Determining the Robustness of Signal Transduction Systems:
A Case Study on Neurons

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Abstract: - In biological signal transduction systems robustness is one of the key system properties that assure reliable and immutable signal processing within and among cells in the tissue. Since signal transduction systems have to respond also very sensitively and flexibly to weak external stimuli, they posses several states, which differ in their robustness. The question arises, how to mathematically quantify and measure the robustness of a particular state. We analyse the robustness of oscillatory states in a mathematical model of an excitable neuron. In accordance with our previous studies for calcium dynamics, we show that the robustness of a particular oscillatory state can be determined by the divergence calculated along the trajectory of the corresponding attractor.

Key-Words: - Robustness, neuronal systems, oscillations, bursting, external forcing, divergence

1 Introduction

Sensitivity, flexibility and robustness are important properties of biological systems. Through the evolution biological systems were compelled to find a compromise between all these properties. This is of special importance for signal transduction systems, which have to be able to detect and respond very flexibly to weak external stimuli. On the other hand, however, they have to be robust against undesirable external influences like noise and other surrounding signals.

At first glance, it appears contradictory that a biological system could be flexible and robust at the same time. Signal transduction systems, for example, possess different dynamical states, which are not only single stationary states but also multistable, periodic, multirhythmic, and non-periodic oscillatory states [1]. In such cases some dynamical states facilitate flexible responses, whereas others guarantee robust functioning of the system. The question arises, however, how to recognise and be able to predict in advance if a given system possesses flexible or/and robust states. Furthermore, it is of interest to quantify the flexibility and robustness of particular states mathematically.

In our previous studies, we have developed mathematical tools for measuring the flexibility and robustness of calcium signalling pathways. Oscillatory changes in cytosolic calcium, the so-called calcium oscillations, play an important role in cellular signalling since they regulate several processes from egg fertilisation to cell death [2]. In order to understand the cellular mechanism of calcium oscillations many mathematical models have been developed, which were recently reviewed in [3]. We studied the flexibility and robustness of several mathematical models for simple and complex calcium oscillations and found that both flexibility and robustness depend on attractive properties of the phase space, which can be mathematically quantified by measuring the divergence along the attractor in the phase space [4-9].

Here we show that the mathematical formalism for determining the flexibility and robustness of oscillatory regimes in the models for calcium dynamics can be applied to other oscillatory systems as well. We demonstrate this on one of the most prominent examples of signal transduction pathways in biological systems, i.e. the neuronal system. We analyse the robustness of oscillatory states in a mathematical model of an excitable neuron and show that in this case the local divergence can also be taken as an appropriate measure for determining the robustness of oscillatory states.

2 Mathematical Model

We use a mathematical model of an idealized nerve membrane model, which was first formulated by FitzHugh and Rinzel in 1976 (unpublished) and latter extensively studied numerically in [10]. The evolution of the model is governed by the following differential equations:

$$\frac{dx}{dt} = x - x^3/3 - y + z + I , \quad (1)$$

$$\frac{dy}{dt} = \delta(x + a - by), \quad (2)$$

$$\frac{dz}{dt} = \varepsilon(-x + c - dz), \quad (3)$$

where $I = 0.3$, $a = 0.7$, $b = 0.8$, $c = -0.9$, $d = 1$, $\delta = 0.08$, and $\varepsilon = 0.0001$. All results presented here were calculated for these values if not otherwise stated in the text or in figure captions. For the chosen parameter values, the model system exhibits elliptic or the so-called "subHopf – fold cycle" bursting oscillations (see [11,12]).

The robustness of the system is examined by studying responses of the model to a well-defined pulsatile external forcing, which has the form

$$f(t) = w \begin{cases} 1, & \text{if } (t > t_f) \text{ and } (t < t_f + u) \\ 0, & \text{else} \end{cases}, \quad (4)$$

where $w = 0.025$ is the amplitude of the forcing signal, t_f is the time of the pulse application, and $u = 20$ is the pulse duration. The pulsatile forcing is taken into account by adding $f(t)$ to the terms in Eq. (1).

3 Results

We study the robustness of the model system by applying the external forcing $f(t)$ at different times t_f. The external forcing is systematically applied during the course of one oscillation period. Figure 1 shows that the response of the system depends significantly on t_f. More precisely, for a given w, there exists a sharp boundary between the "flexible part" (right from the dashed line in Fig. 1) in which the external pulse evokes a new bursting phase, and the "robust part" (left from the dashed line in Fig. 1) in which the external pulse does not evoke a new bursting phase. The robust part corresponds to the well-known refractory period in which the nerve is

unresponsive to external signals (see e.g. [13]). By applying the external forcing, the oscillation period can be reduced down to the extend of the robust part, which characterises the robustness of the oscillatory state. We define the robustness (R) of the signal as a quotient between the time in which the system remains practically unaffected by the external forcing (t_R), and the whole basic oscillation period (t_0) [6]:

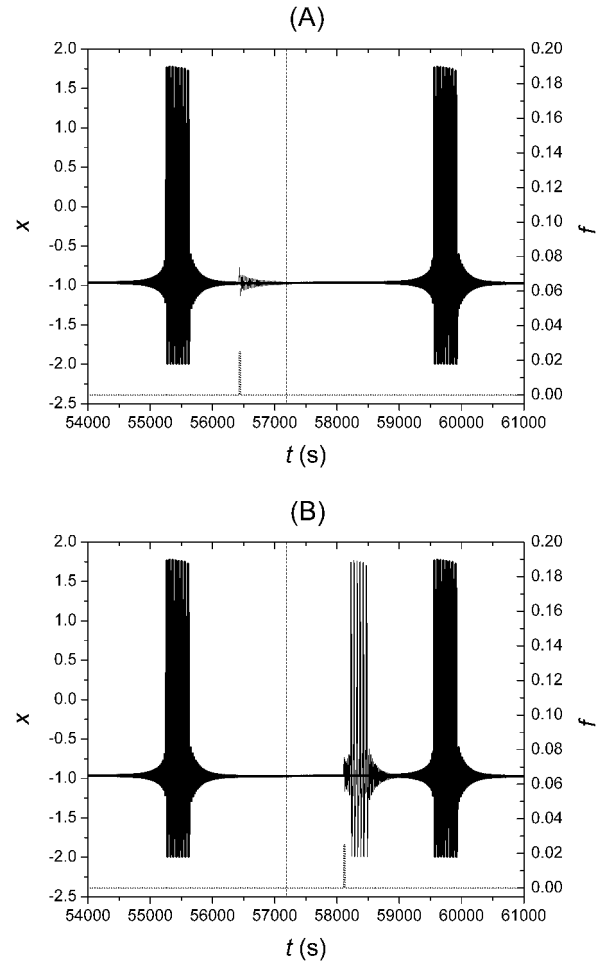$$R = \frac{t_R}{t_0}. \quad (5)$$

Fig. 1 Responses of the model system in the reference state ($I = 0.3$, $a = 0.7$, $b = 0.8$, $c = -0.9$, $d = 1$, $\delta = 0.08$, and $\varepsilon = 0.0001$) to the external forcing ($w = 0.025$, $u = 20$): (A) in the robust part (left from the dashed line) the system remains practically unaffected, (B) in the flexible part (right from the dashed line) the external pulse evokes a new bursting phase.

In the reference case (Fig. 1) the robustness equals 0.44, which means that 44% of the whole oscillatory period is robust in the sense that in this part the system is not considerably disturbed by the external forcing. The question arises why the system responds in one (flexible) part of the oscillation period and does not respond in another (robust) part. To answer this question, we calculate the time course of the local divergence for the corresponding attractor in the phase space. If namely an attractor has a weakly attractive part, i.e. a region with close to zero local divergence, it can easily adapt its shape, thus an alteration of the original time course due to an external forcing is more likely to occur. On the other hand, in regions with considerably negative local divergence the trajectory has a well-defined immutable path in the phase space. Consequently, in these strong attractive areas, it is much more difficult to alter the shape of the attractor and therefore the robustness of these parts is much higher. Thus, the investigation of the interrelation between the local divergence and the robustness of the system seems to be reasonable.

We determine the local divergence for the vector field

$$\mathbf{F} = \left(F_x, F_y, F_z\right) = \left(\frac{\mathrm{d}x}{\mathrm{d}t}, \frac{\mathrm{d}y}{\mathrm{d}t}, \frac{\mathrm{d}z}{\mathrm{d}t}\right) \qquad (6)$$

according to the definition:

$$\nabla \cdot \mathbf{F} = \frac{\partial F_x}{\partial x} + \frac{\partial F_y}{\partial y} + \frac{\partial F_z}{\partial z}. \qquad (7)$$

We calculate the time course of the local divergence for the reference case (Fig. 1). The result is presented in Fig. 2. In the inset of Fig. 2 it is evident that in the flexible part (right from the dashed line) the local divergence is slightly positive, whereas in the robust part (left from the dashed line) the local divergence is slightly negative.

To analyse the relationship between the robustness and the local divergence more systematically, we calculated the robustness (R) for several oscillatory states. The robustness has been calculated for the oscillatory states obtained by varying the current I from $I = 0.27$ to $I = 0.4$. In this parameter region, the oscillatory states are characterised by simple regular bursting oscillations, which enables a relevant comparison of the results. The results are presented in Fig. 3.
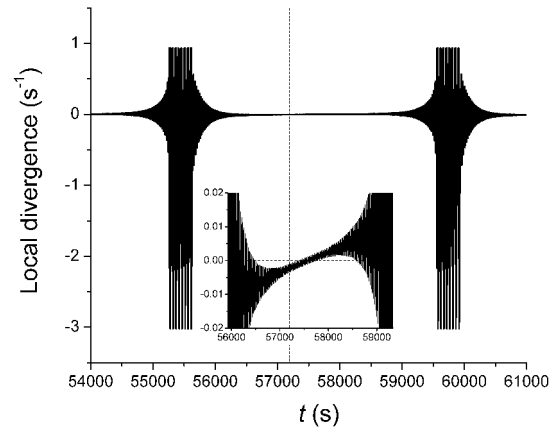

Fig. 2 Time course of the local divergence for the reference case (for the parameter values see text and Fig. 1).
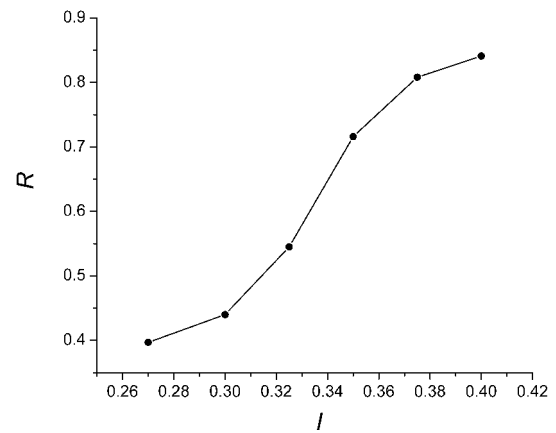

Fig. 3 Robustness (R) of the model system in dependence on the parameter I.

In accordance with the results in Fig. 3, we also calculated time courses of the local divergence for various values of I. The obtained results were qualitatively the same as those presented in Fig. 2; however, the time courses considerably differ in the extension of regions with positive and negative local divergence. To quantify this, we have averaged the local divergence for each oscillatory regime. The results are presented in Fig. 4.

By comparing Figs. 3 and 4, it is evident that the robustness strongly depends on the divergence. Highly robust oscillatory states are characterised by a more negative divergence of the corresponding attractor, whereas less negative values of the divergence characterise less robust systems. Note,

however, that in dissipative systems the time-averaged divergence is negative for every oscillatory as well as non-oscillatory state. It should also be noted that in Fig. 3 the robustness only seemingly approaches to a maximum value. This maximum is directly linked to the chosen value of w, in the sense that for studying the robustness of the system at higher values of I, also the value of w has to be enlarged. The results for larger values of w are qualitatively the same as those shown in Fig. 3.
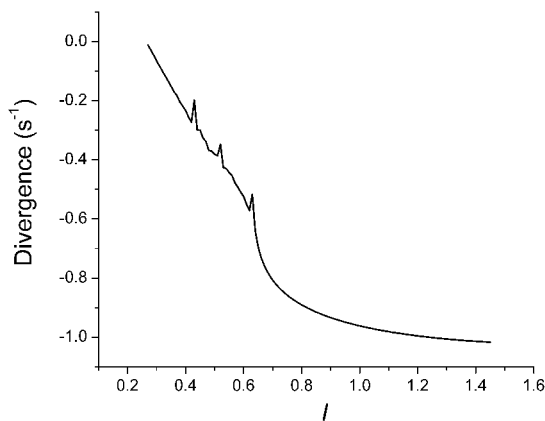

Fig. 4 Time-averaged divergence in dependence on the parameter I.

4 Discussion

We studied the robustness of oscillatory states in a mathematical model of an excitable neuron. The robustness of the system was examined by analysing the responses of the model system to a pulsatile external forcing. In accordance with our previous studies for calcium dynamics [4-9], we show that the robustness of an examined oscillatory state in the neuron model can be determined by the divergence calculated along the trajectory of the corresponding attractor. A more robust oscillator is characterised by a more negative divergence of the corresponding attractor, whereas less negative values of the divergence characterise less robust systems. This can be well explained intuitively. If namely an attractor is weakly attractive, i.e. has a close to zero local divergence, it can easily be shaped by an external forcing, whereas on the other hand the external forcing has practically no effect on robust attractors with a highly negative divergence. It should be noted, of course, that the divergence, usually expressed as the sum of Lyapunov exponents, has been used

before, mainly in the sense of relating it with the entropy production rate (e.g. [14]). However, here the sum of Lyapunov exponents is used for estimating the robustness of a dynamical system.

The studies concerning the flexibility and robustness of dynamical systems are widely applicable. In our previous studies, we showed some applications for calcium oscillations. One of the most direct applications concerns cell coupling by gap junctions. We showed that the coupling ability of an oscillator depends on the local divergence of the corresponding attractor. For a facilitated gap junctional coupling, the system has to be flexible, i.e. the local divergence of the corresponding attractor has to be close to zero [8,9]. These studies, concerning gap junctional coupling of calcium oscillators, seem to be easily transferable to the cell coupling in neuronal systems. In the last decade several new findings have shown that in the neuronal cell networks, involving neurons, astrocytes, microglia, and oligodendrocytes, the gap junctional coupling also plays the key role in maintaining the normal physiological functioning of the system (for review see [15,16]).

Another important application of studies regarding flexibility and robustness of dynamical systems concerns the influences of noise and other sub-threshold signals on the behaviour of a given system. Previously, we studied the effect of noise on the robustness of calcium oscillations [6] and in particular the role of the local divergence in explaining the frequency dependent stochastic resonance [7]. All these results obtained for calcium oscillations could be transferred to neuronal cell networks; however, since we know that calcium plays an important role in the neuronal systems as well, the results should not be simply transferred but also systematically integrated into this area of research, striving towards a deeper understanding of the whole physiological functioning of the system.

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