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Cellular diversity promotes intercellular Ca^{2+} wave propagation

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ABSTRACT

Calcium ions are an important second messenger in living cells. Calcium signals in form of waves serve as a means of intercellular communication and thus represent a vibrant subject for experimental and theoretical investigations. Here we study the role of cellular variability on the occurrence of Ca^{2+} wave propagation in a net of diffusively coupled cells. Dynamics of individual cells is simulated by a mathematical model for Ca^{2+} oscillations. Structural diversity of cells is introduced via variations of the bifurcation parameters, which signify cell sensitivity for external stimulation. Remarkably, for sufficient values of variability Ca^{2+} waves emerge, which are mostly ordered for intermediate variability strength. We analyze the spatial profile via the autocorrelation function, which confirms a resonance-like response due to the cellular variability. Thus, the reported phenomenon is a novel observation of diversity-induced spatial coherence resonance in a tissue-like media.

1. Introduction

The impact of noise on nonlinear systems can cause a variety of interesting and counterintuitive phenomena [1]. Perhaps the most famous is the phenomenon of stochastic resonance where an appropriate intensity of noise evokes the best correlation between a weak deterministic stimulus and the response of the nonlinear system [2]. Even more remarkably, noise alone is also able to induce or enhance temporal order in the dynamics of a nonlinear system, whereby the phenomenon is to date most often addressed as coherence resonance [3]. Especially in biological systems, it is a rather firmly established fact that a certain degree of stochasticity is unavoidable [4]. Therefore, many studies have been devoted to the constructive role of noise in different biological processes. For instance, Douglass et al. [5] have provided experimental evidence that noise enhances the ability of information transfer in crayfish mechanoreceptor cells. Due to the indubitably presence of fluctuations in biological systems, several stochastic models has been developed for describing and studying different cellular processes. It has been shown that noise can induce stochastic Ca^{2+} oscillations in cells operating near a Hopf bifurcation. These oscillations are mostly ordered for some intermediate values of noise [6–8]. Similar studies have also been performed for circadian rhythms [9] as well as genetic regulation [10,11] and neuronal systems [12].

Following initial advances on systems without spatial degrees of freedom, the scope of interest shifted towards spatially extended media, where several noise-induced phenomena have been observed as well [13]. The so-called spatiotemporal stochastic resonance has been reported in [14], while spatial coherence resonance has been reported in several types of spatial extended systems, for example photosensitive Belousov–Zhabotinskii medium [15], in systems near pattern forming instabilities [16], and in excitable media [17,18]. Remarkably, the spatial coherence resonance phenomena has also been reported for diffusively coupled cells [19], where it has been shown that internal stochasticity provokes a characteristic spatial frequency of calcium waves in the medium of coupled cells. Another interesting report was performed by Shuai and Jung [20], who have studied the role spatial clustering of IP_3 receptors in a spatial extended model for intracellular calcium oscillations. Their results indicate that an inhomogeneous distribution of receptors, together with channel noise, warrant more coherent oscillations of Ca^{2+} concentration. The coherence resonance phenomenon has also been studied in more complex spatial extended systems. For instance, Sun et al. [21] have studied the spatial dynamics of Hodgin–Huxley neurons, whose interaction was governed by a small-world network. Remarkably, noise-induced spatial order has also been evidenced experimentally. Kádár et al. [22] have shown that an appropriate intensity of noise sustain wave propagation in a photosensitive Belousov–Zhabotinsky reaction. Another interesting contribution has been reported by Jung et al. [23], who have studied noise-induced calcium waves in astrocyte syncytia. Authors provided evidence that spatiotemporal sizes of single waves that are triggered by noise in a cultured network of glial cells, exhibit a power law distribution.

However, although the phenomena of stochastic and coherence resonance are most commonly associated with dynamic disorder or noise, only recently Tessone et al. [24] succeeded showing that static or quenched disorder can also provoke enhanced collective behavior of bistable and excitable oscillators. Their findings indicate, that many natural systems might profit from their intrinsic diversity. In this manner Chen et al. [25] engaged with analogous investigations in a

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cellular Ca^{2+} signaling system. They have shown that the structural diversity of cells enhances the cellular ability to detect weak extracellular signals in a coupled hepatocytes systems. Specifically, the regularity of Ca^{2+} oscillations exhibits a clear maximum with the variation of cellular diversity. Noteworthy, Glatt et al. [26] have reported that variability is also able to induce pattern formation in a net of subexcitable units, where the most coherent patterns are achieved for intermediate values of parameter variability. In their further investigations [27] interesting findings about the interplay of additive and multiplicative variability in a net of weakly forced bistable elements have been reported.

In the present paper we extend the scope of variability induced pattern formation to the medium of diffusively coupled cells, which local dynamics is driven by a mathematical model for Ca^{2+} oscillations. We show that cellular variability in form of diverse cell-to-cell sensitivity to external stimulation induces Ca^{2+} wave propagation, if the cells are operating near the Hopf bifurcation. Remarkably, the most ordered waves are observed for intermediate values of cellular diversity.

2. Mathematical model

We use a simple mathematical model for Ca^{2+} dynamics determined by theoretical framework of Goldbeter et al. [28] as a building block for our spatially extended system. The model considers changes of free Ca^{2+} concentration in the cytosol (z) and in the intracellular calcium store (y). Individual cells are arranged on a $L\times L(i,j\epsilon[1,L])$ square lattice and are diffusively coupled through the cytosol, which is modeled by an additional flux $D\nabla^2 z_{i,j}$. So, the spatial extension of the model has the following form:

$$\frac{dz_{i,j}}{dt} = v_0 + \beta_{i,j}v_1 - v_2 + v_3 + k_f y_{i,j} - kz_{i,j} + D\nabla^2 z_{i,j}, \tag{1}$$

$$\frac{dy_{i,j}}{dt} = v_2 - v_3 - k_f y_{i,j}, \tag{2}$$

where

$$v_2 = V_{M2}\frac{z_{i,j}^n}{K_2^n + z_{i,j}^n}, \tag{3}$$

$$v_3 = V_{M3}\frac{y_{i,j}^m}{K_R^m + y_{i,j}^m}\frac{z_{i,j}^p}{K_A^p + z_{i,j}^p}. \tag{4}$$

The Laplacian is incorporated into the numerical scheme via a five-point finite difference formula, as described by Barkley [29], using periodic boundary conditions. Parameter values, used in our calculations are quoted in the caption of Fig. 1. Here the model equations are presented only briefly. For details, we refer to the original work of Goldbeter et al. [28]. We would only like to expose the term $\beta_{i,j}v_1$ in Eq. (1), which denotes the IP_3-modulated influx from the IP_3 sensitive store. In particular, the parameter $\beta_{i,j}$ measures the saturation of IP_3 receptors and is selected as the control parameter, which defines the calcium dynamics in the cell. In order to introduce the cellular structural diversity, we assume that values of the control parameter $\beta_{i,j}$ are Gaussian distributed among cells and satisfy $\langle\beta\rangle = \beta_0$:

$$\beta_{i,j} = \beta_0(1 + \sigma\xi_{i,j}). \tag{5}$$

In Eq. (5) σ defines the measure for structural diversity and $\xi_{i,j}$ are uncorrelated random Gaussian numbers with zero mean and unit variance. Clearly, there is a disparity in the cellular structure for $\sigma>0$, which in physiological meaning indicates diverse cell-to-cell sensitivity for external stimulation.

3. Cellular diversity induced Ca^{2+} waves

We set $\beta_0=0.39$ in order to achieve that for $\sigma=0$ all of the cells are just below the Hopf bifurcation, occurring at $\beta_0\approx0.397$. In this case, all cells stay in a stable state and the whole lattice remains quiescent. On the other hand, by introducing the cellular variability, the control parameter, $\beta_{i,j}$ differs from cell to cell and, as a result, some of the cells are placed into the oscillatory regime. In order to visualize the resulting spatial behavior, we show in Fig. 1 characteristic spatial profiles of $z_{i,j}$ for three different values of σ. For a small cellular diversity, the cells remain inactive. However, if σ is increased, ordered Ca^{2+} waves are noticed that are propagating through the medium. As σ increases further, the coherence of waves becomes evidently destroyed.

The basis for the observed phenomenon is the proximity to the Hopf bifurcation point. As already mentioned above, for a non-zero structural diversity, some cells are put into the oscillatory regime. But, if σ is low, the number of oscillatory cells is too small to be capable of activating the other cells and inducing a coherent spatial dynamics. For intermediate values of σ, the fraction of the oscillatory cells in the medium becomes adequate and the steady-state cells are being triggered by small clusters of oscillatory cells, which induce and govern the spatial dynamics of ordered Ca^{2+} waves. However, when σ increases further, the cells become more and more dispersed around the bifurcation point. Consequently, some of the cells are located too far from the bifurcation point and cannot be activated by their neighbors. In addition, several cells are situated in different regions of the oscillatory regime, which occasions different inherent frequencies and amplitudes of oscillations of individual cells. For that reasons larger values of σ obliterate the coherence of the waves. We can thus infer that an optimal cellular diversity should exist for the most coherent intracellular Ca^{2+} wave propagation.

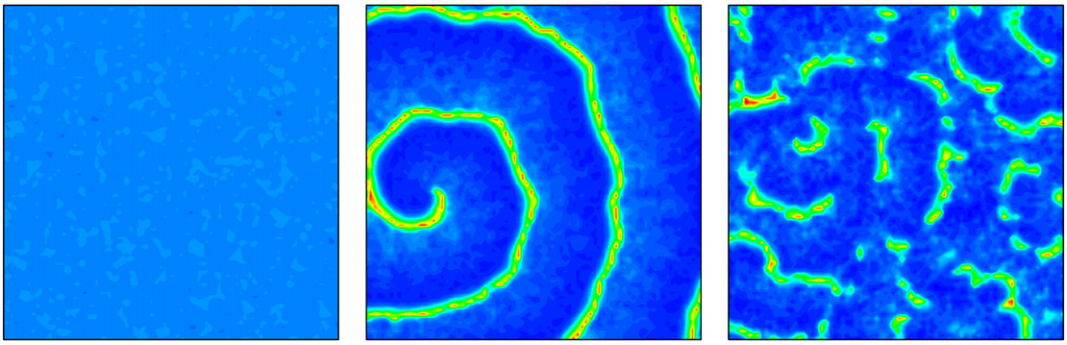

Fig. 1. Characteristic snapshots of the spatial profile $z_{i,j}$ for $\sigma=0.05$ (left panel), $\sigma=0.1$ (middle panel) and $\sigma=0.2$ (right panel). All snapshots are drawn using a linear color profile, blue depicting 0.2 and red 1.2 values of $z_{i,j}$. The employed system parameters are: $v_0=0.5$ μM s^{-1}, $v_1=7.3$ μM s^{-1}, $V_{M2}=65.0$ μM s^{-1}, $V_{M3}=500.0$ μM s^{-1}, $k_f=1.4$ s^{-1}, $k=10$ s^{-1}, $K_2=1.0$ μM, $K_R=2.0$ μM, $K_A=0.9$ μM, $m=n=2$, $p=4$, $\beta_0=0.39$, $D=4.0$ s^{-1}, $L=80$.

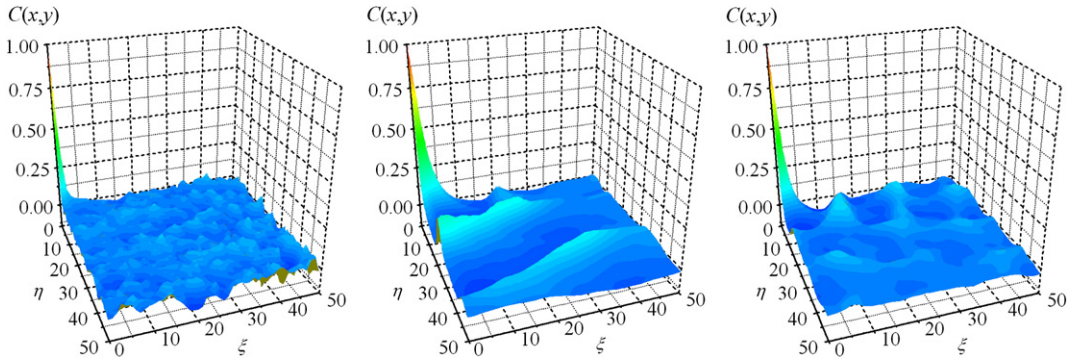

Fig. 2. The average spatial correlation functions of $z_{i,j}$ obtained for the same parameters as in Fig. 1.

To quantify the spatial dynamics of Ca^{2+} waves for different levels of cellular variability, we calculate the normalized autocorrelation function of the spatial domain $z_{i,j}$:

$$g(\xi,\eta) = \frac{\langle \widetilde{z}_{i,j}\widetilde{z}_{i+\xi,j+\eta}\rangle}{\langle z\rangle^2_{i,j}}, \tag{6}$$

where $\widetilde{z}_{i,j}=(z_{i,j}-\langle z\rangle_{i,j})$, $\langle z\rangle_{i,j}$ is the spatial average of the whole lattice at a particular time, and ξ and η are representing spatial lag variables measured as a change in position from the starting i and j values. Fig. 2 shows the results for the same parameters as employed in Fig. 1. As anticipated, for small values of σ, no considerable spatial correlation is noticed. On the other hand, for $\sigma=0.1$, there is an uncontestable spatial correlation. For somewhat larger values of σ, the spatial correlation decreases, which is indicated by a greater decay of the autocorrelation. Note, that the function $g(\xi,\eta)$ shown in Fig. 2, represents the average over several temporal realizations.

Similar as by the characterization of temporal order with the classical temporal autocorrelation function, we calculate the spatial correlation length as:

$$\lambda = \sum_{i=0}^{\xi_0}\sum_{j=0}^{\eta_0} g^2(i,j), \tag{7}$$

in order to determine the optimal cell variability. Namely, the larger the value of λ, the larger the spatial order in the lattice. In the calculations, λ is obtained by averaging over 100 realizations. Fig. 3 features results that confirm a resonance-like behavior with increasing σ, since a clear maximum of the resonance curve can be noticed at $\sigma\approx 0.11$. In addition, we examine how the value λ depends on the distance from the Hopf bifurcation. We can observe, that the overall coherence of the spatial dynamics decreases as the distance from the bifurcation increases, and moreover, the peak of the resonance curves moves towards larger values of σ. Similar findings have been reported for the coherence resonance phenomenon, where the maximal temporal [6] or spatial [19] order that can be induced by noise was also find decreasing with the increasing distance from the Hopf bifurcation.

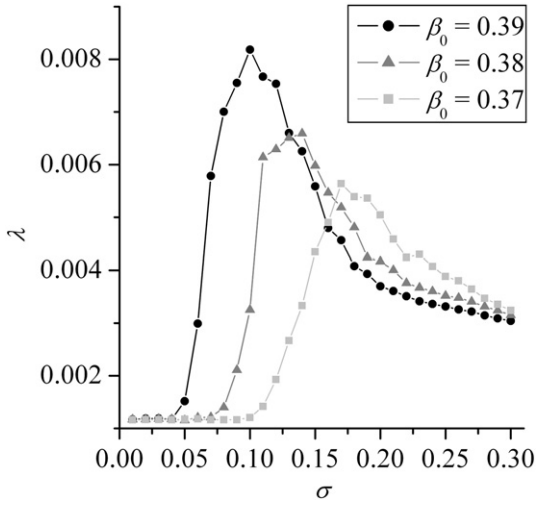

Fig. 3. The dependence of the spatial correlation length on cellular variability for different values of β_0.

4. Discussion

Signals encoded in Ca^{2+} waves regulate multiple cellular functions from cell fertilization to its death [30] and are thus of key importance for normal functioning of living organism. Therefore, investigations of spatio-temporal calcium dynamics represent a vibrant topic in the scientific community. An interesting contribution has been reported by Tordjmann et al. [31,32], who studied the coordination of intercellular Ca^{2+} waves in rat hepatocytes. In their experimental investigations they hypothesize that an assembly of hepatocytes communicating via gap junctions might be regarded as an excitable medium. Furthermore, they discovered that heterogeneity of cell-to-cell sensitivity for the hormone plays a vital role in the coordination of Ca^{2+} waves. Their study also signifies that agonist-induced intercellular waves are initiated by an IP_3 increase in the most sensitive cell, which provides a pacemaker-like mechanism for the regulation of intercellular communication in the liver. These findings were theoretically corroborated by Dupont et al. [33], who examined a model for Ca^{2+} wave propagation, whereby several hepatocytes were differing in sensitivity to the agonist and thus in the intrinsic frequency of calcium oscillations. They revealed that wave propagation occurs in the direction of the gradient of hormonal sensitivity, which has also been confirmed experimentally.

However, in the present study we show that a random heterogeneity in cell-to-cell sensitivity for the external stimulation can provoke Ca^{2+} waves in the medium of diffusively coupled cells. The coherence of the waves exhibits a resonance-like behavior with the variation of structural variability. The phenomenon is a novel observation of diversity-induced spatial coherence resonance in the medium of coupled cells. Remarkably, in the last few years the role of spatial heterogeneities on intercellular dynamics has been emphasized in investigations of cardiac tissues. Bub et al. [34] have provided an explanation for the experimental observations of disturbances of calcium waves in chick embryonic heart cells as the coupling is reduced. On the basis of a simple model they found out that heterogeneity in the spatial arrangement plays the crucial role in wave organization. Recently, the importance of heterogeneities in cardiac tissue has also been emphasized by Woo et al. [35], who have shown that inherent inhomogeneities in the cell culture influence the

cardiac wave dynamics. Our results suggest that cellular variability might play an important role in intercellular calcium signaling or at least may influence other noise-induced effects that are inherent in biological systems. Therefore, when studying intra- and intercellular dynamics and organization, not only dynamical noise, but also cell heterogeneity should be considered.

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