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Noise enhances robustness of intracellular Ca^{2+} oscillations

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Abstract

We investigate responses of a model for intracellular Ca^{2+} oscillations to external pulsatile forcing in the presence of additive Gaussian noise. Our results show that noise makes the system less susceptible to external forcing and thus enhances robustness of Ca^{2+} oscillations. The results can be well explained by the local divergence of limit cycles in the phase space.

Keywords: Robustness; Flexibility; Gaussian noise; Divergence; Calcium oscillations

1. Introduction

Reliable and immutable information processing is vital for flawless functioning of living organisms. One of the key properties that assure such information flow among cells is robustness. Therefore, mathematical models that describe biological systems have to express robustness to various alterations, from parameter changes to external disturbances [1,2]. Moreover, robustness is considered important also in other fields of dynamical system research. There exist many analogies and similar motifs between biological signalling pathways and electronics, where robustness of circuits to various external influences, like for example temperature alterations, is found to be of crucial importance [3,4]. Furthermore, in chained systems the problem of asymptotic stabilization and robustness to external disturbances has recently also attracted much interest cf. [5]. Many studies were also devoted to the robustness of synchronised chaotic states [6–8].

Robustness of a system implies that a particular system property, like for example frequency, amplitude, type or shape of oscillations, is preserved despite changes in the operating environment of the system. These changes in the operating environment can manifest either as shifts in system parameters, different initial conditions or external perturbations. Consequently, there are several ways to define the robustness of a dynamical system, depending on the system properties that change, and how these changes are brought about. A very common way to define robustness of a system is to determine a maximal parameter range in which the qualitative behaviour of the system is not altered, e.g., the system remains oscillating [1,9–11]. However, some authors examine the robustness of a system in dependence on external disturbances [5].

In the present Letter, we study the robustness of intracellular calcium signalling pathways to external perturbations. The study is carried out for a mathematical model that exhibits a broad variety in its dynam-

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ics from simple to complex Ca^{2+} oscillations [12]. It is well known that Ca^{2+} ions are one of the most important second messengers, regulating many cellular processes from egg fertilization to cell death [13]. In order to trigger these different cellular functions, calcium has to play a multiplicity of roles, which requires precisely regulated information encoding of Ca^{2+} oscillations in their frequency [14–20] as well as in their amplitude [21,22]. Therefore, it is of special importance that mechanisms regulating these processes are robust, thereby assuring flawless functioning of living organisms. Previously, Kummer et al. [23] already examined the robustness of a mathematical model for intracellular Ca^{2+} oscillations [24]. They found that bursting oscillations in their model are very unsusceptible to various parameter changes, indicating a high robustness of the system to changes in parameter values. In our work, we examine the robustness of Ca^{2+} oscillations in response to external perturbations. For this study, we use a simple well-defined square-shaped external pulsatile forcing, which enables a systematic analysis of influences of the external forcing on the original signal. We are interested in changes of the form, amplitude and the frequency of Ca^{2+} oscillations caused by the external pulsatile forcing. In real life, these changes of Ca^{2+} oscillations correspond to altering particular information that is encoded by the oscillation frequency and/or the amplitude of Ca^{2+} signals.

The focus of this Letter is to analyse the role of additive Gaussian noise in assuring the robustness of the model system. The robustness of a particular oscillatory regime is quantified by the relative part of the corresponding attractor (limit cycle) that remains unaffected by the applied external perturbations. The positive effect of Gaussian noise on the robustness of the model system is explained by the local divergence of limit cycles in the phase space. In the discussion, the biological importance of the obtained results is discussed.

2. Mathematical model

We use a mathematical model for intracellular Ca^{2+} oscillations, originally proposed by Marhl et al. [12]. The model consists of three basic model compartments, i.e., the cytosol, the endoplasmic reticulum (ER), and the mitochondria (for details see [12]). Consequently, the three main variables are: free Ca^{2+} concentration in the cytosol (Ca_{cyt}), free Ca^{2+} concentration in the ER (Ca_{er}), and free Ca^{2+} concentration in the mitochondria (Ca_{m}). The evolution of the model system is governed by the following differential equations:

$$\frac{\mathrm{d}Ca_{\mathrm{cyt}}}{\mathrm{d}t} = J_{\mathrm{ch}} - J_{\mathrm{pump}} + J_{\mathrm{leak}} + J_{\mathrm{out}} - J_{\mathrm{in}} + J_{\mathrm{CaPr}} - J_{\mathrm{Pr}}, \tag{1}$$

$$\frac{\mathrm{d}Ca_{\mathrm{er}}}{\mathrm{d}t} = \frac{\beta_{\mathrm{er}}}{\rho_{\mathrm{er}}}(J_{\mathrm{pump}} - J_{\mathrm{ch}} - J_{\mathrm{leak}}), \tag{2}$$

$$\frac{\mathrm{d}Ca_{\mathrm{m}}}{\mathrm{d}t} = \frac{\beta_{\mathrm{m}}}{\rho_{\mathrm{m}}}(J_{\mathrm{in}} - J_{\mathrm{out}}), \tag{3}$$

where

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

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

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

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

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

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

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

Concentrations of the free (Pr) and the occupied ($CaPr$) protein binding sites are given by two conservation relations (see [12]):

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

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

Additive Gaussian noise ($\zeta(t)$) with standard deviation $\sigma = 0.367$ and zero mean value is introduced to the model system by adding the term $\beta\zeta(t)$ to Eqs. (1)–(3), where β is the noise intensity. All parameter values are given in figure captions.

3. Results

We examine robustness of the model system by studying responses of the mathematical model to

a well-defined external signal. The external forcing (J_{forcing}) is applied as a pulsatile Ca^{2+} flux through the cell membrane, which has the form of a square-shaped signal ($f(t)$):

$$f(t) = a \begin{cases} 1, & \text{if } (t > t_f) \text{ and } (t < t_f + d) \\ 0, & \text{else,} \end{cases} \tag{13}$$

where a is the amplitude of the forcing signal, t_f is the starting time of the pulse, and d is the pulse duration. The pulsatile Ca^{2+} flux through the cell membrane is taken into account by adding Eq. (13) to the terms in Eq. (1).

We apply the pulsatile forcing systematically in the whole oscillation period of the basic Ca^{2+} oscillations to determine the region in which the system remains unaffected by the external signal. For the model system without inclusion of noise, an example is shown in Fig. 1, where the external forcing with the amplitude $a = 0.05\ \mu\text{M}\,\text{s}^{-1}$ and the duration $d = 3.0$ s is applied in two different parts of the oscillation period. Note that the forcing applied on the left side of the dashed line does not evoke any effect, i.e., the original course (thick solid line) remains unchanged (see Fig. 1(a)), whereas on the right side of the dashed line the response is well expressed in form of a new Ca_{cyt} spike (see Fig. 1(b)). Since the amplitude of the new spike is the same as the amplitude of the original spikes, it is reasonable to study only the frequency robustness of the system.

Fig. 1 shows that the oscillation period can be reduced down to the extend of the robust part on the left side of the dashed line. Therefore, the extend of the robust part of the oscillation period determines the frequency robustness. We define the robustness (R) of the signal related to its frequency as a quotient between the time in which the system remains unaffected by the external forcing (t_R) and the whole basic oscillation period (t_0):

$$R = \frac{t_R}{t_0}. \tag{14}$$

In general, for non-deterministic oscillations, when noise is applied to the system, the robustness (R) is defined by the average values of t_R and t_0:

$$R = \frac{\langle t_R \rangle}{\langle t_0 \rangle}. \tag{15}$$

The average, i.e., the predominant oscillation period ($\langle t_0 \rangle$) for a given β can be obtained by calculating the power spectra of non-deterministic oscillations and applying the equation

$$\langle t_0 \rangle = f_P^{-1}, \tag{16}$$

where f_P is the frequency at which the basic peak value in power spectra occurs. Furthermore, $\langle t_R \rangle$ can be obtained by calculating t_R for several oscillation cycles until a statistically stable average value is gained.

We have calculated the robustness (R) for various levels of the noise intensity (β) and for different amplitudes of the forcing signal (a). Results are presented in Fig. 2. It can be well observed that the robustness of Ca^{2+} oscillations increases by the increasing noise intensity (β). Importantly, this result does not depend on the amplitude of the external perturbation (a). Of course, for larger values of a, thus stronger external forcing, the original time course is altered in a wider part of the oscillation period than for smaller values of a (see Fig. 2). This result is not surprising, since a stronger external perturbation is more likely to affect the original signal.

To explain the results, showing that noise enhances the robustness of Ca^{2+} oscillations to external perturbations, we calculate the time course of the local divergence for the corresponding attractors. If namely 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 close to zero local divergence, it can much easier adapt its shape, thus an alteration of the original time course due to external forcing is more likely to occur (the system is more flexible, see [25]). On the other hand, the trajectory in regions with highly negative local divergence has a strong well-defined immutable path in the phase space. Consequently, in these strong attractive areas, it is much more difficult to alter the shape of an attractor and therefore the robustness of the system is very high. Thus, the investigation of interrelation between the local divergence and the robustness of the oscillator seems to be reasonable. We determine the local divergence for the vector field:

$$\begin{aligned} \mathbf{F}(Ca_{\text{cyt}}, Ca_{\text{er}}, Ca_{\text{m}}) &= (F_{Ca_{\text{cyt}}}, F_{Ca_{\text{er}}}, F_{Ca_{\text{m}}}) \\ &= \left(\frac{\mathrm{d}Ca_{\text{cyt}}}{\mathrm{d}t}, \frac{\mathrm{d}Ca_{\text{er}}}{\mathrm{d}t}, \frac{\mathrm{d}Ca_{\text{m}}}{\mathrm{d}t} \right), \end{aligned} \tag{17}$$

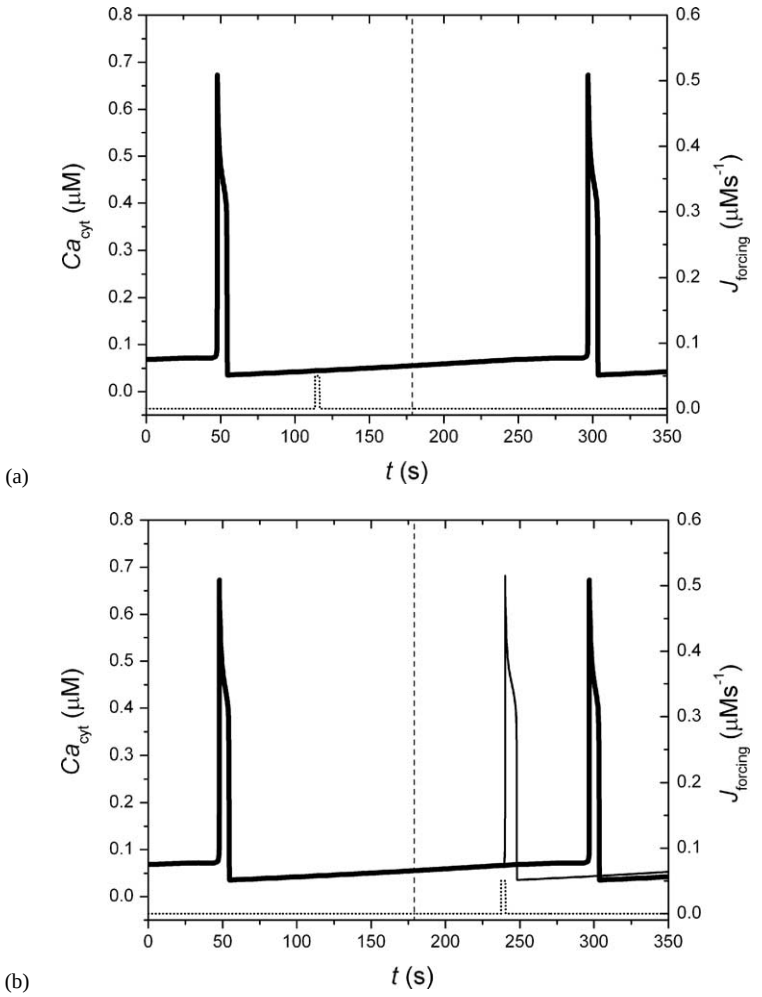

Fig. 1. Responses of the regular oscillatory regime at: $k_{leak} = 0.05\ s^{-1}$, $k_{pump} = 20.0\ s^{-1}$, $k_{in} = 300\ \mu M s^{-1}$, $k_{out} = 125\ s^{-1}$, $k_m = 0.00625\ s^{-1}$, $k_+ = 0.1\ \mu M^{-1} s^{-1}$, $k_- = 0.01\ s^{-1}$, $K_1 = 5.0\ \mu M$, $K_2 = 0.8\ \mu M$, $Ca_{tot} = 90\ \mu M$, $Pr_{tot} = 120\ \mu M$, $\rho_{er} = 0.01$, $\beta_{er} = 0.0025$, $\rho_m = 0.01$, $\beta_m = 0.0025$, $k_{ch} = 495\ s^{-1}$ to the external forcing ($J_{forcing}$, $a = 0.02\ \mu M s^{-1}$, $d = 3.0$ s): (a) time course of Ca_{cyt} (thick solid line) remains unaffected by the external forcing $J_{forcing}$ (doted line) if the pulse is applied in the robust part of the oscillation period (left side of the dashed line), (b) time course of Ca_{cyt} (thick solid line) is altered (thin solid line) by the external forcing $J_{forcing}$ (doted line) if the pulse is applied in the non-robust, susceptible part of the oscillation period (right side of the dashed line).

according to the definition:

$$\nabla \cdot \mathbf{F}(Ca_{cyt}, Ca_{er}, Ca_m) = \frac{\partial F_{Ca_{cyt}}}{\partial Ca_{cyt}} + \frac{\partial F_{Ca_{er}}}{\partial Ca_{er}} + \frac{\partial F_{Ca_m}}{\partial Ca_m}, \tag{18}$$

where $(Ca_{cyt}, Ca_{er}, Ca_m)$ is a point of the limit cycle.

We calculate time courses of the local divergence for the oscillatory regime presented in Fig. 1. Results for the reference case, without adding noise, as well as examples for three different noise intensities (β) are shown in Fig. 3. For $\beta > 0$ typical traces are presented, i.e., traces with the oscillation frequency at which the main peak value in power spectra occurs for a given β. It can be well observed that for increasing noise intensity (larger β) the sensitive parts of the attractor, characterised by the close to zero local divergence, are cut off (see insert of Fig. 3). Therefore, with increasing noise intensity the attractor (limit cycle) becomes stronger attractive, i.e., the system becomes

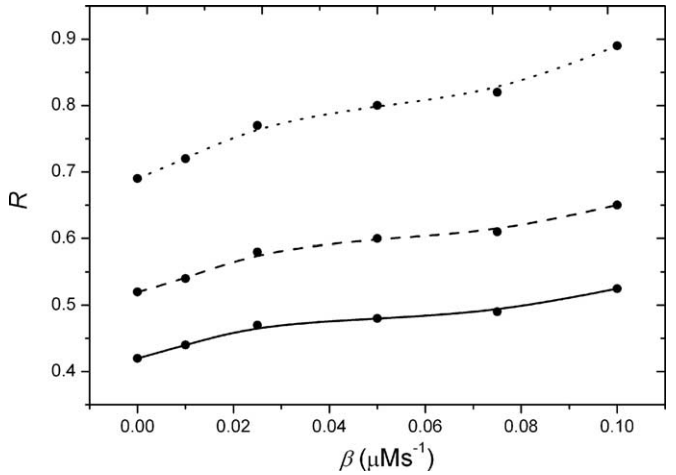

Fig. 2. Robustness of the system in dependence on the noise intensity (β) for various amplitudes of the external signal (a). Solid line, dashed line and doted line stand for $a = 0.1\ \mu\mathrm{M\,s}^{-1}$, $a = 0.05\ \mu\mathrm{M\,s}^{-1}$, and $a = 0.01\ \mu\mathrm{M\,s}^{-1}$, respectively. For other parameter values see caption of Fig. 1.

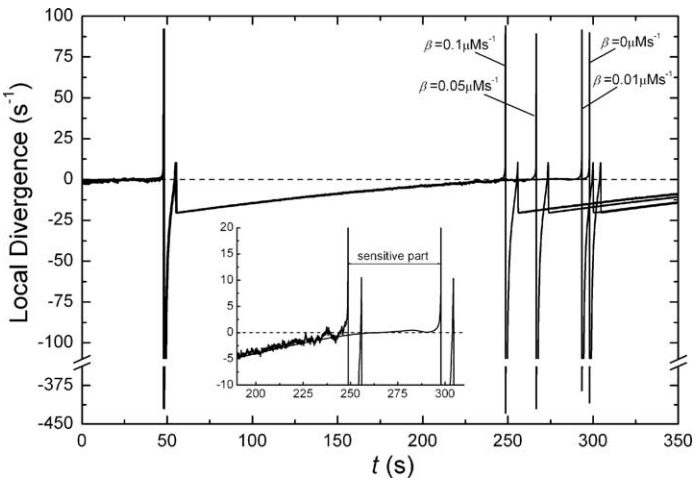

Fig. 3. Time courses of the local divergence for one oscillation period at various noise intensities (β). For parameter values see caption of Fig. 1.

rigid in a broader part of the oscillation period. Consequently, by increasing the noise intensity, the external forcing can alter an ever-smaller part of the oscillation period, thus the robustness of the system increases with increasing noise intensity.

In Fig. 3, it can be well observed that cutting off the flexible parts of attractors by noise results in reducing the oscillation period $\langle t_0 \rangle$. To analyse this more systematically, we separately show $\langle t_0 \rangle$ and $\langle t_R \rangle$ in dependence on β. Fig. 4 shows that $\langle t_0 \rangle$ shortens continuously with increasing β, whereas the time in which the system remains unaffected by the external forcing $\langle t_R \rangle$ remains nearly the same for all noise intensities. According to our definition of R, given by Eq. (15), the robustness of the system increases with increasing noise intensity, as presented in Fig. 2.

4. Discussion

In this Letter, we investigated effects of additive Gaussian noise on robustness of Ca^{2+} oscillations. For

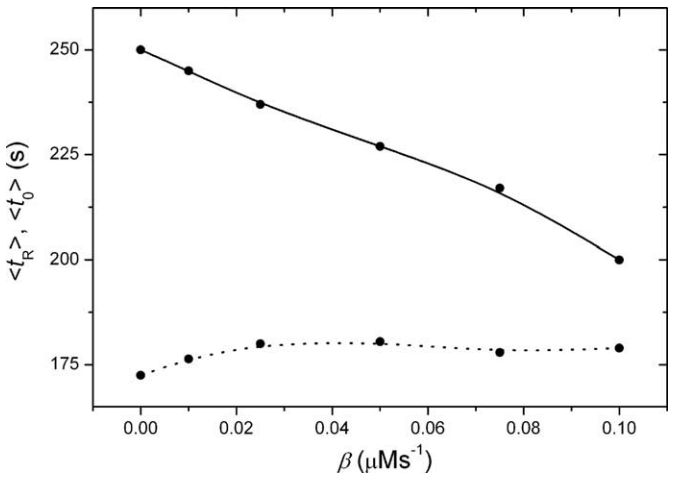

Fig. 4. Time courses of $\langle t_0 \rangle$ (solid line) and $\langle t_R \rangle$ (dashed line) in dependence on the noise intensity (β) for $a = 0.1\ \mu\mathrm{M\,s}^{-1}$. For other parameter values see caption of Fig. 1.

the studied model [12], we found that noise reduces the system susceptibility for external pulsatile forcing, thus enhances the robustness of intracellular Ca^{2+} oscillations. It should be pointed out that the results are independent of the choice of the amplitude of the forcing signal (see Fig. 2).

We explain the obtained results with the local divergence, which represents the attractive properties of limit cycles in the phase space. The local divergence has been previously used for analysing the flexibility of Ca^{2+} oscillations in response to external periodic forcing [25]. In the present study, we found that by applying additive Gaussian noise to the system, the sensitive areas of attractors, characterised by close to zero local divergence, are cut off, while the rigid, non-susceptible parts of the attractor are preserved (see Fig. 3). Consequently, by increasing the noise intensity, the external forcing can alter an ever-smaller part of the oscillation period, i.e., the robustness of the system increases with increasing noise intensity.

Moreover, it should be pointed out that noise predominantly enhances the frequency robustness of the system, thereby assuring robust frequency encoding of information [14–20]. On the other hand, the amplitude robustness of the system is largely unaffected by noise. For excitable systems such as, for example, studied in this Letter, this is a characteristic system property. In the model, oscillations appear via hard excitation [26] characterized by predominantly constant amplitudes in a larger part of the corresponding bifurcation diagram (cf. [17]). This property is also manifested in the time course of the local divergence, which is highly negative at the time the spike occurs, thereby making it virtually impossible for an external signal to alter the system's behaviour at this point.

From the biological point of view, the obtained results are of special importance. In a living environment, there are many external influences to which a biological system has to respond selectively [27]. Accordingly, mechanisms that are essential for living cells have to be able to filter relevant signals from the background successfully [28]. Thus, for Ca^{2+} signalling pathways, for example, only biologically significant signals have to be recognised and further transmitted, while others have to be ignored by the cell. For such a reliable and convincing signal transduction, the cell must have a well-defined threshold, at which it responds to an external signal. In the present study, we showed that noise actively participates in forming the threshold level. In particular, for higher noise intensities the threshold level is shifted higher, whereas for weaker noise the system is able to respond to weaker signals. With a higher threshold level, the confusion with other unreliable weak signals from the environment is avoided. Thereby, our study provides new evidences for a constructive role of noise at the cellular level. This considerably contributes to previous studies analysing the constructive role of noise

in biological systems, like, for example, the noise induced synchronisation of Ca^{2+} oscillations [29], stochastic resonance [30–32], and noise enhanced signal transduction [33].

In further studies, it would be interesting to investigate robustness in relation to other dynamical system properties, like, for example, sensitivity and flexibility of oscillatory regimes. In particular, it is of special interest to clarify, whether the higher robustness of the system can only be achieved by reducing its flexibility. From the evolutionary point of view, it seems reasonable that in biological systems a compromise between sensitivity, flexibility, and robustness is assured.

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