adjusted to 2.85. Most of the concepts about bursting oscillations come from neuron dynamics where bursting is an action potential one. In the present work, bursting is one mode of calcium oscillations, which is resulted from extracellular stimulation with such agonists as ATP and UTP in hepatocytes [27]. In order to elucidate the influence of internal noise, it is necessary to study the corresponding deterministic kinetics for comparison. Eq. (1) is integrated by using the explicit Euler method with a time step 0.0002 s, and the resulted time courses reported in Fig. 1a show the periodic bursting dynamics, where each main spike is followed by a series of secondary oscillations. The power spectrum density (PSD) in Fig. 1b shows the counterparts of the spikes in time courses. As can be readily observed there is one large peak and several low peaks at distinctively different frequencies. The bursting oscillations are consist of short trains of rapid spike oscillations intercalated by quiescent intervals, and they repeat periodically. Therefore Fig. 1b displays a