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Pacemaker enhanced noise-induced synchrony in cellular arrays

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Abstract

We study effects of additive noise on a pacemaker driven excitable cellular array. We find that the subthreshold periodic pacemaker can largely enhance noise-induced synchrony in the array already at very small noise intensities. The phenomenon is tested for robustness against various diffusion coefficients and system sizes. Results are discussed in view of their biological importance.

Keywords: Pacemaker; Coherence resonance; Synchronization; Cellular array

1. Introduction

It is a well-established fact that noise can play an ordering role in temporal as well as spatially extended systems [1–3]. While often the constructive role of noise is revealed in conjunction with a deterministic signal acting on the system [4–16], remarkably, random perturbations alone can also have positive effects on the system's dynamics [17–27]. In the former case one generally speaks of stochastic resonance [28], whereas the solely noise-induced phenomena are often addressed to as coherence resonance [20] or autonomous stochastic resonance phenomena.

Of immediate importance for the present work are articles studying stochastic [7,29–32] and coherence [19,21–23,33,34] resonance phenomena in arrays of coupled systems. It has been discovered that both stochastic and coherence resonance can be largely enhanced by the incorporation of a single system into an array, which lead to terming these phenomena array-enhanced stochastic [7] and coherence [33] resonance, respectively. Another interesting phenomenon is the so-called system size resonance [31,35], where a resonant dependence of the system's response to noisy perturbations was obtained solely by varying the number of units constituting the array, while other parameters such as the coupling and noise strength were left constant. Much interest has also been devoted to the study of effects of different network topologies on stochastic [32] and coherence [34] resonance. In either case it has been discovered that arrays with small-world connectivity [36,37] facilitate the occurrence of constructive effects of noise in comparison to regularly coupled arrays.

Presently, we study a new type of arrays that closely resemble biological real-life configurations in that not all of the array units are subjected to a deterministic periodic forcing but only a single unit. In particular, such array configurations correspond to biological systems that incorporate so-called pacemakers. Pacemakers are isolated cells in the tissue that dictate neighbouring cells the operating rhythm, i.e., pace, and so control the functioning of the whole organ. One of the most prominent organs that has pacemaker cells is the human heart [38,39]. The heart functioning, however, is not the only example of a pacemaker-regulated synchronous process. Also many arteries and arterioles, for example, exhibit rhythmical contractions which are synchronous over considerable distances [40]. A well-known network of pacemaker cells are also the so-called interstitial cells of Cajal (ICC), which regulate the contractility of many smooth muscle cells in several organs, particularly in the gastrointestinal tract [41]. Similarly in the urethra, ICC distributed amongst smooth muscle cells generate rhythmic activity [42]. Recently, non-contractile cells closely resembling ICC were identified also in the wall of portal vein and mesenteric

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artery [43]. Although functions of these cells are not yet fully understood, in portal vein they may act as pacemakers driving the spontaneous activity of the muscle. Moreover, it should be noted that pacemakers are not characteristic only for whole organs or tissue. In some cells, in particular in larger cells like eggs, several parts of a cell can act as pacemakers. For example, in highly polarised egg cells cortical endoplasmic reticulum rich clusters act as pacemaker sites dedicated to the initiation of global calcium waves. These clusters are interconnected into a network supporting the calcium wave propagation throughout the egg [44].

Given the immense importance of pacemakers in various organs and cells, it is of outstanding importance to understand how the inclusion of a pacemaker into a noisy cellular array affect its functioning, whereby noise is introduced to the system under the assumption that random influences are an inseparable part of every real-life process. With this motivation, we study effects of additive Gaussian noise on a pacemaker driven excitable cellular array, which is described by a simple mathematical model of intracellular calcium oscillations [47]. In accordance with previous studies [48], we find that additive noise alone is able to induce synchronous firing of array units. Next, in addition to noise, we introduce to the system a subthreshold periodic pacemaker which affects only one array unit. We find that the excitatory pacemaker can largely enhance the noise-induced synchrony in the array. Moreover, we determine optimal and sufficient conditions with respect to various diffusion coefficients and system sizes for the occurrence of this phenomenon. Finally, obtained results are discussed in view of their biological importance for vascular rhythmicity, contractility of gastrointestinal smooth muscle cells, and intercellular communication.

2. Results

To model the pacemaker-driven array we use a simple model of intracellular calcium oscillations [47] as the basic unit of the system, whilst an artificial periodic pulse train, which is introduced to a single array unit, models the pacemaker. The model takes the form

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = a\frac{y_i x_i^4}{x_i^4 + b^4} - cx_i + dy_i + e - fx_i + D(x_{i-1} + x_{i+1} - 2x_i) + \sigma\xi_i, \tag{1}$$

$$\frac{\mathrm{d}y_i}{\mathrm{d}t} = -a\frac{y_i x_i^4}{x_i^4 + b^4} + cx_i - dy_i, \tag{2}$$

where x_i and y_i are the concentrations of calcium in the cytosol and endoplasmic reticulum, respectively, $a = 1.2$, $b = 3.0$, $c = 2.0$, $d = 0.01$, $e = 0.8$, and $f = 1.0$ are system parameters governing the dynamics of a single noise-free array unit, D is the diffusion coefficient, σ is the standard deviation of the white Gaussian noise term ξ_i satisfying $\langle \xi_i(t)\xi_j(t')\rangle = \sigma\delta_{ij}\delta(t-t')$, whilst $i = 1, \ldots, n$ indexes individual array units. For details regarding the biological meaning of variables and parameter values see [47]. The artificial periodic pulse train modelling the pacemaker is given by

$$\Psi(t) = \begin{cases} g, & (t \bmod t_\Psi) \geqslant (t_\Psi - w), \\ 0, & \text{else}, \end{cases} \tag{3}$$

where t_Ψ is the oscillation period of the pacemaker, w is the width and g the amplitude of each spike, respectively. The pacemaker $\Psi(t)$ is introduced as an additional term to Eq. (1) only for $i = 1$. The whole system is simulated numerically with the Heun method [2] and periodic boundary conditions.

For above given system parameters and $\sigma = 0$ a single array unit is governed by an excitable steady state $(x_i, y_i) = (0.8, 99.76544)$, which we use as the initial condition in all subsequent calculations. Thus, for $\sigma = g = 0$ the array remains quiescent for all t. The excitable steady state looses its stability and enters an oscillatory regime via a Hopf bifurcation at $a = 1.213$, indicating the fact that the system is operated very near the bifurcation point ($a = 1.2$), and thus has a low excitability threshold. Thereby, we set up optimal conditions for studying noise-induced effects on the studied pacemaker-driven system. Importantly, we note that excitable steady states are especially relevant in nature, were it is often the case that quiescence has to be abruptly replaced by oscillatory behaviour upon detection of weak external stimuli. Mathematically this is feasible only when the system with oscillatory states is waiting in an excitable steady state that is very close to the bifurcation point, as is the case presently.

Following this brief introduction elucidating basic dynamical properties of a single deterministic unit of the array, let us start the analysis by studying solely noise-induced oscillations of the system. Thus, we set $g = 0$ and vary σ for some fixed values of the system size n and diffusion coefficient D. As a measure for the array synchrony, i.e., to determine if all array units oscillate with the same noise-induced predominant oscillation frequency, we introduce a similarity function of the form

$$Q(\Delta t) = \frac{1}{n-1}\sum_{i=1}^{n-1}\sqrt{\frac{\langle (x_i(t+\Delta t) - x_{i+1}(t))^2\rangle}{(\langle x_i^2(t)\rangle \cdot \langle x_{i+1}^2(t)\rangle)^{1/2}}}, \tag{4}$$

which simply tests each pair of neighbouring units (x_i, x_{i+1}) for synchrony individually, and then adds contributions of all pairs to yield the final result. Whenever Δt approaches the mutual predominant oscillation period of x_i and x_{i+1} (if the latter exists) for all possible i, $Q(\Delta t)$ exhibits a local minimum. If all array units would oscillate with an oscillation period Δt and were perfectly synchronized, this would yield $Q(\Delta t) \equiv 0$. However, since we are analysing noise-induced oscillations this scenario is not feasible. Instead, we can expect to observe a local minimum of $Q(\Delta t)$ that is better expressed for some σ than other. By evaluating the results presented in Fig. 1, we find that there indeed exists a particular σ for which the array synchrony is well pronounced, whereas small and intermediate σ fail to yield similarly convincing results. In particular, whilst $\sigma = 0.0005$ and $\sigma = 0.00125$ constitute to weak perturbations to evoke synchronous firing with a well-defined oscillation period, note that for $\sigma = 0.003$ all array units fire synchronously with a pre-

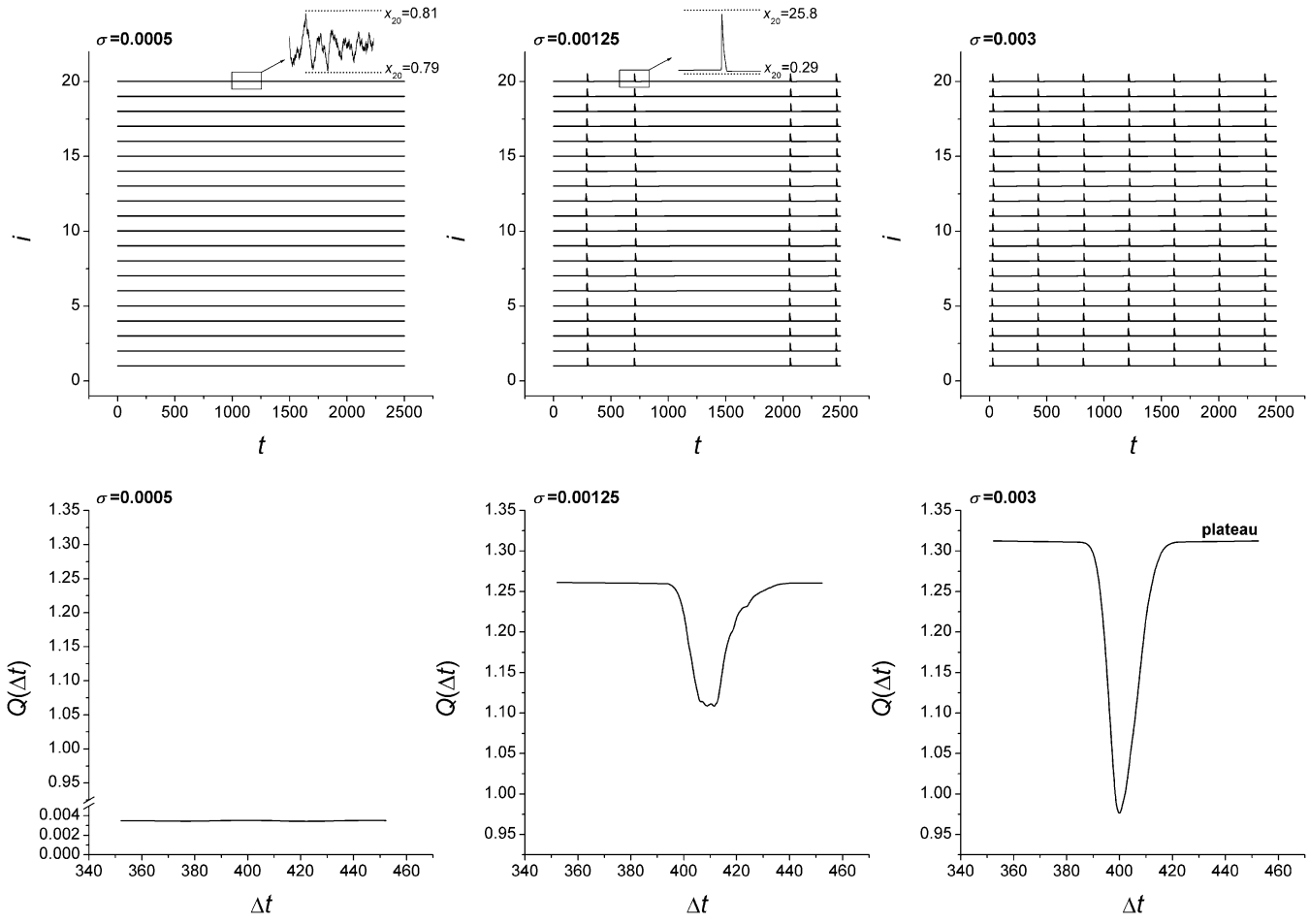

Fig. 1. Solely noise-induced oscillation in the studied cellular array and the corresponding similarity function $Q(\Delta t)$ for various σ. The system size and diffusion coefficient were set to $n = 20$ and $D = 0.01$, respectively.

dominant oscillation period $\Delta t \approx 400$, which manifests as a single well-expressed local minimum at $Q(\Delta t = 400)$. This is the fingerprint of array coherence resonance as previously described in [48], which constitutes that random perturbations are able to evoke ordered and synchronous firing of individual array units even in the absence of additional deterministic inputs.

Next, it is of interest to analyse how the inclusion of a pacemaker affects the observed noise-induced behaviour. For this purpose, we set $t_\Psi = 400$, $w = 2.0$, and $g = 0.008$ in Eq. (3). The pacemaker frequency $(1/t_\Psi)$ is chosen equal to the best-expressed frequency of solely noise-induced oscillations, which also matches the frequency of deterministic oscillations that emerge immediately after the Hopf bifurcation at $a > 1.213$ and is thus also the most probable frequency to be induced by noisy perturbations [16], whilst w and g are chosen so as to prohibit the pacemaker to induce spiking behaviour in the array without the inclusion of noise for any D and n. Moreover, to present the following results in a more compact form, we introduce the so-called synchrony parameter S as $S = Q(\Delta t = 400) - Q(\Delta t = \text{plateau})$ (see Fig. 1), which measures the relative depth of the local minima at $\Delta t = 400$, and thus the quality of synchrony in the array. The more negative the S, the better the quality of synchronization in the array.

First, we study the impact of the pacemaker in dependence on different σ and D by a fixed system size $n = 20$. Results in Fig. 2 show S for the solely noise-driven array and the pacemaker affected noise-driven array separately in the left and right panel, respectively. It is evident that the subthreshold pacemaker is able to enhance noise-induce synchrony in the cellular array for various D, extending over several orders of magnitude. Remarkably also, synchronous firing of array units sets in already at much smaller σ than in the solely noise-driven array. The reported increase of noise sensitivity is rather surprising since the pacemaker is introduced as a subthreshold forcing, affecting only a single array unit. Thus, it appears that the diffusive coupling of individual units into arrays facilitates the transmission of weak signals across tissue, much in accordance with recent experimental findings [40]. Results in the right panel of Fig. 2 also suggest that, in fact, there exist an optimal D that allows the best transmission and amplification of the pacemaker-emitted signal. In our case $D \approx 0.013$. On the other hand, there also exist a lower ($D \approx 0.0003$) and an upper ($D \approx 0.04$) bound for which the pacemaker still has a positive impact on the array synchrony. The lower bound corresponds to the lowest diffusion coefficient, i.e., gap-junctional permeability, that still enables a persuasive (fast and strong) enough transmission of pacemaker-induced excitations to other array

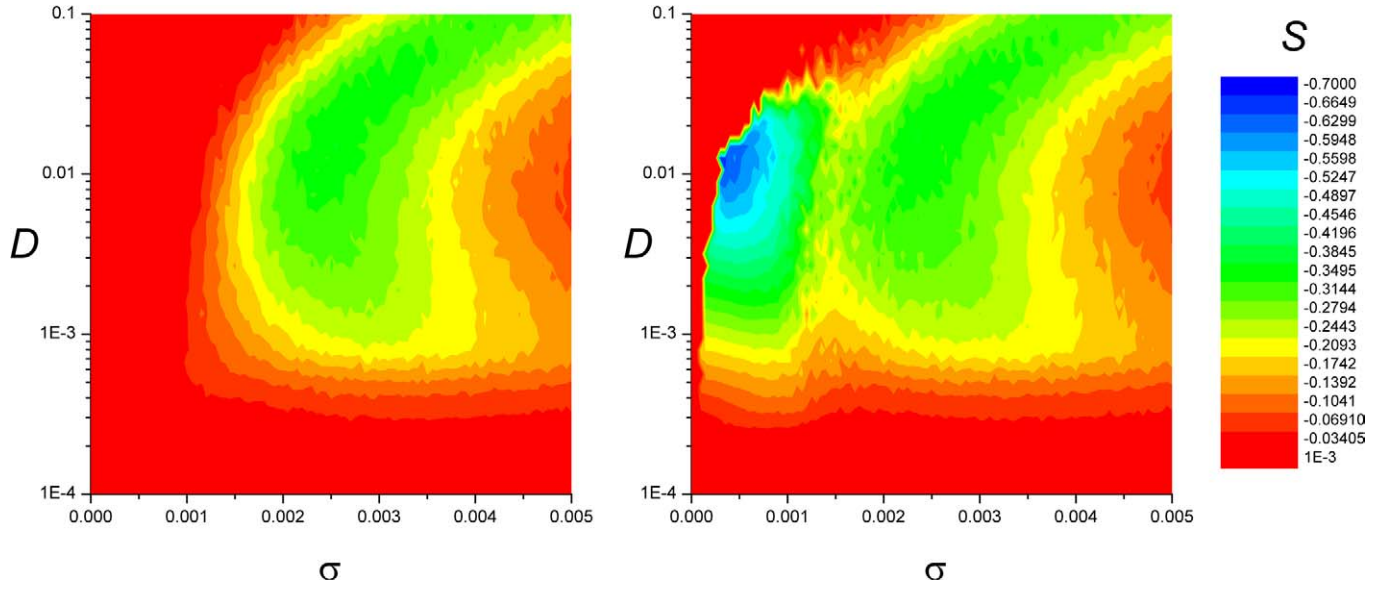

Fig. 2. (Colour online.) Noise-induced synchrony in the studied array for various D and σ, calculated by a fixed system size $n = 20$. The colour map on the left shows results obtained without the inclusion of the pacemaker ($g = 0$), whilst the right panel features results pertaining to the pacemaker-driven noisy array. The most synchronized state is denoted by the blue colour. Note that the abscissa has a logarithmic scale.

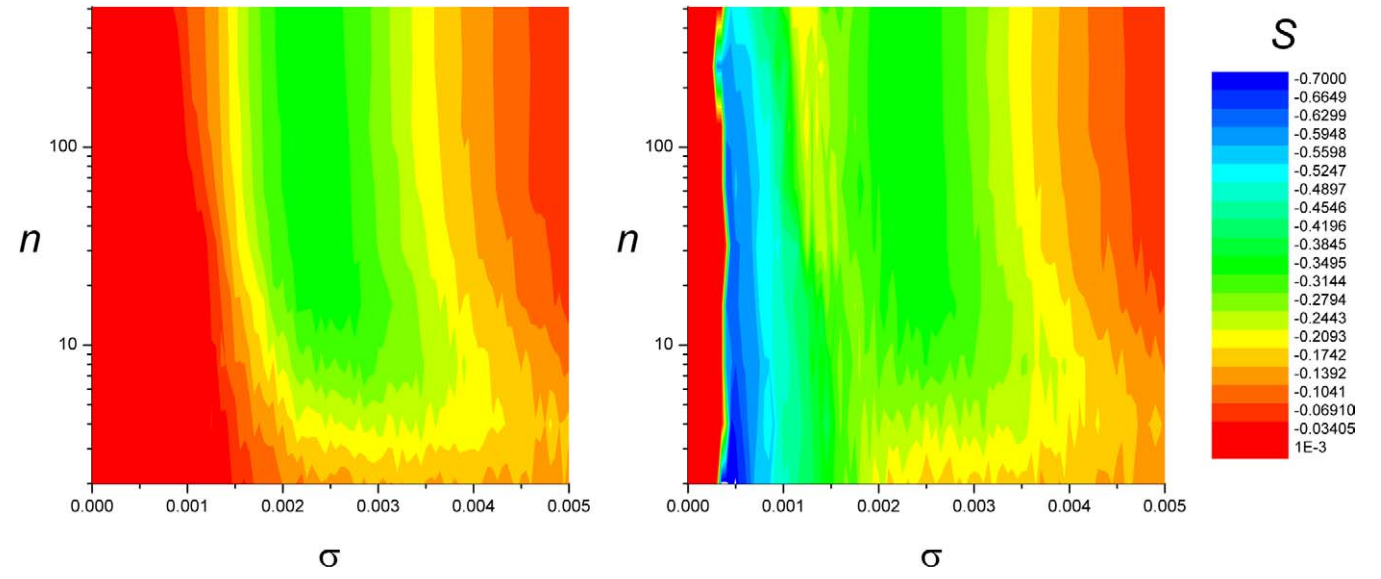

Fig. 3. (Colour online.) Noise-induced synchrony in the studied array for various n and σ, calculated by a fixed diffusion coefficient $D = 0.0126$. Other details are the same as in Fig. 2.

units, whilst the upper bound corresponds to the fastest allowed diffusion that still prevents excitations to average-out and thus fade across the array.

Finally, it remains of interest to verify the robustness of results presented in Fig. 2 against variations of the system size n. Therefore, we set D equal to the value where the inclusion of the pacemaker was most effective, and vary σ and n as presented in Fig. 3. As in Fig. 2, results for the solely noise-driven array and the pacemaker affected noise-driven array are shown separately in the left and right panel, respectively. First, we note that for the solely noise-driven array one can observe that somewhat larger system sizes ($n \geqslant 8$) better support the noise-induced synchrony than smaller ones, thus evidencing the so-called array enhanced coherence resonance in the studied cellular array, similarly as previously reported in [33] for an array consisting of non-identical FitzHugh–Nagumo excitable units. Second, it is evident that the pacemaker assures enhanced synchrony in the array for various n already at very small σ, whereby the positive effect slightly diminishes with the increasing n. This, however, is not surprising since the pacemaker is introduced only to a single array unit, and thus it is only natural to see its effect fade away as locally induced excitations must propagate to increasing numbers of distant array units. We hypothesize, however, that this problem might be overcome by considering not just regularly-coupled but also arrays with small-world connectivity [37]. Thereby, random unit

wiring would enable locally induced excitations to jump instantaneously to a very distinct array site, and from thereon successfully evoke other synchronous excitations that would otherwise not be feasible via a regular route. Confirming this hypothesis would imply that small-world networks might be the natural choice of nature to assure signal transmission and detection at the lowest cost, i.e., with as few energy consuming pacemaker units as possible. Nevertheless, results presently at hand indicate that there exist upper bounds regarding the number of regularly coupled cells that can be effectively driven by a single pacemaker cell, thereby stressing the necessity for their regular occurrence in tissue.

3. Discussion

We study effects of additive Gaussian noise in conjunction with a pacemaker driving on the firing pattern of an excitable diffusively coupled cellular array, which is modelled by a simple model of intracellular calcium oscillations [47]. Mainly, we find that the inclusion of a pacemaker can largely enhance the noise-induced synchrony in the array already at very small noise intensities. Moreover, we show that there exist an optimal diffusion coefficient facilitating the transmission and dissemination of the pacemaker-emitted signal. Not surprisingly, we also find that the pacemaker driving loses its constructive effects as the system size increases, thus indicating the necessity for the existence of a network, rather than a single pacemaker cell to pace an organ. Besides these novel findings, we also show that the so-called array-enhanced coherence resonance, as described previously in [33], is also feasible in excitable cellular arrays modelling diffusively coupled cells in tissue.

Since the theoretical study of effects of pacemakers on spatially extended systems is still in its infancy, there exist several issues that have yet to be addressed properly. As already noted, it would be interesting to elucidate to what extended different network topologies facilitate or hinder pacemaker driving of the system. Recently, it has been shown that depending on the pacemaker frequency and the strength of coupling, the pacemaker can entrain an entire random network, whereas the entrainment window decreases with the depth of the network [49]. It would also be of interest to examine to what extend the pacemaker is able to induce a synchronous response of the array with a frequency different from the inherent, i.e., exclusively noise-induced, one. Our preliminary studies suggest that there exist upper and lower bounds for the frequency a subthreshold pacemaker is able to impose on a noisy array. While the upper bound is due to the fact that the system, having a stable focus as an excitable steady state, needs a finite amount of time for re-settling onto the steady state after an excitation, whereby during that time it is robust against external perturbations, the existence of the lower bound is somewhat more puzzling and needs to be clarified in future studies.

Besides its theoretical value, the present study also has biological relevance, since intracellular calcium oscillations have been found to be of key importance for transmission of vital information amongst various cell compartments as well as coupled cells in tissue. While the mechanisms underlying vascular rhythmicity, for example, have been investigated for many years, significant advances have been made recently with the advent of new imaging techniques for visualizing intracellular calcium release [40]. These methods, when combined with mechanical and electrophysiological recordings, have demonstrated that the vascular rhythm depends on calcium released from intracellular stores within the smooth muscle cells and on cell coupling via gap junctions to synchronise calcium oscillations among adjacent cells. Thus, the basic mechanism for rhythmic activity in arteries differs from its counterpart in non-vascular smooth muscles where specific networks of pacemaker cells generate electrical potentials which drive activity within the otherwise quiescent muscle cells. Similar to the very recent studies in vascular rhythmicity, showing that the basic mechanism of the pacemaker rhythm-regulation is based on store-operated intracellular calcium oscillations [40], for the gastrointestinal smooth muscle cells it has also been shown that the intracellular calcium oscillations in ICC represents the primary pacemaker activity in the gut [45]. Moreover, for intercellular communications, it has been shown that calcium is involved in the gap-junctional connectivity between ICC pacemaker cells and between ICC and smooth muscle cells [46]. Thus, the present study provides numerical results that blend nicely with the existing body of experimental findings, while hopefully providing also some new pointers for future experimental work regarding pacemaker-guided rhythm generation in isolated coupled cells and tissue.

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