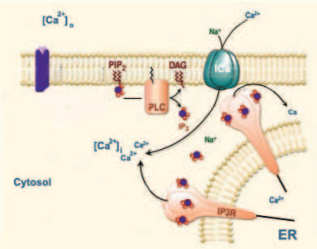


Diffusion and Calcium Oscillation

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Motivation

- In response to signaling molecules, many cell types exhibit intracellular Ca^{2+} oscillation.
- Whole-cell ODE models are commonly used to study Ca^{2+} oscillations

Experimental evidence suggests that a steep intracellular Ca^{2+} gradient often occurs and Ca^{2+} release channels tend to be clustered at specific sites and are tightly modulated by local concentration.

- How does Ca^{2+} oscillation arise in space?
 - Synchronization of smaller oscillators corresponding to each release site
 - Wave propagation from site to site

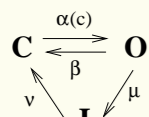
Whole-Cell ODE Model

Assume that the cell is a well-mixed compartment.

Average $[\text{Ca}^{2+}]$

$$\frac{dc}{dt} = \underbrace{G p_o(c) h}_{\text{IPR release}} - \underbrace{k_{up} c}_{\text{uptake/removal}} + \underbrace{k_{lk} (c_{out} - c)}_{\text{background leak}}$$

IP3 Receptor Model



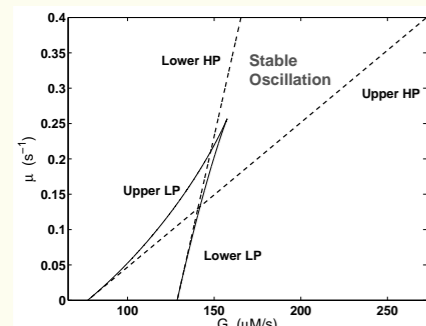
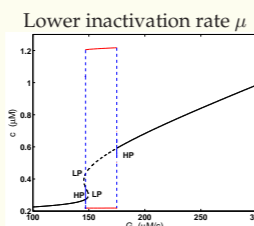
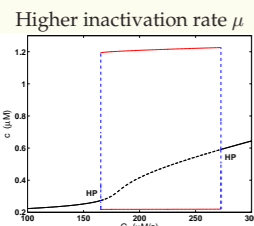
Assuming that transitions between C and O occur rapidly,

$$\frac{dh}{dt} = -\mu p_o(c) h + \nu(1-h)$$

where h is the fraction of the channels in the C and O state and

$$p_o(c) = \frac{\alpha(c)}{\alpha(c) + \beta}$$
 is the fraction of O in h .

Bifurcation Diagrams

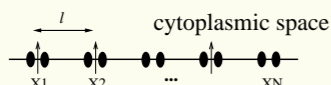


Nullcline Equations

$$h = \frac{\nu}{\mu p_o(c) + \nu}$$

$$h = \frac{1}{G} \frac{Kc - k_{lk}c_{out}}{p_o(c)}$$

Spatially Extended Model



Consider the cell as one-dimensional length of length L with a total of N release sites located at x_i separated from one another by a fixed distance $l = L/N$.

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + \sum_{i=1}^N g p_o(c(x_i, t)) h_i \delta(x - x_i) - k_{up} c + k_{lk} (c_{out} - c)$$

The recovery variable is determined at each site x_i by

$$\frac{dh_i}{dt} = -\mu p_o(c(x_i, t)) h_i + \nu(1 - h_i)$$

Reduction to the ODE model when $D \rightarrow \infty$

Define the average calcium concentration as

$$\bar{c}(t) = \frac{1}{L} \int_0^L c(x, t) dx$$

In the large D limit, we can write $D = 1/\epsilon^2$ where $\epsilon \ll 1$ and $c(x, t)$ should be close to the whole-cell average $\bar{c}(t)$ with small spatially-varying variation.

$$c(x, t) = \bar{c}(t) + \epsilon c_1(x, t)$$

By construction $c_1(x, t)$ has zero average. Substituting into the PDE and taking average of both sides,

$$\frac{d\bar{c}}{dt} = \frac{Ng}{L} p_o(\bar{c}) \bar{h} - k_{up} \bar{c} + k_{lk} (c_{out} - \bar{c})$$

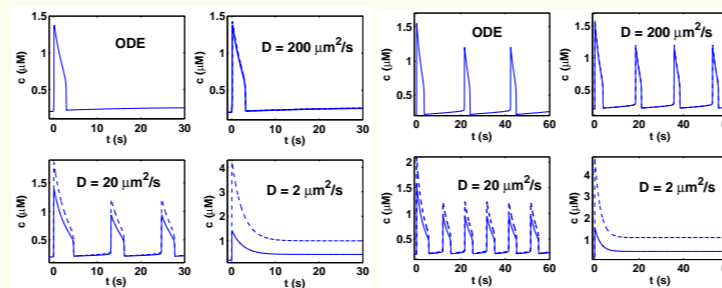
The PDE and the ODE agree in the $D \rightarrow \infty$ limit provided that

$$G = \frac{Ng}{L} = \text{the total release flux spread over the length of the cell.}$$

Result from Numerical Simulation

How does diffusional coupling between release sites alter the global calcium release and oscillation?

- Diffusion transports calcium to and away from a particular release site.



- Decreasing D can cause transition from excitability to oscillatory region as well as to loss of excitability.
- Decreasing D also increases the frequency of oscillation

Summary

- We performed a linear stability analysis of the PDE system to study how diffusional coupling and discrete release site affect calcium release/oscillation.
- Changing the diffusion coefficient can affect the critical parameter value for oscillation onset as well as the frequency of oscillation
- Diffusion coefficient can be reduced in the presence of Ca^{2+} binding protein (buffer) and thus studying compartmentalized ODE model may be insufficient.

Future Directions

- Incorporate a more realistic IP3 receptor model.
- Is there a parameter regime where oscillation caused by wave exist?

References

- A. Skupin, H. Kettenmann, U. Winkler, M. Wartenberg, H. Sauer, S.C. Tovey, C.W. Taylor, M. Falcke (2008). How does intracellular Ca^{2+} oscillate: by chance or by the clock? *Biophys. J.*, 94:2404-2411.
- R. Thul and M. Falcke (2004). Stability of membrane-bound reactions. *Phys. Rev. Lett.*, 93:188103 1-4.
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Steady State Analysis for a Single Cluster

Consider

$$c_t = D c_{xx} + g p_o(c(0, t)) h \delta(x) - k_{up} c + k_{lk} (c_{out} - c)$$

$$\frac{dh}{dt} = -\mu p_o(c(0, t)) h + \nu(1 - h)$$

with periodic boundary condition at $x = \pm \frac{L}{2}$. The steady state solution is found by solving two algebraic equations

- Setting the left hand side of the h equation to zero gives

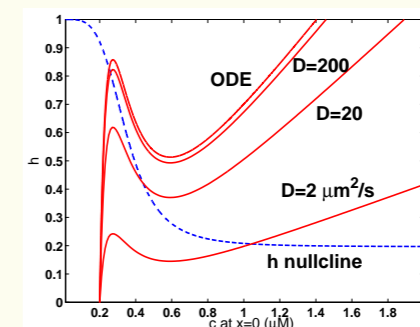
$$h = \frac{\nu}{\mu p_o(c(0)) + \nu}$$

- Solving the boundary value problem for the steady state value of c leads to the following consistency condition

$$h = \frac{\tanh(\phi) K c(0) - k_{lk} c_{out}}{G \phi p_o(c(0))}$$

$$\text{where } \phi = \sqrt{\frac{K}{D}} \frac{L}{2} \text{ and } K = k_{up} + k_{lk}.$$

This is the same algebraic system as the two nullclines equations describing the steady state of the ODE system. The release size G is now modified by a scale factor involving D .



Linear Stability Analysis

Consider the linearized system about the steady state solution.

$$\frac{\partial}{\partial t} \begin{bmatrix} c \\ h \end{bmatrix} = \begin{bmatrix} D \frac{\partial^2}{\partial x^2} - K + g p'_o(c_{ss}(0)) h_{ss} & g p_o(c_{ss}(0)) \\ -\mu p'_o(c_{ss}(0)) h_{ss} & -\mu p_o(c_{ss}(0)) - \nu \end{bmatrix} \begin{bmatrix} c \\ h \end{bmatrix}$$

To solve, we use the eigenfunction expansion.

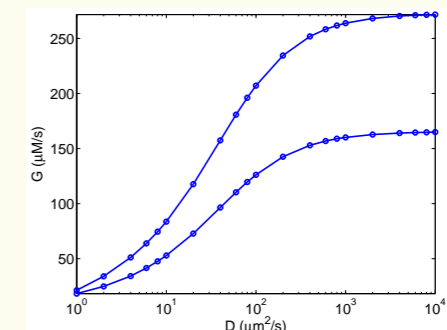
$$\begin{bmatrix} c \\ h \end{bmatrix} = \sum a_n(t) e^{\lambda_n t} \begin{bmatrix} \phi_n \\ h_n \end{bmatrix} \quad \text{where } \mathcal{A} \begin{bmatrix} \phi_n \\ h_n \end{bmatrix} = \lambda_n \begin{bmatrix} \phi_n \\ h_n \end{bmatrix}$$

This leads to the following transcendental equation,

$$2v_n D \tan\left(\frac{v_n L}{2}\right) + g p'_o(c_{ss}(0)) h_{ss} \left(1 - \frac{\mu p_o(c_{ss}(0))}{\lambda_n + \mu p_o(c_{ss}(0)) + \nu}\right) = 0$$

where v_n is related to the eigenvalue by $\lambda_n = -K - D v_n^2$.

A Hopf bifurcation occurs when λ_n crosses the imaginary axis.



The limit-point bifurcation arises when two steady state solutions coalesce.

The limit point curves are thus invariant on the $(G \frac{\phi}{\tanh(\phi)}, \mu)$ plane.

What about the Hopf bifurcation curves?