ELSEVIER

Biophysical Chemistry 120 (2006) 161 – 167

Biophysical Chemistry

http://www.elsevier.com/locate/biophyschem

A minimal model for decoding of time-limited Ca^{2+} oscillations

Marko Marhl [a,*], Matjaž Perc [a], Stefan Schuster [b]

[a] *Department of Physics, Faculty of Education, University of Maribor, Koroška cesta 160, SI-2000 Maribor, Slovenia*

[b] *Department of Bioinformatics, Faculty of Biology and Pharmaceutics, Friedrich Schiller University of Jena, Ernst-Abbe-Platz 2, D-07743 Jena, Germany*

Received 3 October 2005; received in revised form 14 November 2005; accepted 15 November 2005
Available online 9 December 2005

Abstract

Calcium oscillations regulate several cellular processes by activating particular proteins. Most theoretical studies focused on the idealized situation of infinitely long oscillations. Here we analyze information transfer by time-limited calcium spike trains. We show that proteins can be selectively activated in a resonance-like manner by time-limited spike trains of different frequencies, while infinitely long oscillations do not show this resonance phenomenon. We found that proteins are activated more specifically by shorter oscillatory signals with narrower spikes.

Keywords: Signal transduction; Calcium oscillations; Calcium-binding proteins; Decoding; Resonance

1. Introduction

Pulsatile oscillations are very common in a wide variety of chemical [1] and biological [2] nonlinear systems. A prominent example in biology is provided by oscillations of intracellular calcium in a number of electrically excitable and nonexcitable cells (see Refs. [2–4]). Calcium oscillations play an important role in intra- and intercellular signaling. Many cellular processes like egg fertilization, cell division, and cell secretion are regulated by Ca^{2+} oscillations. Soon after the discovery of Ca^{2+} oscillations in non-excitable cells [5], it was shown that the response of a cell stimulated by different concentrations of a hormone is characterized by different frequencies of Ca^{2+} oscillations [6]). The idea of frequency-encoded Ca^{2+} signals was born (cf. [2]) and the mechanism of information encoding in the frequency of Ca^{2+} oscillations has been studied theoretically, starting already by the first model of Ca^{2+} oscillations in non-excitable cells ([7]; for reviews of the models, see Refs. [8,9]).

An intriguing question in the mathematical modeling of Ca^{2+} oscillations is how the oscillatory signal can be decoded to give a stationary output signal, for example, the elevated expression of a gene. In the early 1990s it was suggested that this decoding is performed by Ca^{2+}-dependent kinases, preferably embedded in a kinase-phosphatase cycle [3,10,11]. This hypothesis has later been verified experimentally [12]. This is an impressive example of predictive modeling (cf. [13]).

In most theoretical analyses of Ca^{2+} oscillations, the idealized situation of infinitely long self-sustained oscillations has been considered ([3,10], cf. [8,9]). However, it is clear that biological signals such as Ca^{2+} oscillations act only on limited time spans and activate specific cellular processes that are limited in time as well. For example, specific genes may be switched on only for a certain period during ontogeny. It has been shown that the duration of Ca^{2+} signals modulates gene transcription (cf. [14]). There are also experimental evidences for different durations of Ca^{2+} signals in astrocytes ([15]), neurons ([16]), or in bronchial smooth muscle cells ([17], cf. [18]), for example.

Detailed experimental data are available for the duration of Ca^{2+} signals in oocytes. Upon fertilization of mammalian and ascidian eggs the sperm induces a temporal series of Ca^{2+} spikes, which are then stopped when eggs complete meiosis with the formation of pronuclei [19,20]. The duration of Ca^{2+} oscillations depends on the cell type. In ascidian eggs, Ca^{2+} oscillations are complete by within 25–30 min [19,21], while,

* Corresponding author. Tel.: +386 2 2293643; fax: +386 2 2518180.
E-mail address: marko.marhl@uni-mb.si (M. Marhl).

0301-4622/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.bpc.2005.11.005

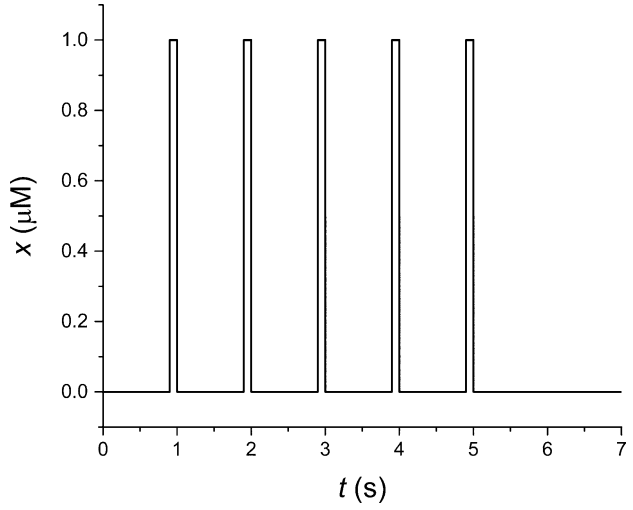

Fig. 1. Square-shaped Ca^{2+} oscillations. Parameter values: $N=5$, $x_{min}=0$, $x_{max}=1$ μM, $p=1$ s, and $d=0.1$ s.

in mammalian eggs, Ca^{2+} spikes stop several hours after sperm fusion [20,22].

In guard cells in plants, Ca^{2+} oscillations regulate the aperture of stomatal pores. It has been shown experimentally that long-term steady-state stomatal closure depends not only on the frequency and amplitude of Ca^{2+} oscillations but also strongly on the duration and number of Ca^{2+} spikes [23]. In particular, long-term steady-state stomatal closure depends on the number of Ca^{2+} spikes in a resonant-like manner. For example, in guard cells of *Vicia faba*, a train of exactly five Ca^{2+} spikes causes maximal half-open-time ([24], cf. [25]).

In the present paper, we study the effects of time-limited Ca^{2+} oscillations on protein activation. We use very simplified model for demonstrating the basic mechanism of how proteins can be selectively activated in a resonance-like manner by time-limited spike trains of different frequencies, while infinitely long oscillations do not show this resonance phenomenon. The time-limited Ca^{2+} spike trains are modeled by square-shaped pulses and the protein activation relies on one protein-binding reaction.

2. Mathematical model

To separate the analysis of decoding of Ca^{2+} oscillations from the studies of their generation and for achieving a controlled change of frequencies, we simulate Ca^{2+} oscillations by artificial square-shaped pulses. Such an approach has also been used in experiment [12] and in mathematical simulations [26–28]. Other artificially generated signals, like sinusoidal patterns, have also been used [29].

Time-limited Ca^{2+} spike trains are here simulated by the following periodic square-shaped signal (Fig. 1):

$$x(t)=\begin{cases} x_{max}, & \text{if } ((t \bmod p)\geq(p-d)\wedge(t<Np)) \\ x_{min}, & \text{else} \end{cases}, \qquad (1)$$

where x_{min} and x_{max} are the minimum and maximum of the oscillation, respectively, p is the period of oscillations, d is the spike width, and N is the number of Ca^{2+} spikes.

We consider proteins that are activated by Ca^{2+} binding. The concentration of the activated proteins is given by the following equation:

$$\frac{dz}{dt}=k_{on}(z_{tot}-z)x^n-k_{off}z, \qquad (2)$$

where k_{on} and k_{off} are the Ca^{2+} binding and dissociation rate constants, respectively; z_{tot} ($z_{tot}=1$ μM in all calculations) is the maximal concentration of activated protein, x is the cytosolic Ca^{2+} concentration, and n ($n=4$ in all calculations) denotes the coefficient of cooperative Ca^{2+} binding to the proteins. It should be noted that the results presented in the paper are qualitatively (and for $x_{min}=0$, $x_{max}=1$ μM exactly) the same for all values of n (also for $n=1$).

3. Results

We study the effects of square-shaped Ca^{2+} spike trains (Fig. 1) on protein activation by using the mathematical model (Eqs. (1), (2)). Time-limited Ca^{2+} spike trains consisting of five spikes ($N=5$) are here used, if not otherwise stated.

3.1. Bell-shaped resonant protein activation

We analyze protein activation for several different classes of proteins which differ in their kinetics of Ca^{2+} binding (k_{on}) and dissociation (k_{off}), while, to demonstrate the effects of the analysis more efficiently, we take the same dissociation constant for all classes of proteins ($K_D=k_{off}/k_{on}=0.01$ μM^4). Therefore, a larger k_{on} implies a larger k_{off} and, thus, an overall faster kinetics of Ca^{2+} binding and dissociation. In Fig. 2,

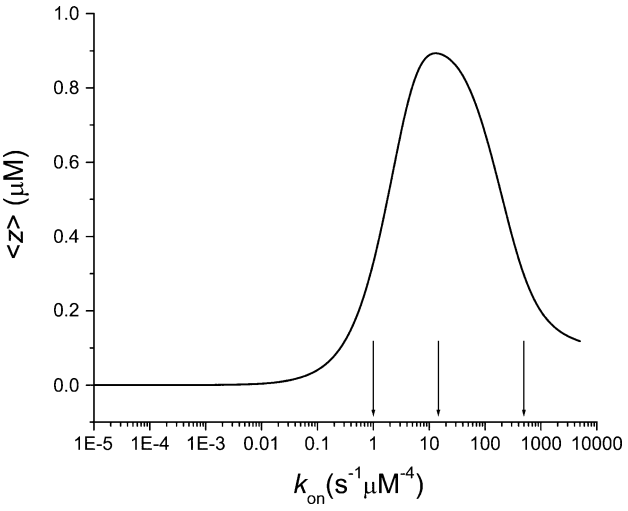

Fig. 2. Average protein activation during the 5th period of Ca^{2+} oscillations as a function of k_{on}. Arrows mark values of k_{on} for which the time courses of protein activation are presented in Fig. 3.