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Analytic description of stochastic calcium-signaling periodicity

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Calcium release is an important tool for cellular signaling processes where chemical signals are converted into spatio-temporal variations of intracellular calcium concentration. We investigated the temporal behavior of a single cluster of inositol-(1,4,5)-triphosphate receptor (IP_3R)-I channels and will present an analytic approach to obtain the spectrum of the calcium signal within the cluster. We compare these results with stochastic simulations and obtain an intermediate number of channels per cluster for optimal signaling periodicity.

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INTRODUCTION

Calcium plays the role of an important intracellular and intercellular messenger in all types of cells and tissues. It is involved in processes ranging from signal transmission across the synaptic cleft to muscle activity and from cell fertilization and proliferation to programmed cell death. This variety of tasks is accomplished by a spatio-temporal variation of the free calcium concentration which interacts with calcium binding proteins which then, on the other hand, fulfill a highly specific task; for a general introduction to calcium signaling see, e.g., Refs. [1–3].

The elevation of free (intracellular or intercellular) calcium concentration is due to the opening of calcium stores, e.g., the endoplasmatic reticulum (ER) or vesicles, regulated by ion channels. These are either sensitive to membrane depolarization (voltage gated) or to ligands binding to their receptors (ligand gated). Of importance for many cellular processes is the ligand gated inositol-(1,4,5)-triphosphate receptor (IP_3R) channel, for review see Ref. [4]. It is present in several types of tissues, e.g., neuronal tissue and smooth muscle. The channel is composed of four subunits, each of which is activated by IP_3 and shows a bell shaped activation dependence on calcium [5], thus calcium induces and limits its own release. De Young and Keizer proposed an eight-state model [6] which was later reduced to a two-state system for this receptor [7,8]. The channel is open if at least three out of four subunits are activated [9].

Although patch clamp techniques and fluorescence microscopy allow single channel characterization and *in vivo* measurements of channel activity on a micrometer scale, respectively, the spatial distribution of ion channels across the ER membrane and its function is not yet fully determined. In Ref. [10] individual Ca^{2+} release sites were observed and it is believed that clusters, each constituted of $O(10–100)$ IP_3R channels, form the signaling basis. In Refs. [11–13] the corresponding cluster signaling properties of a cluster were numerically characterized by power spectra as function on the number of channels constituting one cluster.

We follow this idea that a certain number of ion channels in the cluster creates a common level of noise. By a mean field description for the calcium concentration with imbedded fluctuating subunits, it will be shown analytically that the common noise plays a crucial role for the dynamics of the cluster. As will be inspected by the power spectrum of the calcium concentration, the cluster exhibits collective stochastic oscillations for an optimally selected noise level. The corresponding optimal number of channels in one cluster, for which the quality of oscillation becomes maximal, is compatible with estimates for real cells.

MODEL DESCRIPTION

The analysis presented in this report is based on the Li-Rinzel model for the IP_3R-*I* channel which is obtained by reducing the De Young-Keizer model to a two-state system. This model is valid for a single cluster of N_0 subunits ($N_0/4$ channels) since channel interaction is assumed to be instantaneous via the intracellular calcium concentration $c=[Ca^{2+}]$. Due to fast intracellular calcium diffusion c can be considered spatially constant on a submicrometer scale. We describe the activity of channel subunits with the Li-Rinzel model and the opening probability of a single channel is then given by

$$P_{\text{open}}=x^4+4x^3(1-x), \tag{1}$$

$$x=\frac{pc(1-y)}{(p+K_1)(c+K_5)}. \tag{2}$$

x and y are the probabilities of the subunit being activated or calcium inactivated, respectively, note that x corresponds to one of the four noninhibited states, $p=[IP_3]$ is the concentration of IP_3. If N of the N_0 subunits are in the inactivated state, the master equation for activation and inhibition of a single subunit is

$$\frac{\partial P(N,t)}{\partial t}=-[(N_0-N)K^+ + NK^-]P(N,t)+(N_0-N-1)K^+P(N-1,t)+(N+1)K^-P(N+1,t), \tag{3}$$

with K^- and K^+ being the activation and inactivation rates, respectively,

$$K^+(c)=\frac{2c(K_1k_1k_4+k_2k_4c+k_1k_2p)}{c(k_2+k_4)+2k_1(K_1+p)}, \tag{4}$$

$$K^-=\frac{2[k_{-3}k_{-4}+k_{-2}(k_{-4}+k_3p)]}{k_{-2}+k_{-4}+2k_3(K_3+p)}. \tag{5}$$

Equation (3) can be expanded for $N\gg 1$ to form a Fokker-Planck equation which in turn is equivalent to the Langevin equation (compare Ref. [13])

TABLE I. Numeric model parameters.

$K_1=0.0785\ \mu M$	$k_1=400.0\ (\mu M\ \mathrm{s})^{-1}$	$r_1=0.4\ \mathrm{s}^{-1}$
$K_2=1.049\ \mu M$	$k_2=0.3\ (\mu M\ \mathrm{s})^{-1}$	$r_2=0.02\ \mathrm{s}^{-1}$
$K_3=0.312\ \mu M$	$k_3=400\ (\mu M\ \mathrm{s})^{-1}$	$r_3=2.1\ (\mu M\ \mathrm{s})^{-1}$
$K_4=0.26393\ \mu M$	$k_4=0.3\ (\mu M\ s)^{-1}$	$K_p=0.08\ \mu M$
$K_5=0.0823\ \mu M$	$k_5=80\ (\mu M\ \mathrm{s})^{-1}$	$C_0=2.0\ \mu M$
$p=1.15\ \mu M$	$\alpha=0.185$	

$$\dot{y}=(1-y)K^+-yK^-+\sqrt{\frac{(1-y)K^++yK^-}{N_0}}\xi(t), \quad (6)$$

where $\xi(t)$ is zero-mean Gaussian white noise,

$$\langle\xi(t)\xi(t')\rangle=\delta(t-t'). \quad (7)$$

The intracellular calcium concentration is determined by

$$\dot{c}=(r_1P_{\mathrm{open}}+r_2)(c_{\mathrm{ER}}-c)-r_3\frac{c^2}{c^2+K_p^2}. \quad (8)$$

The first term models the gradient-dependent influx (Ca^{2+} source) while the second term represents the activity of the SERCA pump (Ca^{2+} sink) which re-establishes this gradient; r_1, r_2, and r_3 are channel, leak and pump rates, respectively, $c_{\mathrm{ER}}=(C_0-c)/\alpha$ is the endoplasmatic reticulum calcium concentration, α is the ratio of ER volume to cell volume, and C_0 is a constant, representing a local condition for a fixed amount of total cell calcium; our numeric standard parameters of the whole model, including the dissociation constants $K_i=k_{-i}/k_i$ of the IP_3R-*I*, are given in Table I. Most of them are taken from Ref. [6], some were changed due to new measurements [14] and some were slightly changed by us to investigate other regimes.

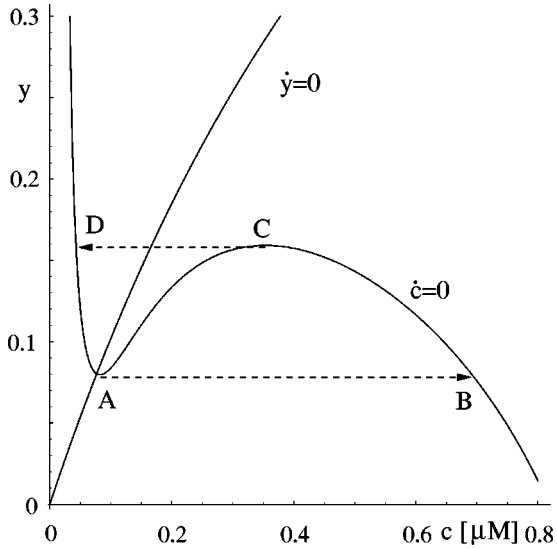

FIG. 1. Nullclines of Eqs. (6,8). In the noisy excitable regime transitions ideally occur along the arrows.

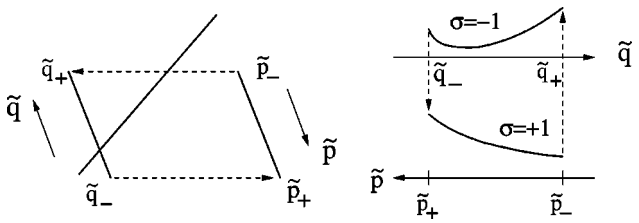

FIG. 2. Linearized nullclines (solid lines, left) and corresponding two-state system (right), transitions are indicated by dashed arrows. One stable fixed point in the system leads to one stable (left branch) and one unstable state (right branch). The solid arrows indicate coordinate directions. $\tilde{q}_-$ and $\tilde{p}_-$ are sinks of probability which is absorbed at $\tilde{p}_+$ and $\tilde{q}_-$, respectively, thus realizing the flow of probability J_0.

MODEL REDUCTION

In order to find an analytic description we make further simplifications. Analysis of the nullclines of the noise-free Eqs. (6,8), cf. Fig. 1, shows one fixed point at $(c^s,y^s)=(0.0768625\ \mu M,0.080218)$ in an excitable system. We assume a fast transition after an overthreshold disturbance out of the fixed point to the right branch of the $\dot{c}=0$ nullcline ($A\rightarrow B$) followed be a slow inhibition process (increasing y, $B\rightarrow C$) along this branch, this corresponds to the slow calcium inhibition of the IP_3R-I–the parameters r_i and K_p were chosen accordingly. When reaching the local maximum of $\dot{c}=0$ another fast transition occurs to the left branch ($C\rightarrow D$) and the trajectory slowly relaxes towards the fixed point. Although time scale separation is small ($[r_1+r_2]/K^-=1.6$) for the sake of analytic treatment perfect time scale separation is assumed. This defines a two-state process switching between low and high intracellular calcium concentration. Shuai *et al.* [13] numerically described this process and computed its spectrum. The following approach provides an analytical basis.

Firstly, we linearly approximate the relevant branches of the nullclines, cf. Fig. 2, and the Langevin equations take the form

$$\dot{c}_a=F_\pm(c_a)-Y_1y_a \quad (9)$$

$$F_\pm(c_a)=\begin{cases}Y_+^0-Y^mc_a & \text{right branch}\\ Y_-^0-Y^mc_a & \text{left branch,}\end{cases} \quad (10)$$

$$\dot{y}_a=\gamma c_a+\gamma_0-Y_2y_a+\sqrt{2Q}\xi(t). \quad (11)$$

The left branch is approximated by a line through the points *A* and *D* determining the slope $Y^m=2.022\ \mathrm{s}^{-1}$, the right branch is substituted by a line with the same slope Y^m through point C; the linearized nullcline $\dot{y}_a=0$ is determined by the two intersections of $\dot{y}=0$ with the linearized nullclines $y_a=F_\pm(c_a)$; other values are: $\{Y_+^0,Y_-^0\}=\{0.873,0.246\}\ \mu M\ \mathrm{s}^{-1}$, $\gamma=0.773\ \mu M^{-1}\,\mathrm{s}^{-1}$, $\gamma_0=0.0215\ \mathrm{s}^{-1}$, $Y_1=1\ \mu M\ \mathrm{s}^{-1}$, and $Y_2=1\ \mathrm{s}^{-1}$. Computing the noise along an excitation cycle, it varies by a factor of 3; here we neglect this fact and replace the phase state dependent noise by its intensity taken in the fixed point,

$$Q=\frac{(1-y^s)K^++y^sK^-}{2N_0}\approx\frac{0.0153453\ \mathrm{s}^{-1}}{N_0}. \quad (12)$$

This is justified if one considers the main effect of the noise being the disturbance of the trajectory from the fixed point, which determines how often excitations occur. Inserting Eq. (9) into Eq. (11), introducing a dimensionless time τ

$$\tau = \nu_0 t, \quad \nu_0 = Y_2 + \frac{\gamma Y_1}{Y^m}, \tag{13}$$

and performing the variable transformations,

$$\tilde{q} = y_a - \left(\frac{\gamma Y_-^0}{Y^m} + \gamma_0 \right) \Big/ \nu_0 \quad \text{and}$$

$$\tilde{p} = -y_a + \left(\frac{\gamma Y_+^0}{Y^m} + \gamma_0 \right) \Big/ \nu_0, \tag{14}$$

one obtains a set of symmetric Langevin equations with boundary conditions (cf. Fig. 2),

$$\dot{\tilde{q}} = -\tilde{q} + \sqrt{2D}\xi(\tau) \quad \text{and} \quad \dot{\tilde{p}} = -\tilde{p} + \sqrt{2D}\xi(\tau), \tag{15}$$

with the rescaled noise intensity $D = Q/\nu_0$.

RESULTS

Reference [15] gives the solution to a two-state system $\sigma = \pm 1$, cf. Fig. 2, possessing the dynamics of Eq. (15). The spectrum has the form [16]

$$N(\omega) = \int_{-\infty}^{\infty} d\tau \langle \sigma(t)\sigma(t+\tau)\rangle e^{i\omega\tau}$$

$$= \frac{8J_0}{\omega^2} \mathrm{Re}\left(\frac{[1 - W_{\tilde{q}}(\omega)][1 - W_{\tilde{p}}(\omega)]}{1 - W_{\tilde{q}}(\omega) W_{\tilde{p}}(\omega)} \right). \tag{16}$$

The stationary current J_0 and the Fourier transforms $W_{\tilde{q},\tilde{p}}(\omega)$ of the waiting time distributions are given by

$$J_0 = \left[\int_{\tilde{q}_-/\sqrt{2D}}^{\tilde{q}_+/\sqrt{2D}} dz e^{z^2} \mathrm{erfc}(z) + \int_{\tilde{p}_-/\sqrt{2D}}^{\tilde{p}_+/\sqrt{2D}} dz e^{z^2} \mathrm{erfc}(z) \right]^{-1} \Big/ \sqrt{\pi}, \tag{17}$$

$$W_{\tilde{q}}(\omega) = \frac{e^{(\tilde{q}_+^2 - \tilde{q}_-^2)/4D} U\left(-i\omega - \frac{1}{2}, \tilde{q}_+/\sqrt{D} \right)}{U\left(-i\omega - \frac{1}{2}, \tilde{q}_-/\sqrt{D} \right)}, \tag{18}$$

$$W_{\tilde{p}}(\omega) = \frac{e^{(\tilde{p}_+^2 - \tilde{p}_-^2)/4D} U\left(-i\omega - \frac{1}{2}, \tilde{p}_+/\sqrt{D} \right)}{U\left(-i\omega - \frac{1}{2}, \tilde{p}_-/\sqrt{D} \right)}, \tag{19}$$

where $U(a,z)$ denotes the parabolic cylinder function. The stationary current J_0 determines a frequency

$$\omega_m = 2\pi J_0, \tag{20}$$

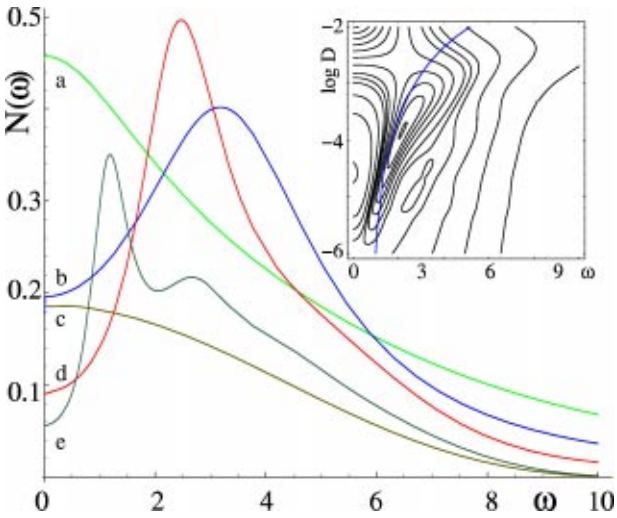

FIG. 3. Power spectra $N(\omega)$ of the linearized analytic model, noise values are in the order (a)–(e): $D = 0.005$, 10^{-3}, 10^{-6}, 10^{-4}, and 10^{-5}. The inset shows a contour plot of $N(D,\omega)$ and the mean frequency ω_m from Eq. (20).

which corresponds to the time scale given by the sum of mean first passage times for $\tilde{q}_+ \to \tilde{q}_-$ and $\tilde{p}_+ \to \tilde{p}_-$.

The spectrum for the linearized system is depicted in Fig. 3. For a small noise intensity (large number of channels) the power spectrum is a monotonous function of ω. As noise increases (reducing the number of channels per cluster) a peak appears which shifts to higher frequencies for rising noise, it finally vanishes if noise surpasses a certain value (few channels) above which the spectrum becomes monotonously decreasing again. For some small noise levels the second harmonic of the peak is visible. There exists an intermediate noise level for which the quantity

$$G = \frac{N_{\max}}{\sqrt{\Delta N^2}} \approx \frac{N_{\max}}{2\sqrt{\Delta_{1/2} N^2}} \tag{21}$$

reaches a maximum value; this indicates coherence resonance and for the corresponding number of channels calcium signaling can be considered most regular.

The above assumptions and simplifications entitle to question the validity of the description for the underlying stochastic system. We therefore performed stochastic simulations of the unreduced Li-Rinzel model [17]. Each of the four channel subunits was treated according to the Li-Rinzel model, i.e., the process $y(t) = 0$ or 1, to decide for transitions between these two states uniformly distributed random numbers $\rho \in [0,1]$ were computed and if $\rho_1 \Delta t < K^{\pm}$ the corresponding transition was set. For noninhibited subunits another random number $\rho_2 < x$ selects the activated state out of the four possible noninhibited states. A channel opens if three or four subunits are in the open state and the fraction N^{open}/N_0 of open channels substituted P_{open} in Eq. (8). The evolution of $c(t)$ was sampled with $\Delta t = 0.01$ s for a time $T = 2621.44$ s and the time series was then zero averaged and fast Fourier transformed. In order to obtain a smooth power spectrum, we averaged over 300 runs and the results are displayed in Fig. 4.

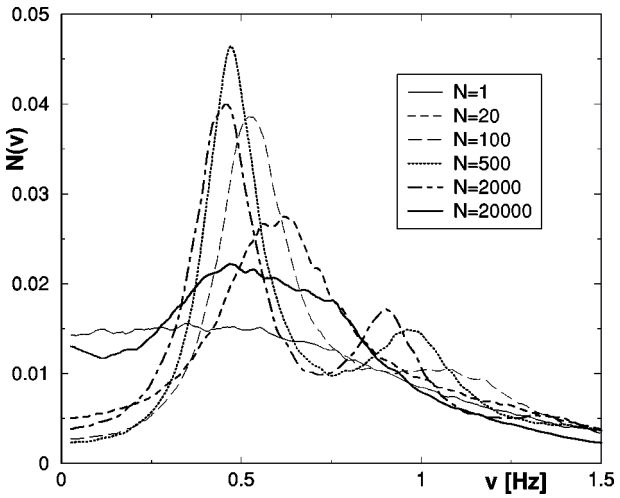

FIG. 4. Power spectra $N(\omega)$ of the stochastic model for different numbers N of subunits in the cluster, smoothed by applying a 10-point average filter to the mean of 300 runs (150 runs for $N=20000$).

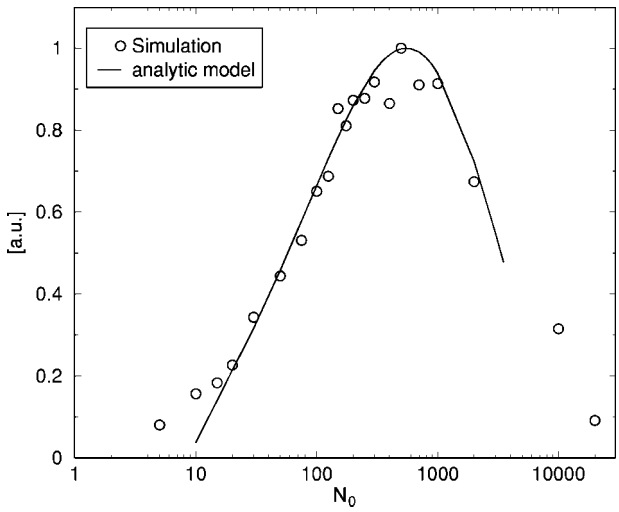

FIG. 5. The quality of oscillations, G from Eq. (21), dependent on the number of subunits per cluster N_0 of the stochastic simulation (circles) is compared with the analytic result (solid line) and shows very good agreement. The maximum for $N_0 \approx 450$ indicates optimal signaling periodicity. The maximum value of G was rescaled to unity.

For a single channel (maximal noise level) the spectrum shows no peak, but monotonically falls off for increasing frequencies. If the number of subunits N_0 is increased, i.e., the system noise is reduced, a peak emerges, reaches a maximum value, and later starts to disappear again for very large clusters. Thus, the simulations show the same qualitative behavior as our simplified model discussed above. For the comparison of Figs. 3 and 4 please note the different frequency axes: while Fig. 4 already uses the natural frequency, in Fig. 3 one obtains the natural frequency after rescaling according to $\nu=\nu_0\omega/2\pi\approx 0.22\omega\ \mathrm{s}^{-1}$.

CONCLUSION

To answer the key question—what is the optimal number of channels per cluster with respect to signaling periodicity—we calculated the quantity G of Eq. (21) which represents the quality of the stochastic oscillation. Due to the second harmonic peak in the spectrum it is not possible to obtain an exact value for the full peak width at half maximum and therefore, we use the left sided version. The comparison of analytic and stochastic calculations is given in Fig. 5 and shows excellent agreement, for $N_0>3000$ the peak in $N(\omega)$ starts to vanish and thus G was indeterminable for these values.

In a numeric first approach similar results were obtained in Refs. [11–13], which showed the existence of a certain range of cluster size where signaling properties become most periodic. Here, we presented analytic evidence for that in a cluster of IP_3R-I calcium ion channels which interact instantaneously. We found a range of 80–3000 subunits (corresponding to 20-750 channels) per cluster optimal for signaling periodicity. The key parameter is the cluster size, i.e., the number of subunits or channels, governing the fluctuations in the clusters mean open probability.

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