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Local dissipation and coupling properties of cellular oscillators A case study on calcium oscillations

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Abstract

Synchronised signal transduction between cells is crucial, since it assures fast and immutable information processing, which is vital for flawless functioning of living organisms. The question arises how to recognise the ability of a cell to be easily coupled with other cells. In the present paper, we investigate the system properties that determine best coupling abilities and assure the most efficient signal transduction between cells. A case study is done for intercellular calcium oscillations. For a particular diffusion-like coupled system of cellular oscillators, we determined the minimal gap-junctional permeability that is necessary for synchronisation of initially asynchronous oscillators. Our results show that dissipation is a crucial system property that determines the coupling ability of cellular oscillators. We found that low dissipation assures synchronisation of coupled cells already at very low gap-junctional permeability, whereas highly dissipative oscillators require much higher gap-junctional permeability in order to synchronise. The results are discussed in the sense of their biological importance for systems where the synchronous responses of cells were recognised to be indispensable for appropriate physiological functioning of the tissue.

Keywords: Calcium oscillations; Cell coupling; Gap junctions; Dissipation; Lyapunov exponents

1. Introduction

Synchronised signal transduction is of crucial importance, since it assures fast and immutable information processing. For example, it has been shown experimentally that beta cells, which form pancreatic islets must function highly coordinated in order to produce enough insulin [1]. Moreover, experimental studies on several other cell types also showed that Ca^{2+} signals propagate through tissue in a highly organized manner in time and space [2–6]. Several experimental [7–9] as well as theoretical studies [10,11] emphasize the importance of inositol trisphosphate (IP_3) as an important messenger in many cells, inducing synchronised Ca^{2+} oscillations in tissue. In some other cells, electrical coupling plays a vital role assuring synchronised oscillations among coupled cells [12–15]. However, the calcium ions seem to be the most important second messengers assuring cell synchronisation in general [16–22].

The importance of calcium ions is well established at the intra- as well as intercellular level (for review see Refs. [23,24]). In excitable as well as in non-excitable cells, a significant part of signal transduction from receptors at the cell membrane to enzymes, controlling the complex behaviour of the biological systems, is performed by the oscillatory changing of free cytosolic Ca^{2+} concentration. Cytosolic Ca^{2+} oscillations regulate many cellular processes from egg fertilization to cell death [25]. The mechanisms of these oscillations have been intensely investigated both from experimental and theoretical point of view (for review see Refs. [24,26]).

At the intercellular level, synchronisation of cytosolic Ca^{2+} oscillations plays a vital role in the communication between adjacent cells in tissue. During the last decade, experimental evidences of intercellular spread of Ca^{2+} oscillations have been provided (for review see Refs. [23,27,28]). For example, in hepatocytes [9,16,18], spinal cord astrocytes [29], chromaffin cells [13], epithelial cells [8,30], cholangiocytes [22], keratinocytes [21] and different

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malignant cells [19,20] synchronised Ca^{2+} oscillations between coupled cells have been found. The majority of intercellular communications via calcium ions relies on gap-junctional signal trunsduction ([16–22], for review see Refs. [23,27,28]). Gap junctions are intercellular channels that connect the interiors of coupled cells and have an important function in maintaining tissue homeostasis and are thus a critical factor in the life and death balance of cells. Sáez et al. [16] showed that hepatocytes can communicate directly via calcium transmission through gap junctions. Tjordmann et al. [18] studied connected hepatocytes pairs and triplets, which were connected through gap junctions. They found that calcium diffusion between adjacent cells guaranties synchronised oscillations of Ca^{2+} in the coupled cells. In cholangiocytes, Bode et al. [22] discovered that apical exposure to ATP induced Ca^{2+} oscillations that were coordinated among neighbouring cells. Furthermore, they showed that inhibition of gap junctions permeable to Ca^{2+} ions desynchronised the Ca^{2+} oscillations. Korkiamaki et al. [21] found that the type 1 of neurofibromatosis is related with altered calcium-mediated signalling between keratinocytes. Calcium signalling through gap junctions was also found between malignant glioma cells and astrocytes [19]. Malignant cells are prominent examples of Ca^{2+} based communications through gap junctions. They form gap-junctional connections with healthy cells across the tissue and so spread, causing cell death. Krutovskikh et al. [20] showed that Ca^{2+} ions are the most probable cell-killing messengers that spread through gap-junctional connections between healthy and malignant cells of tissue.

Coupling of calcium oscillations has also been studied by use of mathematical modelling (for review see Ref. [24]). Höfer [31], for example, showed that hepatocytes, with initially different oscillation frequencies, when coupled by gap junctions, synchronise because of calcium diffusion between adjacent cells. Moreover, Höfer et al. [32] studied the interrelation between the cytoplasmic Ca^{2+} diffusion coefficient and the required gap-junctional permeability for synchronised calcium oscillation among coupled cells. They also examined effects of varying calcium buffer concentration and the cytoplasmic inositol trisphospahte level on coupling properties of cellular oscillators. Zhang et al. [33] reported the phenomenon of internal stochastic resonance in a diffusion-like coupled model. They coupled identical cells with the same oscillation frequency and induced asynchronous oscillations by using different initial conditions for individual oscillators. Their results indicate that noise can induce synchronisation in the initially unsynchronised system. Similar results were obtained by Gracheva et al. [34]. They found that stochastic effects in the coupled system improve agreement with experimental results. All these theoretical analyses [31–34] show that if the permeability of gap junctions, which are permeable to calcium ions, is high enough, and/or the stochastic effects are taken into account, synchronisation of initially asynchronous Ca^{2+} oscillations in a coupled system can be achieved. The question arises, however, which are those system properties that determine the highest coupling abilities of coupled cells, i.e. under which internal system conditions the minimal gap-junctional permeability is needed in order to synchronise the initially asynchronously oscillating coupled cells.

In the present paper, we study the system properties of a single oscillator, under which synchronisation of initially unsynchronised cells is most easily to achieve. We introduce local dissipation as a measure for coupling ability of cellular oscillators. The local dissipation reflects the attractive properties of a limit cycle in phase space at a given time. The limit cycle in the phase space corresponds to Ca^{2+} oscillations in a single cell. Therefore, local dissipation seems to be a good measure for determining adaptation ability of the system to external perturbations and thus, synchronisation properties of individual oscillators. First, the interrelation between the local dissipation and the synchronisation ability with a well-defined cell-independent external forcing signal is studied. This gives basis for better understanding of the mechanisms involved in adaptation processes within single cells, which are crucial for understanding the synchronisation of coupled cells. The interrelation between the synchronisation properties of coupled cells and the local dissipation is studied for a diffusion-like coupled system of two cellular oscillators. In dependence on the local dissipation of the particular oscillator in the coupled system, we look for the minimal gap-junctional permeability that is necessary for synchronisation of initially asynchronous oscillators. Local dissipation and coupling properties of the dynamical system seem to be in close interrelation. The results obtained for two coupled oscillators can be easily generalised to multi-cellular systems. In Discussion, the biological importance of the results is discussed and some further applications of our findings are proposed for systems of coupled cells with other heterogeneities than studied in this paper.

2. Mathematical model

The role of local dissipation in synchronisation of Ca^{2+} oscillations is studied in a model for simple and complex Ca^{2+} oscillations [35]. In the model, the endoplasmic reticulum (ER) as well as mitochondria are taken into account as intracellular Ca^{2+} stores. After cell stimulation with a hormone, Ca^{2+} is released from the ER through IP_3-sensitive Ca^{2+} channels. The cytosolic Ca^{2+} concentration increases very rapidly due to calcium-induced calcium release (CICR) and begins oscillating. Calcium oscillations result from the Ca^{2+} exchange across the ER membrane, Ca^{2+} sequestration in mitochondria and Ca^{2+} binding to cytosolic proteins. Here, the model equations are only briefly presented (for details see Ref. [35]). The

Table 1
Model parameters for which all results are calculated unless otherwise stated

Parameter	Value
Total concentrations	
Ca_{tot}	90 μM
Pr_{tot}	120 μM
Geometric parameters	
ρ_{er}	0.01
ρ_{m}	0.01
β_{er}	0.0025
β_{m}	0.0025
Kinetics parameters	
k_{ch}	480–4650 s^{-1}
k_{leak}	0.05 s^{-1}
k_{pump}	20 s^{-1}
k_{in}	300 μM s^{-1}
k_{out}	125 s^{-1}
k_{m}	0.00625 s^{-1}
k_{+}	0.1 μM^{-1} s^{-1}
k_{-}	0.01 s^{-1}
K_1	5 μM
K_2	0.8 μM
Coupling parameters	
h	0–0.16 s^{-1}
a	0.02 s^{-1}

free Ca^{2+} concentrations in the cytosol (Ca_{cyt}), in the ER (Ca_{er}) and in the mitochondria (Ca_{m}) are calculated by the following differential equations (for parameter values see Table 1):

$$\frac{dCa_{cyt}}{dt} = J_{ch} - J_{pump} + J_{leak} + J_{out} - J_{in} + J_{CaPr} - J_{Pr}, \tag{1}$$

$$\frac{dCa_{er}}{dt} = \frac{\beta_{er}}{\rho_{er}}(J_{pump} - J_{ch} - J_{leak}), \tag{2}$$

$$\frac{dCa_{m}}{dt} = \frac{\beta_{m}}{\rho_{m}}(J_{in} - J_{out}), \tag{3}$$

where

$$J_{ch} = k_{ch}\frac{Ca_{cyt}^2}{Ca_{cyt}^2 + K_1^2}(Ca_{er} - Ca_{cyt}), \tag{4}$$

$$J_{pump} = k_{pump}Ca_{cyt}, \tag{5}$$

$$J_{leak} = k_{leak}(Ca_{er} - Ca_{cyt}), \tag{6}$$

$$J_{Pr} = k_{+}Ca_{cyt}Pr, \tag{7}$$

$$J_{CaPr} = k_{-}CaPr, \tag{8}$$

$$J_{in} = k_{in}\frac{Ca_{cyt}^8}{Ca_{cyt}^8 + K_2^8}, \tag{9}$$

$$J_{out} = \left(k_{out}\frac{Ca_{cyt}^2}{Ca_{cyt}^2 + K_1^2} + k_{m}\right)Ca_{m}. \tag{10}$$

The concentrations of free and occupied protein binding sites of proteins (Pr and $CaPr$, respectively) are calculated by conservation relations for the total protein binding sites in the cytosol (Pr_{tot}) and for the total Ca^{2+} concentration in the cell (Ca_{tot}):

$$Pr = Pr_{tot} - CaPr, \tag{11}$$

$$CaPr = Ca_{tot} - Ca_{cyt} - \frac{\rho_{er}}{\beta_{er}}Ca_{er} - \frac{\rho_{m}}{\beta_{m}}Ca_{m}. \tag{12}$$

In the basic model, described by Eqs. 1–12, Ca_{tot} is constant, while in case of cell coupling, this quantity is variable (see below).

Coupling properties are studied for the system of two cells coupled via a passive diffusion-like calcium transfer through gap junctions, which is justified by experimental evidences [16–22]. The calcium diffusion through gap junctions is modelled by an additional Ca^{2+} flux through the cell membrane [31–33]. Consequently, differential equations for the cytosolic Ca^{2+} concentration in each cell read:

$$\frac{dCa_{cyt,1}}{dt} = J_{ch,1} - J_{pump,1} + J_{leak,1} + J_{out,1} - J_{in,1} + J_{CaPr,1} - J_{Pr,1} + h\cdot(Ca_{cyt,2} - Ca_{cyt,1}), \tag{13}$$

$$\frac{dCa_{cyt,2}}{dt} = J_{ch,2} - J_{pump,2} + J_{leak,2} + J_{out,2} - J_{in,2} + J_{CaPr,2} - J_{Pr,2} + h\cdot(Ca_{cyt,1} - Ca_{cyt,2}) \tag{14}$$

where indexes 1 and 2 denote the two coupled cells and h is the effective gap-junctional calcium permeability.

The total concentration of calcium in the ith cell, $Ca_{tot,i}$, is due to coupling no longer constant. Therefore, additional differential equations are needed for calculating changes in

the total Ca^{2+} concentration in the first ($Ca_{tot,1}$) and in the second cell ($Ca_{tot,2}$):

$$\frac{dCa_{tot,1}}{dt} = h \cdot (Ca_{cyt,2} - Ca_{cyt,1}), \quad (15)$$

$$\frac{dCa_{tot,2}}{dt} = h \cdot (Ca_{cyt,1} - Ca_{cyt,2}), \quad (16)$$

All results are calculated for the parameter values given in Table 1 if not otherwise stated.

3. Results

We examine the coupling properties of two coupled cells for different levels of agonist stimulation (k_{ch}). The two cells are coupled via a passive diffusion-like calcium flux through gap junctions (see Eqs. (13) and (14)), which is very common in a large variety of cell types [16–22]. Initially, the two cells oscillate asynchronously, which is a consequence of different initial conditions, whereas the parameter values of both cells are identical (for parameter values see Table 1). The coupling ability of the cells is measured by determining the minimal coupling constant (h), for which the cells oscillate synchronously.

However, in order to analyse the system properties, which facilitate cell coupling, we first study the easiest way of a quasi-cell coupling. We examine cell responses to a cell-independent well-defined external signal. The external forcing ($J_{forcing}$) is applied in form of a pulsatile Ca^{2+} flux through the cell membrane. The term $h \cdot (Ca_{cyt,2} - Ca_{cyt,1})$ in Eq. (13) is replaced by the $J_{forcing}$, which has the form of Ca^{2+} spikes characteristic for the unforced model ($F(t)=Ca_{cyt}(t)$):

$$J_{forcing} = aF(t), \quad (17)$$

where a is a constant regulating the amplitude of the forcing signal.

First, the response ability of regular oscillations at k_{ch}=480 s^{-1} is examined. We apply the external signal ($J_{forcing}$) with given amplitude determined by the factor a=0.02 s^{-1}. The same signal is applied to the basic Ca^{2+} oscillations at two different times. In Fig. 1A, the first case is shown in which the basic Ca^{2+} oscillations (thick solid line) do not respond to the external signal (dotted line), whereas in Fig. 1B the response is well expressed in form of a new Ca_{cyt} spike (thin solid line), which emerges as a consequence of the external forcing. We applied the forcing signal systematically in the whole oscillation period of the basic Ca^{2+} oscillations to determine the region of response to the external signal with given form and amplitude (a=0.02 s^{-1}). The dashed line in Fig. 1A and B represents the boundary between the rigid part (left side) and the flexible part (right side). If the external signal $J_{forcing}$ with

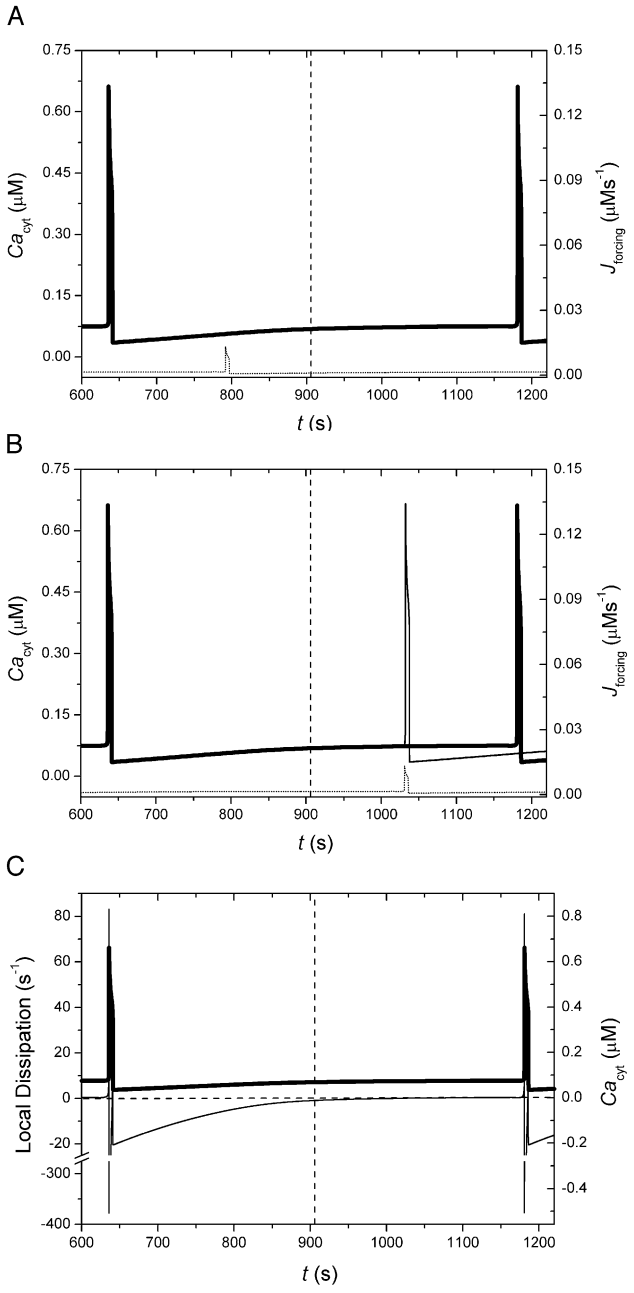

Fig. 1. Responses of the regular oscillatory regime at k_{ch}=480 s^{-1} to the external forcing ($J_{forcing}$, a=0.02 s^{-1}): (A) time course of Ca_{cyt} (thick solid line, left y-axis) remains unaffected by the external forcing (doted line, right y-axis) if it is applied in the rigid part of the oscillation period (left side of the dashed line); (B) time course of Ca_{cyt} (thick solid line, left y-axis) is altered (thin solid line, left y-axis) by the external forcing (doted line, right y-axis) if it is applied in the flexible part of the oscillation period (right side of the dashed line); (C) time course of the local dissipation (thin solid line, left y-axis) and time course of Ca_{cyt} (thick solid line, right y-axis) for one oscillation period.

a=0.02 s^{-1} is applied in the rigid part, there is no response, and contrary, a new spike emerges if the external signal is applied in the flexible part.

To understand these response abilities of the system presented in Fig. 1A and B, the time course of the local

dissipation should be considered. If an attractor in form of a limit cycle that corresponds to oscillations of cytosolic calcium in the cell is weakly attractive, i.e. has a low local dissipation, it seems much easier to alter its shape, thus a response to the external signal is more likely to occur. Therefore, the investigation of interrelation between the local dissipation and the response ability of the oscillator is reasonable. We calculate the local dissipation as the sum of diagonal elements of the Jacobian matrix for Eqs. 1–3. In Fig. 1C, the time course of local dissipation, together with the time course of Ca_{cyt} for k_{ch}=480 s^{-1} is presented. By comparing Fig. 1A–C, we see that the flexible region (on the right side of the dashed vertical line) is characterized by a very low, i.e. close to zero dissipation, whereas the rigid non-flexible region (on the left side of the dashed vertical line) is characterized by an increasingly higher dissipation.

In Fig. 2A and B, another example of the response ability of the model system is shown for the regular oscillatory regime at k_{ch}=480 s^{-1}. Again, the external periodic forcing of the same amplitude as above (a=0.02 s^{-1}) is applied to the basic Ca^{2+} oscillations at two different times. In Fig. 2A, the original time course (thick solid line) remains unaffected by the external forcing, whereas in Fig. 2B, a new Ca_{cyt} spike (thin solid line) appears due to the external perturbation. Like in Fig. 1A and B, the dashed vertical line in Fig. 2A and B represents the boundary between the rigid, non-flexible part and the well-adaptable, flexible part of one oscillation period. We see that for the oscillatory regime at k_{ch}=500 s^{-1} the line of separation is shifted much more to the right, compared to the oscillatory regime at k_{ch}=480 s^{-1}, thus the non-rigid, flexible region is much smaller. To explain this, we calculate the time course of local dissipation for the parameter value k_{ch}=500 s^{-1}. In Fig. 2C, the time course of the local dissipation, together with the time course of Ca_{cyt} for k_{ch}=500 s^{-1} is presented. By comparing the two time courses of local dissipation presented in Figs. 1C and 2C, we see that the time interval in which the dissipation is low, i.e. very close to zero, is much smaller in Fig. 2C than in Fig. 1C. This shows that the local dissipation plays an important role in determining the adaptation properties of a dynamical system and gives strong evidences that small values of local dissipation are a necessary condition for high response and adaptation ability that characterise a flexible system.

To demonstrate the interrelation between the local dissipation and the response ability of the model system even further, we examine the regular oscillatory regime at k_{ch}=800 s^{-1}, which is characterised by a time course of the local dissipation that is close to zero only in an extremely narrow time interval (see Fig. 3). The consequence of the predominant rigid part of the oscillation regime is that no effects occur due to external forcing with the same amplitude as used in the previous calculations (a=0.02 s^{-1}). An external forcing with much higher amplitude is necessary to provoke an effect, i.e. alteration of the basic Ca^{2+} oscillations.

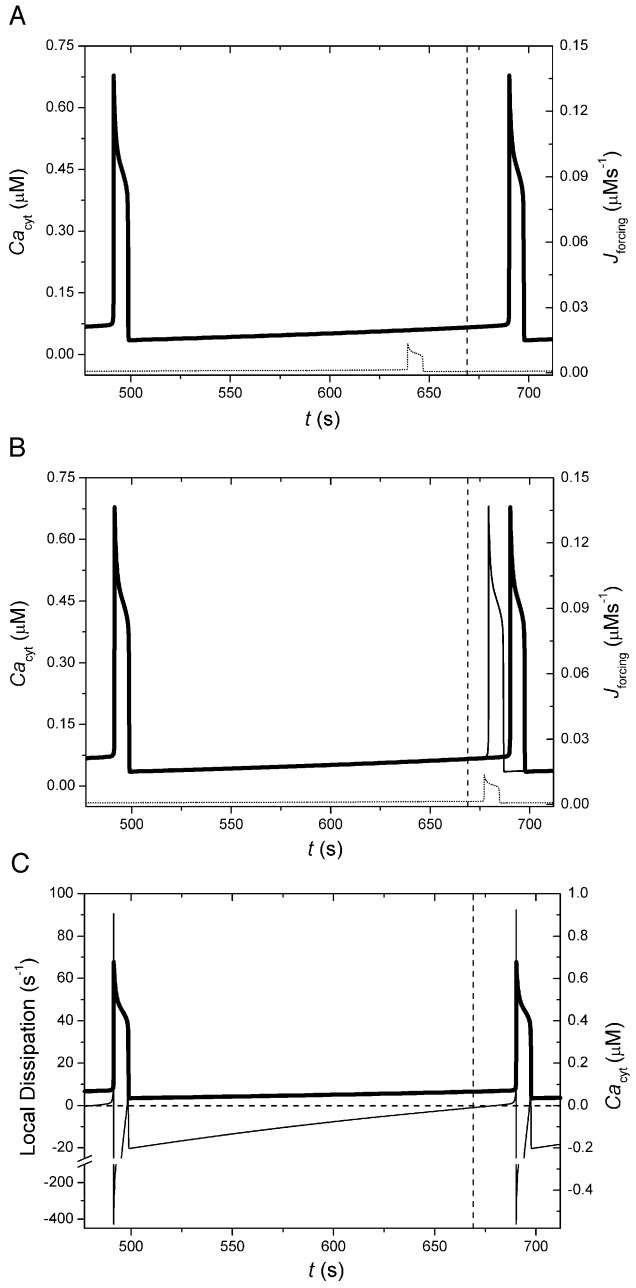

Fig. 2. Responses of the regular oscillatory regime at k_{ch} = 500 s^{-1} to the external forcing ($J_{forcing}$, a = 0.02 s^{-1}): (A) time course of Ca_{cyt} (thick solid line, left y-axis) remains unaffected by the external forcing (doted line, right y-axis) if it is applied in the rigid part of the oscillation period (left side of the dashed line); (B) time course of Ca_{cyt} (thick solid line, left y-axis) is altered (thin solid line, left y-axis) by the external forcing (doted line, right y-axis) if it is applied in the flexible part of the oscillation period (right side of the dashed line); (C) time course of the local dissipation (thin solid line, left y-axis) and time course of Ca_{cyt} (thick solid line, right y-axis) for one oscillation period.

We showed that for a high flexibility of the model system a larger region of low, i.e. close to zero, local dissipation is needed. This is reflected in a low time-averaged dissipation (usually called just dissipation) over the whole oscillation period, which we calculate as the sum of Lyapunov expo-

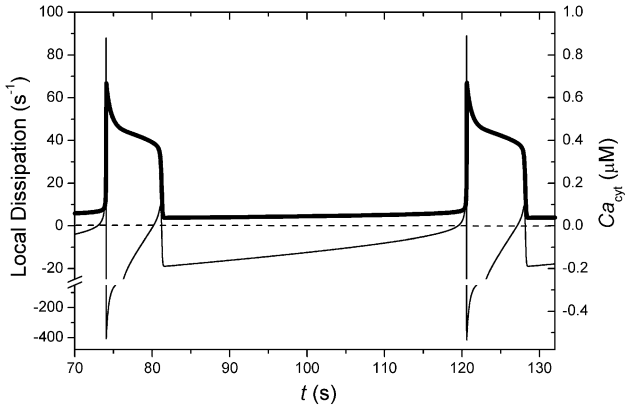

Fig. 3. Local dissipation for the regular oscillatory regime at k_{ch}=800 s^{-1}. Time course of the local dissipation (thin solid line, left y-axis) and time course of Ca_{cyt} (thick solid line, right y-axis) for one oscillation period.

nents according to the algorithm proposed by Wolf et al. [36]. Indeed, Fig. 4 shows that for k_{ch}=480 s^{-1} the dissipation is much closer to zero than for k_{ch}=500 s^{-1} and k_{ch}=800 s^{-1}. As shown above (see Figs. 1 and 2) the oscillatory regime at k_{ch}=480 s^{-1} has a much wider region of the oscillation period with a close to zero local dissipation and is therefore more flexible and adapts much better to external forcing than the oscillatory regimes at k_{ch}=500 s^{-1} and k_{ch}=800 s^{-1}.

The examination of the response ability of Ca^{2+} oscillations to pulsatile external forcing in dependence on the local dissipation gives basis for studying the interrelation between the local dissipation and the coupling properties of the oscillators. Since we showed that the dissipation of the model system vary upon different agonist stimulation (changes in k_{ch}), we now examine the interrelation between the coupling abilities of the system and its local dissipation

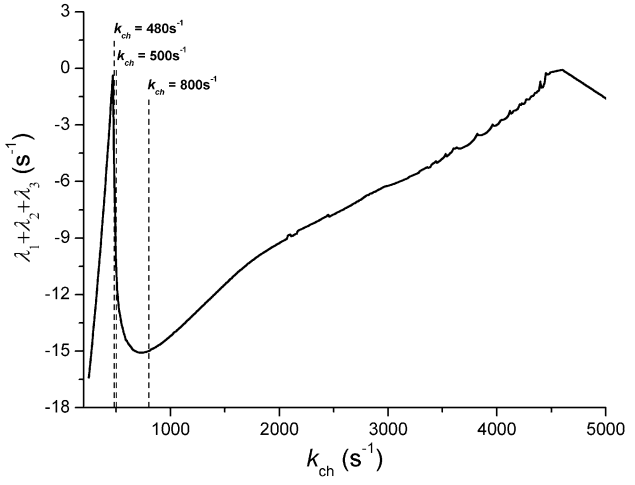

Fig. 4. Dissipation of the model system, i.e. the sum of the Lyapunov exponents ($\lambda_1+\lambda_2+\lambda_3$), is plotted versus parameter k_{ch}. Studied oscillatory regimes at k_{ch}=800 s^{-1}, k_{ch}=500 s^{-1} and k_{ch}=800 s^{-1} are marked with vertical dashed lines.

for different values of k_{ch}. We couple identical cells, i.e. equations as well as parameter values are the same for all cells coupled in the system. The initially asynchronous oscillations in the system are set by different initial conditions for the individual cells. As a result a phase shift (φ) between the oscillations of Ca^{2+} in the two cells occurs, whereas the basic oscillation frequency of calcium in each cell remains the same. We choose the initial conditions in such a way that $\varphi=\pi$ (see Fig. 5A). If the coupling constant (h) is zero, the two cells continue to oscillate asynchronously (see Fig. 5A). By increasing the value of parameter h, we achieve synchronisation of Ca^{2+} oscillations in both cells (see Fig. 5B).

We have determined the minimal value of the coupling constant (h) for different values of agonist stimulation (k_{ch}). The results are presented in Table 2. They show that the time-averaged dissipation is a suitable index determining the coupling properties of the cells. Low dissipation is a good guarantee for efficient coupling, i.e. a smaller value of h is sufficient for the synchronisation. On the other hand, high dissipation characterizes oscillations that are more rigid in

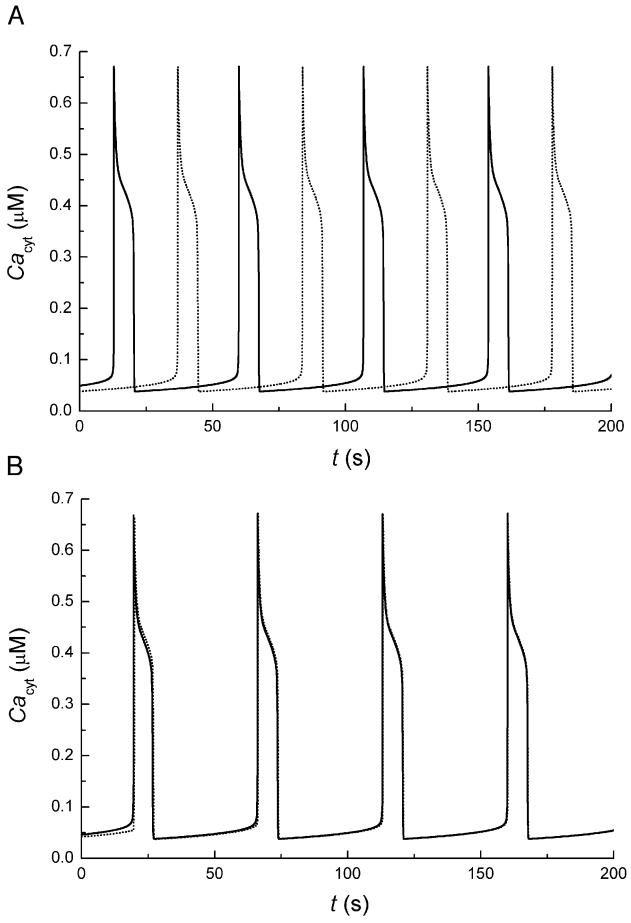

Fig. 5. Time courses of Ca_{cyt} in the first (solid line) and in the second (dashed line) coupled cell for the oscillatory regime at k_{ch}=800 s^{-1}: (A) h=0 s^{-1}. (B) h=0.16 s^{-1}.

Table 2
Coupling ability of cells at different levels of agonist stimulation

k_{ch} (s^{-1})	h (s^{-1})	$\lambda_1+\lambda_2+\lambda_3$ (s^{-1})
480	0.000016	−4.52
485	0.0024	−5.99
490	0.0067	−7.42
500	0.062	−10.5
550	0.11	−13.1
800	0.16	−14.4
2950	0.060	−6.32
3450	0.048	−5.04
4100	0.040	−2.51
4300	0.036	−1.62
4550	0.14	−0.14
4570	0.085	−0.11
4590	0.061	−0.087

For oscillatory regimes at different values of k_{ch}, the minimal value of coupling constant h and the time-averaged dissipation ($\lambda_1+\lambda_2+\lambda_3$) are calculated.

the sense that larger values of h are required for the synchronisation (see Table 2).

However, the time-averaged dissipation alone cannot be taken as an absolute measure for determining the coupling abilities of the system. For example, the two oscillatory regimes at k_{ch}=485 s^{-1} and k_{ch}=2950 s^{-1} have almost the same time-averaged dissipation, but their critical coupling coefficients differ considerably (see Table 2). Furthermore, the oscillatory regime at k_{ch}=4550 s^{-1} has a very low time-averaged dissipation but requires a comparatively high coupling coefficient in order to synchronise. These seemingly deceiving results appear due to the fact that for various values of k_{ch} the system expresses different oscillatory behaviours, from simple spiking, complex bursting as well as sinus-like oscillations. Haberichter et al. [37] made a detailed analysis of different oscillatory regimes for the same model system as studied in this paper. They found that the system exhibits simple spiking oscillations for 473<k_{ch}<1800 s^{-1}, complex bursting oscillations for 1800<k_{ch}<4500 s^{-1} and sinus-like oscillations for 4500<k_{ch}<4603 s^{-1}. For the three different oscillatory regimes, we graphically show the dependency between the minimal coupling constant that is required for synchronisation (h) and the time-averaged dissipation separately in Fig. 6. It can be well observed that within a particular oscillatory regime the time-averaged dissipation largely determines the coupling abilities of the system.

The fact that two different oscillatory regimes have almost the same time-averaged dissipation, but posses rather distinct coupling properties (see Fig. 6), can be well explained by calculating, in addition to the time-averaged dissipation, also the local dissipation of the system. This gives a better insight into the system properties of cellular oscillators, which enable efficient coupling of cells. In Fig. 7, the local dissipation for the complex bursting oscillatory regime at k_{ch}=4300 s^{-1} is presented. We see that the local dissipation oscillates around zero in a wide range of the oscillation period, which results in a low time-averaged

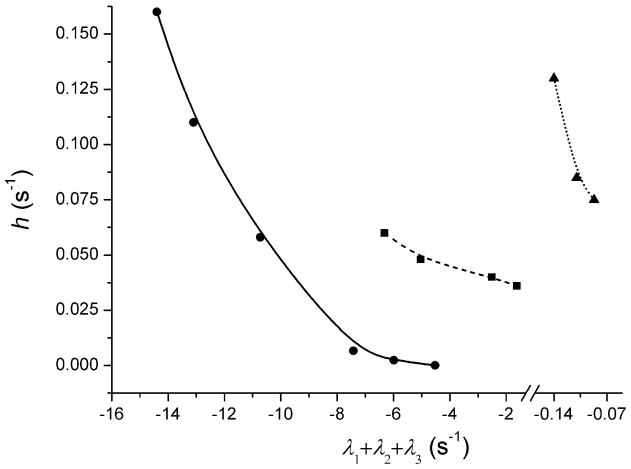

Fig. 6. Dependency between the minimal coupling constant (h) and the time-averaged dissipation, i.e. the sum of the Lyapunov exponents ($\lambda_1+\lambda_2+\lambda_3$), for simple spiking (circles connected by a solid line), complex bursting (squares connected by a dashed line) and sinus-like (triangles connected by a dotted line) oscillations.

dissipation. However, the oscillatory part of the low local dissipation is not so close to zero as in the case presented in Fig. 1C (k_{ch}=480 s^{-1}), for example. Therefore, the cell requires a slightly larger external input from the neighbouring cell (larger h) to synchronise (as shown in Table 2 and Fig. 6).

The local dissipation is also necessary to explain the coupling properties for the sinus-like oscillatory regime at k_{ch}=4550 s^{-1}. The oscillatory regime at k_{ch}=4550 s^{-1} has a very low time-averaged dissipation (see Table 2) but is rather difficult to synchronise (a large value of h is required). This result could be deceiving, since it may suggest that the system is rigid and feebly adaptable. In fact, in accordance to the low time-averaged dissipation the system behaviour can be altered already by very weak external signals. In case of coupling, the cells alter each others behaviour extensively already by much smaller coupling constant than it is required for the synchronisation (results

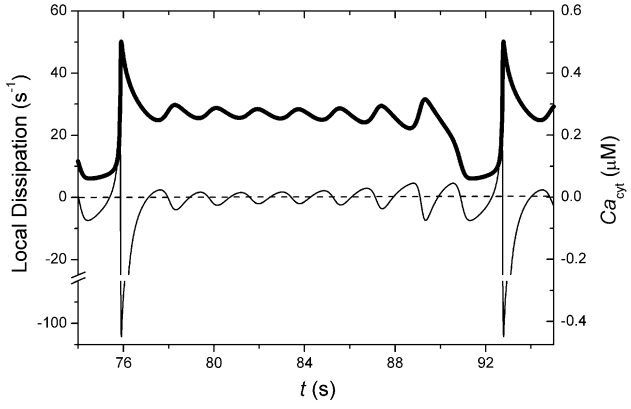

Fig. 7. Local dissipation for the regular oscillatory regime at k_{ch}=4300 s^{-1}. Time course of the local dissipation (thin solid line, left y-axis) and time course of Ca_{cyt} (thick solid line, right y-axis) for one oscillation period.

not shown). However, under low gap-junctional permeability (smaller values of h) oscillations in both cells are highly irregular and far from being synchronised. That is, under such conditions oscillations are characterized by a variety of different amplitudes and frequencies, which at a given time do not coincide in both cells. For biological systems, this is not the desired effect, which would contribute to better synchronisation and signal transmission between cells. In order to efficiently transmit relevant information, biological systems must respond controlled and immutably, i.e. their response has to be synchronised and precisely encoded in its frequency as well as in its amplitude [2–6]. To explain the results presented in Table 2 and in Fig. 6, we calculate the local dissipation of the model system for the parameter value k_{ch}=4550 s^{-1}, which is presented in Fig. 8. It can be well observed that the very low time-averaged dissipation results from the sinus-like time course of the local dissipation (Fig. 8). In accordance to our previous statement, the low dissipation implies high flexibility of the system, which is here expressed as a possibility of altering the system behaviour already with very weak external signals. However, in order to have a flexible system with well-defined responses, in addition to the low dissipation, the local dissipation has to express some asymmetry, like in (Figs. 1C, 2C and 7). For the larger part of the oscillation period, the local dissipation either has to be close to zero or should closely oscillate around zero. This contributes to the low time-averaged dissipation and represents the flexible part of the time course. However, in addition to this flexible part, there must also be at least one well-expressed negative dell of dissipation (see (Figs. 1C, 2C and 7)). This assures the system to have a strong attractive region in phase space to which the system returns with higher probability. Herewith, the forcing signal cannot change these rigid parts of the time course but only alters the system's behaviour in regions of low dissipation. Therefore, in this case (k_{ch}=4550 s^{-1}) the higher coupling constant is necessary not because the system would be rigid and non-flexible (like for example at k_{ch}=800 s^{-1}) but because a firm and well-determined external signal is needed to prevent uncontrolled behaviour and assure synchronised responses in the frequency as well as in the amplitude.

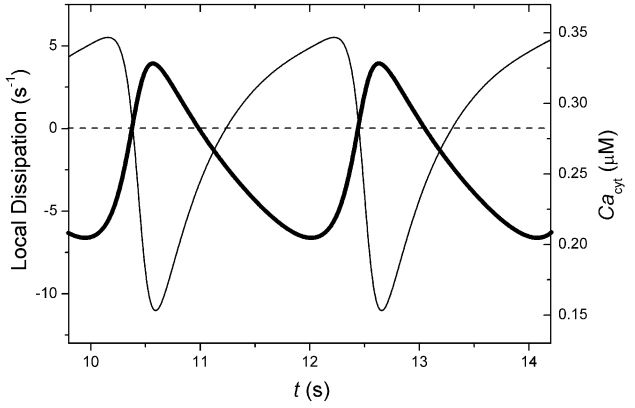

Fig. 8. Local dissipation for the regular oscillatory regime at k_{ch}=4550 s^{-1}. Time course of the local dissipation (thin solid line, left y-axis) and time course of Ca_{cyt} (thick solid line, right y-axis) for one oscillation period.

4. Discussion

In the paper, the influence of local and time-averaged dissipation on coupling properties of calcium oscillations in diffusion-like coupled cells is examined. Our results show that Ca^{2+} oscillations synchronise easily, i.e. at low coupling constants, in regimes with low time-averaged dissipation, and rather difficult, i.e. at high coupling constants, in regimes with high time-averaged dissipation. We argue that the time-averaged dissipation is a suitable index in characterizing the coupling properties of the system.

However, the time-averaged dissipation cannot be taken as an absolute measure for estimating the coupling properties of the system. For better insight into the system ability to efficiently adapt its oscillations to the neighbouring oscillator and thereby to synchronise, in addition to the time-averaged dissipation, its whole time evolution, the so-called local dissipation, has to be taken into account. The crucial system property, which efficiently facilitates synchronisation of Ca^{2+} oscillations in coupled cells, is the predominantly close to zero local dissipation. This contributes to the low time-averaged dissipation and represents the flexible, well-adaptable part of the time course. Intuitively, if an attractor in form of a limit cycle that corresponds to oscillations of cytosolic calcium in the cell is weakly attractive, i.e. has a very low dissipation, it seems much easier to alter its shape, thus adapting its basic Ca^{2+} oscillations to the Ca^{2+} oscillations in adjacent cells. It should be noted, however, that in addition to this predominant flexible part, there must also exist localised but well-expressed negative dells of dissipation (see, e.g. Figs. 1C and 2C). They act as stabilizers and enable well controlled immutable responses of Ca^{2+} oscillations to external perturbations. The same reasoning in explaining responses of a system to external perturbations was tested also for other model system for intracellular Ca^{2+} oscillations than studied in this paper [38–40]. In particular, for the model system proposed by Kummer et al., [40], we were able to show that dissipation largely determines sensitivity and flexibility of regular as well as chaotic Ca^{2+} oscillations [41]. Therefore, we conclude that dissipation seems to be a suitable system property for determining response abilities of the system also for mathematical models with different heterogeneities than studied in this paper.

From the biological point of view, the relation between low dissipation and high flexibility of Ca^{2+} oscillations also seems to be of special importance. Dissipation is closely related with the free energy consumption, which all living organisms tend to minimise. For signal transmission processes, the free energy consumption and the information-processing rate, which can be well determined [42,43], is of

high biological interest [44]. Since highly important and permanently active physiological functions that are vital for normal functioning and reproduction of living organisms depend on synchronous Ca^{2+} oscillations, it is important that these processes consume as little free energy as possible. For example, periodic release of luteinizing hormone-releasing hormone (LHRH) from the hypothalamus, which is essential for normal reproductive functions, requires coordinated intercellular communication based on Ca^{2+} [45]. Furthermore, also proper insulin secretion relies on synchronised Ca^{2+} oscillations in pancreatic islets [1]. All these functions require fast and efficient synchronisation of initially asynchronous oscillations throughout the organism, with as little free energy consumption as possible. Therefore, in view of low free energy consumption, dissipation of biological systems should be minimised [46]. In order to give more precise information about the energy consumption for different oscillatory regimes, one would require quantitative estimates of the metabolic energy used to maintain calcium oscillations, being mainly due to ATP breakdown by the ER and plasma membrane Ca^{2+} ATPases. However, the determination of the energy consumption for different oscillatory regimes requires quite extensive calculations [47] and is therefore beyond the scope of the present paper.

In previous studies, there were only modest attempts to explain the phenomenon of faster and more efficient synchronisation of Ca^{2+} oscillations for one set of system parameters than for another. For example, Zhang et al. [33] suggested a possible role of thrirhythmicity in occurrence of internal stochastic resonance. Intuitively, this proposal seems to be reasonable since due to coexisting oscillatory states the system has additional degrees of freedom. In case of thrirhythmicity, for the same parameter values, three different oscillatory regimes exist between which the system can choose. In general, these oscillatory regimes differ in their amplitudes as well as in their frequencies [37]. Therefore, one could hypothesise that the system in a thrirhythmic regime should be more flexible, and could easily adapt to oscillations in adjacent cells. Despite this intuitive interrelation between multirhythmicity and coupling properties of oscillators, our results did not confirm this hypothesis (see Table 2 at k_{ch}=3450 s^{-1} and the analysis of thrirhythmicity for the same model system [37]). Moreover, our calculations show that in determining coupling abilities of the system, complexity of calcium oscillations does not play a role at all. We tested very complex forms of bursting chaotic regimes, which appear in our system (e.g. at k_{ch}=2950 s^{-1}, see Refs. [35,37]). Since chaotic regimes poses a broad multitude of different amplitudes as well as frequencies, they appear to be able to respond even more sensitive and flexible to external perturbations than the multirhythmic regimes. Therefore, one could hypothesise that chaotic Ca^{2+} oscillations should be extremely adaptable to signals from adjacent cells. Galvanoskis and Sandblom [48,49], for example, studied effects of external forcing on regular and chaotic Ca^{2+} oscillations. Their results suggested a possible role of chaotic processes in detection of weak signals within cells. Considering these signals to come from adjacent cells, one could hypothesise that chaotic regimes are more appropriate for efficient coupling of cells than regular oscillatory regimes. We investigated a possible interrelation between chaotic regimes and a higher coupling ability of the system very carefully. In general, no such interrelations could be observed. However, in many cases (but not true in general, see, e.g. Ref. [50]) complex system behaviours may coincide with regions of lower dissipation (the case in several mathematical models, e.g. [38–40]). Therefore, special care has to be taken in order to interpret the results in such models correctly.

In further studies it would be interesting to test coupling properties of cells, which are initially not just phase shifted but also have different basic oscillation frequencies. Some studies [18,51] suggest that this is of great biological relevance since adjacent cells may indeed have slightly different oscillation frequencies due to non-homogenous agonist stimulation over the whole tissue. Furthermore, it is also possible that only a few cells are exposed to sufficient agonist stimulation, while other remain quiescent. Therefore, possibilities of switching from quiescent to oscillatory regimes that may appear in consequence of diffusion-like calcium transfer through gap junctions should also be examined. Our preliminary studies suggest that these properties also strongly depend on dissipation of the system, and additionally on the type of bifurcation, that characterises the transition between the quiescent and the oscillatory regime. However, this topic is beyond the scope of the present paper and further studies will be necessary to clarify these statements.

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