Global noise and oscillations in clustered excitable media

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(Received 11 September 2008; published 24 April 2009)

We study the effects of global noise on waves in heterogeneous, spatially clustered, reaction-diffusion systems with possible applications to calcium signaling. We first discuss how clustering of the excitability determines the dynamics by shifting bifurcation points and creating new oscillatory solutions. We then consider the specific situation, where intrinsic noise, due to the smallness of the excitable patches, destroys the global oscillatory state. We show that additional small global fluctuations, however, can partially restore temporal and spatial coherence of the oscillatory signal.

DOI: 10.1103/PhysRevE.79.041923 PACS number(s): 87.16.Xa, 05.45.–a, 05.40.Ca

I. INTRODUCTION

Recently, considerable attention has been paid to the constructive effects of noise in nonlinear systems [1]. One of the widely studied phenomena is stochastic resonance and coherence resonance, where additional noise can improve a system’s response to a weak periodic signal [2], or even in the absence of a periodic driving [3,4]. In complex biological systems, different sources of fluctuations are present, often characterized as extrinsic and intrinsic noises. It has been shown that intrinsic fluctuations can improve the encoding of small signals [5], or enhance the periodicity of spiking in a chain of coupled neurons [6]. Furthermore, multiple noise sources can generate novel and unexpected phenomena, such as effective noise cancellation [7], noise suppression by noise [8], or modulation of coherence resonance [9].

In this paper we discuss the synergistic effects of spatially independent and global fluctuations on a spatially clustered oscillating system. We show that a small optimal intensity of extrinsic, global noise can restore temporally and spatially coherent oscillations destroyed by intrinsic noise due to the smallness of the excitable clusters. In contrast to the standard stochastic-resonance scenario, where a deterministically periodic state is turned into a periodic state, the coherence of a deterministically periodic state is enhanced by the interaction of various noises.

As a working model, we consider a model for intracellular calcium dynamics. This model used here does not contain biophysical details of the calcium signaling machinery, but is rather focused on the important consequences of clustering of excitability, an important source of intrinsic noise. Calcium ions are an important second messenger in living cells [10], and calcium signals have been subject of experimental and theoretical investigations [18–29] in recent decades. Intracellular calcium is released from internal Ca2+ stores, most notably the endoplasmic reticulum (ER), through inositol 1,4,5-trisphosphate receptor channels (IP3Rs). Recent experiments revealed that the IP3Rs are distributed in clusters, spaced a few micrometers apart and with a few tens of channels per cluster [14]. Hence, Ca2+ liberation occurs at discrete release sites as puffs or sparks [11,13]. Each local release event is stochastic due to intrinsic stochasticity of channel opening and closing [11,13,14]. Local release events can merge to form global release events in the form of oscillations and waves.

It has been shown that rich and complex behaviors can be found in calcium dynamics, such as the shifts of bifurcations [30,31] and multiple stable states with hysteresis [32]. By investigating the global spike trains of four cell types, it has been suggested that Ca2+ spikes are caused by random wave nucleation with a regular regime arising from the array enhanced coherence resonance with IP3R clusters [17]. Hence, the stochastic effects in such a system are not only curious from a physics perspective but are also relevant for open problems in cell biology. In Sec. IV of this paper, we show that the clustered organization of the release channels induces rich and complex dynamics of Ca2+ waves with a corresponding bifurcation diagram. We report in Secs. V and VI on a mechanism for generating spatially and temporally oscillations through the interaction of stochastic channel dynamics and global fluctuations of the concentration of the second messenger IP3.

II. A SIMPLE MODEL FOR INTRACELLULAR CALCIUM DYNAMICS

We model the cytosolic space as a two-dimensional sheet, in which the calcium concentration, i.e., \( C(x,y,t) \), is described by the following reaction-diffusion equation:

\[
\frac{\partial C}{\partial t} = D \nabla^2 C + f(x,y)J_C - J_P + J_L, \tag{1}
\]

where \( D \) denotes an effective diffusion constant, \( J_C \) channel flux from ER to the cytosol through clusters of IP3Rs, \( J_P \) pump flux from the cytosol to ER through SERCA pumps, and \( J_L \) leakage flux from ER to the cytosol. The proteins that constitute pumps and leakage are assumed homogeneously distributed over the ER membrane. The IP3Rs are distributed in clusters positioned on a regular lattice, described by the
form-function \( f(x, y) \) which is unity at the location of the clusters and zero elsewhere.

The three fluxes in Eq. (1) are given by

\[
J_C = v_C g \frac{N_{\text{open}}}{N} (C_{\text{ER}} - C)
\]

\[
J_P = v_P \frac{C^2}{k^2 + C^2}
\]

\[
J_L = v_L (C_{\text{ER}} - C),
\]

where \( C_{\text{ER}} \) describes the high concentration of Ca\(^{2+}\) in ER. For this study, which does not focus on physiologic detail, we assume that the concentration of Ca\(^{2+}\) in ER remains unchanged everywhere and is thus chosen to be a constant. The parameters \( v_C, v_P, \) and \( v_L \) describe the maximum flux through a cluster of IP\(_3\)Rs, maximum pump flux, and leakage rate, respectively. The flux \( J_C \) through a cluster (i) with \( N \) channels is determined by the fraction of open IP\(_3\)Rs in this cluster, i.e., \( N_{\text{open}}/N \). For the gating of IP\(_3\)R, we use the Li-Rinzel model [19]. The Li-Rinzel model is a simplification of the DeYoung-Keizer model [18], in which each channel has three subunits with each a binding site for IP\(_3\) (i.e., \( m \)-gate), and two binding sites for Ca\(^{2+}\), one for activation (i.e., \( n \)-gate) and one for inactivation (i.e., \( h \)-gate). The channel is open if all three subunits are activated, i.e., IP\(_3\) and activating Ca\(^{2+}\) are both bound. In the Li-Rinzel simplification, binding probabilities of IP\(_3\) and activating Ca\(^{2+}\) are instantaneous and represented by their quasisteady states,

\[
m_x = \frac{p}{p + d_m},
\]

\[
n_x = \frac{C}{C + d_n},
\]

where \( p \) represents the IP\(_3\) concentration, giving rise to the factor \( g = m_x n_x^3 \) in Eq. (2).

Ca\(^{2+}\)-inactivation (\( h \)-gate) is slow and described by the binding and dissociation rates \( \alpha \) and \( \beta \), given by

\[
\alpha = a d_2 \frac{p + d_1}{p + d_3},
\]

\[
\beta = a C.
\]

In case that the number of channels per cluster is large and the fluctuations are small, \( N_{\text{open}}/N \) can be replaced by the continuous fraction \( h \), obeying the linear rate equations [19],

\[
\frac{dh}{dt} = \alpha (1 - h) - \beta h.
\]

The parameters \( k, d_m, d_n, d_1, d_2, d_3, \) and \( a \) in Eqs. (2)–(7) are specified in Table I.

Due to its large diffusion coefficient, IP\(_3\) spreads out quickly through the cell after generated locally, acting as a global signal in the intracellular space [12] and is thus often treated as a common variable [20,21,24]. The dynamics of the IP\(_3\) concentration \( p \) around its steady-state concentration \( p_0 \) are determined by [18],

\[
\frac{dp}{dt} = \frac{p_0 - p}{\tau},
\]

with the degradation rate of \( 1/\tau \). According to [33], we chose \( \tau = 10.0 \) s here.

In this paper we will go one step further by taking into account stochasticity in the local production of IP\(_3\) (e.g., through variable amounts of agonist binding to receptors on the plasma membrane), which through the rapid spread through the entire cell becomes a global, stochastic signal.

In our model, the IP\(_3\)Rs are distributed in equally sized clusters with \( N = 36 \) channels each, positioned on a regular array at a distance of \( L = 3 \) \( \mu \)m. The small size of the clusters facilitates rapid equilibration of calcium within the cluster and one can therefore assume that all channels in one cluster experience the same calcium concentration [20]. We further approximate the clusters as point sources where the actual size of the cluster appears as a prefactor of \( v_C \) [25], i.e., the form function \( f(x, y) \) becomes a sum of \( \delta \) functions located at the clusters. In the simulation, an area of \( 60 \times 60 \) \( \mu \)m\(^2\) membrane ER is discretized and represented by a grid with distance \( \Delta x = 0.5 \) \( \mu \)m. Nonflux boundary conditions are applied in the model. The parameter values given in Ref. [24] are used in the present study (Table I).

### III. UNIFORM CALCIUM CONCENTRATION

In this section we discuss the behavior of the model in the limit of a large diffusion coefficient of Ca\(^{2+}\), resulting in a rapid formation of a uniform Ca\(^{2+}\) concentration. All IP\(_3\)Rs of all clusters are clamped to the same, but variable, Ca\(^{2+}\) concentration. Thus, the Laplacian in Eq. (1) vanishes, the number \( N \) becomes the total number of channels 10 000, and the fraction \( N_{\text{open}}/N \) becomes continuous (\( h \)), leaving us with a set of ordinary differential equations for cytosolic Ca\(^{2+}\) concentration, i.e.,

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GLOBAL NOISE AND OSCILLATIONS IN CLUSTERED... PHYSICAL REVIEW E 79, 041923 (2009)

FIG. 1. Bifurcation diagram of the model as a function of IP$_3$ messenger $p$ for intracellular calcium dynamics [Eqs. (1)–(7)] with uniform cytosolic Ca$^{2+}$ concentration, i.e., for $D=\infty$. Oscillatory branches are depicted by the minimum and the maximum of the amplitude.

\[
\frac{dC}{dt} = J_C - J_p + J_L,
\]

\[
\frac{dh}{dt} = a(1-h) - \beta h,
\]

where the channel flux becomes $J_C = \rho C m^3 n^3 h^3 (C_{\text{ER}} - C)$ with the modified maximum flux $\rho C = \nu C/36$ [24]. The other terms are the same as given in Eqs. (3)–(7). Stochastic effects of gating can be ignored here for the large number $N$ (fluctuations are of the $1/\sqrt{N_{\text{tra}}}$) [22].

For this deterministic model [Eq. (9)], the bifurcation diagram of stable attractors of Ca$^{2+}$ signal is shown in Fig. 1 as a function of $p$. For IP$_3$ concentrations $p$, between 0.24 $\mu$M and 1.1 $\mu$M, Ca$^{2+}$ oscillations are observed, while for lower and higher IP$_3$ concentrations, stationary concentrations are found. This bifurcation diagram sets the stage for further studies of the behavior of the system without the constraints to large diffusion coefficients of Ca$^{2+}$ and large numbers of channels.

IV. CHANNEL-CLUSTERING AND DYNAMIC BIFURCATIONS IN THE ABSENCE OF STOCHASTIC EFFECTS

We now lift the constraint of a large diffusion coefficient and allow for gradients in the overall Ca$^{2+}$ concentration. We do, however, at this point neglect stochasticity in the cluster conductance due to spontaneous opening and closing of IP$_3$Rs. Hence, we consider the deterministic dynamics and pattern formation in a spatially clustered excitable system.

To quantify the effects of spatial gradients for the dynamics and stable attractors, we consider the dynamics of cell-averaged Ca$^{2+}$ concentrations, i.e., we solve Eqs. (1)–(5) and then perform a spatial average. In Figs. 2(A) and 2(B) we show the bifurcation diagrams of cell-averaged calcium $C_{\text{Cell}}$ as a function of $p$ at $D=30$ and 15 $\mu$m$^2$/s, respectively. These diffusion coefficients are biologically meaningful as they incorporate the effect of buffers [12].

At $D=30$ $\mu$m$^2$/s the dynamic behavior resembles very much the system with uniform Ca$^{2+}$ concentrations, i.e., the oscillations of Ca$^{2+}$ signal are found for the range of $0.18 \mu$M $< p < 0.84 \mu$M. The minimum and the maximum amplitudes in Fig. 2 depict oscillations. The onset and termination of oscillations are shifted to smaller values of $p$.

At $D=15$ $\mu$m$^2$/s, however, we find a bifurcation diagram which is qualitatively very different [Fig. 2(B)]. The range of IP$_3$ concentrations for which we find stable oscillations is even smaller, and the bistable range (a fixed point and an oscillatory attractor) just before the bifurcation back to steady state (i.e., close to $p > 0.69 \mu$M) has shrunk [Fig. 2(B)].

Most interestingly, however, a new steady-state branch $F$ in the interval $0.15 \mu$M $< p < 0.23 \mu$M and a new oscillatory branch $P_2$ in the interval $0.23 \mu$M $< p < 0.29 \mu$M emerged. The new branch of fixed point $F$ coexists with the oscillatory state $P_1$. Closer inspection of the spatiotemporal patterns represented by $P_1$ and $P_2$ shows that these are two phase shifted, propagating intracellular Ca$^{2+}$ waves (data not shown).

In the following, we focus our attention to the region of $0.23 \mu$M $< p < 0.29 \mu$M, where a propagating Ca$^{2+}$ wave ($P_1$) coexists with a steady-state concentration. We will next take into account intrinsic channel noise and global fluctuations in the IP$_3$ concentration $p$, and study the fate of the spatiotemporal dynamics of calcium signal. We will show that the channel noise alone will destroy the wave and the associated spatial and temporal coherence. Small global fluctuations of IP$_3$, however can partially restore temporal and spatial coherence of the intracellular calcium oscillation.

V. Ca$^{2+}$ SIGNALING MODEL WITH INTRINSIC CHANNEL NOISE

For a small number of channels in each cluster, the fraction of open channels in a cluster is stochastic due to the
In this case, the channel fluxes at the various cluster sites (i) can be expressed as

$$J^{(i)} = v_{CG} \frac{N_{h,\text{Open}}^{(i)}}{N} (C_{ER} - C^{(i)}),$$

where $N_{h,\text{Open}}^{(i)}$ denotes the number of noninhibited IP$_3$Rs of cluster (i), and $C^{(i)}$ the cytosolic calcium concentration at cluster site (i). In order to determine the number $N_{h,\text{Open}}^{(i)}$, we perform a Markov-simulation of the gating scheme of IP$_3$Rs as described in [22] with the binding and dissociation rates given in Eq. (6).

We combine the Markov simulations of the clusters with 36 IP$_3$Rs per cluster with the solution of Eq. (1) to find the stochastic spatiotemporal Ca$^{2+}$ dynamics. Averaging the noisy Ca$^{2+}$ concentrations over the entire system we can compare the resulting bifurcation diagram [Fig. 3(A)] with that obtained in the absence of channel noise at $D$ = 15 $\mu$m$^2$/s [Fig. 2(B)]. Some of the detail of the nonstochastic bifurcation diagram [Fig. 2(B)] vanishes in the presence of channel noise. The two branches $P_1$ and $P_2$ in Fig. 2(B) describing propagating calcium waves merge into a single state. The steady-state branch $F$ in Fig. 2(A) merges with $P_1$ to yield stochastic calcium fluctuation around the steady state [see Fig. 3(B)]. The power spectrum of calcium fluctuation at $p_0 = 0.25$ $\mu$M indicates little periodicity, as shown in Fig. 4 ($\eta = 0$). The coherence and periodicity of the intracellular Ca$^{2+}$ wave signal are destroyed by the spatially independent fluctuations of channel conductance. In Sec. VI, we show that an optimal amount of extrinsic fluctuations in the global IP$_3$ concentration can restore the temporally and spatially coherent Ca$^{2+}$ waves, which were destroyed by the channel noise at $p_0 = 0.25$ $\mu$M.

VI. INTERACTION BETWEEN INTRINSIC CHANNEL NOISE AND EXTRINSIC IP$_3$ FLUCTUATION

We now take into account global stochasticity of the IP$_3$ concentration $p$. Global IP$_3$ fluctuations are likely to occur whenever IP$_3$ is generated as a response to extracellular agonist binding to metabotropic receptors distributed locally on the plasma membrane or through local release of caged IP$_3$ through application of light in experiment [11,14].

Assuming a narrow Gaussian distribution of the IP$_3$ concentration around the average value of $p_0 = 0.25$ $\mu$M, the dynamics of $p$ is described by the stochastic differential equation,

$$\frac{dp}{dt} = \frac{p_0 - p}{\tau} + \eta \xi(t),$$

where $\eta$ denotes the noise strength, and $\xi(t)$ white Gaussian noise with zero mean, i.e.,

$$\langle \xi(t) \rangle = 0$$

$$\langle \xi(t_1) \xi(t_2) \rangle = 2\delta(t_1 - t_2).$$

Artifacts such as negative values for $p$ do not typically occur since we only use small values of $\eta$. The variance of the Gaussian distribution of $p$ is given by $\tau \eta^2$. Hence for $\eta = 0.03$, i.e., the largest value of $\eta$ we are using, one has $\tau \eta^2 = 0.009$ $\mu$M$^2$. Thus, the standard deviation $\sqrt{\tau \eta^2} = 0.095$ $\mu$M, which is much smaller than the average $p_0 = 0.25$ $\mu$M, and so the chance of negative values of $p$ is very small.

In Figs. 3(C)–3(E), we show the effect of global fluctuations of IP$_3$ on the calcium dynamics at the center cluster of the cell model for various fluctuation strengths $\eta$. Visible
inspection of the data suggests that an increase in global IP$_3$ fluctuation results in a more periodic Ca$^{2+}$ signal with an optimal value of about $\eta=0.006$ $\mu$M/s$^{1/2}$ [Fig. 3D], hence periodicity and signal encoding are restored at an optimal value of IP$_3$ fluctuation. Comparing the normalized power spectra of the calcium trajectories of the center cluster we further assess this effect. The corresponding power spectra are shown in Fig. 4 for trajectories at $\eta=0.0, 0.001, 0.006$, and $0.03$ $\mu$M/s$^{1/2}$. The spectrum at $\eta=0.006$ $\mu$M/s$^{1/2}$ clearly demonstrates the restored periodicity at a frequency of 0.075 Hz.

The periodicity of the Ca$^{2+}$ signal can be characterized by

$$\kappa = H_p \frac{f_p}{\Delta f},$$

where $H_p$ represents the peak height of the spectrum $P(f)$, $f_p$ the frequency at the peak, and $\Delta f$ the frequency width at half peak height. A larger value of $\kappa$ indicates a better periodicity [3]. Figure 5A shows that the periodicity first increases with increasing global fluctuations $\eta$, reaching a maximum at $\eta=0.006$ $\mu$M/s$^{1/2}$, and then decreases with larger $\eta$.

The peak frequency is also shifted with increasing $\eta$ as shown in Fig. 5B. At small $\eta$ the peak frequency is about 0.087 Hz, while at large $\eta$ the peak frequency approaches 0.07 Hz, which is close to the oscillation frequency of the system in the absence of any noise (i.e., 0.067 Hz).

### VII. Discussion and Conclusions

We have found that global noise, generated through rapid diffusion of the second messenger IP$_3$, can restore global periodicity of the cellular Ca$^{2+}$ signal, which has been destroyed by channel conductance fluctuations, and hence increase cellular signaling capability. In this section we discuss the underlying mechanism for this unexpected behavior.

To explain this effect, we consider first a single cluster of IP$_3$Rs in the absence of interaction with other clusters in the presence of channel noise and IP$_3$ fluctuation. This is realized by considering one cluster and setting the diffusion constant zero. More concrete, we solve Eq. (1) with $D=0$, the channel flux given in Eq. (10) with a cluster size of $N=36$ channels, and the stochastic differential equation for IP$_3$ concentration $p$ given in Eq. (11). In Fig. 6, we show the power spectra of the single cluster for a range of fluctuation intensities $\eta$ of the IP$_3$ concentration. All power spectra are very similar and do not show an increase in periodicity at any value of $\eta$. Hence, the dynamics of a single cluster is not the origin of the increase in global periodicity in the presence of coupling to other clusters.

To further substantiate the hypothesis that the increased periodicity is related to the diffusive coupling between clusters, we study the correlation between local Ca$^{2+}$ dynamics at the center cluster $C_{cent}$ and the global cell-averaged Ca$^{2+}$ dynamics $C_{cell}$, i.e.,

$$F(\tau) = \frac{\langle (C_{cell}(t) - \langle C_{cell} \rangle) \cdot (C_{cent}(t) - \langle C_{cent} \rangle) \rangle}{\sqrt{\langle (C_{cell}(t) - \langle C_{cell} \rangle)^2 \rangle \cdot \langle (C_{cent}(t) - \langle C_{cent} \rangle)^2 \rangle}}.$$  

A simple measure for the overall correlation is the correlation time [24],

$$\tau_0 = \int_0^\infty F^2 dt,$$

which is shown in Fig. 7 for the model discussed in Figs. 4 and 5. The correlation time increases with increasing global IP$_3$ fluctuations until it reaches a maximum at the same value where the local Ca$^{2+}$ dynamics are most periodic (see Fig. 4).

Hence, periodicity is linked to large spatial correlations, allowing a simple interpretation of the main result in this paper. Global IP$_3$ fluctuations, although small, slightly bias
the clusters to correlated occurrence of Ca\(^{2+}\) release. Ca\(^{2+}\) released at one site diffuses to other nearby clusters and further correlates the clusters through calcium-induced calcium release.

In the paper we report an unexpected effect of global fluctuations in a clustered excitable medium. We show that spatiotemporal coherence, destroyed by the fluctuations borne by the small size of the number of ion channels in a cluster generating the excitability, can be partly restored by global fluctuations acting on all excitable clusters of the system.

This effect has been studied in a simple model for calcium signaling which does not contain much biophysical detail.

For example, we ignore suspected large gradients in the calcium concentrations in the vicinities of open channels and their consequences for the onset of oscillations. It thus remains an open problem how robust this effect is and whether it maybe relevant for intracellular calcium signaling.

ACKNOWLEDGMENTS

P.J. thanks for funding by the U.S. National Science Foundation through Grant No. IOS-0744798. J.W.S. thanks for funding by the National Science Foundation of China through Grant No. 10775114.