



# SYNCHRONIZATION OF REGULAR AND CHAOTIC OSCILLATIONS: THE ROLE OF LOCAL DIVERGENCE AND THE SLOW PASSAGE EFFECT A Case Study on Calcium Oscillations

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In this paper, coupling properties of regular and chaotic calcium oscillations are examined. Synchronized calcium signals among coupled cells in tissue, where calcium ions were found to be one of the most important second messengers, have proven indispensable for proper and reliable functioning of living organisms. When modeling such systems, it is of particular interest to determine, which internal system properties guarantee best coupling abilities and herewith physiologically the most efficient signal transduction between cells. We found that local contractive properties of attractors in phase space, quantified by the local divergence, represent one of the crucial system properties that determine synchronization abilities of coupled regular and chaotic oscillators. In particular, parts of attractors with close to zero local divergence largely facilitate synchronization of initially unsynchronized oscillators. For bursting oscillations, this is fully in agreement with previous studies showing that synchronization abilities of bursters are closely related with the slow passage effect. We extended this concept with the help of local divergence and succeeded to apply our theory also to other oscillatory regimes, like regular spiking and complex chaotic oscillations.

*Keywords:* Synchronization; local divergence; slow passage; intermittency; bursting; calcium oscillations.

## 1. Introduction

Recently, synchronization of coupled oscillators has attracted much interest. Many theoretical studies analyzing coupling properties of oscillators were carried out for regular spiking and bursting as well as chaotic oscillations. Leung [1999], for example, studied coupling properties of nonchaotic van der Pol oscillators with added dissipative drive in dependence on different system parameters. He found that the examined conservative system could not be synchronized without an external dissipative drive. Moreover, for chaotic systems, many coupling procedures that assure synchronization at minimum coupling strength were developed. Junge

and Parlitz [2001] showed that suppression of the initial exponential divergence of nearby trajectories along noncontracting directions in the phase space facilitates synchronization of coupled chaotic oscillators. They developed a procedure that can be used for an arbitrary chaotic dynamical system, and demonstrated the effectiveness of their method on the Hénon map. Furthermore, Wang [2002] found that two initial weakly coupled chaotic systems could achieve synchronization by adaptively reducing their speed and/or enhancing the coupling strength. He developed an explicit adaptive algorithm for speed reduction and employed it on the Lorenz system. Effects of noise on the dynamics

of coupled oscillators were also studied extensively. Pravitha *et al.* [2002] found that uniformly distributed noise can induce synchronization of two coupled chaotic Rössler systems already at very low coupling strength. A similar phenomenon was reported by Zhang *et al.* [2001]. They observed the phenomenon of stochastic resonance after perturbing a system parameter with Gaussian noise. Gracheva *et al.* [2001] also found that stochastic effects in a coupled system improve the agreement with experimental results. On the other hand, Andrade and Lai [2001] found that additive white noise can induce phase slips, i.e. hinders synchronization of coupled chaotic oscillators. Moreover, there exist several theoretical studies on coupling properties of biochemical oscillators (see [Wolf & Heinrich, 1997, 2000; Höfer, 1999, 2001a, 2001b; Varona *et al.*, 2001; Schuster *et al.*, 2002]). In these studies, effects of varying different biologically relevant system parameters on coupling properties of oscillators are examined. Some authors also report that coupling can lead to more complex behaviors than originating from the individual systems only, such as cascades of period doubling and multiple periodic solutions as well as chaos (see [Bindschadler & Sneyd 2001; De Vries & Sherman, 2001; Tsumoto *et al.*, 2002]).

Although many theoretical as well as experimental studies (see e.g. [Arecchi *et al.*, 2003]) have been devoted to investigate the synchronization of coupled oscillators, the question remains, which are those internal system properties that determine the highest synchronization abilities. That is, under which internal system conditions the minimal coupling strength is needed in order to synchronize initially asynchronous oscillators. Some authors have already dealt with similar questions. Izhikevich [2000a, 2000b, 2001] made a detailed analysis of coupling properties for different bursting oscillations. He showed that best synchronization abilities have those oscillators that are characterized by the so-called slow passage effect. The latter was extensively studied during the last two decades (see [Nejshadt, 1985; Baer *et al.*, 1989; Holden & Erneux, 1993a, 1993b]). The main characteristic of the slow passage effect is a slow transition of the trajectory through a Hopf bifurcation. Due to this phenomenon, a delayed transition of the trajectory from the unstable foci branch to the stable periodic branches occurs. Since the trajectory stays close to the unstable foci branch for a considerable

amount of time after passing the bifurcation point, that region is extremely susceptible to noise (see [Baer *et al.*, 1989]) or any other external influences, like for example signals coming from the neighboring oscillators (see [Izhikevich, 2000a, 2000b, 2001]). Therefore, such systems can adapt very flexibly to external perturbations, which provides a powerful mechanism for instantaneous synchronization of bursters even when they have essentially different intrinsic oscillation frequencies.

The aim of the present study is to extend the analysis of system properties that determine the highest synchronization abilities of coupled oscillators. First, the results, previously obtained by Izhikevich [2000a, 2000b, 2001] are interpreted in a more general concept of the local divergence. The local divergence appears to be a general and wide applicative measure for determination of coupling abilities. With the local divergence, we are able to extend the existing theory of coupling properties of bursting oscillations also to regular spiking as well as chaotic oscillations. Intuitively, the role of local divergence in adaptation processes, i.e. coupling properties of dynamical systems, is well understandable since the local divergence reflects the contractive properties of attractors in the phase space. Therefore, if an attractor in form of a limit cycle is weakly attractive, it seems much easier to alter its shape, thus adapting the oscillation frequency of the system to the oscillation frequency of the neighboring system. By use of several examples, we show that in general local divergence and coupling properties of a dynamical system are in a close interrelation. The results obtained for two coupled oscillators can be easily generalized to multioscillator systems.

For demonstrating the influences of local divergence on the synchronization abilities of coupled systems, we use a biochemical model that describes intracellular  $\text{Ca}^{2+}$  oscillations in nonexcitable cells, previously proposed by Marhl *et al.* [2000]. Calcium ions were shown to be very important second messengers assuring synchronized signal transduction between cells (see [Sáez *et al.*, 1989; Goodenough *et al.*, 1996; Tordjmann *et al.*, 1997; Zhang *et al.*, 1999; Krutovskikh *et al.*, 2002; Korkiamaki *et al.*, 2002; Bode *et al.*, 2002]), which was proved to be indispensable for proper functioning of many important biological functions. For example, periodic release of luteinizing hormone-releasing hormone (LHRH) from the hypothalamus,

which is essential for normal reproductive functions, requires synchronized signal transduction between cells (see [Richter *et al.*, 2002]). Furthermore, also proper insulin secretion relies on synchronized oscillations in pancreatic islets (see [Charollais *et al.*, 2000]). Moreover, Saito and Urano [2001] showed that neurosecretory cells use intervals of synchronized periodic burst discharges to fit the levels of secretory activity to physiological requirements. Therefore, the present study is also of significant biological importance. It shows that the mathematical analysis of coupled cellular oscillators, expressing simple periodic, complex bursting as well as chaotic oscillations, can considerably improve our understanding of the physiologically important synchronization phenomenon in signal transduction that is found to be of vital importance for all living organisms.

## 2. Mathematical Model

To study the interrelations between the local divergence, the slow passage effect, and the coupling properties of  $\text{Ca}^{2+}$  oscillations, we use the model proposed by Marhl *et al.* [2000]. For different values of parameters, the model exhibits a broad variety of different dynamical behaviors, like simple periodic spike-like oscillations, complex bursting as well as chaotic  $\text{Ca}^{2+}$  oscillations. In the model, the slow passage effect can also be well observed for bursting  $\text{Ca}^{2+}$  oscillations (see [Perc & Marhl, 2003a]). The model consists of three basic model compartments, i.e. the cytosol, the endoplasmic reticulum (ER) and the mitochondria (for details see [Marhl *et al.*, 2000]). Consequently, the three main system variables are: free  $\text{Ca}^{2+}$  concentration in the cytosol ( $Ca_{\text{cyt}}$ ), free  $\text{Ca}^{2+}$  concentration in the ER ( $Ca_{\text{er}}$ ), and free  $\text{Ca}^{2+}$  concentration in the mitochondria ( $Ca_{\text{m}}$ ). The evolution of the model system is governed by the following differential equations:

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

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

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

where

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

$$J_{\text{pump}} = k_{\text{pump}} Ca_{\text{cyt}}, \quad (5)$$

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

$$J_{\text{Pr}} = k_+ Ca_{\text{cyt}} Pr, \quad (7)$$

$$J_{\text{CaPr}} = k_- Ca Pr, \quad (8)$$

$$J_{\text{in}} = k_{\text{in}} \frac{Ca_{\text{cyt}}^8}{Ca_{\text{cyt}}^8 + K_2^8} \quad (9)$$

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

$$Pr = Pr_{\text{tot}} - Ca Pr, \quad (11)$$

$$Ca Pr = Ca_{\text{tot}} - Ca_{\text{cyt}} - \frac{\rho_{\text{er}}}{\beta_{\text{er}}} Ca_{\text{er}} - \frac{\rho_{\text{m}}}{\beta_{\text{m}}} Ca_{\text{m}}. \quad (12)$$

The parameter values are listed in Table 1, whereas their meaning and biological relevance are fully explained in the original work (see [Marhl *et al.*, 2000]).

Synchronization properties are studied for the system of two cells coupled via a passive diffusion-like calcium transfer through gap junctions. The calcium diffusion through gap junctions is modeled by an additional  $\text{Ca}^{2+}$  flux through the cell membrane (see e.g. [Höfer, 1999, 2001a, 2001b; Zhang *et al.*, 2001; Schuster *et al.*, 2002]). Consequently, the total concentration of calcium in the cell ( $Ca_{\text{tot}}$ ) is no longer constant. Therefore, additional differential equations are needed for calculating changes of total  $\text{Ca}^{2+}$  concentrations in the first ( $Ca_{\text{tot},1}$ ) and in the second cell ( $Ca_{\text{tot},2}$ ):

$$\frac{dCa_{\text{tot},1}}{dt} = h \cdot (Ca_{\text{cyt},2} - Ca_{\text{cyt},1}), \quad (13)$$

$$\frac{dCa_{\text{tot},2}}{dt} = h \cdot (Ca_{\text{cyt},1} - Ca_{\text{cyt},2}). \quad (14)$$

Due to the calcium transfer through gap junctions, differential equations for the free cytosolic  $\text{Ca}^{2+}$

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

Parameter	Value
<i>Total concentrations</i>	
$Ca_{\text{tot}}$	90 $\mu\text{M}$
$Pr_{\text{tot}}$	120 $\mu\text{M}$
<i>Geometric parameters</i>	
$\rho_{\text{er}}$	0.01
$\rho_{\text{m}}$	0.01
$\beta_{\text{er}}$	0.0025
$\beta_{\text{m}}$	0.0025
<i>Kinetics parameters</i>	
$k_{\text{ch}}$	480–4100 $\text{s}^{-1}$
$k_{\text{leak}}$	0.05 $\text{s}^{-1}$
$k_{\text{pump}}$	20 $\text{s}^{-1}$
$k_{\text{in}}$	300 $\mu\text{M}\text{s}^{-1}$
$k_{\text{out}}$	125–250 $\text{s}^{-1}$
$k_{\text{m}}$	0.00005 $\text{s}^{-1}$
$k_{+}$	0.1 $\mu\text{M}^{-1} \text{s}^{-1}$
$k_{-}$	0.01 $\text{s}^{-1}$
$K_1$	5 $\mu\text{M}$
$K_2$	0.8 $\mu\text{M}$
<i>Coupling parameters</i>	
$h$	0–0.34 $\text{s}^{-1}$

concentration in each cell [see Eq. (1)] have to be modified:

$$\begin{aligned} \frac{dCa_{\text{cyt},1}}{dt} = & J_{\text{ch},1} - J_{\text{pump},1} + J_{\text{leak},1} \\ & + J_{\text{out},1} - J_{\text{in},1} + J_{\text{CaPr},1} - J_{\text{Pr},1} \\ & + h \cdot (Ca_{\text{cyt},2} - Ca_{\text{cyt},1}), \end{aligned} \quad (15)$$

$$\begin{aligned} \frac{dCa_{\text{cyt},2}}{dt} = & J_{\text{ch},2} - J_{\text{pump},2} + J_{\text{leak},2} \\ & + J_{\text{out},2} - J_{\text{in},2} + J_{\text{CaPr},2} - J_{\text{Pr},2} \\ & + h \cdot (Ca_{\text{cyt},1} - Ca_{\text{cyt},2}), \end{aligned} \quad (16)$$

In Eqs. (13)–(16) indices 1 and 2 denote the two coupled cells, whereas parameter  $h$  stands for the effective gap-junctional calcium permeability.

The complete set of model equations is given by Eqs. (1)–(16). In the paper, all results are calculated for the parameter values given in Table 1 if not otherwise stated.

### 3. Methods

#### 3.1. Fast–slow subsystem analysis

The bifurcation analysis of  $\text{Ca}^{2+}$  oscillations was carried out with the method proposed by Rinzel

[1985]. By this method, the system is separated into a “fast” and a “slow” subsystem. Therefore, we address to it as the fast–slow subsystem analysis. Each variable that changes rapidly during the oscillation period is a part of the “fast” subsystem whereas the variables that vary slowly represent the “slow” subsystem. We accomplish the fast–slow subsystem analysis by calculating the bifurcation diagram of the “fast” subsystem using the “slow” variables as bifurcation parameters. All bifurcation diagrams were calculated with the numerical continuation software AUTO97 [Doedel *et al.*, 1997] and XPPAUT [Ermentrout, 1996].

#### 3.2. Local divergence

For the vector field:

$$\begin{aligned} \mathbf{F}(Ca_{\text{cyt}}, Ca_{\text{er}}, Ca_{\text{m}}) = & (F_{Ca_{\text{cyt}}}, F_{Ca_{\text{er}}}, F_{Ca_{\text{m}}}) \\ = & \left( \frac{dCa_{\text{cyt}}}{dt}, \frac{dCa_{\text{er}}}{dt}, \frac{dCa_{\text{m}}}{dt} \right), \end{aligned} \quad (17)$$

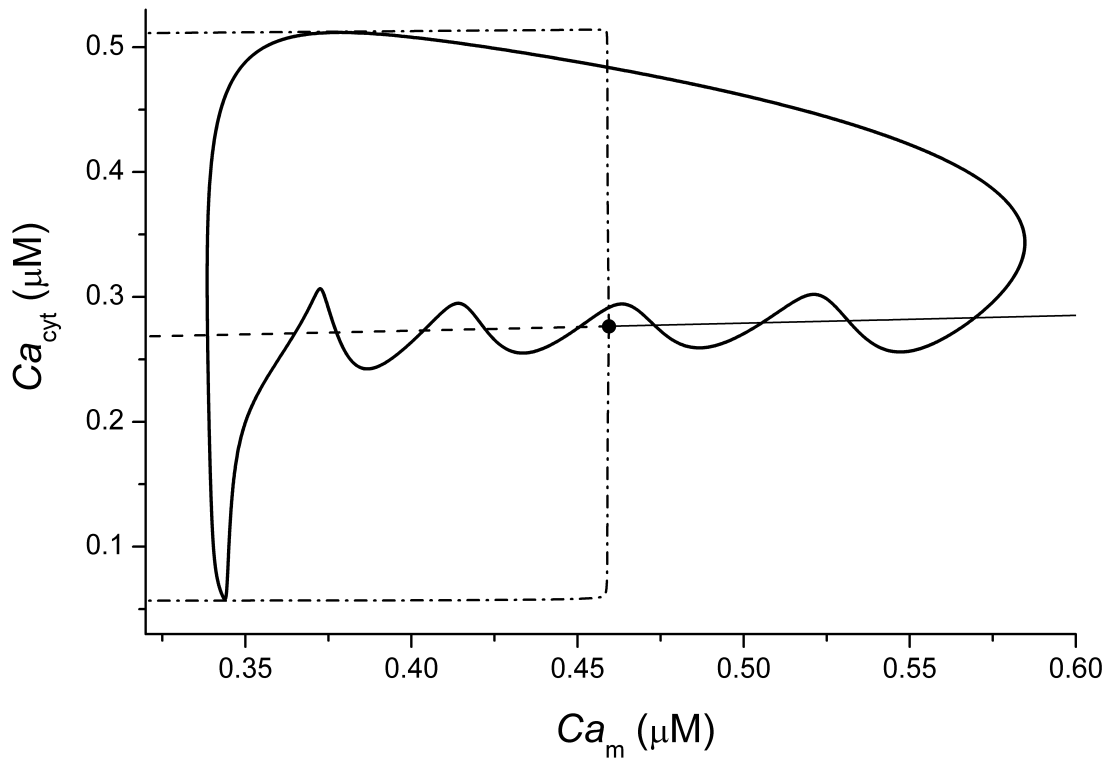
the local divergence is defined as:

$$\begin{aligned} \nabla \cdot \mathbf{F}(Ca_{\text{cyt}}, Ca_{\text{er}}, Ca_{\text{m}}) \\ = & \frac{\partial F_{Ca_{\text{cyt}}}}{\partial Ca_{\text{cyt}}} + \frac{\partial F_{Ca_{\text{er}}}}{\partial Ca_{\text{er}}} + \frac{\partial F_{Ca_{\text{m}}}}{\partial Ca_{\text{m}}}, \end{aligned} \quad (18)$$

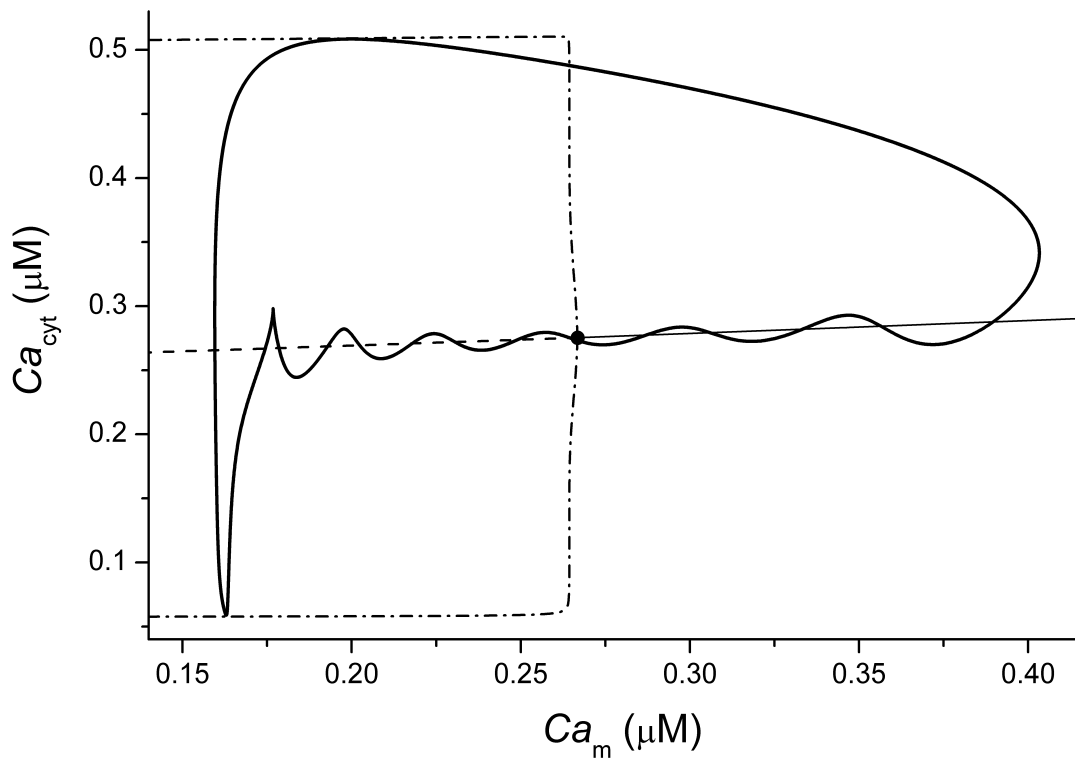
where  $(Ca_{\text{cyt}}, Ca_{\text{er}}, Ca_{\text{m}})$  is a point of the limit cycle. The local divergence determines the local attraction properties of the limit cycle and enables us to identify parts of the limit cycle that are characterized by weak attraction. The weak attractive parts facilitate synchronization since in these regions the system behavior can easily be modified by the neighboring oscillators. Therefore, we use the local divergence as a measure for estimating the synchronization abilities of the system.

### 4. Results

We examine synchronization properties of two coupled cells [Eqs. (1)–(16)] for different values of parameter  $k_{\text{out}}$ , which determines the rate of  $\text{Ca}^{2+}$  efflux from mitochondria. By changing the value of  $k_{\text{out}}$ , we can prolong the silent phase between two main calcium spikes. The prolonged silent phase is characterized by a better-expressed slow passage effect, which for certain parameter values exist in the examined mathematical model (see [Perc & Marhl, 2003a]). Since Izhikevich [2000a, 2000b, 2001] showed that elliptic bursters, also known as

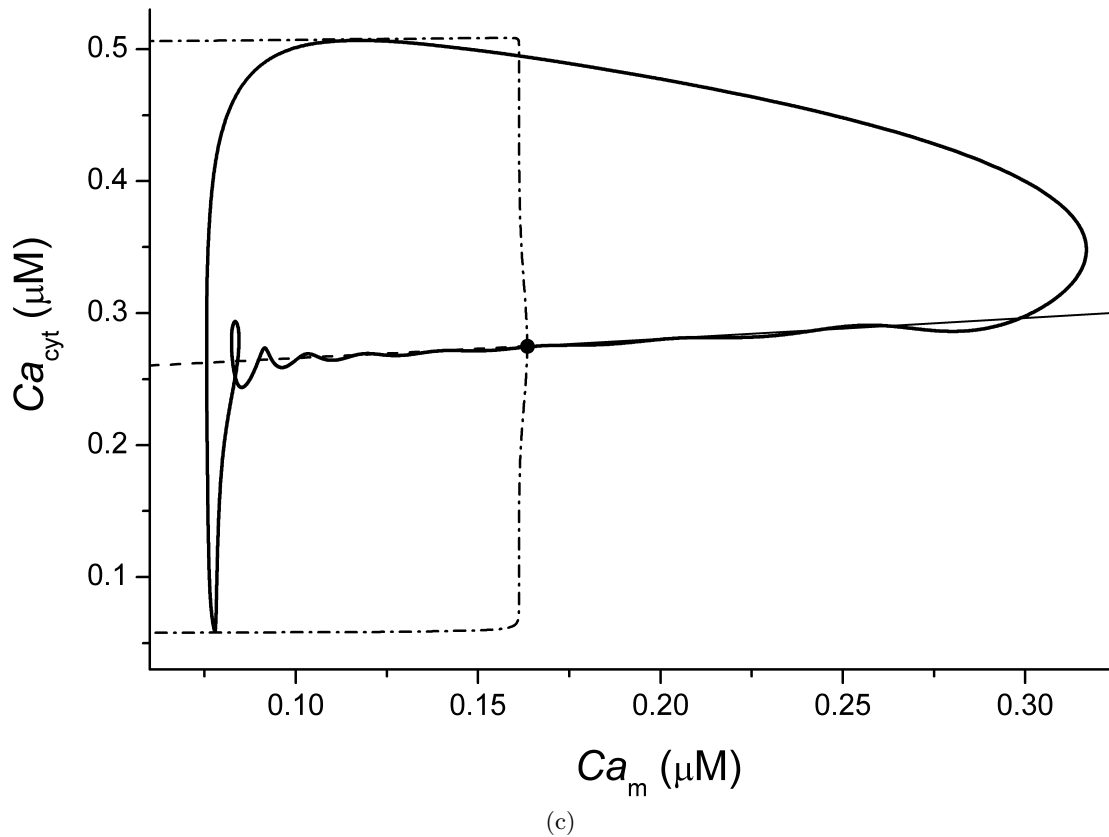


(a)



(b)

Fig. 1. Bifurcation diagram of the fast subsystem (only  $Ca_{\text{cyt}}$  is depicted), whereas the slow variable ( $Ca_m$ ) is used as the bifurcation parameter, for the bursting oscillatory regime at  $k_{\text{ch}} = 4100 \text{ s}^{-1}$ . Solid (dashed) lines represent stable (unstable) steady states. Dashed-dotted lines represent stable periodic solutions. Circle represents the supercritical Hopf bifurcation. The thick solid line represents the 2D projection of the trajectory. (a)  $k_{\text{out}} = 125 \text{ s}^{-1}$ . (b)  $k_{\text{out}} = 175 \text{ s}^{-1}$ . (c)  $k_{\text{out}} = 250 \text{ s}^{-1}$ .

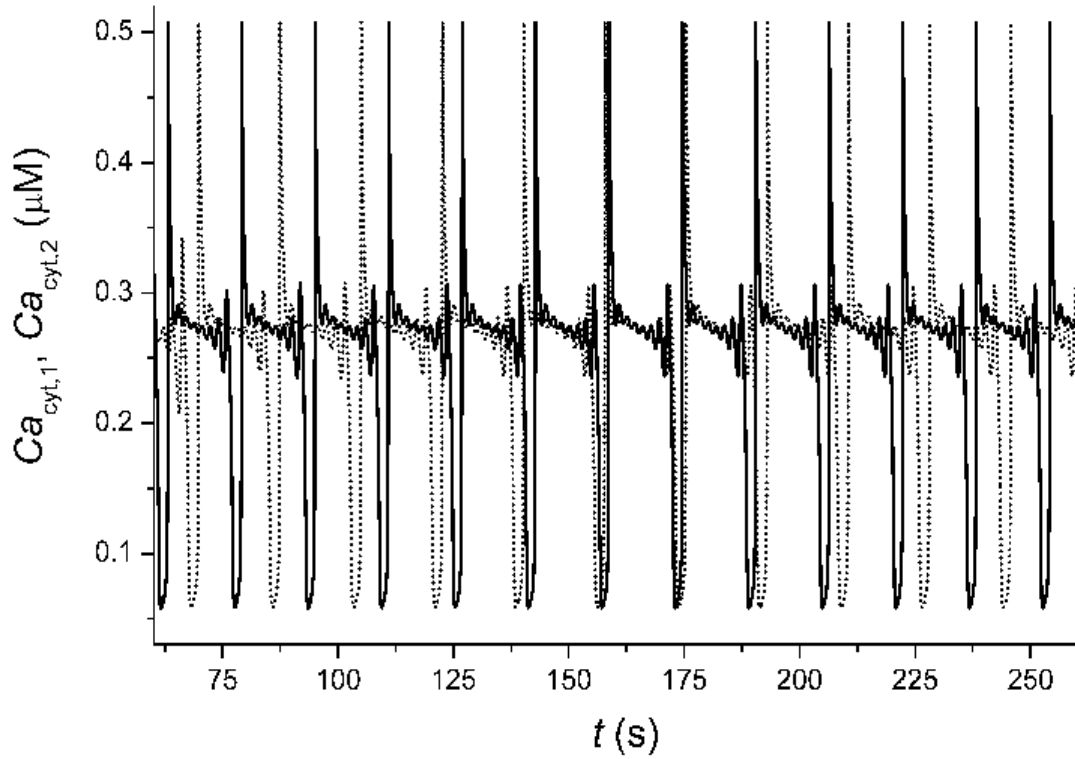
Fig. 1. (*Continued*)

type III bursters (see [Bertram *et al.*, 1995]), with the slow passage effect synchronize almost instantaneously even when they are weakly coupled, it seems reasonable to investigate coupling abilities of our system in dependence on the parameter  $k_{\text{out}}$ .

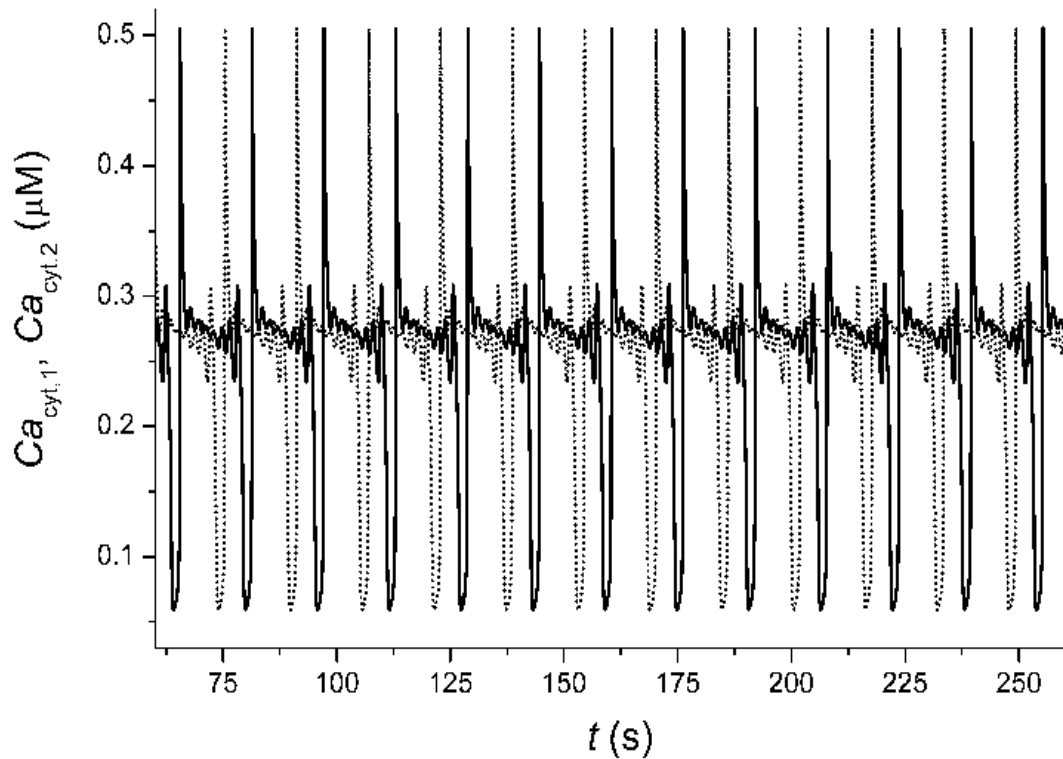
Results obtained by the fast-slow subsystem analysis for different values of parameter  $k_{\text{out}}$  are presented in Figs. 1(a)–1(c). In Fig. 1(a) the bifurcation diagram is presented for  $k_{\text{out}} = 125 \text{ s}^{-1}$ , whereas in Figs. 1(b) and 1(c)  $k_{\text{out}}$  was enlarged by 40% and 100%, respectively. In all three figures [Figs. 1(a)–1(c)], the trajectory remains close to the steady state for a considerable amount of time before it unfolds to the stable periodic branches (dashed-dotted line), despite the fact, that the stable foci branch turns unstable (dashed line) after the supercritical Hopf bifurcation is exceeded. This behavior is known as the slow passage effect (see [Nejsttadt, 1985; Baer *et al.*, 1989; Holden & Erneux, 1993a, 1993b]). Note that all cases presented in Fig. 1 are characterized by the slow passage effect. However, the slow passage effect is much better expressed, i.e. the transition of the trajectory through the bifurcation point is much

smoother, for higher than for smaller values of  $k_{\text{out}}$  [compare Figs. 1(a)–1(c)].

Coupling properties of the examined model system [Eqs. (1)–(12)] are studied by coupling two cells via a passive diffusion-like calcium flux through gap junctions [Eqs. (13)–(16)]. Initially, the two cells oscillate asynchronously due to different intrinsic oscillation frequencies. The initial difference between oscillation frequencies is obtained by multiplying all differential equations governing the time evolution of  $\text{Ca}^{2+}$  in the first and second cells with constant factors  $f_1$  and  $f_2$ , respectively, while all other parameter values are left identical for both oscillators (for parameter values see Table 1). This procedure is known as the time scaling method (see e.g. [Goldbeter, 1996; Reijnga *et al.*, 2002]). We choose  $f_1 = 0.95$  and  $f_2 = 1.05$ , which yield a relative difference between the two oscillation frequencies of 10.5%. If the coupling constant ( $h$ ) is zero, the two cells continue to oscillate asynchronously [see Fig. 2(a)]. By increasing the coupling constant  $h$ , we achieve synchronization of  $\text{Ca}^{2+}$  oscillations in both cells [see Fig. 2(b)]. To determine, if both coupled cells oscillate with the same oscillation frequency,

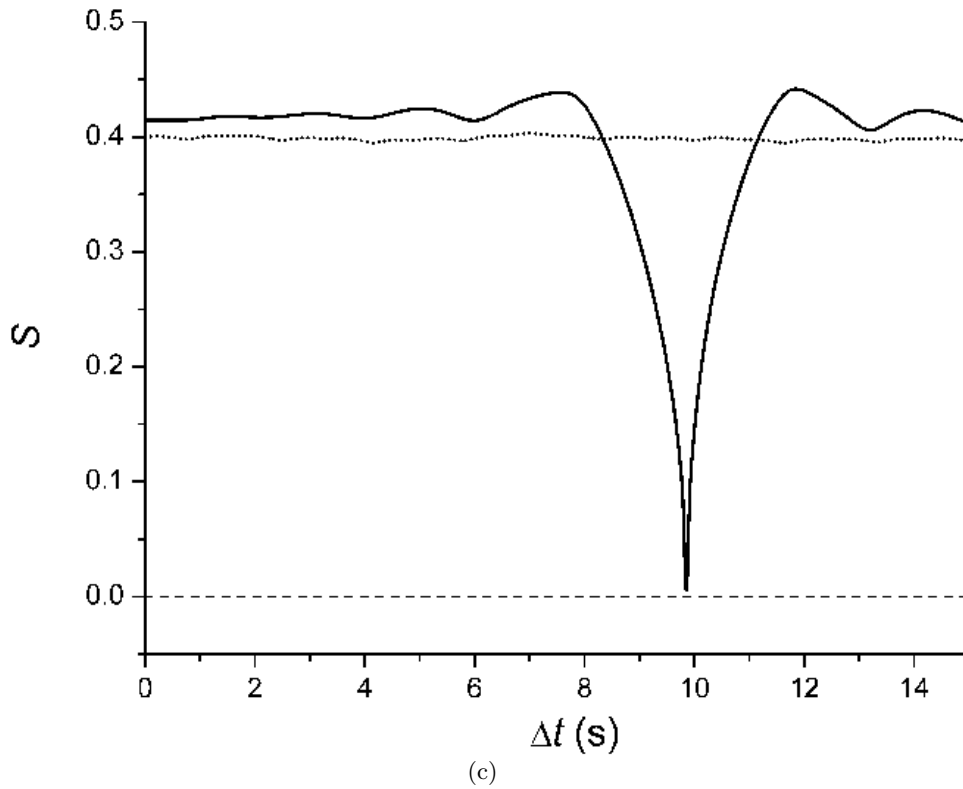


(a)



(b)

Fig. 2. Time courses of  $Ca_{\text{cyt}}$  in the first (solid line) and in the second (dotted line) coupled cell for the bursting oscillatory regime at  $k_{\text{ch}} = 4100 \text{ s}^{-1}$  and  $k_{\text{out}} = 200 \text{ s}^{-1}$ . (a)  $h = 0 \text{ s}^{-1}$ . (b)  $h = 0.036 \text{ s}^{-1}$ . (c) The similarity function for the unsynchronized (dotted line) and synchronized (solid line) oscillations.

Fig. 2. (*Continued*)

i.e. they are synchronized, we calculate the similarity function  $S$  (see e.g. [Masoller & Zanette; 2001]), which is defined by the following equation:

$$S^2(\Delta t) = \frac{\langle (Ca_{\text{cyt},1}(t + \Delta t) - Ca_{\text{cyt},2}(t))^2 \rangle}{(\langle Ca_{\text{cyt},1}^2(t) \rangle \cdot \langle Ca_{\text{cyt},2}^2(t) \rangle)^{1/2}}. \quad (19)$$

If  $Ca_{\text{cyt},1}(t)$  and  $Ca_{\text{cyt},2}(t)$  are independent time series, with different intrinsic frequencies, then  $S > 0$ . On the other hand, if the two oscillators have the same intrinsic frequency as well as the same shape of oscillations, then  $S \cong 0$  at a given  $\Delta t$ . If in this case  $\Delta t = 0$ , there is no phase shift between the two synchronized time series, whereas if  $\Delta t = t_p$ , this means that one signal is phase shifted with regard to the other with a time delay  $t_p$ . The similarity functions for oscillations, shown in Figs. 2(a) and 2(b), are presented in Fig. 2(c), where the dotted line represents the similarity function for unsynchronized  $\text{Ca}^{2+}$  oscillations [Fig. 2(a)], and the solid line represents the similarity function for synchronized oscillations [Fig. 2(b)]. The similarity function shows that in case of synchronized oscillations, presented in Fig. 2(b),  $S \cong 0$  at  $\Delta t = 9.85$  s, which means that oscillations in the second cell follow the oscillations in the first cell with a time delay of 9.85 s, whereas

the oscillation frequency as well as the form of  $\text{Ca}^{2+}$  oscillations in both cells are the same. In case of unsynchronized oscillations, the similarity function has a nearly constant positive value, which means that the average of their square differences does not depend on the time shift between them, which can only be achieved if the two cells have different intrinsic oscillation frequencies.

As already shown by Izhikevich [2000a, 2000b, 2001], bursters with the slow passage effect synchronize easily, i.e. even if they are weakly coupled, whereas bursters that are not characterized by the slow passage effect possess no such property. Here we investigate this system property in more detail by comparing bursters that have differently pronounced slow passage effects. In Figs. 1(a)–1(c), we showed that in the examined mathematical model the slow passage effect becomes more expressed by increasing  $k_{\text{out}}$ . Therefore, we determine the synchronization ability of the model system by calculating the minimal coupling constant  $h$  for different values of  $k_{\text{out}}$ . The results are presented in Table 2. They show that the better-expressed slow passage effect, obtained at larger values of  $k_{\text{out}}$ , assures better synchronization properties of coupled cells,



Table 2. Synchronization abilities of bursting calcium oscillations. For oscillatory regimes at  $k_{\text{ch}} = 4100 \text{ s}^{-1}$  and different values of  $k_{\text{out}}$ , the minimal value of coupling constant  $h$  is calculated.

$k_{\text{out}} \text{ (s}^{-1}\text{)}$	$h \text{ (s}^{-1}\text{)}$
125	0.34
150	0.17
175	0.11
200	0.036
225	0.019
250	0.014

meaning that synchronization of bursters can be achieved at lower coupling constants if the slow passage effect is more pronounced.

Although we showed that bursters with a more pronounced slow passage effect have better synchronization abilities, the question remains, which is the general system property that assures facilitated synchronization. In our previous work, we showed that the divergence can be taken as a good measure for estimating the system ability to respond synchronously to an external periodic signal (see [Perc & Marhl, 2003b; Marhl & Schuster, 2003]). Since effects on an individual system due to coupling are very similar to that caused by the external forcing, the same reasoning can also be used for explaining synchronization properties of coupled oscillators. If, namely an attractor in form of a limit cycle that corresponds to oscillations of  $\text{Ca}^{2+}$  in the cell is characterized by weakly attractive regions, i.e. parts that have a very close to zero local divergence, it has a partially weakly imposed spatial persistence in the phase space. Therefore, those regions can be altered even by the weakest external inputs from the neighboring oscillator. Consequently, the whole limit cycle can easily change its shape and so the system can adapt its oscillation frequency to the external signal. Therefore, the investigation of interrelation between the local divergence and the coupling properties of oscillators seems to be reasonable.

We calculate the local divergence [Eq. (18)] for all attractors corresponding to  $\text{Ca}^{2+}$  oscillations studied in Table 2. The local divergence for parameter values  $k_{\text{out}} = 125 \text{ s}^{-1}$ ,  $k_{\text{out}} = 175 \text{ s}^{-1}$  and  $k_{\text{out}} = 250 \text{ s}^{-1}$  is presented in Figs. 3(a)–3(c), respectively. The  $x$ – $y$  projection of the 3D curve

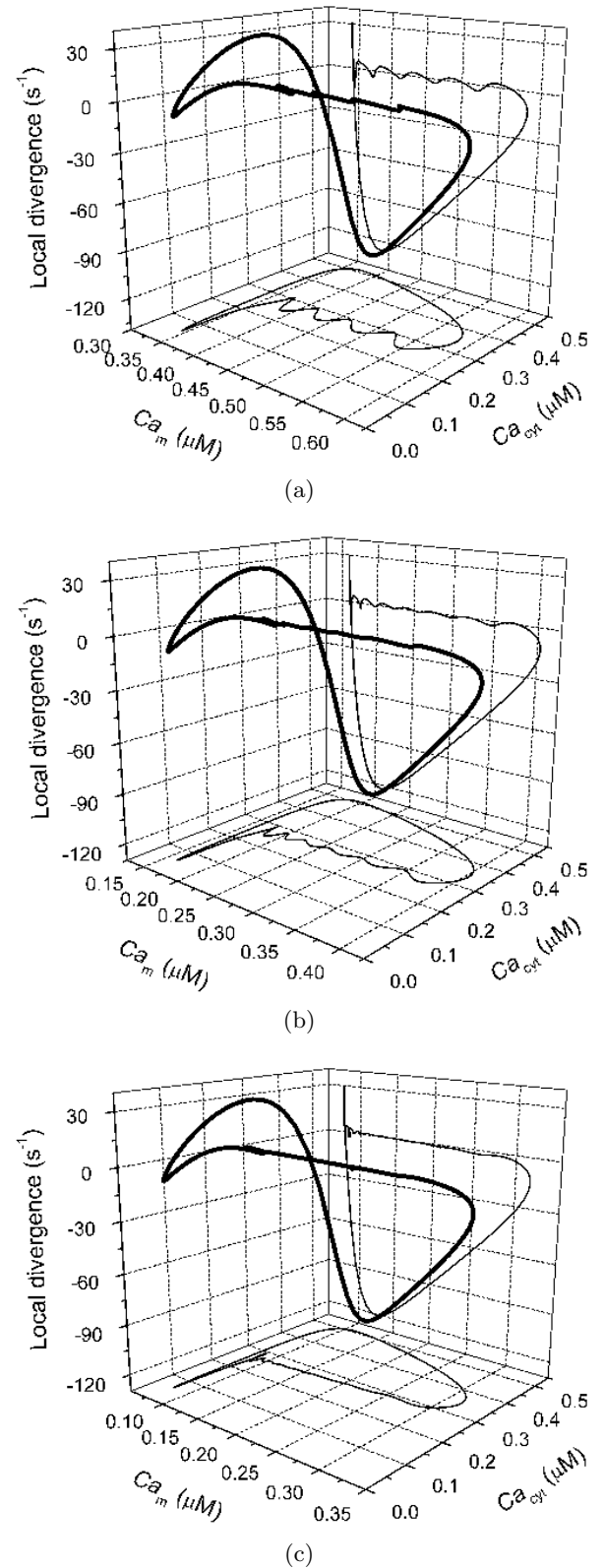


Fig. 3. Local divergence ( $z$ -axis) together with the 2D projection of the trajectory ( $x$ – $y$  plane) for the bursting oscillatory regime at  $k_{\text{ch}} = 4100 \text{ s}^{-1}$ . The  $x$ – $z$  projection shows the outlay of the local divergence in dependence on the slow system variable ( $\text{Ca}_m$ ). (a)  $k_{\text{out}} = 125 \text{ s}^{-1}$ . (b)  $k_{\text{out}} = 175 \text{ s}^{-1}$ . (c)  $k_{\text{out}} = 250 \text{ s}^{-1}$ .

corresponds to the  $Ca_m$ - $Ca_{\text{cyt}}$  projection of the trajectory in phase space, as shown in Figs. 1(a)–1(c), whereas the  $x$ - $z$  projection represents the local divergence of the system in dependence on  $Ca_m$ . By comparing Figs. 1(a)–1(c) with Figs. 3(a)–3(c), respectively, it can be well observed that the slow passage effect is always characterized by a more or less close to zero oscillating local divergence. Since in this area the phase space is very weakly contractive, the system passes slowly through the bifurcation point. Therefore, the trajectory feels only weak spatial persistence in that region, which results in a slow passage through the Hopf bifurcation. At  $k_{\text{out}} = 125 \text{ s}^{-1}$ , the local divergence oscillates with a rather high amplitude around zero, whereas the oscillations of the local divergence at  $k_{\text{out}} = 175 \text{ s}^{-1}$  are already much more suppressed. Furthermore, at  $k_{\text{out}} = 250 \text{ s}^{-1}$  the local divergence ceases oscillating almost altogether and is nearly zero during the slow passage. Consequently, at  $k_{\text{out}} = 250 \text{ s}^{-1}$  the weakest attraction of the phase space, expressed by the zero local divergence during the slow passage phase, assures excellent adaptation properties, and hence the best synchronization abilities of the model system (see Table 2).

By introducing the local divergence as a measure for synchronization properties of the coupled model system, we showed that the slow passage effect indeed facilitates synchronization of coupled bursters, and thereby confirm the previously obtained results by Izhikevich [2000a, 2000b, 2001]. Moreover, we carried out a more detailed analysis of synchronization abilities of the system for differently expressed slow passage effects and showed that better synchronization of bursters can be achieved if the slow passage effect is more pronounced. In the following, we would like to extend our study about the interrelation between the local divergence and the synchronization properties from bursting oscillations to regular spiking and intermittent chaotic oscillations, which can be found in our model.

Haberichter *et al.* [2001] carried out a detailed analysis of different oscillatory regimes that can be found in the mathematical model studied here. They showed that for the same parameter values as listed in Table 1, simple spiking oscillations could be found for values of agonist stimulations below  $k_{\text{ch}} = 1800 \text{ s}^{-1}$ . Therefore, we analyze synchronization abilities of simple spiking oscillations at two different levels of agonist stimulation, namely at

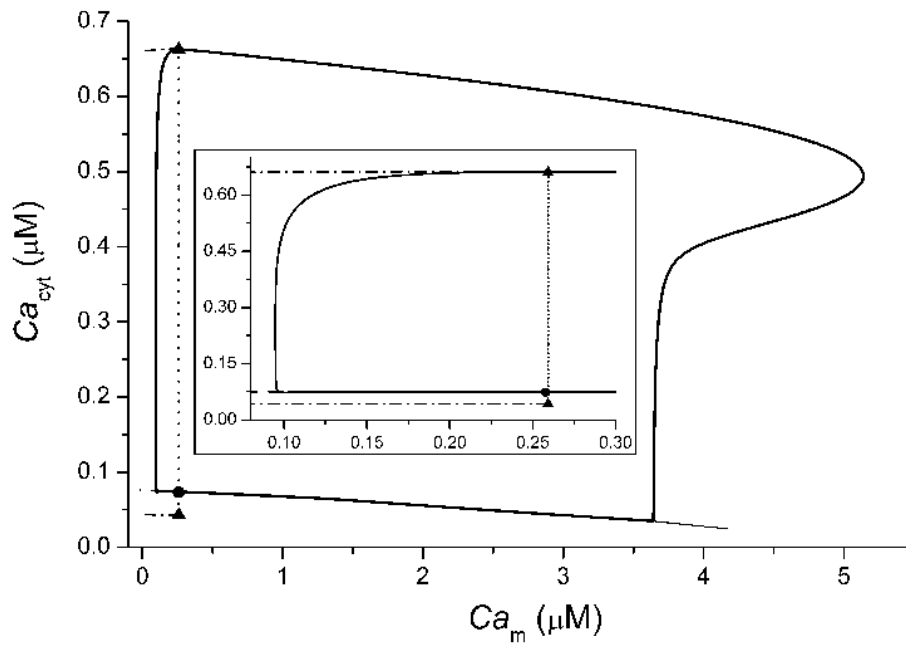
Table 3. Synchronization abilities of simple spike-like calcium oscillations. For oscillatory regimes at different values of  $k_{\text{ch}}$ , the minimal value of coupling constant  $h$  is calculated.

$k_{\text{ch}} \text{ (s}^{-1}\text{)}$	$h \text{ (s}^{-1}\text{)}$
480	$1e^{-7}$
800	0.090

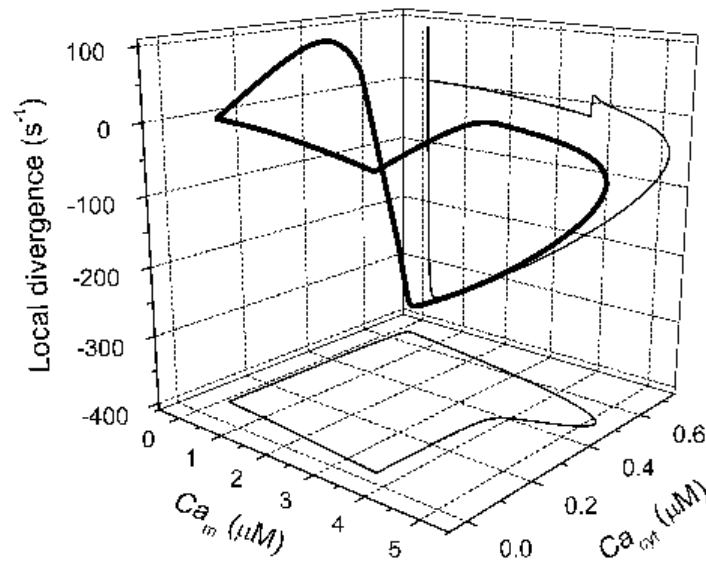
$k_{\text{ch}} = 480 \text{ s}^{-1}$  and  $k_{\text{ch}} = 800 \text{ s}^{-1}$ . To obtain the initial relative difference in oscillation frequency of 10.5% between both coupled cells, we again use the time scaling method (see e.g. [Goldbeter, 1996; Reijenga *et al.*, 2002]). The minimal values of the coupling constant  $h$ , at which the two oscillators are able to synchronize, are presented in Table 3.

We begin by explaining the results obtained for spiking  $Ca^{2+}$  oscillations at  $k_{\text{ch}} = 480 \text{ s}^{-1}$ . The bifurcation diagram obtained by the fast-slow subsystem analysis is presented in Fig. 4(a). From the inset in Fig. 4(a), where the enlarged area around the subcritical Hopf bifurcation is presented, the slow passage effect can be well observed. The delayed transition from the unstable foci branch (dashed line) to the stable periodic branches (dashed-dotted lines) is a characteristic property indicating the slow passage effect. Note that the trajectory passes through the subcritical Hopf bifurcation very smoothly. There are no signs of any oscillations during the transition, like for example shown in Figs. 1(a) and 1(b). The slow passage phase is characterized by a very close to zero local divergence, as shown in Fig. 4(b). This assures the system to have excellent synchronization abilities. The two cellular oscillators are able to nullify the initial relative frequency difference of 10.5% (the same as for previous results presented in Table 2) already at  $h = 1e^{-7} \text{ s}^{-1}$  (see Table 3). This is an extremely low coupling constant, which is nevertheless not surprising since the local divergence is during the long and well-expressed slow passage phase very close to zero. This makes the system very flexible in this part and allows it to synchronize at the very low coupling constant.

Another analysis of synchronization abilities for simple spiking oscillations was carried out for  $k_{\text{ch}} = 800 \text{ s}^{-1}$ . In this case, the two oscillators need to be much stronger coupled, i.e. a much



(a)

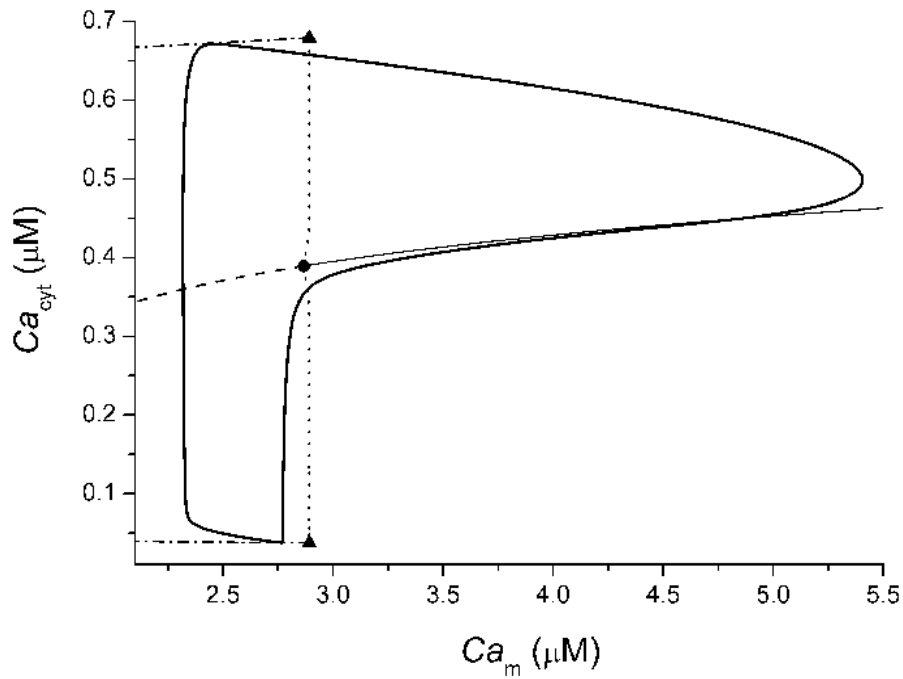


(b)

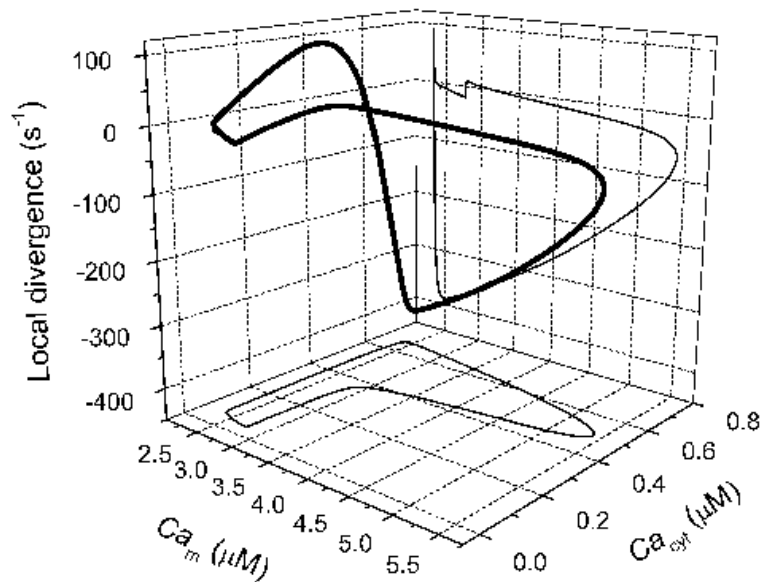
Fig. 4. Bifurcation diagram and the outlay of the local divergence for spiking oscillatory regime at  $k_{\text{ch}} = 480 \text{ s}^{-1}$  and  $k_{\text{out}} = 125 \text{ s}^{-1}$ . (a) Solid (dashed) lines represent stable (unstable) steady states. Dashed-dotted (dotted) lines represent stable (unstable) periodic solutions. Circle (up-triangle) represents the subcritical Hopf (fold limit cycle) bifurcation. The thick solid line represents the 2D projection of the trajectory. (b) The 2D projection of the trajectory ( $x$ - $y$  plane), whereas the  $x$ - $z$  projection shows the outlay of the local divergence in dependence on the slow system variable ( $Ca_m$ ).

larger  $h$  is required for synchronization than at  $k_{\text{ch}} = 480 \text{ s}^{-1}$  (see Table 3). For the oscillatory regime at  $k_{\text{ch}} = 800 \text{ s}^{-1}$  the bifurcation diagram and the local divergence are presented in Figs. 5(a) and 5(b), respectively. In Fig. 5(b) it can be well observed that the region, in which the local divergence is close to zero, is very small, i.e. the divergence just

shortly intersects the zero line. Therefore, the system does not have a well-adaptable, flexible region in the phase space. Thus, a much larger external input from the neighboring cell is required for synchronization. Consequently, since the trajectory is always subjected to a rather strong spatial persistence, the slow passage effect is not present in this



(a)



(b)

Fig. 5. Bifurcation diagram and the outlay of the local divergence for spiking oscillatory regime at  $k_{\text{ch}} = 800 \text{ s}^{-1}$  and  $k_{\text{out}} = 125 \text{ s}^{-1}$ . (a) Solid (dashed) lines represent stable (unstable) steady states. Dashed-dotted (dotted) lines represent stable (unstable) periodic solutions. Circle (up-triangle) represents the subcritical Hopf (fold limit cycle) bifurcation. The thick solid line represents the 2D projection of the trajectory. (b) The 2D projection of the trajectory ( $x$ - $y$  plane), whereas the  $x$ - $z$  projection shows the outlay of the local divergence in dependence on the slow system variable ( $Ca_m$ ).

case [see Fig. 5(a)]. The bifurcation diagram shows a typical transition from the unstable foci branch to the stable periodic branches; hence, the trajectory immediately diverges from the unstable foci branch after the subcritical Hopf bifurcation is exceeded.

Local divergence can also be applied for analyzing synchronization properties of intermittent chaotic  $\text{Ca}^{2+}$  oscillations. Intermittent chaos is characterized by a well-expressed predominant oscillation frequency as well as almost constant shape

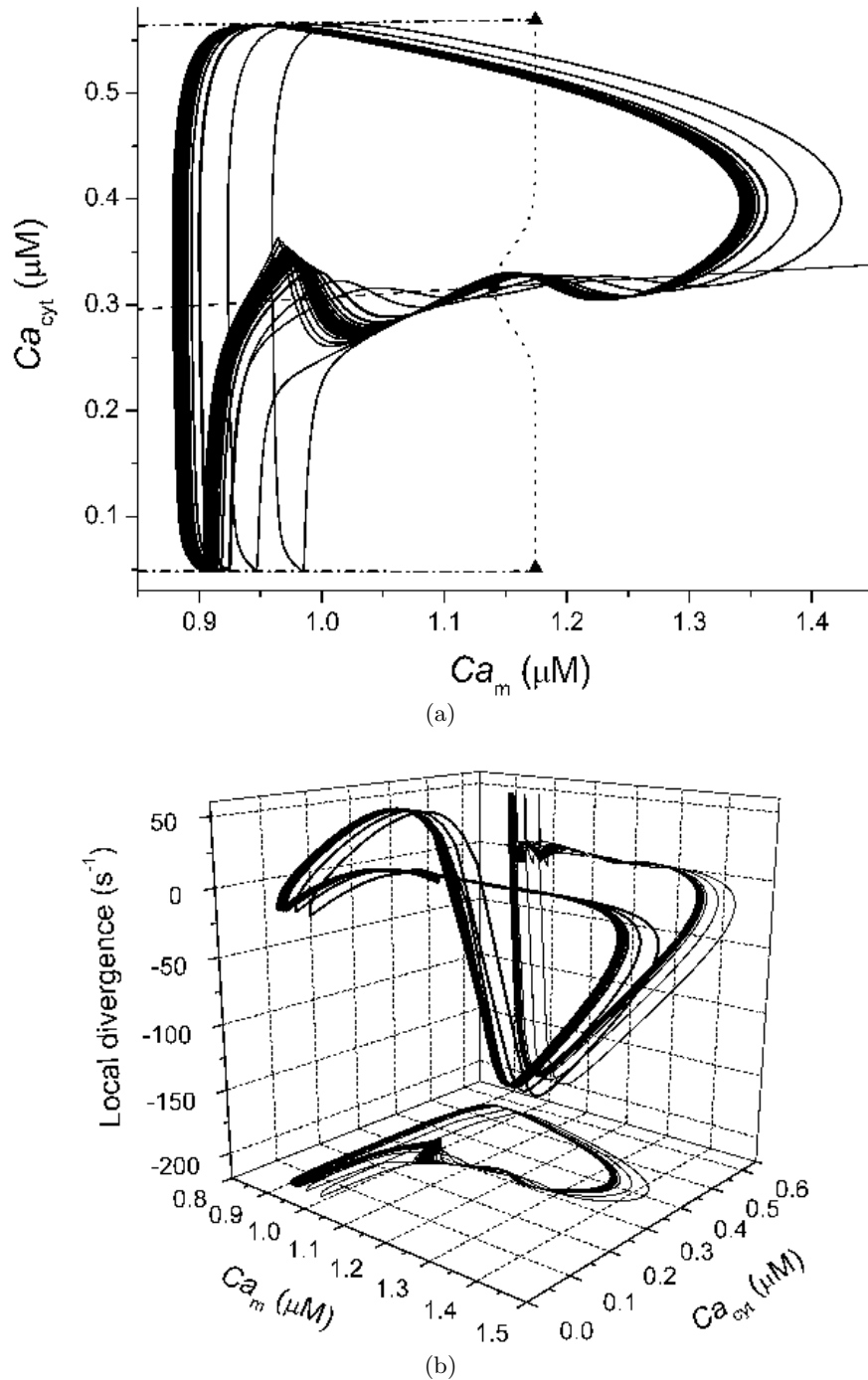


Fig. 6. Bifurcation diagram and the outlay of the local divergence for chaotic oscillatory regime at  $k_{ch} = 2950 \text{ s}^{-1}$  and  $k_{out} = 125 \text{ s}^{-1}$ . (a) Solid (dashed) lines represent stable (unstable) steady states. Dashed-dotted (dotted) lines represent stable (unstable) periodic solutions. Circle (up-triangle) represents the subcritical Hopf (fold limit cycle) bifurcation. The thick solid line represents the 2D projection of the trajectory. (b) The 2D projection of the trajectory ( $x$ - $y$  plane), whereas the  $x$ - $z$  projection shows the outlay of the local divergence in dependence on the slow system variable ( $Ca_m$ ).

of oscillations, with irregularly occurring intermittent deviations (see [Haberichter *et al.*, 2001; Perc & Marhl, 2003a]). Therefore, for intermittent chaotic oscillations the local divergence along the attrac-

tor still has a well comparable outlay for most oscillation periods. Consequently, the local divergence still applies as a good measure for estimating the synchronization abilities of coupled oscillators.

In the studied mathematical model, intermittent chaotic behavior can be found for the agonist stimulation  $k_{\text{ch}} = 2950 \text{ s}^{-1}$ , for example (for details see [Haberichter *et al.*, 2001]). The coupling properties of the intermittent chaotic  $\text{Ca}^{2+}$  oscillations were analyzed in the same way as the above studied coupled systems (results presented in Tables 2 and 3). We found that the coupled chaotic oscillators are able to nullify their initial relative frequency difference of 10.5% at  $h = 0.14 \text{ s}^{-1}$ . By comparing this result to that obtained previously for regular bursting oscillations presented in Table 2, we see that it is comparable with the oscillatory regime calculated for  $k_{\text{out}} = 175 \text{ s}^{-1}$  at  $k_{\text{ch}} = 4100 \text{ s}^{-1}$ . Indeed, the bifurcation diagram as well as the outlay of the local divergence for the chaotic regime presented in Figs. 6(a) and 6(b), respectively, are very similar to that presented in Figs. 1(b) and 3(b), which were made for the regular bursting regime. Figure 6(b) shows that also in case of intermittent chaotic behavior, regions with close to zero local divergence represent well-adaptable, flexible parts of the attractor. These parts of the chaotic attractor can be easily altered by external signals coming from the neighboring oscillators. Therefore, the local divergence seems to be a useful measure for determining coupling abilities also for intermittent chaotic oscillators. Additionally, from the bifurcation diagram a kind of quasi- slow passage effect can be well observed, which sets in for the majority of oscillation cycles in a well-expressed manner [see Fig. 6(a)].

## 5. Discussion

In this paper, we investigate the influence of local divergence on synchronization abilities of calcium oscillations in diffusion-like coupled cells. Moreover, the interrelation between the local divergence and the slow passage effect is studied. Our results show that close to zero local divergence is the crucial system property, which assures good coupling abilities of  $\text{Ca}^{2+}$  oscillations, i.e. a low coupling constant suffices for synchronization, whereas an around-zero oscillating outlay of the local divergence reduces the possibilities of synchronization at low coupling constants. We argue that the local divergence is an appropriate measure for characterizing the coupling properties of regular spiking, complex bursting as well as intermittent chaotic oscillations. Furthermore, concerning the interrelation between the local divergence and the slow passage effect, our

results are fully in agreement with those obtained previously by Izhikevich [2000a, 2000b, 2001], showing that the slow passage effect largely facilitates synchronization of coupled bursters. Moreover, we made a more detailed coupling analysis for oscillators with differently pronounced slow passage effects, and found that coupled oscillators can be more easily synchronized if the slow passage effect is more pronounced. This can be well explained by the outlay of the local divergence during the transition through the bifurcation point.

The local divergence enables a deeper insight into the system ability to adjust its oscillation frequency when coupled with another system. The crucial system property, which efficiently facilitates synchronization of  $\text{Ca}^{2+}$  oscillations in coupled cells, is the well-expressed close to zero local divergence. Those areas represent the flexible, well-adaptable parts of the attractor. Intuitively, if an attractor, e.g. a limit cycle, that corresponds to oscillations of cytosolic calcium in the cell is weakly attractive, i.e. has a very low local divergence, it seems much easier to alter its shape, thus adapting its basic  $\text{Ca}^{2+}$  oscillations to the  $\text{Ca}^{2+}$  oscillations in adjacent cells. On the other hand, if the local divergence oscillates around zero this indicates a less adaptable system. Consequently, it is more difficult to alter the shape of such an attractor and a stronger external input from the neighboring cell is necessary for synchronization. Nevertheless, it should be noted that close to zero local divergence is only the necessary condition that assures good synchronization abilities. We previously showed that externally forced systems with highly flexible attractors must, in addition to the zero local divergence parts, also have localized but well-expressed negative dells of local divergence (see [Perc & Marhl, 2003b]). This assures the system to have strong attractive regions in the phase space, which act as stabilizers, and enable well-controlled responses of oscillators to external influences. These strong attractive regions can be well observed in all examples that we have studied in the paper [see negative cells of local divergence in Figs. 3(a)–3(c), Fig. 4(b), Fig. 5(b), and Fig. 6(b)]. Without these strong attractive regions, the system would respond very vividly to the signals from adjacent cells and the synchronization would be very hard to achieve.

Moreover, we point out an important interrelation between the local divergence and the slow passage effect. Our results show that the slow pas-

sage effect is always characterized by close to zero local divergence. A smoother outlay of the local divergence is linked with a better-expressed slow passage effect. By way of several examples, we showed that this holds not just for bursting  $\text{Ca}^{2+}$  oscillations, to which the slow passage effect was predominantly related (see e.g. Izhikevich [2000a, 2000b, 2001]), but also for simple spiking and intermittent chaotic oscillations [see Figs. 1(a)–1(c), 4(a) and 6(a)]. We also made some preliminary studies for other model systems describing intracellular  $\text{Ca}^{2+}$  oscillations, where the slow passage effect was also found, like for example in the model proposed by Borghans *et al.* [1997] (for the bifurcation analysis see [Perc & Marhl, 2003a]). We found that in the model by Borghans *et al.* [1997] the slow passage effect is also characterized by a very close to zero local divergence (results not shown).

Therefore, by introducing the local divergence as a measure for the estimation of coupling properties, we extend the existing theory of determining the synchronization properties of coupled bursters by considering the slow passage effect, as earlier proposed by Izhikevich [2000a, 2000b, 2001]. We generalize this idea in the sense of trying to find a more accurate and widely applicable internal system property, i.e. the local divergence, which incorporates the slow passage effect, as well as enables the estimation of synchronization properties for simple spiking, complex bursting and intermittent chaotic oscillations. We tested the presented theory also on other model systems and obtained qualitatively the same results. For example, studying coupling properties in the model describing bursting oscillations in thalamocortical neurons presented by Hindmarsh and Rose [1984], as well as the nonchaotic regimes in the mathematical model for intracellular  $\text{Ca}^{2+}$  oscillations proposed by Shen and Larter [1995], the interrelation between the coupling properties and the local divergence obey the presented theory. In all cases, oscillatory regimes that are characterized by extensive regions with close to zero local divergence synchronize at low coupling constants, whereas regimes with now such properties require a much higher coupling coefficient in order to synchronize. Moreover, our investigations on other mathematical models show that in particular for spike-like oscillations and bursting oscillations with excitable properties the local divergence is most useful and very clearly indicates coupling properties of the system. On the other hand, for predominantly sinus-like oscillatory regimes changes in

the outlay of the local divergence for certain parameter ranges might not be so clearly visible, and thus determination of coupling properties is difficult (see also [Perc & Marhl, 2003b]). Special care should also be exercised when dealing with oscillatory regimes close to bifurcation points since due to coupling the oscillatory regimes might change and consequently the outlay of the local divergence of a single system before coupling no longer determines its coupling properties.

Furthermore, an open question remains if the local divergence is still a good measure for estimating the synchronization abilities of chaotic oscillatory regimes, which come into existence through the period doubling root, like for example the chaotic regime in the model proposed by Shen and Larter [1995] (for the analysis see [Perc & Marhl 2003a]). The present study shows that for intermittent chaotic behavior the local divergence plays a decisive role in determining coupling properties, since in this case the system still has a rather well defined predominant frequency as well as shape of oscillations, with only some intermittent alterations. Therefore, the local divergence, calculated along an attractor of intermittent chaotic oscillations, is similar for many oscillation cycles and can be treated nearly the same as it would be calculated for a regular oscillator. However, for chaotic oscillations, which come into existence through the period doubling route and consequently have no predominant oscillation frequency and shape, the local divergence considerably varies from one oscillation cycle to another and is therefore probably a less appropriate measure for determining coupling properties of the system. Therefore, in further studies, we are going to determine not just the attractive properties of a particular attractor, but also the attractive properties of the whole surrounding phase space. Thereby, we expect to get a topological picture of the whole phase space, which would enable a deeper understanding of coupling properties in general.

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