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Periodic calcium waves in coupled cells induced by internal noise

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Abstract

We show that internal stochasticity, originating from finite cell sizes and related small numbers of reactant ions participating in the dynamics, is able to extract a characteristic spatial frequency of calcium waves in the medium of diffusively coupled cells. Internal noise is thereby the only agent acting on the system. As the spatial periodicity is best pronounced at an intermediate level of stochasticity the reported phenomenon is thus a novel observation of internal noise spatial coherence resonance in biochemical tissue-like media. In addition, results shed light on the stochastic versus deterministic nature of dynamics at the cellular and tissue level.

1. Introduction

Spatial dynamics in chemical and biochemical media, like propagating waves and pattern formation, has attracted much interest in the past decades. Patterns observed in the early experiments with the Belousov–Zhabotinskii medium [1,2] are epitome and visually compelling examples of self-organization in chemical systems. Conceptually related studies of spatial dynamics in chemical media [3–6] continue to have a remarkable impact in the scientific community even today. Coherent spatial structures have also been observed in cardiac muscles [7] as well as biological cells and tissue [8].

Due to lurking biomedical and pharmacological applications, the spatiotemporal dynamics of intra and intercellular Ca^{2+} signalling has been studied particularly extensive [8,9]. The cytosolic Ca^{2+} is an important second messenger in most excitable and non-excitable cells. Upon the impact of agonists, like hormones or neurotransmitters, the concentration of free cytosolic Ca^{2+} increases, either in form of locally evoked puffs and sparks, or global waves that emerge due to local Ca^{2+} elevations that are transmitted throughout the cell. Importantly, signals encoded in calcium waves regulate several cellular processes from cell fertilisation to its death [10], and are thus of key importance for normal functioning of living organisms. In order to gain a better understanding of the physiological role of these waves, the spatiotemporal Ca^{2+} dynamics has been analysed by different conditions, like altered kinetics of calcium binding to cytosolic proteins, endoplasmic reticulum pump activity, and calcium sequestration in mitochondria, for example [8].

While intra and intercellular spatiotemporal Ca^{2+} dynamics has been extensively studied in response to external agonist signals and other deterministic pacemaker activities, it has also been discovered that noise alone often suffices to induce spatiotemporally ordered behaviour in systems as diverse as optical devices and biochemical media [8,11]. In particular, spatiotemporal stochastic resonance has been first reported in [12] for excitable systems. Moreover, there also exist studies reporting noise-induced spiral growth and enhancement of spatiotemporal order [13–15], noise sustained coherence of space-time clusters and self-organized criticality [16], noise induced excitability [17], noise induced propagation of harmonic signals [18], as well as noise sustained and controlled synchronization [19] in spatially extended systems.

The constructive role of noise on the dynamics of calcium has been studied for single and coupled cells [8], albeit for later in a substantially lesser extend. Also, we have been

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unable to find studies focusing explicitly on the spatial dynamics of noise-induced calcium waves, although latter appear vital for calcium to play out its central role in intra and intercellular signalling. Moreover, not only for spatial calcium dynamics but also in general, little attention has been devoted to the explicit analysis of characteristic spatial frequencies of nonlinear media. Spatial coherence resonance has been introduced in [20] for systems near pattern forming instabilities, and the concept has recently been extended to excitable media in [21–23].

Presently, we aim to fill the gap by analysing spatial frequency spectra of calcium waves in the medium of diffusively coupled cellular oscillators that are locally described by a model of intracellular Ca^{2+} oscillations [24]. We show that internal stochasticity in diffusively coupled cells is able to extract an inherent spatial frequency of the system in a resonant manner. In particular, the spatial periodicity of calcium waves is best pronounced at an intermediate level of internal noise. Thereby, the internal stochasticity is attributed to finite compartment sizes and related small numbers of reactant ions participating in forming the Ca^{2+} dynamics of each individual cell. The phenomenon is a novel observation of internal noise spatial coherence resonance in biochemical tissue-like media. Presented results are discussed in view of the stochastic versus deterministic nature of dynamics at the cellular and tissue level.

2. Mathematical model

We use a minimal model for calcium dynamics proposed by Goldbeter et al. [24] as the building block for the spatially extended system. While several models for intracellular calcium oscillations in non-excitable cells have been developed over the years [8,9], the presently used captures all essential dynamical features with a modest computational effort. The model interrelates changes of free Ca^{2+} concentration in the cytosol (Z) and in the intracellular Ca^{2+} store (Y). We introduce diffusive coupling between individual cells by adding an additional flux of the form $D\nabla^2 Z_{i,j}$ to the differential equation modelling changes of cytosolic Ca^{2+} concentration in each of the coupled cells on the $L \times L$ ($i,j \in [1, L]$) square lattice. The Laplacian is integrated into the numerical scheme via a first-order

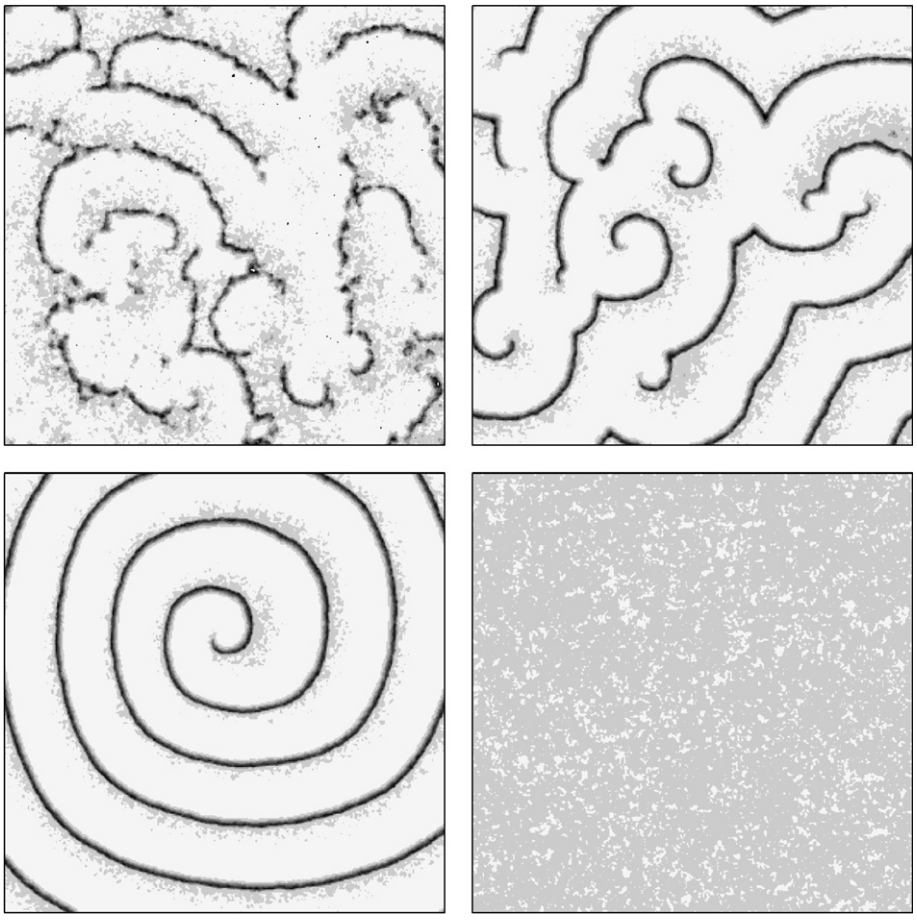

Fig. 1. Characteristic snapshots of the spatial profile of $Z_{i,j}$ for $\chi = (0.3; 1.1; 1.9; 2.1)$ μm^3 increasing from the top left towards the bottom right panel. All snapshots are depicted on square grids of linear size $L = 256$. The colour mapping is linear, white depicting 0.2 and black 1.2 values of $Z_{i,j}$. Other system parameters, as introduced in [24], are: $\beta = 0.26$, $v_0 = 1.5\ \mu M s^{-1}$, $v_1 = 7.3\ \mu M s^{-1}$, $V_{M2} = 65\ \mu M s^{-1}$, $V_{M3} = 500\ \mu M s^{-1}$, $k_f = 1.6\ s^{-1}$, $k = 10\ s^{-1}$, $K_2 = 1.0\ \mu M$, $K_R = 2.0\ \mu M$, $K_A = 0.9\ \mu M$, $m = n = 2$, $p = 4$.

numerical approximation $D(Z_{i-1,j}+Z_{i+1,j}+Z_{i,j-1}+Z_{i,j+1}-4Z_{i,j})$ and no-flux boundary conditions, whereby $D=5\ \mu\mathrm{Ms}^{-1}$ already incorporates the spacing between individual cells. Other parameter values, with the same notation as introduced in [24], are listed in the caption of Fig. 1. Each cell forming the medium is initially placed in a steady state just before the Hopf bifurcation occurring at $\beta=0.2806$ in the deterministic model. Thus, without taking into account internal stochasticity due to finite cell sizes and related small numbers of reactant ions participating in the dynamics, the medium would remain forever quiescent. Internal stochasticity is taken into account by integrating the resulting spatially extended system with the Gillespie's τ-leap simulation method [25]. Although, being only an approximation of the exact stochastic simulation method [26], the τ-leap method is much faster which is presently of essence as we consider a spatially extended system with 256×256 coupled cells. Importantly, since we are presently dealing with partial differential equations governing the dynamics of calcium, the τ-leap method is employed as proposed by Gracheva et al. [27], where the fluxes, constituting the differential equations of the system, determine the probability that the concentration of a particular reactant (Z or Y) will increase or decrease. Reaction probabilities, defined by the fluxes of the differential equations, are ascribed to the reaction mechanism as described in [27]. In accordance with the reaction probabilities, a discrete change of concentration of the form $k_x/(N_A\chi)$ is performed at each iteration, where k_x is proportional to the flux of the corresponding reactant during time τ, N_A is the Avogadro's number, and χ is the volume of each individual cell.

In Fig. 1 we show characteristic snapshots of the spatial grid for four different volumes χ of individual cells. Importantly, χ directly determines the level of internal noise to which the medium is exposed. Small cellular volumes correspond to large levels of stochasticity, while increasing values of χ eventually introduce deterministic steady state solutions in the dynamics of each individual cell and ultimately result in a quiescent medium. It can be observed nicely that there exists an intermediate cellular volume for which the spatial dynamics of the medium is optimally ordered. In particular, an optimally pronounced internal stochasticity is able to induce coherent spatial waves throughout the medium, while smaller or larger values of χ clearly fail to have the same effect. At this point, we emphasize once more that the studied spatial dynamics is induced solely by internal noise. Moreover, it is important to note that the exact visual outlay of the waves presented in Fig. 1 would differ if the calculations had been repeated with a different noise seed, however, the subsequent analysis of spatial periodicity would yield similar results irrespective of particularities such as the position of the centre of the spiral wave. In what follows, we will show that there exists an optimal level of internal stochasticity for which a particular spatial frequency of calcium waves is resonantly enhanced, thus providing first evidences for internal noise spatial coherence resonance in biochemical tissue-like media.

3. Spatial dynamics

To quantify effects of different levels of internal noise on the spatial dynamics of the studied medium we calculate the structure function according to the equation

$$P(k_x,k_y)=\langle H^2(k_x,k_y)\rangle, \tag{1}$$

where $H(k_x, k_y)$ is the spatial Fourier transform of the $Z_{i,j}$ field at a particular time t and $\langle\ldots\rangle$ is the ensemble average over different temporal realizations of the spatial grid. To study results obtained according to Eq. (1) more precisely, we exploit the circular symmetry of $P(k_x, k_y)$ as proposed in [20]. In particular, we calculate the circular average of the structure function according to the equation.

$$s(k)=\int_{\Omega_k}P(\vec{k})\,\mathrm{d}\Omega_k, \tag{2}$$

where $\vec{k}=(k_x,k_y)$, and Ω_k is a circular shell of radius $k=|\vec{k}|$. Fig. 2 shows results for various χ. It is evident that there indeed exists a particular spatial frequency $k=k_{\max}$ that is resonantly enhanced for a particular cellular volume χ defining an intermediate level of internal stochasticity to which the medium is exposed.

To quantify the ability of a particular cellular volume to extract the characteristic spatial periodicity of calcium waves in the medium more precisely, we calculate the signal-to-noise ratio according to $\rho=s(k_{\max})/\tilde{s}$, where $\tilde{s}=[s(k_{\max}-\Delta k_a)+s(k_{\max}+\Delta k_b)]/2$ is an approximation for the level of background fluctuations in the system, and $(\Delta k_a,\ \Delta k_b)$ determine the width of the peak around $k_{\max}$ [local minima of $s(k)$ on both sides of $k_{\max}$]. Thus, ρ measures the normalized height of the peak at $k_{\max}$ for each particular χ. Fig. 3 shows how ρ varies with χ. It is evident that there exists an optimal intensity of internal noise

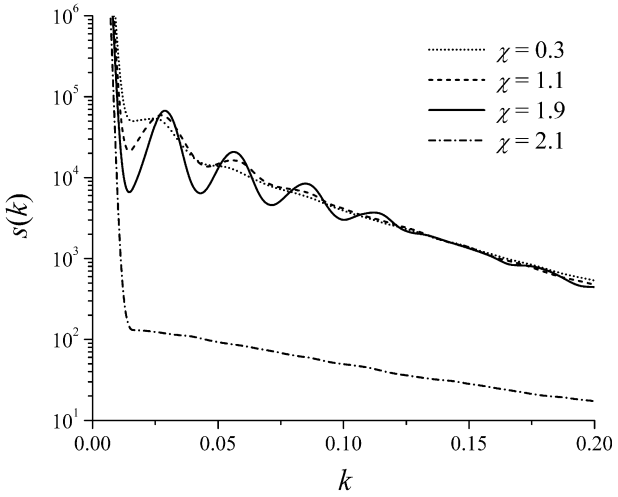

Fig. 2. Circular average of the structure function for different cellular volumes χ.

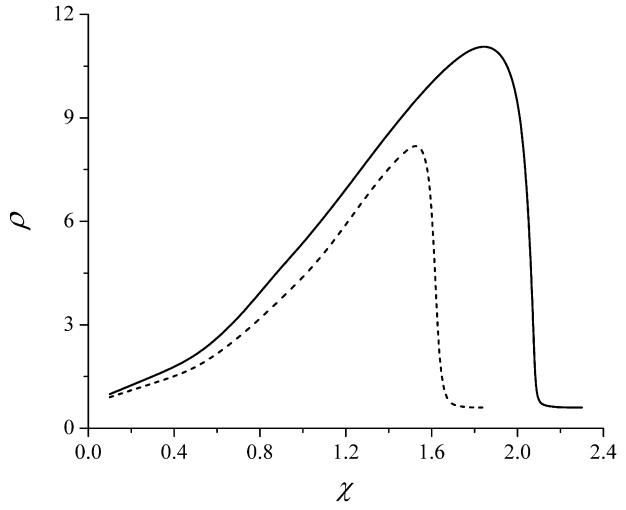

Fig. 3. Internal noise spatial coherence resonance in the studied medium. Signal-to-noise ratio ρ has a clear maximum in dependence on the level of internal stochasticity χ. The solid line shows results for $\beta = 0.26$ and the dashed line for $\beta = 0.25$.

for which the peak of the circularly averaged structure function is best resolved, thereby indicating the existence of internal noise spatial coherence resonance in the studied medium. Not surprisingly, the peak value of ρ decreases and shifts towards smaller χ as individual units are set further away from the Hopf bifurcation at $\beta = 0.2806$ (see dashed line in Fig. 3) because the threshold for inducing excitations rises. This result is also in agreement with findings obtained on a single cell [28], where the maximal temporal order that can be induced by internal stochasticity was also find decreasing with the increasing distance from the Hopf bifurcation. Moreover, it is instructive to relate the asymmetric shape of the resonance curve with the formation of spatial waves. In particular, as χ decreases to the value where first calcium waves emerge ρ increases rapidly because these waves travel on the minimal noisy support needed that still warrants their existence. Hence, they are minutely perturbed by noise and thus smooth and ordered, resulting in maximal ρ. As χ decreases further, the increasing stochasticity indents the ordered spatial waves, and thus induces the downfall of ρ. However, this process is gradual, thus resulting in a near-linear dependence of ρ on χ. The above reasoning can be beautifully collaborated by snapshots presented in Fig. 1, where the swift transition from quiescence to superbly ordered spiral calcium waves is inferable from the two bottom panels, while the gradual deterioration of spatial order due to increasing stochasticity is evident in the upper two panels.

Before we finally turn to explaining the results, we emphasize that it is fascinating to notice that above findings outline also a transition from stochasticity, present at the level of each individual cell, towards deterministic behaviour often observed at the organic level. In particular, while temporal traces of intracellular calcium oscillations at real-life conditions show clear traits of stochasticity [29], the recordings of functions at the level of an organ are often deterministic [30]. While results in [29] show the transition from stochasticity towards determinism for the temporal dynamics of coupled cells, present results show that in fact also the spatial dynamics may become prevalently deterministic as individual cells are coupled to form a tissue-like medium.

To shed light on the above-reported internal noise spatial coherence resonance, we first briefly summarize findings obtained when studying spatial coherence resonance in excitable media [21]. It has been argued that, since individual excitable units have a noise robust characteristic firing time τ [31], additive spatiotemporal noisy perturbations are able to extract a characteristic spatial frequency of waves in a resonant manner so that $k_{\max} \propto 1/\sqrt{\tau D}$. Presently, each individual cell may also exhibit rapid elevations of calcium concentration by an appropriate level of internal stochasticity. Also, the duration of the elevation phase is, as by excitable units, fairly robust against noise and thus warrants the observation of temporal internal noise coherence resonance if only the system is near a Hopf bifurcation point [28]. However, even by fairly large levels of noise, elevations of calcium cannot follow each other immediately one after the other, as this is the case by excitable units whose steady states are nodes, but there exists a certain refractory time after each elevation that is needed for the internal store of calcium in the cell to be refilled. Mathematically, this manifest so that the steady state of the present model is not a stable node but a focus. Due to the refractory times, a randomly induced wave of calcium, emerging identically as by excitable media, is temporarily unable to transmit information to the opposite site of its propagation direction. Thus, once the wave leaves the absorbing boundaries of the spatial grid the system has little or no recollection, depending on the duration of the refractory time and the size of the spatial grid, of its existence. If, however, the refractory time is short enough and the spatial grid large, as is presently the case, spatial periodicity may still emerge out of noise. The general mechanism behind this so-called emergence of spatial periodicity in the presence of memory loss has been studied precisely for additive spatiotemporal noise in [23], while here we show that internal stochasticity, being an innate property of constitutive units of the medium, can have a conceptually identical impact on the spatial dynamics thus warranting the observation of internal noise spatial coherence resonance.

4. Discussion

We show that internal cellular stochasticity in the medium of diffusively coupled cells is able to extract an inherent spatial frequency of calcium waves in a resonant manner. The phenomenon is a novel observation of internal noise spatial coherence resonance in biochemical tissue-like media.

It should be noted that although coherence resonance phenomena have been extensively studied in arrays of

dynamical systems [32,33], our work focuses explicitly on the spatial [20,21] rather than temporal or spatiotemporal system scale. Moreover, we do not apply additive or multiplicative external noise, but show that a characteristic spatial frequency of calcium waves in the medium of diffusively coupled cells can be a consequence of internal cellular stochasticity only.

It is fascinating that the internal stochasticity, present at the level of each individual cell, may lead to deterministic behaviour often observed at the level of an organ [30]. In contrast to the results in [29], reporting the transition from stochasticity towards determinism for the temporal dynamics of coupled cells, present results show that also the spatial dynamics may become prevalently deterministic as individual noisy cells are coupled to form a tissue-like medium. Since it is well established that virtually all real-life phenomena at the cellular level are heavily affected by internal stochasticity [8,34], the prevalence of determinism at larger levels may appear somewhat puzzling. Our theoretical results suggest that this discrepancy can be attributed to the temporal [29] and, as evidence here, also to spatial self-organisation of individual cellular oscillators due to influences from neighbouring cells. Remarkably, thereby the intensity of stochasticity at the level of constitutive units appears vital for the behaviour at larger scales, thus intimately linking tissue and organ functioning with intracellular processes, in turn suggesting interesting possibilities for further theoretical as well as experimental studies.

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