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Effects of noise on the off rate of Ca^{2+} binding proteins in a coupled biochemical cell system

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Abstract

We investigated numerically the kinetic properties of calcium binding proteins by using a three-calcium store model and discussed the response of a two-way coupled biochemical cell system, whose subsystems were coupled via diffusion-like cytosolic calcium transfer through gap junctions, to the external stimulation. When we used noise to modulate the off rate of the Ca^{2+} binding proteins in simulation, an SR-like phenomenon of synchronous oscillations is observed. In addition, the interaction involving noise, coupling and the dynamics of Ca^{2+} binding proteins is discussed.

Keywords: Synchronization; Ca^{2+} binding proteins; Coupling; Off rate

1. Introduction

Calcium ions are considered to be one of the most important secondary messengers in the cytosol of majority of living cells [1]. Cytosolic calcium oscillations play a vital role as a communication mechanism between distinct parts of the cell or between different adjacent cells in the tissue. Since the 1980s, after self-sustained calcium oscillations were found experimentally [2], many further experimental and theoretical studies have been carried out to explain the mechanism of Ca^{2+} oscillation and waves [3,4]. Recently, it has been shown that in a large number of cell types, in the presence of external stimulation, calcium signals are highly organized in time and space [5–8]. Bertuzzi et al. explored the rhythmic changes in the cytosolic Ca^{2+} concentration occurring in response to stimulatory glucose concentration and found Ca^{2+} signal propagation synchronously within islet cells [9,10]. Hinman et al. reported that injury would initiate calcium signals in nearby survivors [11]. Intercellular Ca^{2+} signal communication can be propagated by mechanical stimulation via ATP release and purinergic receptor activation [12].

At a sub-cellular level, it is widely agreed that the endoplasmic reticulum (ER) represents the main calcium store and plays the predominant role in generating sustained calcium oscillations in the

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cell [13]. The roles of the store Ca-ATPases in regulating both the upstroke and downstroke of a Ca^{2+} spike has also been investigated by Morgan et al.; they demonstrated experimentally that the smooth endoplasmic reticulum Ca^{2+} plays a powerful and dynamic role in regulating Ca^{2+} oscillations in human umbilical vein endothelial cells [14]. Falcke and Hudson [15] showed that mitochondrial Ca^{2+} efflux can be adjusted by prolonging the recovery time of IP_3Rs from a refractory state, under which conditions the Ca^{2+} dynamics can be controlled. In recent models of Ca^{2+} oscillations and waves, the important role of Ca^{2+} binding proteins has been acknowledged [16–18]. In Marhl et al. [19] and Haberichter et al. [20], the authors presented a more perfect model: a three-store model, and demonstrated that both the mitochondria and the Ca^{2+} binding proteins play important roles in formation of the complex calcium oscillation.

It is well-known that complex bodily rhythms are ubiquitous in living organisms and many bodily activities require the synchronization of cellular activities [21]. These rhythms arise from the interaction between non-linear biological systems and a fluctuating environment [22]. It seems likely that synchronous oscillations often take place in neuronal systems, such as in the central nervous system [23] and in the cat retina [24–26]. However, in our paper, we investigated the dynamics of the calcium binding protein modulated by external stimulation, and found that the synchronization phenomena can also be observed in the other cell chain systems. Our numerical simulation shows that a fluctuation at one end of a cell coupling chain can lead to internal order. This means the synchronous oscillations can be explained by the interaction of the specific Ca kinetics of all three intracellular Ca^{2+} stores, especially the cytosolic Ca^{2+} binding proteins, with the fluctuating environment. It suggests that the dynamics of Ca^{2+} binding proteins in living cells may play an important role in generating and propagating life information.

2. Dynamic model

The model used in our work was presented in detail in Marhl et al. [19]. The main characteristics of this system are three different calcium stores: the ER, mitochondria and calcium binding proteins in the cytosol. The complex calcium oscillations of the free calcium concentration in cytosolic ER and mitochondria can be described by the following equations, respectively:

$$\frac{\mathrm{dCa_{cyt}}}{\mathrm{d}t} = J_{\mathrm{ch}} + J_{\mathrm{leak}} - J_{\mathrm{pump}} + J_{\mathrm{out}} - J_{\mathrm{in}} + k_{-} * \mathrm{CaPr} - k_{+}\mathrm{Ca_{cyt}} * \mathrm{Pr} = f_x \tag{1}$$

$$\frac{\mathrm{dCa_{ER}}}{\mathrm{d}t} = \frac{\beta_{\mathrm{ER}}}{\rho_{\mathrm{ER}}} * (J_{\mathrm{pump}} - J_{\mathrm{ch}} - J_{\mathrm{leak}}) = f_y \tag{2}$$

$$\frac{\mathrm{dCa_m}}{\mathrm{d}t} = \frac{\beta_{\mathrm{m}}}{\rho_{\mathrm{m}}} * (J_{\mathrm{in}} - J_{\mathrm{out}}) = f_z \tag{3}$$

where k_{-} and k_{+}, denote the off and on rate constants of the Ca^{2+} binding, respectively; and constant factors ρ_{ER} and ρ_{m} represent the volume ratio between the ER and the cytosol and between the mitochondria and the cytosol, respectively. The concentrations of free Ca^{2+} in the cytosol, the ER, the mitochondria are denoted by $\mathrm{Ca_{cyt}}$, $\mathrm{Ca_{ER}}$ and $\mathrm{Ca_m}$. The concentration of free (bounded) Ca^{2+} binding site on the cytosolic proteins represented by Pr (CaPr). The Ca^{2+} flux J_{ch}, J_{leak}, J_{pump}, J_{out}, J_{in} are related to the half-saturation constants for calcium and other parameters through the following equations:

$$J_{\mathrm{ch}} = k_{\mathrm{ch}} \frac{\mathrm{Ca_{cyt}^2}}{\mathrm{K_1^2} + \mathrm{Ca_{cyt}^2}} (\mathrm{Ca_{ER}} - \mathrm{Ca_{cyt}}),\ J_{\mathrm{leak}} = k_{\mathrm{leak}} * (\mathrm{Ca_{ER}} - \mathrm{Ca_{cyt}});$$

$$J_{\mathrm{pump}} = k_{\mathrm{pump}} * \mathrm{Ca_{cyt}},\ J_{\mathrm{in}} = k_{\mathrm{in}} \frac{\mathrm{Ca_{cyt}^8}}{\mathrm{K_2^8} + \mathrm{Ca_{cyt}^8}};$$

$$J_{\mathrm{out}} = \left(k_{\mathrm{out}} \frac{\mathrm{Ca_{cyt}^2}}{\mathrm{K_3^2} + \mathrm{Ca_{cyt}^2}} + k_{\mathrm{m}} \right) Ca_{\mathrm{m}} \tag{4}$$

A more detailed description of the dynamics is given in Marhl et al. [19], and the parameters used in this paper can be found in table 1 of Haberichter et al. [20]. In this study, we chose k_{-}, which represents the off rate of the Ca^{2+} binding to the buffering proteins, as an adjustable parameter. The dynamic characteristics of synchronous oscillation in coupled biochemical cell systems have been

studied when the off rate was subjected to noise or external field.

The transfer of calcium ions through gap junctions is known to occur in a large number of cell types [27]. For a linear array of a two-coupled system by passive diffusion-like calcium transfer, we only consider that cytosolic calcium is coupled, and select the zero boundary condition so that the evolution equations are of the form:

$$\frac{dx_i}{dt} = f_x + k_d(x_{i+1} - x_i) \qquad (i=1) \tag{5}$$

$$\frac{dx_i}{dt} = f_x + k_d(x_{i+1} + x_{i-1} - 2*x_i) \quad (i=2,3...N-1) \tag{6}$$

$$\frac{dx_i}{dt} = f_x + k_d(x_{i-1} - x_i) \qquad (i=N) \tag{7}$$

The subscripts i denote the i-th cell, and k_d is a coupling constant. The second terms in Eqs. (5)–(7) denote the cytosolic Ca^{2+} exchange between adjacent cells via diffusion-like transfer from one cell to its nearest neighbors.

In Marhl et al. [19], the authors report that, in the generation of high-frequency calcium oscillation between the main spikes characterizing the bursting oscillations, the Ca binding dynamics of proteins also play a crucial important role. In phase I (in Fig. 3 of Marhl et al. [19]), the Ca^{2+} release from the ER is the dominating process, but in the bursting phase (phase II), a slow release of Ca^{2+} from the mitochondria begins, and then transfers to the cytosolic proteins, so we can see the concentration of CaPr increasing, but at the end of the bursting phase (phase II) the silent phase (III) begins, during which the dissociation of the CaPr complex is the major process. The dissociation rate determines the duration of the silent phase. It is quite natural for us to think about what will happen in the cytosolic calcium oscillation among the coupled cells, when we adjust the duration interval of the silent phase by perturbing the off rate of Ca binding proteins by the external stimulation.

To investigate the effects of noise on the dynamics of CaPr in the coupled system, in the present simulation, we fixed k_d (the only critical coupling is considered to be $k_d = 0.005$; this means that only when k_d is equal to this value can the synchronization be realized by adjusting the noise intensity). Then we perturb the control parameter k_- with Gaussian noise, i.e.:

$$k_- = k_-^0(1 + \beta\zeta(t)) \tag{8}$$

with $\langle\xi(t)\rangle = 0$ and $\langle\zeta(t)\zeta(t')\rangle = \delta(t-t')$. In our simulation, we chose the noise intensity β as an adjustable parameter; the meaning and detailed values of the parameters are shown by Haberichter et al. [20], table l. The simulation was done by using the fourth order Runge–Kutta method with the time step being taken as 0.1 ms and the time series of $x_i(Ca_{cyt})$ were obtained by averaging over 50 runs.

3. Results and discussion

Let us consider that the coupled system is perturbed by noise and only the first cell is subjected to external noise. Fig. 1a shows that subsystems oscillate without noise, owing to the initial conditions being different from each other, and as each sub-system is initially run in an oscillatory state with a distinct cycle, respectively, no synchronous oscillation appears. Fig. 1b,c shows the time series of cytosolic calcium oscillations in each cell. One can see the occurrence of the noise-induced synchronization of oscillations when the noise intensity is appropriate (for example, $\beta = 0.005$). To quantify the spatio-temporal behavior of synchronization in this coupled system, a factor η can be defined as below:

$$\eta = \frac{\sum_{i=1}^{N} t_i}{NT} \times 100\% \tag{9}$$

where N, T represent the number of cells and the total experimental time; t_i denotes the time interval during which i-th cell can oscillate synchronously with the first cell. We fixed $N = 8$, $T = 40$ s, $k_{ch} = 3450$ (in this region, the system is characterized by an occurrence of trirhythmicity, see also Haberichter et al. [20]; the bifurcation diagram is not shown). The factor η vs. various noise levels is plotted in Fig. 3a. For example, with no noise

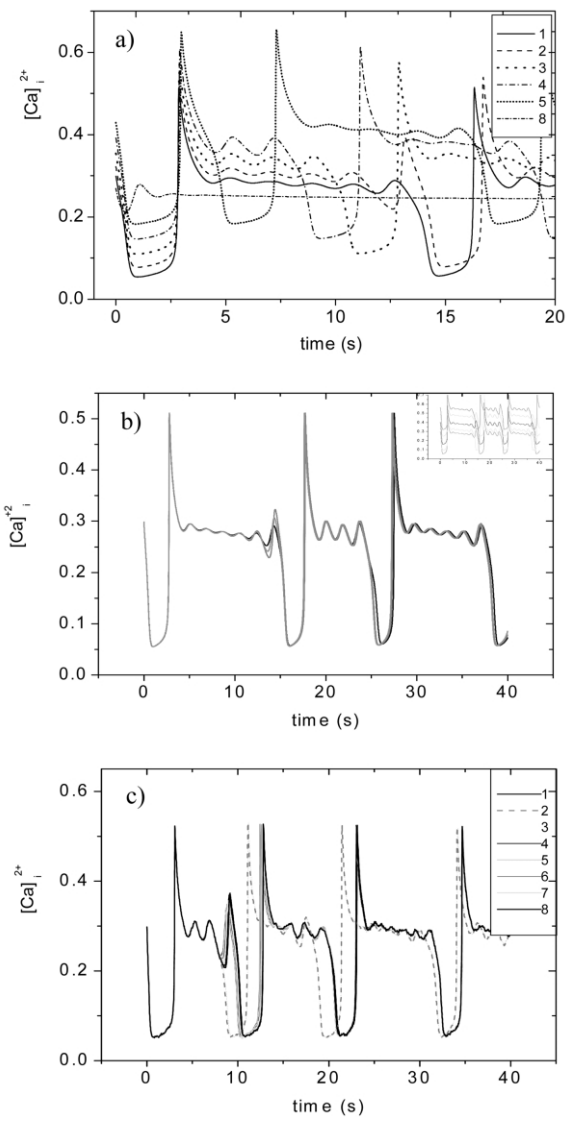

Fig. 1. The plots of calcium oscillation for all sub-systems, $k_d=0.005$, $N=8$. Curves 1,2,…8 correspond to $cell_1$, $cell_2$,….$cell_8$, respectively. (a) No synchronization without noise (cells 6,7 are not shown); (b) synchronous oscillations induced by noise, $\beta=0.005$. Inset: cells are displayed for convenient comparison; and (c) the extent of synchronous oscillations descends, $\beta=0.08$.

present ($\beta=0$), the sub-systems behave like independent systems (Fig. 1a), so $\eta=0$, only when all the other cells oscillate synchronously with the first cell, i.e. $t_1=t_2=\ldots=t_N=T$, $\eta=1$, otherwise $t_i<T$, and $\eta<1$. In Fig. 3a, one can see that with the increment of noise level, the factor moves upward, then goes through a maximum plateau and descends at a higher noise level. This curve indicates the occurrence of the SR. In order to display the synchronous oscillation extent of all cells handily, we use gray scale maps in Fig. 2 to show the cytosolic calcium oscillations for all subsystems. It clearly indicates that the noise effect on the off rate of Ca binding proteins, transferring from the first cell to the following cells, changes with noise intensity β, i.e. when β is, respectively, 0.0 (see also Fig. 1a), 0.001, 0.005 (see also Fig. 1b), and 0.08 (see also Fig. 1c). One can see that the synchronous oscillation extent changed with the noise, and when the noise intensity is appropriate ($\beta=0.005$), all the sub-systems oscillate together.

In fact, the synchronous effect, transferring from the first cell to the following cells, is a cooperative phenomenon involving noise, coupling and the dynamics of calcium binding proteins. We investigated the eighth cell and plotted its time courses of cytosolic calcium for one cycle, i.e. between two basic spokes, vs. various noise intensities. (8 presents the eighth cell and the first cell is plotted for comparison). We know the key link of the synchronization is the effect of noise on the dynamics of Ca^{2+} binding protein. In Fig. 3b, one can see, with the enhancement of noise, the off rate increases and the CaPr will dissociate and Ca^{2+} (binding to the buffering proteins) is released into the cytosol. This leads to the prolonging of the bursting phase (phase II) and shorting of the phase III (see also Marhl et al. [19] Fig. 3a). Resorting to the coupling, these noise effects can propagate along the cell chain to the following cells. For example, we can see this tendency from Fig. 3b. If β is smaller, the effect of noise on the binding proteins cannot be transferred far away from the first cell along the cell chain, but with the increment of noise intensity, the bursting phase of the eighth cell becomes longer at first and then shorter, so the oscillations synchronization can be realized while the noise is appropriate (see the curve in Fig. 3b, $\beta=0.005$).

Another interesting feature is why a plateau exists in the curve in Fig. 3a. This is because the

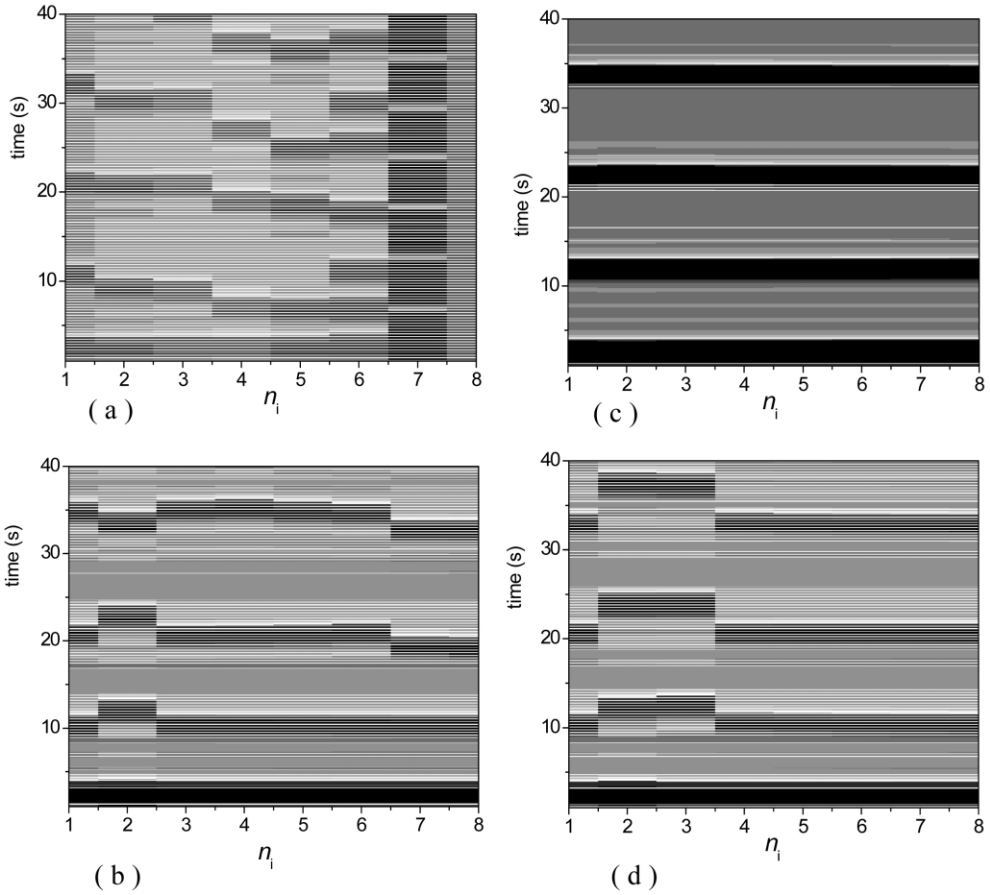

Fig. 2. The gray scale maps of oscillations for all eight subsystems vs. various noise intensities. (a) $\beta = 0.0$, (see also Fig. 1a); (b) $\beta = 0.001$; (c) $\beta = 0.005$, (see also Fig. 1b); and (d) $\beta = 0.08$ (see also Fig. 1c).

off rate constants of the Ca^{2+} binding has a saturation point. When noise increases and makes the k_- value reach saturation point, the CaPr does not dissociate any longer, so in this region the factor η does not increase with noise intensity. However, upon further increase, the noise will stimulate passive effects and put the coupled system into disorder, so that the synchronous factor η falls quickly.

On the other hand, we have investigated the influence of external field on the dynamic of Ca^{2+} binding proteins, and also found the spatio-temporal orders of the whole system induced by the external signal (unpublished).

4. Conclusion

Physiological function is derived from the interactions of cells with each other, and with external inputs, will generate the rhythms essential for life. In general, physiological oscillations can be synchronized to appropriate external or internal stimuli [28–33]. Our numerical results indicate that external stimulation, coupling, and intrinsic properties of the sub-system can cooperate to organize the spatio-temporal order in the coupled biochemical cell systems and to induce synchronization phenomena. This results may be important in living cell systems in which information is transmitted

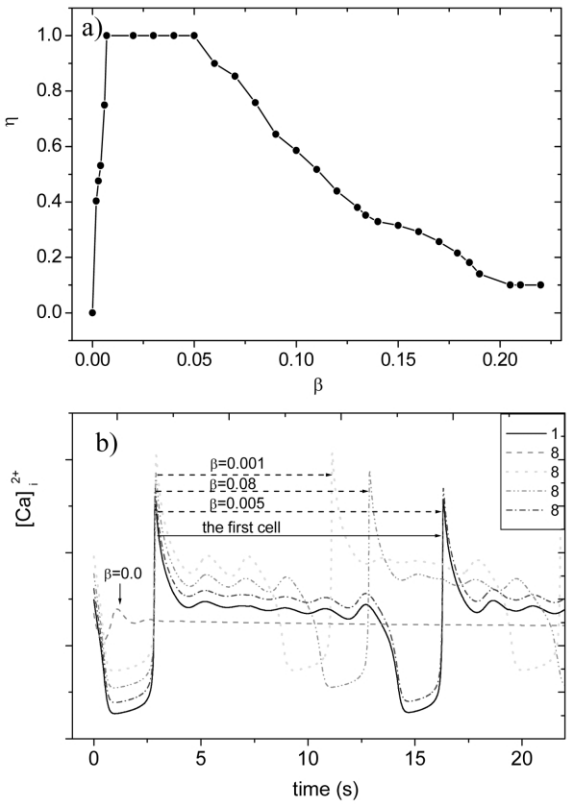

Fig. 3. (a) The factor η as a function of noise intensity β. (b) The oscillation in $Cell_8$ for different noise levels, $\beta = 0.0$, 0.001, 0.005 and 0.08, respectively; $k_d = 0.005$. 8 denotes the eighth cell, the first cell is plotted for comparison.

along a cell chain, i.e. if one end of the cell chain is subjected to a fluctuation, ordered internal signal by coupling which may represent life rhythms or contain special life information can be received. It means that the spatio-temporal order can occur, not only in the nervous system, but also in a large number of other kinds of cell types. In addition, our simulation give another possible way of controlling synchronous effects in the coupled system by modulation of the dynamics of sub-cellular organization, such as the Ca^{2+} buffering proteins. We hope our study can arouse new interest of scientists in associated fields. Further experimental and theoretical work will be helpful to future research.

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