Computational Modeling of Calcium Dynamics Near Heterogeneous Release Sites

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ABSTRACT

Background: Calcium is known to play an important role in many physiological processes, such as egg fertilization and heart muscle functions. Several recent theoretical studies ([4], [1]) investigated calcium dynamics near so-called release sites – clusters of calcium-regulated channels on the intracellular calcium stores. Interest in the synchronized openings of channels within a release site has increased because these openings are thought to be the building blocks of global calcium events.
Methods: We conduct computational studies of the effect of heterogeneity in the make-up of the release site on the resulting calcium dynamics. We introduce heterogeneity into the model of the release site by (1) including channels with two distinct modes of calcium regulation and (2) by using channels with the same type of calcium regulation but varied transition rates between open, closed or inactivated states and a varied ability to release calcium. The first case models release sites made up channels that are both activated and inactivated by calcium (such as type I inositol 1,4,5-triphosphate receptors or IP_3R) and channels with calcium activation only (such as ryanodine receptors or RyR). The second case examines the effect of natural variation among channels.
Results: Our computations show that as the number of channels with both activation and inactivation (IP_3R) increases in a release site, so does the range of radius values for which cooperative opening of channels is possible. We show that the precise position of the IP_3R channels within a release site matters, as IP_3R in the middle of a release site are able to exert a greater influence over the calcium dynamics than IP_3R near the perimeter. We also show that natural variation within a channel type does not produce significant changes in the ability of the channels to open cooperatively.
Conclusions: Heterogeneity resulting from different types of channels inside a release site of calcium-regulated calcium channels has a significant effect on the calcium dynamics. However, heterogeneity resulting from natural variation in the same type of channels does not significantly alter the dynamics.

1 Introduction

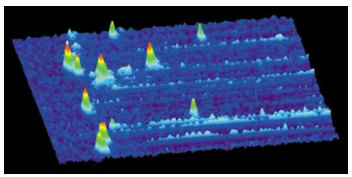


Figure 1. Ian Parker, UC Irvine

- Heterogeneity of Ca^{2+}-regulated Ca^{2+} channel types contributes to the diversity of local and global Ca^{2+} signals observed ([3])
- We present a computational study of a stochastic release site consisting of **(a)** distinct receptor types, **(b)** identical channel types with natural variation
- Significance: **(a)** diversity of local Ca^{2+}dynamics may be crucial to understanding variation in global Ca^{2+} signals ([2]); **(b)** physical heterogeneity of release sites is difficult to study experimentally

2 Methods

2.1 Mathematical Model

Based on Nguyen et al [4] we describe a release site of coupled channels with a stochastic generator matrix. Our release site consists of two simple stochastic models of Ca^{2+}-regulated intracellular Ca^{2+} channels: Ca^{2+}-activated channel (representing type II IP_3R or RyR):

$$C\,(\text{closed}) \underset{k_-}{\overset{k_+[Ca^{2+}]_{\text{local}}}{\rightleftharpoons}} O\,(\text{open})$$

2.1 Mathematical Model (cont.)

Channel with Ca^{2+}-activation and Ca^{2+}-inactivation (type I IP_3R) :

$$\begin{array}{ccccc} & & \overset{k_a^+ c}{\rightleftharpoons} & & \\ \text{(closed)} \quad C_1 & & & O & \quad \text{(open)} \\ & \overset{k_d^+ c}{\underset{k_d^-}{\uparrow\downarrow}} & & \overset{k_b^-}{\underset{k_b^+ c}{\uparrow\downarrow}} & \\ & & \underset{k_c^+ c}{\rightleftharpoons} & & \\ \text{(inact.)} \quad C_3 & & & C_2 & \quad \text{(inact.)} \end{array}$$

The generator matrix for a 2-state channel is:

$$Q = (q_{ij}) = \begin{pmatrix} -k^+ c^\eta & k^+ c^\eta \\ k^- & -k^- \end{pmatrix}.$$

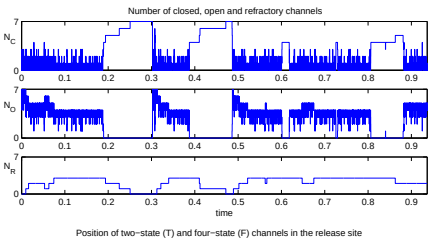
For a release site of two interacting two-state channels:

$$Q = \begin{pmatrix} \star & k^+ c_\infty^\eta & k^+ c_\infty^\eta & 0 \\ k^- & \star & 0 & k^+ (c_\infty + c_{21})^\eta \\ k^- & 0 & \star & k^+ (c_\infty + c_{12})^\eta \\ 0 & k^- & k^- & \star \end{pmatrix}$$

where $\star$ denotes the element to ensure row sum 0 and c_{ij} is the $[Ca^{2+}]$ increase experienced by channel j when channel i is open.
The $[Ca^{2+}]$ is computed as the steady state of the "excess buffer approximation". (Note that $r_{ii} = r_d$, the distance between binding site and channel pore).

$$c_{ij} = \frac{\sigma_0}{2\pi D r_{ij}} e^{-r_{ij}/\lambda}.$$

2.2 Visualization of the Simulations



Position of two−state (T) and four−state (F) channels in the release site

T F
F T F
T T

Figure 2. Release site dynamics

3 Results

3.1 Type I and II IP_3 Receptors Within a Release Site

- Mean-field approximation: average the contribution of all other channels to channel i.
- Measure of channel synchronicity based on Nguyen ([4]):

$$Score = \frac{\mathrm{Var}[f_O]}{\mathrm{E}[f_O]}$$

where $[f_O]$ is the fraction of open channels.
- Parameters in Figures 5 and 6 are drawn from a Gamma distribution with mean of the original parameter value and variance of α times the original value. Standard deviation is collected but not reported here.

3.1.1 Mean-field approximations

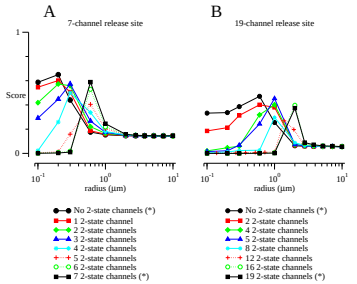


Figure 3.Score as a function of the radius for two release sites. Stars indicate results previously obtained by Nguyen et al ([4]).

3.1.2 Spatial position and a fixed number of channels

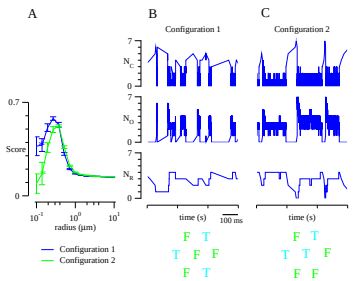


Figure 4. Score and trajectories for two distinct release site configurations. The stars in panel **A** show the radius value used to generate the trajectories in panels **B** and **C**.

3.2 Natural variation in Type I IP_3R

3.2.1 Variation in the transition rates

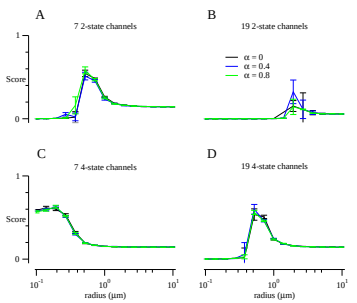


Figure 5. Channel kinetic parameter values given below in Section 3.2.3.

3.2.2 Variation in the source amplitude

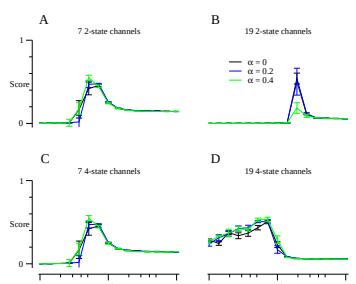


Figure 6. Parameter values for σ in Section 3.2.3

3.2.3 Parameter values

Channel kinetic parameters: *two-state channels:* $k^+ = 1.5\mu$ M^{-2} ms^{-1}, $k^- = 0.5$ ms^{-1}; *four-state channels:* $k_a^+ = k_c^+ = 0.5$, $k_b^+ = 0.001$, $k_d^+ = 0.01$ in μ M^{-2} ms^{-1}, and $k_a^- = k_c^- = 1$, $k_b^- = 0.001$ in ms^{-1}.
Parameters for the calcium domain: $c_\infty = 0.05\mu$M, $\eta = 2$, $D = 250\mu M^2 s^{-1}$, $r_d = 0.05\mu$m, $\lambda = 5\mu$m, $\sigma = 518.24\mu moles s^{-1}$ (= 0.05 pA).

4 Conclusions

- Calcium dynamics depend on the physical composition of the release site and the exact spatial position of the different types of channels.
- Synchronous channel activity is possible with any composition of channels for a certain range of radius values.
- Increasing the number of channels with inactivation increases the range of radius values for which the cooperative channel activity occurs.
- Natural variation in the transition rates does not significantly alter the release site dynamics. Although small amount of variation can be ignored, calcium puffs are sensitive to changes in the source amplitude of calcium-gated calcium channels.

5 Further Directions

- Develop improved mean-field calculations averaging over the same channel types only
- Use additional statistical measures such as inter-puff interval and puff-duration to distinguish between Ca^{2+}dynamics near homogeneous and heterogeneous release sites

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References

[1] DeRemigio H et al, *Cell Calcium*, **38(2):73-86**, (2005).
[2] Marchant JS, Parker I., *EMBO Journal*, **20(1&2):65-76**,(2001).
[3] Miyakawa T, Maeda A, Yamazawa T, Hirose K, Kurosaki T, Iino M. *EMBO Journal*, **18(5): 1303-1308**, (1999).
[4] Nguyen V et al,*Bull. Math. Bio.*, **67(3):393-432**, (2005).