Period distributions of intracellular Ca^{2+} oscillations

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1 Introduction

The dynamics of cytosolic Ca^{2+} concentrations is the dynamics of uptake and release by intracellular storage compartments. It was shown in recent years by several modelling studies that fluctuations drive spatial and temporal structures in intracellular Ca^{2+} dynamics [1, 3]. Fluctuations arise from the random opening and closing of release channels on the membrane of the endoplasmic reticulum. The state of the channels is controlled by binding of Ca^{2+} and IP_3 to binding sites on the subunits of the tetrameric channel molecule. The source of randomness in the channel behavior is the random binding and dissociation of Ca^{2+} and IP_3 at the channel subunits.

Long period oscillations can be comprehended as repetitive wave nucleation: The cooperative release activity of a few neighbored channel clusters creates a wave spreading through the whole cell [2, 1]. The creation of global events by this process is stochastic, too. The stochasticity of the elemental events causes randomness of global events. Thus, periods of oscillations are not regular anymore but exhibit variability and a distribution instead of a single sharp value. We present period distributions in this paper and analyze them with respect to the wave nucleation rate.

2 Method and Results

We simulated Ca^{2+} release patterns on an array of clusters of IP_3 receptor channels as described previously [1]. The concentration field is a superposition of single cluster profiles. A single cluster profile is the stationary solution of the diffusion problem describing a single cluster in an infinitely large cell. The state of each subunit of each channel is simulated as a Markov process. Channels are open, if at least 3 out of 4 subunits have IP_3 and activating Ca^{2+} bound.

The IP_3 concentration sets the ability of the channel cluster array to support wave propagation. It determines the fraction of channels which can be opened by Ca^{2+} binding at the activating binding sites of the subunits. There is a minimum IP_3 concentration for global events. Wave nucleation sets in with very large (most likely infinite) period above this minimum concentration. Distributions of intervals between global events - which we call periods in lack of a better term - are broad and decay exponentially towards large periods in this concentration range (see Fig. 1). The exponential decay is illustrated by the fit in Fig. 1. It shows that the creation of the next global wave is determined by a process with a single constant probability per unit time. That is compatible with the idea of wave nucleation and the fact that the average local channel state is constant before nucleation of a wave in long period oscillations [1]. Hence, the time constant of the exponential decay of period distributions towards large periods is a measure of the wave nucleation rate. That allows for definition of the two components of the period: One part determined by the dynamics of the channel state $T_{channel}$ and another part set by the wave nucleation rate. Periods in dependence on IP_3 are shown in Fig. 2. The

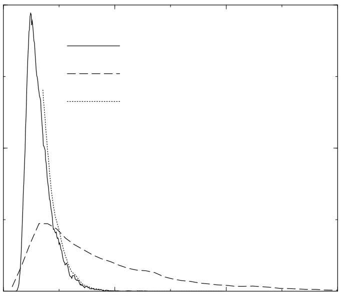

Figure 1: Period distributions for [IP$_3$]=0.155μM (long dashed line) and [IP$_3$]=0.170μM (full line).

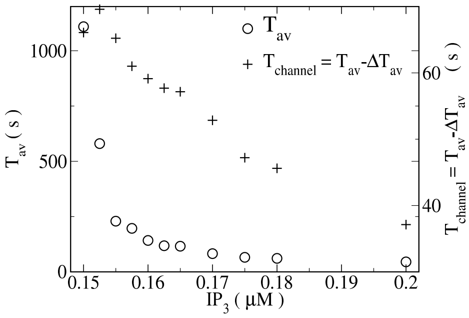

Figure 2: Average periods of Ca^{2+} oscillations due to wave nucleation T$_{av}$ and the channel time scale T$_{av}$-ΔT$_{av}$.

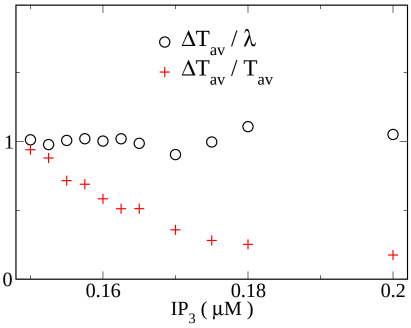

Figure 3: Relative standard deviation of periods ΔT$_{av}$/T$_{av}$ and comparison of ΔT$_{av}$ and the nucleation rate λ for a range of [IP$_3$].

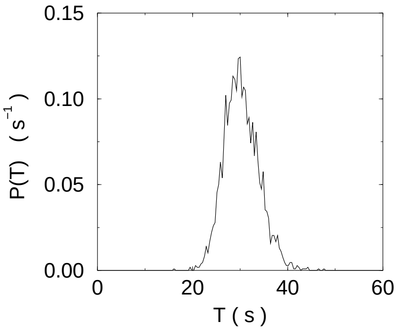

Figure 4: Period distribution for [IP$_3$]=0.3μM.

period and its standard deviation (see Fig. 3) decrease with increasing IP$_3$ concentration. While the total average period changes by about a factor of 40, T$_{channel}$ changes by about a factor of 2 only. Comparison of the time constants λ obtained from period distributions with the standard deviation of the period ΔT$_{av}$ shows good agreement for these two values for average periods down to about 40s (see Fig. 3). These are periods frequently encountered in experiments. Hence, ΔT_{av}^{-1} is a good approximation for the nucleation rate. That approximation breaks down for short period distributions like shown in Fig. 4. It shows a relative standard deviation of 11% only which is determined by the fluctuations in the channel state transition times.

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