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System-Size Induced Coherence Resonance in Coupled Minimal Cytosolic Ca^{2+} Oscillation Models *

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We have investigated the collective behaviour of an array of coupled minimal cytosolic Ca^{2+} oscillation models by numerical methods, taking into account the external noise resulting from the random extracellular stimulation. It is found that the system size, i.e. the number of minimal cytosolic Ca^{2+} oscillation models, has an optimal value, at which the system collective dynamics shows the best performance. The effect of the coupling strength has also been studied. Such a phenomenon of system-size resonance has been found for different coupling strengths, but the optimal system size increases when the coupling strength increases.

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It is well known that intercellular calcium (Ca^{2+}) often acts as a second messenger in the cytosol of living cells. The oscillations of the intracellular Ca^{2+} have been reported in a variety of non-excitable cells,[1] and appear to be important in the control of many cellular processes.[2] For example, Ca^{2+} oscillations increase the efficiency and specificity of gene expression,[3] Ca^{2+} regulates the phosphorylation–dephosphorylation cycle process involved in glycogen degradation,[4] etc. Thus great attention has been paid to the nonlinear dynamics of Ca^{2+} oscillation models,[5,6] especially to the constructive effects of noise in the stochastic Ca^{2+} oscillation models. A lot of interesting phenomena have been found, such as noise-induced bursting and coherence resonance,[5] which shows that a type of complex oscillation (bursting-like) can occur in the cytosolic Ca^{2+} concentration and coherence resonance phenomenon can be produced through the histogram of interspike intervals and the characteristic time of Ca^{2+} concentration when the extracellular stimulation is random. Internal noise stochastic resonance,[6] where stochastic calcium oscillations appear when the internal noise is considered and there is an optimal internal noise intensity at which such oscillations show best performance. In Ref. [6], the internal noise intensity is proportional to $1/\sqrt{\Omega}$, where Ω is the total cell volume, hence this reported phenomenon is in fact a type of system-size resonance (SSR) where the system size (i.e., the total cell volume Ω) plays an constructive role.

Very recently, a new and quite interesting SSR phenomenon has gained much attention.[7,8] For instance, Pikovsky *et al.* showed that in an array of coupled noise-driven bistable systems subjected to an external periodic forcing, an optimal response is obtained when the number of elements in the system has an optimal value.[7] Similar effects have also been reported in Ref. [8]. This effect was explained by reduction to the usual phenomena of stochastic resonance and coherence resonance with effective noise intensity depending on the number of coupled elements, that is to say, the system size (the number of coupled elements) plays a role in changing the effective noise intensity that is subjected to the mean field. In fact, it is a cooperate effect of the noise and the element number, which is an problem of optimization.[9] Motivated by the biological applications suggested in Ref. [7], we expect that this kind of SSR can also be observed in coupled Ca^{2+} oscillation models. Thus in this Letter, we consider the collective dynamic behaviour of an array of coupled minimal calcium models,[10] each subjected to uncorrelated random extracellular stimulations. We show that for an optimal system-size, the number of calcium models, the collective behaviour of the system has a maximal order. The effect of coupling strength has also been investigated.

The model discussed in the present study is based on the minimal model for intracellular calcium oscillations with the mechanism of calcium induced calcium release (CICR).[10] Although there are many different models of intracellular calcium oscillations, this minimal model has been frequently studied even in recent years.[5,6,11] Here, we choose such a minimal model to simply illustrate how the system-size would influence the calcium oscillations. The dynamics of a single minimal cytosolic Ca^{2+} oscillation model can be described by the following equations:[10]

$$\frac{dZ}{dt} = v_0 + v_1\beta - v_2 + v_3 + k_f Y - kZ, \qquad (1)$$

$$\frac{dY}{dt} = v_2 - v_3 - k_f Y, \qquad (2)$$

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with

$$v_2 = V_{M2}\frac{Z^n}{K_2^n + Z^n},$$
$$v_3 = V_{M3}\left(\frac{Y^m}{K_R^m + Y^m}\right)\left(\frac{Z^p}{K_A^p + Z^p}\right). \qquad (3)$$

In these equations, Z and Y denote the concentration of free Ca^{2+} in the cytosol and in the IP3-insensitive pool, respectively; v_0 refers to a constant influx of Ca^{2+} from the extracellular medium; v_1 denotes the IP_3-modulated influx from the IP_3-sensitive store. The rates v_2 and v_3 refer to the pumping of Ca^{2+} into the IP_3-insensitive store and the release of Ca^{2+} from this store into the cytosol in a process activated by cytosolic Ca^{2+}; V_{M2} and V_{M3} denote the maximum values of these rates; k_f is a rate constant measuring the passive linear leak of Y to Z; k relates to the assumed linear transport of cytosolic Ca^{2+} into the extracellular medium. Parameter K_2, K_R and K_A are the threshold constants for pumping, release, and activation; n, m and p denote the Hill coefficients characterizing these processes. Especially, the parameter β measures the saturation of IP_3 receptor and is selected as the control parameter, which rises with the level of the stimulus and varies from 0 to 1. The detailed meanings of these parameters can be found in Ref. [10]. The parameter values employed are as follows: $k_f = 0.7\ \mathrm{min}^{-1}$, $k = 10\ \mathrm{min}^{-1}$, $v_0 = 1\,\mu\mathrm{M min}^{-1}$, $c_1 = 5.7\,\mu\mathrm{M min}^{-1}$, $V_{M2} = 30\,\mu\mathrm{M min}^{-1}$, $V_{M3} = 325\,\mu\mathrm{M min}^{-1}$, $K_2 = 0.5\,\mu\mathrm{M}$, $K_R = 1.7\,\mu\mathrm{M}$, $K_A = 0.46\,\mu\mathrm{M}$, $n = 2$, $m = 2$ and $p = 4$.

With the above parameter values and setting the control parameter $\beta = 0.1$, a low steady-state level of cytosolic Ca^{2+} is established.[5] If considering the effects of random extracellular stimulation, we add additive noise terms $\xi_Z(t)$ and $\xi_Y(t)$ on the right of Eqs. (1) and (2), respectively. Here $\xi_Z(t)$ and $\xi_Y(t)$ is the Gaussian white noise with zero mean, and the correlation function is $\langle \xi_a(t)\xi_b(t')\rangle = 2D\delta_{ab}\delta(t-t')$ $(a, b = Z, Y)$. D denotes the intensity of noise.

Now the dynamics of an array coupled minimal cytosolic Ca^{2+} oscillation models can be described by the following equations:

$$\frac{dZ_i}{dt} = v_0 + v_1\beta - v_{2i} + v_{3i} + k_f Y_i - kZ_i + \varepsilon(Z_{i-1} + Z_{i+1} - 2Z_i) + \xi_{Zi}(t), \qquad (4)$$
$$\frac{dY_i}{dt} = v_{2i} - v_{3i} - k_f Y_i + \xi_{Yi}(t), \qquad (5)$$

where

$$v_{2i} = V_{M2}\frac{Z_i^n}{K_2^n + Z_i^n},$$
$$v_{3i} = V_{M3}\left(\frac{Y_i^m}{K_R^m + Y_i^m}\right)\left(\frac{Z_i^p}{K_A^p + Z_i^p}\right), \qquad (6)$$

with $1 \le i \le N$. Here N is the number of minimal cytosolic Ca^{2+} oscillation models; periodic boundary conditions are used; ε is the coupling strength. To study the collective behaviour of the coupled system, we introduce the average values of Z_i,

$$Z'(t) = \frac{1}{N}\sum_{i=1}^{N} Z_i(t).$$

Numerical integration of Eqs. (4)–(6) is carried out by explicit Euler with a time step 0.001 min. In each calculation, the time evolution of the system lasted 4000 min after transient was discarded.

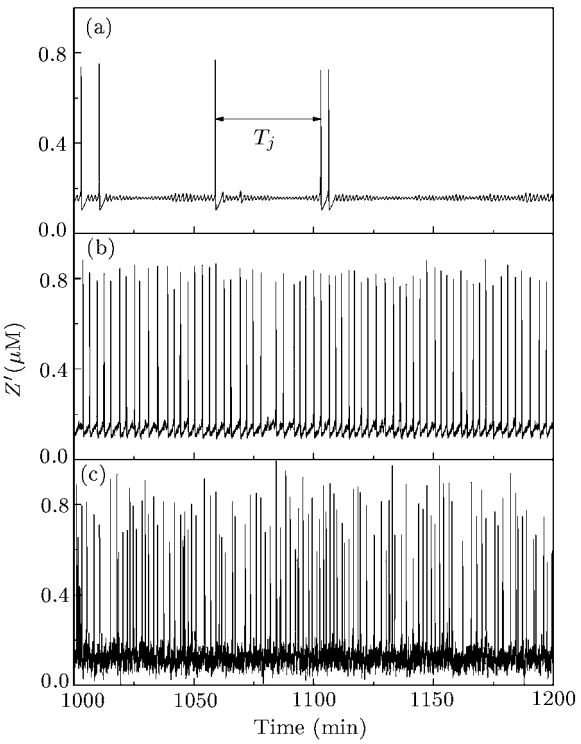

Fig. 1. The spike trains of Z' of a single minimal cytosolic Ca^{2+} oscillation model for different noise strengths: (a) $\log D = -2.82$, (b) $\log D = -1.42$, (c) $\log D = -0.72$.

For a single minimal cytosolic Ca^{2+} oscillation model ($N = 1$), the noise-induced spikes can be observed as shown in Fig. 1. When the noise is weak, the cytosolic calcium concentration only shows small-amplitude oscillations with very few occasional firing spikes, as shown in Fig. 1(a). If the noise intensity is too large, although the spike firing becomes more frequently, the regularity of the spike train is smeared (Fig. 1(c)). Consequently, for intermediate noise intensity, the spike train is more regular (Fig. 1(b)). To characterize the regularity of the spike train, we have calculated R, which is defined as

$$R = \frac{\langle T\rangle}{\sqrt{\langle T^2\rangle - \langle T\rangle^2}}.$$

Here $\langle T\rangle$ and $\langle T^2\rangle$ are the mean and mean-squared interspike intervals, respectively; a spike occurs each

time, and Z' crosses $0.4\,\mu$M. Note that R represents a measure of the spike coherence. The spike train is the more ordered, the larger R is obtained. The dependence of R on the noise intensity for a single model is displayed in Fig. 2. It shows that R goes through a maximum at around $D \approx 0.038$ ($\log D = -1.42$), corresponding to the best regularity of the spike train. This phenomenon has been termed as coherence resonance.

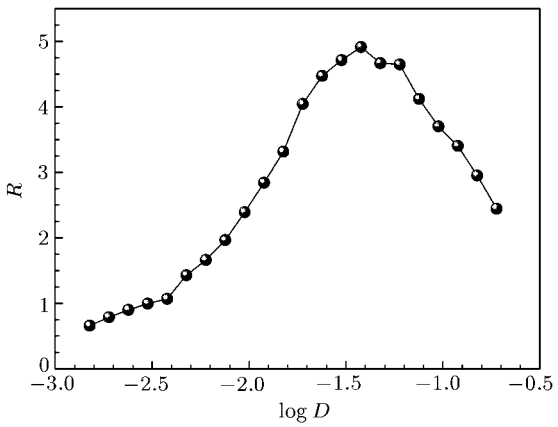

Fig. 2. The spike coherence R versus D of a single minimal cytosolic Ca^{2+} oscillation model. The maximal R shows the coherence resonance.

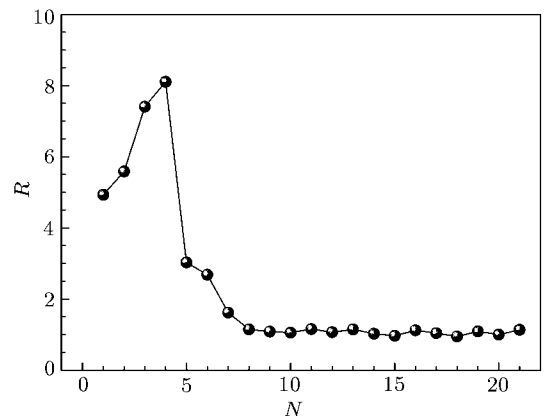

Fig. 3. The spike coherence R versus N for a given noise intensity ($\log D = -1.42$). The maximal R shows the system-size resonance. The coupling strength $\varepsilon = 2.0$.

We now turn to the collective behaviour of $N(>1)$ coupled models. The coupling strength is $\varepsilon = 2.0$ unless specially specified. For a given noise intensity, e.g., $D \approx 0.038$ ($\log D = -1.42$), we find that R goes through a maximum when array size N changes, as depicted in Fig. 3. Therefore, there is an optimal number of elements at which the spike train is most ordered, demonstrating the existence of system-size resonance.

To obtain a global view, we have scanned the system-size N and noise intensity D simultaneously over a relatively wide parameter range, keeping other parameters unchanged. The results are shown in Fig. 4(a). We find a clear "optimal island" inside the $N - D$ parameter plane where the value of R reaches the maximum, indicating that the collective behaviour becomes even better ordered when both the system size and the noise intensity have optimal values. In other words, the optimal number of coupled cells subjected to optimal external noise works the best.

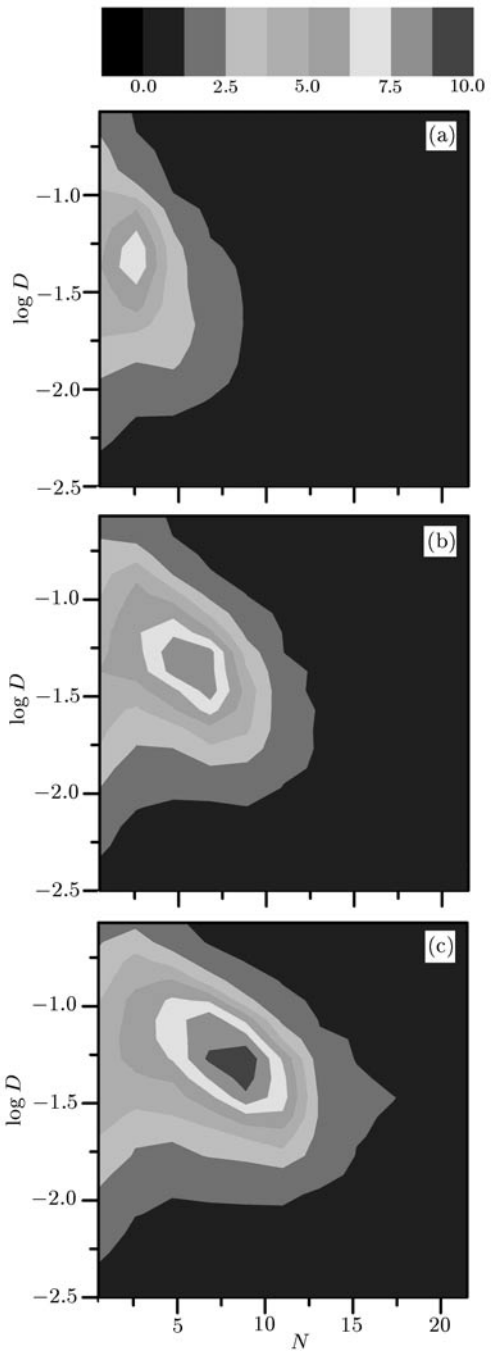

Fig. 4. The contour plot of the spike coherence R as a function of N and D for different coupling strengths: (a) $\varepsilon = 2.0$, (b) $\varepsilon = 4.0$, (c) $\varepsilon = 6.0$.

In real systems, the coupling strength is also an important parameter, and the collective behaviour of the coupled system may strongly depend on the

coupling strength. To further demonstrate this behaviour, we have also investigated the effect of the coupling strength, and the results are also shown in Fig. 4. For Figs. 4(b) and 4(c), the coupling strengths read $\varepsilon = 4.0$ and $\varepsilon = 6.0$, respectively. For different coupling strengths we obtain the similar results, expect that the optimal island position shifts along the direction of the increasing system size N and the coupling strength.

In conclusion, we have studied the collective behaviour dynamics of an array of coupled minimal cytosolic Ca^{2+} oscillation models. The Models are tuned in a regime which is sub-threshold for the deterministic oscillatory dynamics. In such a regime, stochastic calcium oscillations are observed, which are induced by the random extracellular stimulation. The collective response of the system, the average cytosolic calcium oscillations, becomes the most regular when the number of cells N and the noise intensity D has optimal values. Namely, the system size resonance and coherence resonance occur. Our findings may find interesting applications for intercellular calcium signaling processes in vivo.

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