Applied Mathematical Modelling 35 (2011) 2682–2687

Contents lists available at ScienceDirect

Applied Mathematical Modelling

journal homepage: www.elsevier.com/locate/apm

Propagation and enhancement of the noise-induced signal in a coupled cell system

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ARTICLE INFO

Article history:
Received 14 September 2009
Received in revised form 23 November 2010
Accepted 24 November 2010
Available online 5 December 2010

Keywords:
Coupled cell system
Hopf bifurcation
Calcium oscillation
The noise induced signal

ABSTRACT

The response of an array of unidirectional coupled cells to local external noise is investigated. The cells are all tuned near the Hopf bifurcation point for calcium oscillation. It is found that when the first cell of the chain is perturbed by noise, stochastic calcium oscillation can be induced and propagates along the chain with considerable enhancement and a rather regular signal output is obtained at the end of the chain. It indicates that noise can result in the internal order, which is likely to show the rhythm of life in life systems. It is demonstrated that the occurrence of such a phenomenon depends on the coexistence of three factors: being close to the Hopf bifurcation point, unidirectional coupling and optimal coupling strength. It is important to note that this phenomenon is quite different from the noise enhanced signal propagation, where a larger coupling strength is always more favorable. Our result may find important applications in calcium signaling processes in vivo.

1. Introduction

The constructive roles of noise in nonlinear systems, especially stochastic resonance (SR), have gained much attention in the last two decades. Recently, the frontier of this attention has shifted to spatially extended systems, such as spatio-temporal stochastic resonance [1,2], array enhanced stochastic resonance [3], array enhanced coherence resonance [4], noise enhanced signal propagation [5–7], noise enhanced synchronization [8–10], noise sustained wave propagation [11,12], noise enhanced signal detection [13], and so on. Specially, in one dimensional system, an interesting phenomenon is noise-enhanced signal propagation (NESP), where it is found that a regular signal can propagate along a chain of coupled nonlinear dynamic elements via the help of noise. In real systems, however, it often happens that an array of coupled dynamic elements is subjected to external stimulus, which may not be a periodic signal, but a noisy stimulus. So it is significant to study the role of noise in these systems, especially the signaling processes in living systems.

It is well known that intracellular calcium (Ca^{2+}) is one of the most important second messengers in the cytosol of living cells [14,15]. Cytosolic calcium oscillations play a vital role as a communication mechanism between distinct parts of the cell or between adjacent cells in the tissue. Many cellular processes [15–17], like intracellular and extracellular signaling processes, muscle contraction, cell fertilization, cell secretion, cell metabolism, gene expression, and so on, are all controlled by the oscillatory regime of the cytosolic calcium concentration. Many studies have been carried out to show the energetic role of noise for calcium signaling in a single cell, for example, noise-enhanced robustness of intracellular calcium oscillations [18], internal noise-increased sensitivity of calcium response [19], noise-enhanced hormonal signal transduction through intracellular calcium oscillation [20], internal noise enhanced detection of hormonal signal [21] and weak signal

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0307-904X/$ - see front matter
doi:10.1016/j.apm.2010.11.063

[22] through intracellular calcium oscillations, and so on. But in real systems, cells are often coupled together to collectively accomplish some specific functions. So far, some constructive effects of noise in coupled cell systems have been reported, including noise-induced synchronization of calcium oscillation [23], array enhanced coherence resonance [24], internal noise enhanced detection of weak stimulation [13], and so on. Nevertheless, to our knowledge, few studies have been focused on the signaling processes in coupled cell systems.

In the present paper, we have investigated how the coupled cells, which are all tuned near the Hopf bifurcation (HB) point for calcium oscillation, response to local external noise.

2. Model and simulation

The model we used in the present paper is given by the inositol 1,4,5-trisphosphate cross-coupling (ICC) model produced by Meyer and Stryer [25], which describes dynamics of calcium ions in cytosol. The evolution equations are [26]:

$$\begin{aligned}\frac{dx}{dt} &= f_x = -\frac{dy}{dt} = vJ_{channel} - J_{pump},\\ \frac{du}{dt} &= f_u = k_{PLC} - Du,\\ \frac{dv}{dt} &= f_v = F_v(1-v) - E_v x^4 v,\end{aligned} \tag{1}$$

where x, y, u represent the concentration of three key species: the cytosolic Ca^{2+} (Ca_i), the calcium ions sequestered in an intracellular store (Ca_s), and the inositol 1,4,5-trisphosphate (IP_3), respectively; v denotes the fraction of open channels through which the sequestered calcium is released into cytosol; the flux $J_{channel}$ associates with the release of sequestered calcium from an internal store, the flux J_{pump} corresponds to calcium sequestration and k_{PLC} is the rate of IP_3 production, which are given by

$$J_{channel} = \left[\frac{Au^4}{(u+K_1)^4}\right]y, \quad J_{pump} = \frac{Bx^2}{x^2+K_2^2}, \quad k_{PLC} = C\left[1 - \frac{K_3}{(x+K_3)(1+R)}\right]. \tag{2}$$

In Eqs. (1) and (2), D, F_v, E_v, A, B, C, K_1, K_2, and K_3 are constants, the detailed descriptions and values of these parameters can be found in Ref. [26]. We choose R which represents the fraction of activated cell surface receptors as an adjustable parameter and the parameter path contains two Hopf bifurcations at $R = 0.02570$ and $R = 0.58068$. A more detailed description of the dynamics is given by Ref. [26].

Assuming that, only the first cell is disturbed by noise and a diffusion-like passive transport process of cytosolic calcium and IP_3 occurs presumably via gap junctions between the cells. Then the unidirectional coupled ICC system for the simplest linear case can be described by:

$$\begin{aligned}\frac{dx_i}{dt} &= f_{x_i} + k_d(x_{i-1} - x_i),\\ \frac{du_i}{dt} &= f_{u_i} + k_d(u_{i-1} - u_i),\\ \frac{dv_i}{dt} &= f_{v_i},\end{aligned} \tag{3}$$

where k_d is the coupling constant, $i = 1, 2, \ldots, N$ and N is the number of coupled cells. Zero boundary condition is selected, that is:

$$x_0 = x_1, \quad u_0 = u_1, \quad x_N = x_{N+1} \quad u_N = u_{N+1}.$$

Although we do not find that the cell system must be based on the unidirectional coupling in researches, many studies [27–29] have taken into account this coupling way for the coupled life system. So, we also assume the unidirectional coupling way in our following study.

3. Results and discussion

We keep all the control parameters R_i to be the same value $R_0 = 0.600$, which is slightly above the right Hopf bifurcation (HB) value so that all the cells are at a stable state in the absence of noise. And then we assume the first cell is perturbed by an external noise, i.e., $R_1 = R_0[1 + \beta\xi(t)]$ where $\xi(t)$ is the Gaussian white noise with zero mean value $\langle\xi(t)\rangle = 0$ and unit variance $\langle\xi(t)\xi(t')\rangle = \delta(t-t')$; β denotes the noise intensity. All the other cells have the same parameter $R_i = R_0 (i = 2, 3, \ldots, N)$. Since the behavior of the first cell is not affected by the coupling, one would expect to find noise induced oscillation (NIO) and internal signal stochastic resonance (ISSR). Indeed, we can observe the phenomenon of noise induced calcium oscillation. We use an effective signal-to-noise ratio (SNR) to measure the relative performance of the NIO, see Ref. [30] for the more detailed description of the calculation of SNR. Then one can see the existence of a maximum SNR of the NIO with the variation of the noise intensity β, indicating the occurrence of ISSR, shown in Fig. 1(a).

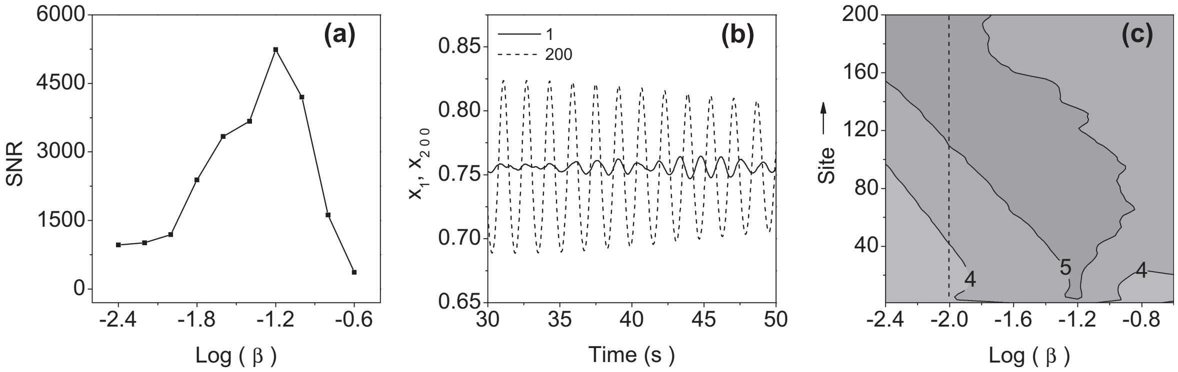

Fig. 1. (a) The effective SNR as a function of noise intensity β in a single cell; (b) the time series for site 1 and site 200. Parameters are $k_d = 4.0$ and $\beta = 0.01$ and (c) contour plot of SNR (in logarithmic scale) for different site and noise intensity. The coupling strength is $k_d = 4.0$.

When we investigate the dynamic behavior of the cells one by one, we find that the NIO triggered at the first cell can propagate along the cell chain with considerable enhancement, and at the other end of the chain, a rather regular signal output with large amplitude and clear periodicity can be obtained. The results obtained for $N = 200$, $k_d = 4.0$ and $\beta = 0.01$ are shown in Fig. 1(b) and (c). In Fig. 1(b), the time series of x_1 and x_{200} are shown. The regularity and periodicity of the 200th cell are obviously well than the 1st one. The SNR of x_{200} is much larger than that of x_1, which is shown in Fig. 1(c). Fig. 1(c) fully pictured the contour plot of SNR for different site and noise intensity. The dash line refers to the case of $\beta = 0.01$ used in Fig. 1(b). It can be observed that for small noise intensity β, for example $\log(\beta) = -2.4$, the SNR value increases monotonously along the cell chain and becomes much larger than that of site 1 around $N = 160$. With the increases of the noise intensity, for example $\log(\beta) = -2.0$, the SNR value still increases monotonously and quickly reaches a maximum corresponding to a smaller N (N $\sim$ 110). When the noise intensity increases further, for example $\log(\beta) = -1.2$, although the SNR value reaches a maximum corresponding to a even smaller N (N $\sim$ 10), it will then damps out when the calcium signal has not yet reached the end of the chain. When the noise intensity is very large, for example $\log(\beta) = -0.8$, although the SNR value increases monotonously, the maximal SNR is smaller than that of other smaller noise intensity. That is to say, there exists an optimal noise intensity, for example $\log(\beta) = -2.0$, at which the noise induced calcium signal can propagate along the chain to the end site and with considerable enhancement. In short, previous discussions show the main results of the present paper, that is, when an array of unidirectional coupled cells tuned near the HB point stimulated by external noise only at the first cell, noise induced calcium oscillations triggered at the first cell can propagate along the chain with considerable enhancement and a rather regular signal output can be obtained at the end of the chain.

To check if such a phenomenon depends on the state of the system, we have also studied other cases.

Firstly, if the system is far from the HB point, we find that larger noise intensity is required to make the NIO propagate farther along the chain, and at the same time, the distance of propagation is shortened. Fig. 2 shows the contour plot of SNR for $R_0 = 0.603, 0.605, 0.610, 0.615$ respectively. Comparing with Fig. 1(c), it is obvious that the NIO can propagate more effectively when the system is tuned closer to the HB point.

Secondly, if the cells are bidirectional coupling, the NIO cannot propagate to the end site at all no matter what the noise intensity is, as shown in Fig. 3. When comparing with the results of the unidirectional coupling, we found that the noise-induced propagation is favored with the unidirectional coupling, but not with the bidirectional coupling. As to why, we still cannot confirm before carrying out further research. We think it is probably related to the coupling mechanisms: when the coupling is bidirectional, the two adjacent cells will influence each other; but when the coupling is unidirectional, the cell behind will not influence the front one.

To further understand the phenomenon, we have also studied the influence of coupling strength. The SNR plots for some coupling constants are shown in Fig. 4. It can be seen that the coupling strength also plays an important role in the propagation of the NIO. For small coupling strength, the NIO triggered at the first cell damps monotonously along the chain and cannot reach the end site, as shown in Fig. 4(a), larger noise intensity is favorable for the signal propagation. While for large coupling strength, the SNR undergoes a clear maximum along the chain for some given noise intensity and then damps out before reaching the end site, as shown in Fig. 4(d), smaller noise intensity is better for the signal propagation. For an intermediate coupling strength, e.g., $k_d = 4.0$, the SNR of the NIO increases monotonically along the chain for small and large noise intensity; even though the SNR value undergoes a maximum and then damps out for intermediate noise intensity, the SNR level at the end site is still large, which is shown in Fig. 4(c). Therefore, an optimal coupling strength exists for the propagation and enhancement of the NIO. We should note that this phenomenon of the existence of an optimal coupling strength for the signal propagation and enhancement is quite different from the noise enhanced (external) signal propagation (NESP), where it was demonstrated that a larger coupling strength is always more favorable [7].

It should be pointed out that the coupling strength for calcium coupling and IP_3 coupling via gap junctions is not necessarily the same. In our article, we studied the influence of the same coupling strength and found that there existed an optimal

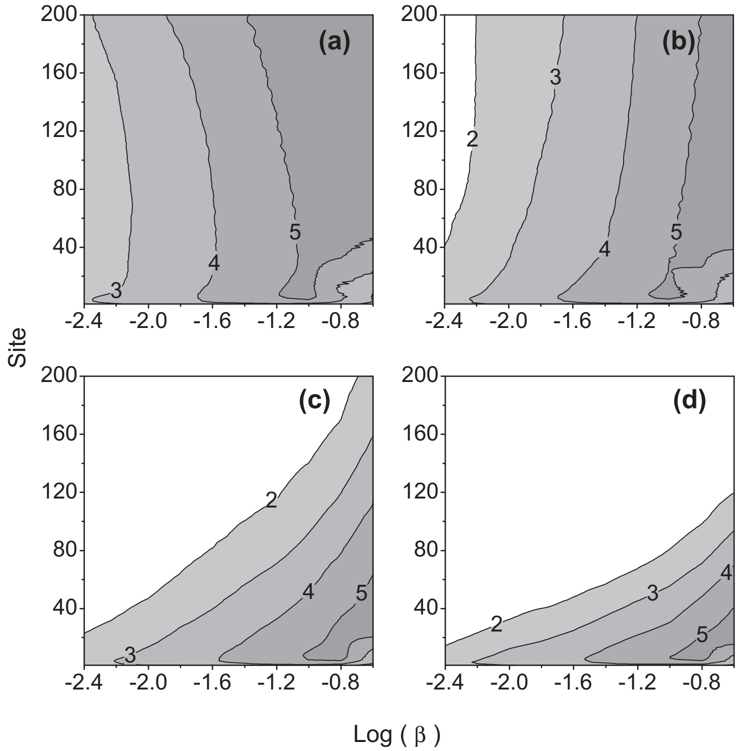

Fig. 2. The contour plot of SNR for (a) $R_0 = 0.603$, (b) $R_0 = 0.605$, (c) $R_0 = 0.610$, (d) $R_0 = 0.615$, respectively with the coupling strength $k_d = 4.0$. The SNR values are all in logarithmic scale.

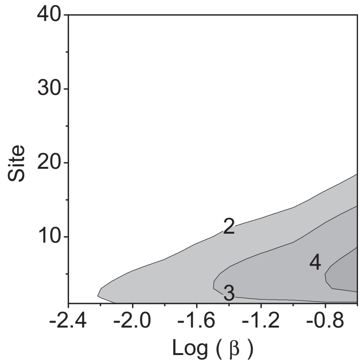

Fig. 3. The contour plot of SNR for bidirectional coupling with the coupling strength $k_d = 4.0$ and control parameter $R_0 = 0.600$. The SNR values are in logarithmic scale.

coupling strength for the propagation and enhancement of the noise induced oscillation. When we consider the different coupling strengths for calcium coupling and IP_3 coupling, we think that similar result can also be found that there will exist a pair of coupling strengths for calcium coupling and IP_3 coupling which is the best benefit for the propagation and enhancement of the calcium oscillation. But in order to find this pair of coupling strengths, a lot of simulation work will be needed. In our study, we studied a simple case of the same coupling strength, only to illustrate the existence of the optimal coupling strength, rather than looking for the optimal values of the coupling strengths, so we think it is sufficient to only study the simple case of the same coupling strength.

4. Summary

In conclusion, we have investigated the response of an array of unidirectional coupled cells, all tuned near the Hopf bifurcation point for calcium oscillation, to local external noise. Stochastic calcium oscillation can be induced and propagates

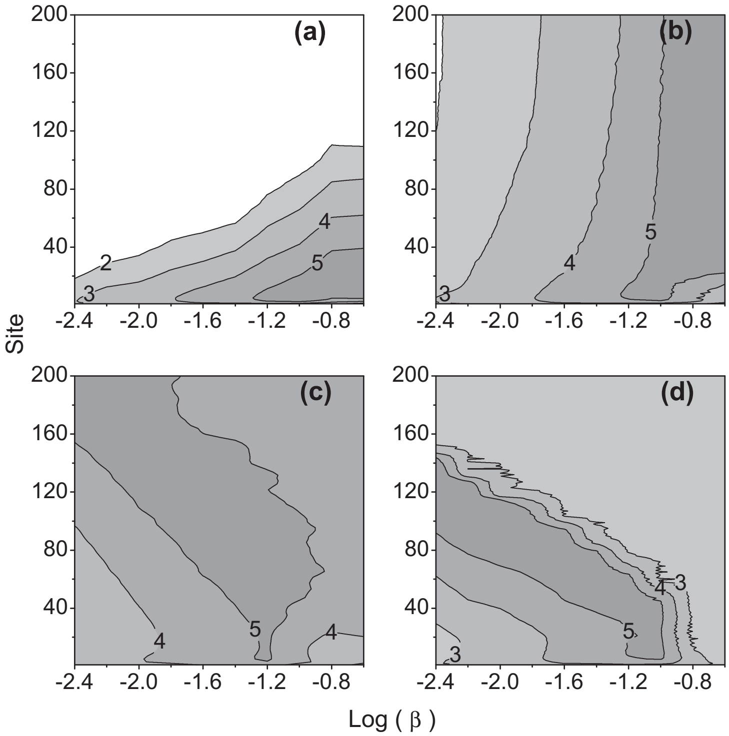

Fig. 4. The contour plot of SNR (in logarithmic scale) for different coupling strength. From (a) to (d), the coupling constant is 2.0, 3.0, 4.0, 6.0, respectively.

along the chain with considerable enhancement and a rather regular signal output is obtained at the end of the chain. It indicates that noise can result in the internal order, which is likely to show the rhythm of life in life systems. We demonstrated that the occurrence of such a phenomenon depended on the coexistence of three factors: being close to the Hopf bifurcation, unidirectional coupling and optimal coupling strength. We know that cells are often coupled together to collectively accomplish some specific functions, environmental fluctuations around life systems are unavoidable, and recent studies have shown that some real systems, especially sensory systems, such as hearing system, often works in the vicinity of the Hopf bifurcation point through a self-tuned mechanism [31,32]. So, our results may find interesting applications in these systems. It could happen that these systems may effectively response to ambient noisy faint sounds with regular electrical signals using the mechanism described in the present paper.

Acknowledgements

This work is supported by the National Science Foundation of China (20673106) and Natural Science Foundation of Higher Education of Anhui Province of China (KJ2009B066Z).

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