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

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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,

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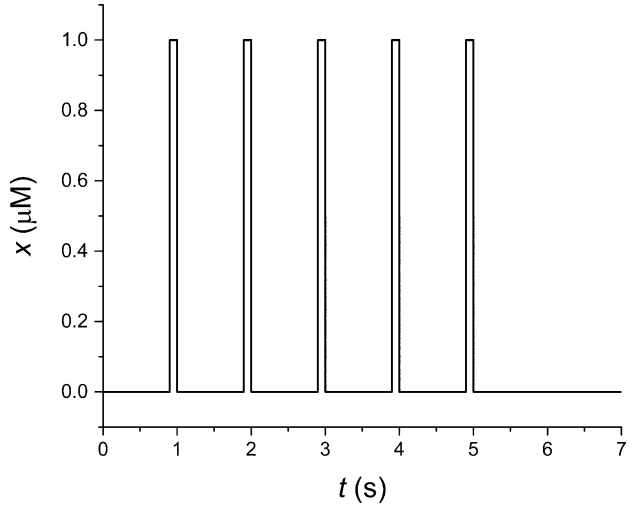

Fig. 1. Square-shaped Ca^{2+} oscillations. Parameter values: $N=5$, $x_{min}=0$, $x_{max}=1$ μM, $p=1$ s, and $d=0.1$ s.

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,

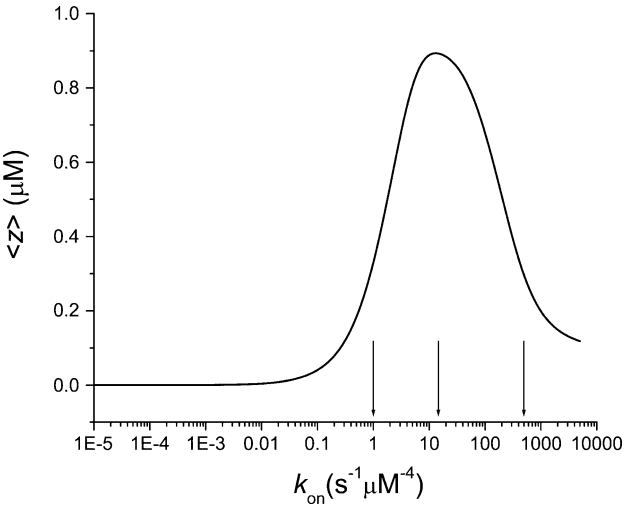

Fig. 2. Average protein activation during the 5th period of Ca^{2+} oscillations as a function of k_{on}. Arrows mark values of k_{on} for which the time courses of protein activation are presented in Fig. 3.

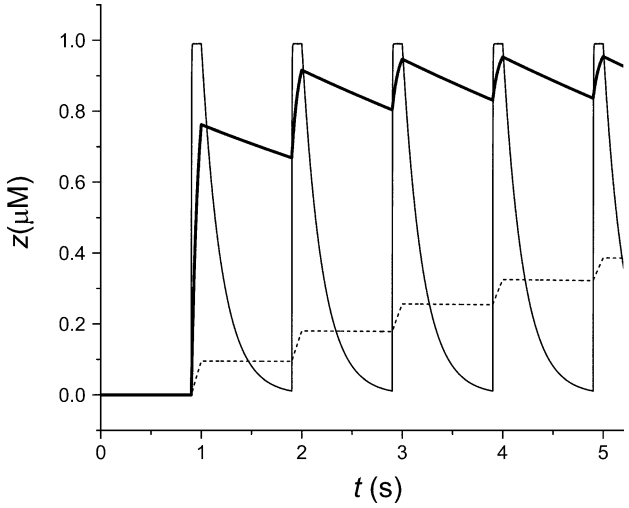

Fig. 3. Time courses of protein activation for the values of k_{on} marked in Fig. 2: k_{on}=1 s^{-1} μM^{-4} (dashed line), k_{on}=14.54 s^{-1} μM^{-4} (thick solid line, this value corresponds to the maximum protein activation in Fig. 2), and k_{on}=500 s^{-1} μM^{-4} (thin solid line).

protein activation is plotted in dependence on k_{on}. Since the Ca^{2+} signal is time-limited and the average protein activation does not always reach its steady state value during this time, Fig. 2 shows the average protein activation, denoted by $\langle z \rangle$, during the last (5th) period of Ca^{2+} oscillations.

The results in Fig. 2 show that for a given time-limited oscillatory Ca^{2+} signal an optimal protein kinetics exists for which the activation of proteins is maximum. To explain these results we analyze the time-course of protein activation. For three values of k_{on} (marked with arrows in Fig. 2) the dynamics of protein activation is presented in Fig. 3. It can be seen that if the kinetics of Ca^{2+} binding to proteins is very slow, the duration of the Ca^{2+} signal is too short to allow the average protein activation to reach its maximal steady state value (dotted line in Fig. 3). On the other hand, if the kinetics of Ca^{2+} binding to proteins is very fast, Ca^{2+} binding to the proteins is fast enough to reach the maximal possible protein activation. However, since K_D is constant the dissociation of Ca^{2+} is also very fast, and thus the average value of protein activation is small again (thin solid line in Fig. 3). In fact, if the rate constants were infinitely high, the bound calcium would follow the calcium signal perfectly because the binding reaction would always be in equilibrium, that is, it would show a square-shaped pattern in the case considered here. This shows that neither very slow nor very fast kinetics of Ca^{2+} binding to proteins can lead to the maximal protein activation.

The optimal resonant response in protein activation is reached if the kinetics of Ca^{2+} binding to proteins is fine-tuned with the kinetics of the oscillatory Ca^{2+} signal (thick solid line in Fig. 3). In analogy to stochastic resonance (see Ref. [30]), we suggest using the term “finiteness resonance” for this phenomenon because it requires finite spike trains. The basic idea of this fine-tuning is that for a rather low dissociation constant, an optimal on-rate constant exists which allows a quasi-equilibrium binding during the calcium spike while the off-rate constant is not high enough to allow a quasi-equilibrium during the resting phase. To explain this fine-tuning effect in more detail, we analyze the Ca^{2+} binding to proteins separately for the Ca^{2+} spike and for the inter-spike interval.

First, we analyze protein activation during the interspike interval. Since, in the time between two successive Ca^{2+} spikes, the value of x is zero, Eq. (2) simplifies to:

$$\frac{dz}{dt} = -k_{off} z. \tag{3}$$

The solution of Eq. (3) is:

$$z = z_0 e^{-k_{off} t}, \tag{4}$$

where $z_0 = z(0)$, taking $t = 0$ at the beginning of the interspike interval (see Fig. 4a).

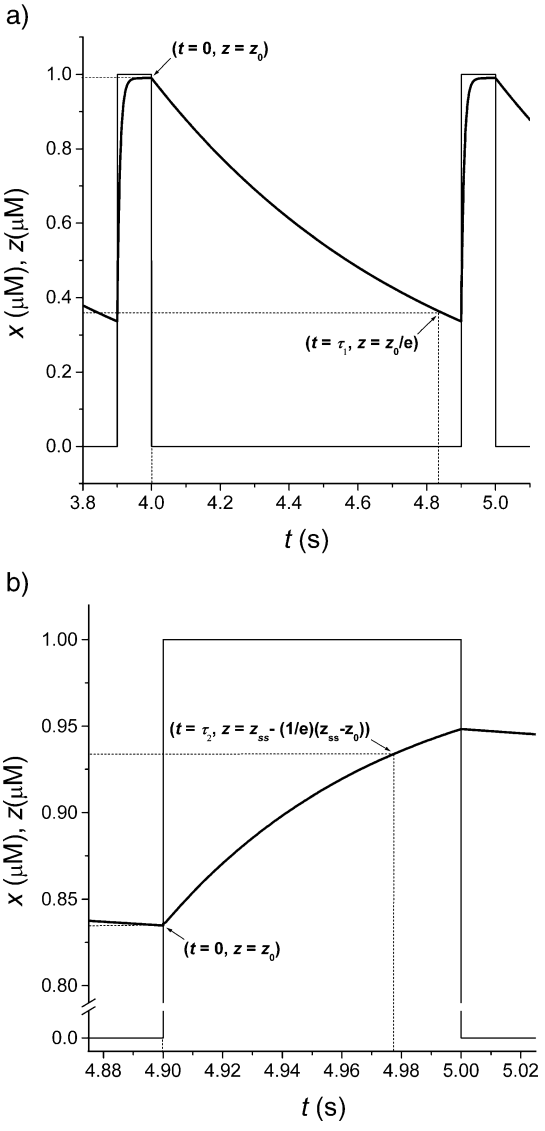

Fig. 4. Detailed analysis of Ca^{2+} binding to proteins: (a) protein deactivation during the interspike interval, (b) protein activation during the Ca^{2+} spike. Thick solid line, time course of activated proteins (k_{on}=120 s^{-1} μM^{-4} in (a) and k_{on}=13 s^{-1} μM^{-4} in (b)); thin solid line, Ca^{2+} oscillations; thin dashed line, characteristic time τ_1 in (a) and τ_2 in (b).

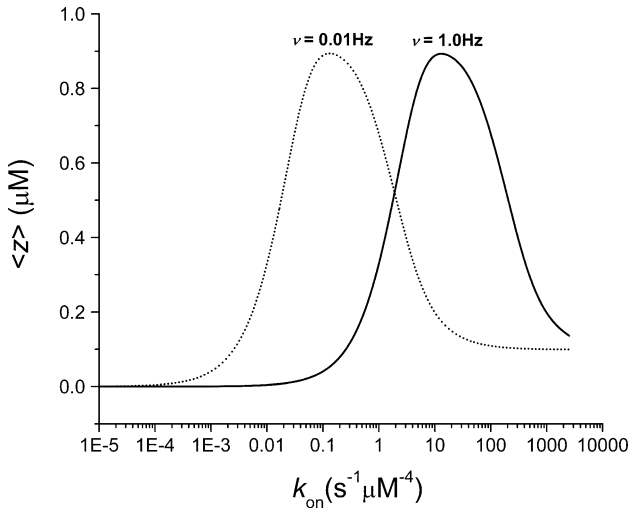

Fig. 5. Average protein activation during the 5th period of Ca^{2+} oscillations as a function of k_{on} for two different frequencies of Ca^{2+} oscillations: $\nu = 0.01$ Hz (dotted line) and $\nu = 1.0$ Hz (solid line) with $d/p = 0.1$ (see Fig. 1).

The characteristic time, τ_1, of this process is:

$$\tau_1 = \frac{1}{k_{off}}. \tag{5}$$

Eq. (5) implies the first condition for an optimal resonant response in protein activation:

$$\frac{1}{k_{off}} > p. \tag{6}$$

If, for example, $k_{off} = 1.2\ s^{-1}$, Ca^{2+} spikes should be less than 0.83 s apart.

The analysis of Ca^{2+} binding to proteins during the Ca^{2+} spike is only slightly more complex, because the Ca^{2+} level is constant during the spike. Therefore, Eq. (2) can be written as:

$$\frac{dz}{dt} = k^*_{on}(z_{tot} - z) - k_{off} z, \tag{7}$$

where $k^*_{on} = k_{on} x^n = \text{const.}$ The solution of Eq. (7) is:

$$z = z_{ss} - (z_{ss} - z_0) e^{-\left(k^*_{on} + k_{off}\right)t}, \tag{8}$$

where z_{ss} is the steady state solution, $k^*_{on} z_{tot}/(k^*_{on} + k_{off})$, fulfilling the condition $dz/dt = 0$ at $x = \text{const.} = 1.0$ μM, and $z_0 = z(0)$, taking $t = 0$ at the beginning of the Ca^{2+} spike (see Fig. 4b).

The characteristic time, τ_2, at which $z = z_{ss} - (1/e)(z_{ss} - z_0)$ is:

$$\tau_2 = \frac{1}{k^*_{on} + k_{off}}. \tag{9}$$

The importance of τ_2 is demonstrated in Fig. 4b. For effective protein activation Ca^{2+} spikes should not be shorter than τ_2. Therefore, Eq. (9) implies another condition for optimal resonant response in protein activation (in addition to Eq. (6)):

$$\frac{1}{k^*_{on} + k_{off}} < d. \tag{10}$$

If, for example, $k^*_{on} = 13\ s^{-1}$ and $k_{off} = 0.13\ s^{-1}$, Ca^{2+} spikes should not be shorter than 0.076 s.

Relations (6) and (10) represent conditions linking the protein kinetics to the Ca^{2+} signal, which ensure an optimal resonant response in the protein activation (see Fig. 2). For Ca^{2+} spiking oscillations with given d and p values, optimal k_{on} values can be estimated by combining the relations (6) and (10):

$$\frac{1}{K_D p} > k_{on} > \frac{1}{(x^n + K_D) d}, \tag{11}$$

where $K_D = k_{off}/k_{on}$. For the parameter values used in Fig. 2, for example, we obtain $100\ \mu M^{-4}\ s^{-1} > k_{on} > 10\ \mu M^{-4}\ s^{-1}$, which is quite a good estimate. Interestingly, if the parameter values are such that $1/K_D p$ is less than the term on the right-hand side in relation (11), so that this relation cannot be fulfilled, the resonance property is much less pronounced or even lost completely (not shown).

3.2. Frequency-dependent resonant protein activation and specificity of activation

The bell-shaped resonant protein activation (see Fig. 2) points to the possibility of specific activation of proteins that differ in their kinetics. We analyze protein activation by Ca^{2+} signals that differ in their frequency. Let us vary the frequency of Ca^{2+} oscillations at constant ratio d/p (in our case $d/p = 0.1$). This amounts to a scaling of time in Eq. (1). Fig. 5 shows that proteins with higher rate constants for Ca^{2+} binding and dissociation are more efficiently activated by Ca^{2+} oscillations with higher frequencies.

The reference Ca^{2+} signal, represented in Fig. 1, consists of 5 spikes. Now we prolong this signal and study the resulting protein activation. In Fig. 6 the results are shown for five different lengths of Ca^{2+} signals: 5, 10, 20, 2000, and extremely many spikes ($N \to \infty$). It can be seen that the

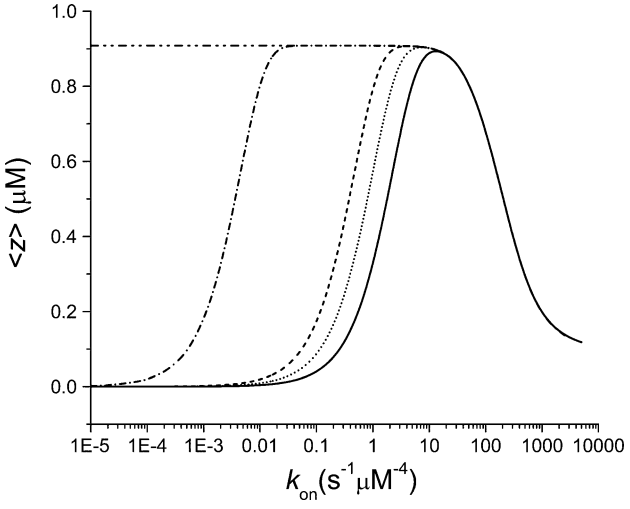

Fig. 6. Average protein activation during the 5th (solid line), 10th (dotted line), 20th (dashed line), 2000th (dashed-dotted line), and Nth ($N \to \infty$; dashed-dot-dotted line) period of Ca^{2+} oscillations as a function of k_{on}. For parameter values see caption of Fig. 1 and description of Eq. (2).

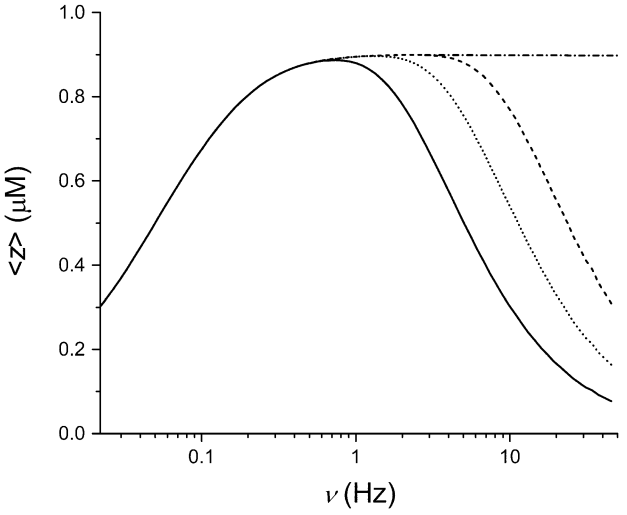

Fig. 7. Average protein activation during the 5th (solid line), 10th (dotted line), 20th (dashed line), and Nth ($N\to\infty$; dashed-dotted line) period of Ca^{2+} oscillations as a function of the frequency of Ca^{2+} oscillations at constant ratio between spike width and interspike interval ($d/p=0.1$). Other parameter values: $k_{on}=10\ s^{-1}\ \mu M^{-4}$, $k_{off}=0.1\ s^{-1}$.

specificity of resonant protein activation depends on the number of Ca^{2+} spikes. The specificity is larger for shorter Ca^{2+} signals. For very long Ca^{2+} signals, the specificity is practically lost (see Fig. 6). This can be explained as follows. If the binding and dissociation are very fast, the fraction of bound calcium follows the calcium signal immediately because it is in quasi-equilibrium. Therefore, the average protein activation practically does not depend on the number of spikes. By contrast, in the case of slow binding and dissociation, a large spike number implies that the average protein activation can build up to a higher level (see also the dotted curve in Fig. 3). Therefore, in Fig. 6, the plateau is extended to the left by increasing the spike number.

Moreover, the specificity of protein activation depends not only on the number of spikes, but also slightly on the width of Ca^{2+} spikes, even at constant number of spikes and constant frequency of the signal. The proteins are activated more specifically by Ca^{2+} oscillations with narrower spikes. However, the level of activation then decreases due to smaller amounts of Ca^{2+} in the cytosol. Thus, a compromise between the spike width and a physiological reasonable threshold level of protein activation has to be found.

Now we consider the activation of one given protein class, with specific k_{on} and k_{off} values ($k_{on}=10\ s^{-1}\mu M^{-4}$, $k_{off}=0.1\ s^{-1}$), in dependence on the frequency of time-limited Ca^{2+} oscillations (Fig. 7). The frequency of Ca^{2+} oscillations is changed by the scaling of time in Eq. (1), which means that $d/p=$const. (in our case $d/p=0.1$).

Fig. 7 shows that proteins are able to decode the frequency of time-limited Ca^{2+} signals. A given class of proteins is optimally activated by the resonant frequency of Ca^{2+} spike trains, which means that protein activation is maximum when the protein kinetics of Ca^{2+} binding is fine tuned with the Ca^{2+} dynamics. This resonant protein activation enables selective activation of different protein classes by only changing the frequency of oscillations. The specificity of resonant protein activation depends on the number of spikes. In Fig. 7 the results are shown for four different lengths of Ca^{2+} signals: 5, 10, 20, and extremely many spikes ($N\to\infty$). It can be seen that the specificity decreases with the number of Ca^{2+} spikes. For very long Ca^{2+} signals, the resonance and, thus, specificity are lost.

4. Discussion

In this paper, the decoding of time-limited Ca^{2+} spike trains is analyzed, which in addition to the known importance of oscillatory signals in comparison to stationary ones (see, e.g. Ref. [31] for experimental evidences and [28] for theoretical reasoning), points out the importance of time limitation of the Ca^{2+} signals. In general, constant (non-oscillatory) Ca^{2+} signals are less efficient in protein activation than Ca^{2+} oscillations with the same average value, but of course not with the same amplitude value, which can be seen from Eq. (2). Moreover, constant signals cannot activate proteins in a resonance-like manner, and constant elevated calcium levels are harmful to the cell. Our simulation results show that also infinitely long Ca^{2+} oscillations do not show the resonance phenomenon, but the proteins can be activated in a resonance-like manner by finite Ca^{2+} spike trains. We demonstrate that the frequency optimum of protein activation depends on the binding properties of the protein. Therefore, it can be concluded that the time limitation of Ca^{2+} signals is crucial for a selective activation of proteins. In living cells, this is of particular importance, because it allows different processes to be selectively regulated. Proteins that regulate cellular processes differ in their rate constants [32]. In our simulations, proteins with higher rate constants for Ca^{2+} binding and dissociation turned out to be more efficiently activated by Ca^{2+} oscillations with higher frequencies.

The specificity of protein activation depends on the duration of Ca^{2+} signals. We found that proteins are activated more specifically by shorter oscillatory signals. For biological systems, shorter signals seem to be of advantage because they are time-efficient and require less energy consumption. As mentioned in the Introduction, there are many experimental evidences about time-limited Ca^{2+} signals. Although biological signal transduction processes are always time-limited, in some cases oscillatory signals are indeed very short. Upon fertilization of frog eggs [20], or in bronchial smooth muscle cells under caffeine stimulation [33], for example, Ca^{2+} signals consist of only one spike. Experiments on isolated mitochondria show that only two or three Ca^{2+} spikes are necessary to effectively open the permeability transition pore (PTP) [34–36]. Time-limited Ca^{2+} oscillations provide a conductance switch between two open conformations of the PTP. Detailed experimental [34] and theoretical [37] analyses show that the number of Ca^{2+} spikes necessary for a certain effect strongly depends on the frequency of Ca^{2+} oscillations. High frequencies of Ca^{2+} oscillations enable effective opening of the PTP after only two or three Ca^{2+} spikes, because the threshold in pH is reached very fast for high-frequency oscillations. The dynamics of the pH can be directly compared with the time

evolution of the Ca^{2+} binding to the proteins in our model. Importantly, this shows the universality of the presented mechanisms for decoding of Ca^{2+} oscillations.

We have also tested for our model that the specificity of protein activation can be increased even further by Ca^{2+} signals consisting of narrower spikes. In experiments, Ca^{2+} signals with narrow spikes are a common observation (see, e.g. Ref. [6]). In addition, this may have further evolutionary reasons. It is known that long exposure to high Ca^{2+} concentrations is toxic for living cells (cf. [8]). Therefore, short Ca^{2+} signals with narrow spikes provide secure and energy-saving signal transduction which guarantees reliable and, as we show here, increased specific protein activation.

It should be noted that the proposed mathematical model represents a minimal model for selective protein activation, and hence indicates a simplest possible mechanism for selective regulation of cellular process, for the case that the frequency of Ca^{2+} oscillations is varied at constant ratio d/p (in our case $d/p=0.1$). If the frequency of Ca^{2+} oscillations is varied at constant spike duration (d), for example, the cellular mechanisms providing selective regulation of cellular processes become more complex [38].

In some cases, process regulation does not mainly depend on the frequency but much more on the duration of Ca^{2+} signals and the number of Ca^{2+} spikes. Such an example has recently been found for plant cells: the long-term steady-state stomatal closure depends on the number of Ca^{2+} spikes in a resonant-like manner. In guard cells of *V. faba*, for example, exactly five Ca^{2+} spikes cause maximal half-open-time of stomatal pores ([24]; cf. [25]). This indicates that several different mechanisms exist for optimal decoding of intracellular signals and further studies will be needed to clarify all these questions.

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