

Decoding of calcium oscillations by phosphorylation cycles

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1 Introduction

Hormones and neurotransmitters induce oscillations in the concentration of cytosolic calcium. The amplitude and frequency of Ca^{2+} oscillations carry information for the activation of signaling targets and the regulation of cellular functions. Experiments on calcium-dependent gene expression suggest that oscillations can be advantageous when compared to constant signals [1]. Several models have considered the activation of specific enzymes by calcium oscillations [2,3]. Here we aim to elucidate general properties of oscillatory signal transduction. We show under which conditions Ca^{2+} oscillations increase efficiency, speed, and specificity of activation of target proteins.

2 Results and discussion

Mathematical model. We consider the activation of a protein by Ca^{2+} , e.g., through a Ca^{2+} -dependent kinase. The fraction of active protein X obeys $X'(t) = \alpha(t) - (\alpha(t) + \beta)X(t)$, where the activation rate constant $\alpha(t) = \hat{\alpha}S(t)^n / (K^n + S(t)^n)$ incorporates cooperative activation by Ca^{2+} , as observed, e.g., for calmodulin. $S(t)$ denotes the Ca^{2+} concentration, K the half-saturation constant, and n the Hill-coefficient. Oscillations of $S(t)$ are modelled as piecewise constants functions with period T , amplitude S_0 , and spike width Δ (Fig. 1A, top). For inactivation, e.g., by dephosphorylation, we take $\beta = \text{const}$.

Efficiency of activation. When an oscillatory Ca^{2+} signal is initiated, the time-averaged activity of the protein increases and reaches a stationary value \bar{X} , which we take as a measure of the target response (Fig. 1A, bottom). In the limits of short periods ($T \rightarrow 0$) or low activation ($X \ll 1$), the average activity of the protein is given by

$$\bar{X} = \frac{\hat{\alpha} \gamma \bar{S}^n}{\bar{S}^n + (K\gamma)^n} \bigg/ \left(\beta + \frac{\hat{\alpha} \gamma \bar{S}^n}{\bar{S}^n + (K\gamma)^n} \right) \quad (1)$$

where $\gamma = \Delta/T$ is the duty ratio and $\bar{S} = \gamma S_0$ the average Ca^{2+} concentration in an oscillation period. Comparing the responses to constant Ca^{2+} elevation and Ca^{2+} oscillations with the same average, Eq. (1) shows that oscillations greatly enhance the detection of low-amplitude stimuli (Fig. 1B). This requires cooperativity of Ca^{2+} sensing ($n > 1$), causing the oscillations to periodically exceed the threshold for activation, while the constant Ca^{2+} signal remains below the threshold (Fig 1C). Oscillations are more efficient when the average Ca^{2+} concentration is below the critical value $\bar{S}_c = K \sqrt[n]{(\gamma - \gamma^n)/(1 - \gamma)}$, approaching the half-saturation constant K for large values of n (Fig. 1D).

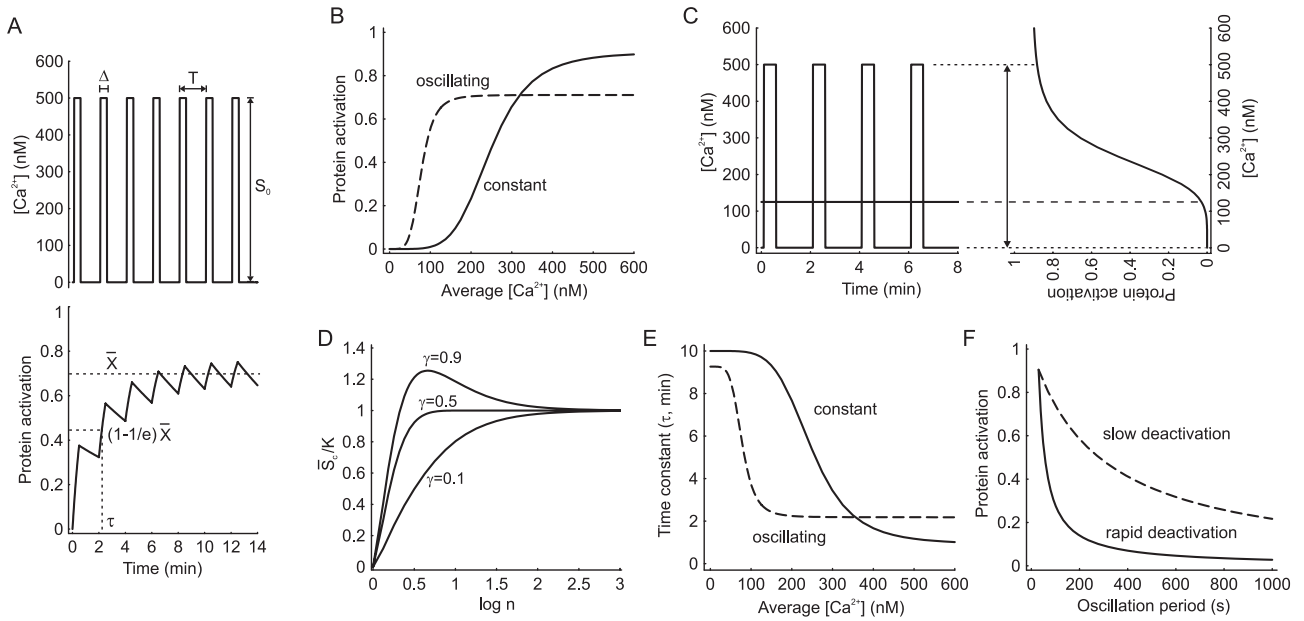


Figure 1: Oscillations increase efficiency and specificity of protein activation at low levels of stimulation

Speed of activation. The transient time τ for protein activation (see Fig 1A, bottom) can be shorter in response to oscillations than to a constant signal. Again, for low periods or non-saturated proteins, τ can be calculated analytically

$$\tau = \left(\frac{\hat{\alpha} \gamma \bar{S}^n}{\bar{S}^n + (K\gamma)^n} + \beta \right)^{-1}, \quad (2)$$

showing that oscillations accelerate the response to comparatively low-amplitude stimuli (Fig. 1E).

Target specificity. Ca^{2+} -regulated proteins differ in their activation and inactivation kinetics. We compare two proteins which attain the same activity for a constant Ca^{2+} signal but have different kinetics. Slow oscillatory signals activate preferentially the slowly responding protein and thus discriminate between the two targets (Fig. 1F). Further analysis suggests that the deactivation rate constant β of the protein is critical for period sensitivity of activation. This finding is in agreement with the period dependence of the activation of the transcription factors NF κ B and NFAT by Ca^{2+} oscillations [1]. The activity of NF κ B, which is counteracted by a slow, transcription-dependent mechanism, extends to much longer periods than NFAT activity, which is opposed by a faster mechanism of phosphorylation and nuclear export. We also found that low-amplitude oscillations, with frequent narrow spikes or, alternatively, with less frequent but broad spikes, are more efficient for proteins which slowly deactivate. If the protein is rapidly deactivated, an optimal response is obtained for a train of high-amplitude broad spikes. Thus Ca^{2+} oscillations, through variation of period, amplitude, and spike width, may discriminate between different target proteins. Furthermore, we found that oscillatory signals also enhance both the efficiency and specificity of signalling pathways involving multisite phosphorylation and positive feedback loops [4].

References

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