



# Internal noise induced pattern formation and spatial coherence resonance for calcium signals of diffusively coupled cells



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## HIGHLIGHTS

- Effects of internal noise in coupled square-lattice calcium cells are studied in the context of chemical Langevin equation.
- Internal noise can induce coherent spatial patterns and spatial coherence resonance occurs.
- Internal noise does not always promote coherence of the spatial pattern.
- Spatial coherence of the spatial pattern can also be enhanced by the coupling.

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## ABSTRACT

The effects of internal noise in a square-lattice Höfer calcium oscillation system have been studied numerically in the context of chemical Langevin equations. It was found that spatial pattern can be induced by internal noise and, interestingly, an optimal internal noise strength (or optimal cell size) exists which maximizes the spatial coherence of pattern, indicating the occurrence of spatial coherence resonance. The effects of control parameter and coupling strength on system's spatial coherence have also been investigated. We found that larger internal noise strength is needed to induce spatial pattern for a small control parameter or a stronger coupling strength, and spatial coherence can be enhanced by coupling.

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## 1. Introduction

The noise induced nontrivial phenomenon in nonlinear systems has received much attention over the last two decades. Among them, the most famous are stochastic resonance (SR) and coherence resonance (CR) [1–6]. Both SR and CR effects have been demonstrated experimentally in many systems, including excitable chemical reactions, excitable optical system and biological systems [7–12]. Noise has also other positive effects. For example, it can induce (or enhance) synchronization [13–15], and so on.

With the development of SR and CR studies, more and more attention has been paid to SR-like phenomena. For instance, SR and CR in spatially extended systems have been intensively studied [16–30]. The phenomenon of SR or CR in a system of coupled units can be effectively enhanced by coupling, and such a phenomenon is called array-enhanced stochastic resonance [16–18]. It was found that the collective behavior of coupled noisy dynamical elements can be the most ordered by adjusting the elements' number to an optimal value, which is called system-size resonance [19–24]. Spatiotemporal stochastic resonance and spatial coherence resonance (SCR) in a two-dimensional excitable medium have been reported

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in the literature [25–31]. It was shown that there exists an optimal noise level at which noise-sustained rotating spiral waves can appear, which indicates the occurrence of spatiotemporal stochastic resonance [25]. SCR means that noise can induce excitable media to exhibit an optimal intrinsic spatial scale, and SCR has also been studied in many different types of spatially extended systems [26–31]. Carrillo et al. [26] showed that SCR existed in the chlorine dioxide–iodine–malonic acid reaction. SCR in excitable media has been first reported by Perc [27]. They showed that there exists an optimal level of additive noise for which the spatial periodicity of the system is best pronounced [27]. Gosak has shown that cellular diversity could promote intercellular  $\text{Ca}^{2+}$  wave propagation [28] and induce the SCR phenomenon. Most above studies of SCR are focused on a single dynamical element or dynamical elements on regular coupled networks. In recent years, the effects of complex network connectivity on noise induced patterns and SCR in excitable media have been widely studied [32–38], and the emergence of spatiotemporal stochastic resonance and SCR are observed.

The presence of noise is inevitable in all real processes, especially in biochemical reaction systems. Many kinds of noises have been studied, such as Gaussian color noise, dichotomous noise, Gaussian white noise, non-Gaussian noise [39,40] and so on. Usually the noise terms are added to the dynamical equations directly, multiplicatively or additively. These noises are called external noises, whose intensity and correlation time are assumed to be controllable parameters and have no relevance to the system's dynamic features or the system's size. But for chemical reactions in small-scale systems, such as biochemical reaction taking place in living cell or catalytic reactions happening on nano-scale crystal surfaces, another source of noise, the internal noise, must be taken into account. The internal noise is uncontrollable, which depends on the details of the reaction dynamics as well as the system size. Internal noise induced SR-like phenomena have been intensively studied [22,29,41–48]. However, little attention has been paid to the effects of internal noise on SCR. For example, SCR induced by internal noise has been reported in the spatially extended FitzHugh–Nagumo model and a minimal model for calcium dynamics [29,49].

In the present work, the SCR phenomenon induced by the internal noise in diffusively coupled Höfer calcium models has been studied numerically with the chemical Langevin equation method. By scanning the cell size  $V$  in a wide range, an optimal cell size has been found, with the observation of coherent spatial patterns. Since the magnitude of the internal noise is related to the system size, these phenomena also indicate the existence of SCR. In addition, the effects of control parameter and coupling strength on system's spatial coherence have been investigated. In particular, the occurrence of the SCR phenomenon depends on the value of control parameter. Furthermore, it was found that a smaller cell size is needed to induce spatial pattern for a smaller control parameter when this control parameter is below the threshold. Similarly, a smaller cell size is needed to induce spatial pattern for a stronger coupling strength. Moreover, spatial coherence can be enhanced by coupling.

## 2. Model: square-lattice of locally coupled cells with internal noise

There are a number of models of intracellular and intercellular calcium oscillations and waves [50]. Herein we adopt the model proposed by Höfer [51,52] and Gracheva [53], which describes the dynamics of  $\text{Ca}^{2+}$  in a single cell of rat hepatocytes. The calcium signaling in a single cell involves the interplay of fluxes from and into the endoplasmic reticulum (ER) and across the plasma membrane. In the case of noise free, the dynamical equations of this calcium oscillation model in a single cell are

$$\begin{aligned} \frac{dx}{dt} &= \rho \left\{ v_0 + v_c \frac{p}{k_0 + p} - v_4 \frac{x^2}{k_4^2 + x^2} + \frac{\alpha k_r(x, p)}{\beta} [z - (1 + \beta)x] - \alpha v_3 \frac{x^2}{k_3^2 + x^2} \right\} \\ \frac{dz}{dt} &= \rho \left( v_0 + v_c \frac{p}{k_0 + p} - v_4 \frac{x^2}{k_4^2 + x^2} \right) \\ k_r(x, p) &= k_1 \left\{ \frac{d_2 (d_1 + p) p x}{(d_p + p) (d_a + x) [d_2 (d_1 + p) + x (d_3 + p)]} \right\}^3 + k_2 \end{aligned} \quad (1)$$

where  $x$  and  $z$  represent the concentrations of cytosolic  $\text{Ca}^{2+}$  and the total  $\text{Ca}^{2+}$  in the cell. The model parameters are (see Ref. [51] for more details):  $\rho = 0.2 \text{ L} \cdot \mu\text{mol}^{-1}$ ,  $\alpha = 2.0 \text{ L} \cdot \mu\text{mol}^{-1}$ ,  $\beta = 0.1 \text{ L} \cdot \mu\text{mol}^{-1}$ ,  $v_0 = 0.2 \mu\text{mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$  describes a calcium leakage from the background,  $v_c = 4.0 \mu\text{mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$  denotes the maximum rate of calcium influx induced by  $\text{IP}_3$  (inositol 1, 4, 5-trisphosphate),  $v_3 = 9.0 \mu\text{mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$  denotes the maximum rate of ER uptake calcium from the cytosol, and  $v_4 = 9.0 \mu\text{mol} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$  is the maximum rate of calcium efflux through the plasma membrane. The values of the other parameters are  $k_0 = 4.0 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $k_1 = 40.0 \text{ s}^{-1}$ ,  $k_2 = 0.02 \text{ s}^{-1}$ ,  $k_3 = 0.12 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $k_4 = 0.12 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $d_1 = 0.3 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $d_2 = 0.4 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $d_3 = 0.2 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $d_p = 0.2 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $d_a = 0.4 \mu\text{mol} \cdot \text{L}^{-1}$ .  $k_r(x, p)$  is the  $\text{IP}_3$  receptor release function.

Parameter  $p$  is the concentration of  $\text{IP}_3$  in the cell, which describes the level of the agonist simulations and is viewed as the control parameter. With the variation of  $p$ , the bifurcation diagram of Eq. (1) is shown in Fig. 1. It is clearly shown that there are two Hopf bifurcation points at  $p = 1.45 \mu\text{mol} \cdot \text{L}^{-1}$  and  $p = 8.89 \mu\text{mol} \cdot \text{L}^{-1}$ , and the system has three states: steady state, small oscillation and relaxation oscillation. Fig. 1 is constructed from our own simulations and agrees with the previous studies [54,55].

To account for the effects of internal noise on the spatial dynamics of coupled Höfer calcium models, mesoscopic stochastic models should be used instead of the deterministic models, and these mesoscopic stochastic models are coupled by linear diffusion on a square-lattice, as shown in Fig. 2. Here,  $i = 1, \dots, N$  and  $j = 1, \dots, N$  are the labels of the cells'

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