

A reaction-diffusion model for calcium in neurons

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The inspiring paper

D. Holcman and Z. Schuss

Modeling calcium dynamics in dendritic spines

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Langevin equation

Calcium Ca^{2+} ions dynamics given by

$$\dot{\boldsymbol{x}} = \boldsymbol{V}(\boldsymbol{x}, t) + \sqrt{2D(\boldsymbol{x}, t)}\dot{\boldsymbol{w}}$$

\boldsymbol{w} is a Brownian motion

$\boldsymbol{V}(\boldsymbol{x}, t)$ is the cytoplasmic flow field

$D(\boldsymbol{x}, t)$ is the diffusion coefficient

Existence of motion if

$$|\boldsymbol{V}(\boldsymbol{x}, t)| + |D(\boldsymbol{x}, t)|^2 \leq C(1 + |\boldsymbol{x}|)$$

Fokker-Planck or

Backward Kolmogorov equation

$$\partial_t M(\mathbf{x}, t) = -\nabla \cdot \mathbf{J}(\mathbf{x}, t)$$

$$\mathbf{J}(\mathbf{x}, t) := -D(\mathbf{x}, t)\nabla M(\mathbf{x}, t) + M(\mathbf{x}, t)\mathbf{V}(\mathbf{x}, t)$$

$\mathbf{J}(\mathbf{x}, t)$ is the flux of the concentration of Ca^{2+} ions $M(\mathbf{x}, t)$

Dynamics in the cytoplasm

Cytoplasmic fluid is incompressible $\nabla \cdot \mathbf{V} = 0$

Ω is the domain inside the dendritic spine where the Ca^{2+} ions can move

No obstacles $\Rightarrow \Omega$ is the interior of the dendrite and D is constant (Holcman *et al*)

Obstacles (organelles and macromolecules) \Rightarrow exterior domains and $D = D(\mathbf{x}, t)$.

Same results if $D \in C^1$ and $D(\mathbf{x}, t) \geq \delta > 0$

Two types of boundary conditions

1. An absorbing boundary $\partial\Omega_a$ where the ions leave the spine and never return. Ca^{2+} pumps and the bottom of the spine neck (where the ions enter the dendrite)

$$M(\mathbf{x}, t) = 0 \quad \text{on } \partial\Omega_a$$

2. A reflecting boundary $\partial\Omega_r$ with no flux boundary conditions for the ions

$$\mathbf{J}(\mathbf{x}, t) \cdot \mathbf{n}(\mathbf{x}, t) = 0 \quad \text{on } \partial\Omega_r$$

The proteins come into the game

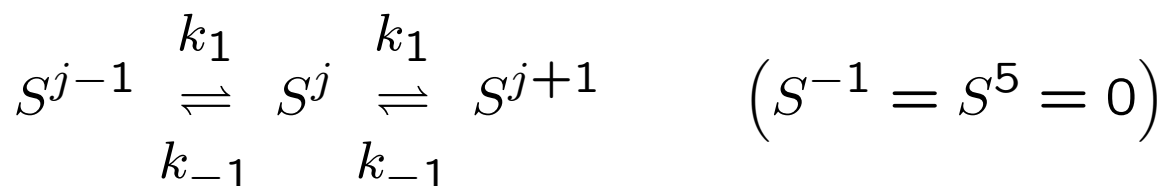
“Fixed” proteins calmodulin (CaM), actin-myosin (AM) and calcineurin that can carry up to four Ca^{2+} ions

$M(\mathbf{x}, t)$ is the number of free calcium ions

$S^j(\mathbf{x}, t)$ for $0 \leq j \leq 4$ is the number of proteins that contains j bound ions

k_1 is the (binding) rate of the reaction $S^j + M \rightarrow S^{j+1}$

k_{-1} is the (unbinding) rate of the reaction $S^j \rightarrow S^{j-1} + M$



Modeling the reactive part

Hybrid description:

Model the chemical reactions at each binding site separately (fine-grained description)

Model the dynamics at the sites using the Law of Mass Action (coarse-grained description)

Law of Mass Action

The rate of a reaction is proportional to the product of the concentrations of the reactants



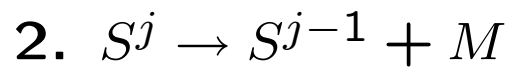
The Law of Mass Action implies

$$\frac{dS^j}{dt} = \alpha M S^{j-1}$$

S^{j-1} has $4 - (j - 1) = 5 - j$ free sites

The ion that binds can choose any free site with rate k_1

$$\alpha = (5 - j)k_1$$



The Law of Mass Action implies

$$\frac{dS^j}{dt} = -\beta S^j$$

S^j has j occupied sites

The ion that unbinds can come from any occupied site with rate k_{-1}

$$\beta = jk_{-1}$$

Reaction-diffusion system

$$\begin{aligned}\partial_t M &= -\nabla \cdot \mathbf{J} \\ &\quad -k_1 M \left[\sum_{j=0}^4 (4-j) S^j \right] + k_{-1} \left[\sum_{j=0}^4 j S^j \right] \\ \partial_t S^j &= k_1 M \left[(5-j) S^{j-1} - (4-j) S^j \right] \\ &\quad -k_{-1} \left[j S^j - (j+1) S^{j+1} \right] \quad (1)\end{aligned}$$

$\sum_{j=0}^4 (4-j) S^j(\mathbf{x}, t)$ is the number of free binding sites

$\sum_{j=0}^4 j S^j(\mathbf{x}, t)$ is the number of occupied binding sites

Initial conditions

$$\begin{aligned}M(\boldsymbol{x}, 0) &= m_0(\boldsymbol{x}) \\S^0(\boldsymbol{x}, 0) &= \frac{1}{4}A(\boldsymbol{x}) \\S^j(\boldsymbol{x}, 0) &= 0 \quad 1 \leq j \leq 4\end{aligned}$$

$S^0(\boldsymbol{x}, 0)$ is the total number of proteins

$A(\boldsymbol{x})$ is the total number of binding sites

$$\sum_{j=0}^4 S^j(\boldsymbol{x}, t) = \frac{1}{4}A(\boldsymbol{x}) \quad \text{for all } t \geq 0$$

Boundary conditions

$$\begin{aligned}M(\boldsymbol{x}, t) &= 0 && \text{on } \partial\Omega_a \\ \boldsymbol{J}(\boldsymbol{x}, t) \cdot \boldsymbol{n}(\boldsymbol{x}, t) &= 0 && \text{on } \partial\Omega_r\end{aligned}$$

Reduction 1

Define

$$U(\mathbf{x}, t) := \sum_{j=0}^4 (4 - j) S^j(\mathbf{x}, t)$$
$$W(\mathbf{x}, t) := \sum_{j=0}^4 j S^j(\mathbf{x}, t)$$

Then the system (1) becomes

$$\begin{aligned}\partial_t M &= -\nabla \cdot \mathbf{J} - k_1 M U + k_{-1} W \\ \partial_t U &= -k_1 M U + k_{-1} W \\ \partial_t W &= k_1 M U - k_{-1} W\end{aligned}$$

Initial conditions

$$M(\mathbf{x}, 0) = m_0(\mathbf{x}) \quad U(\mathbf{x}, 0) = A(\mathbf{x}) \quad W(\mathbf{x}, 0) = 0$$

Reduction 2

The identity

$$U(\mathbf{x}, t) + W(\mathbf{x}, t) = 4 \sum_{j=0}^4 S^j(\mathbf{x}, t) = A(\mathbf{x})$$

implies

$$\begin{aligned}\partial_t M &= -\nabla \cdot \mathbf{J} - [k_1 M + k_{-1}]U + k_{-1}A \\ \partial_t U &= -[k_1 M + k_{-1}]U + k_{-1}A\end{aligned}\quad (2)$$

This is the system we will study

On the positivity of solutions

Theorem 1 “Almost” positivity

Suppose that $M(\mathbf{x}, t)$ is a solution of the problem (2) and define

$$Z(\mathbf{x}, t) := k_1 M(\mathbf{x}, t) + k_{-1}$$

Then $Z(\mathbf{x}, t) \geq 0$

This implies “almost positivity”, i.e.

$$M(\mathbf{x}, t) \geq -\frac{k_{-1}}{k_1}$$

Positivity in the particular cases $k_{-1} = 0$ and $D = 0, \mathbf{V} = 0$

Energy estimates

Estimation of $U(\mathbf{x}, t)$

$$0 \leq U(\mathbf{x}, t) \leq A(\mathbf{x})(1 + k_{-1}t)$$

Theorem 2 Energy estimates

For any $\varepsilon > 0$ there exists a constant $C = C(\varepsilon) > 0$ such that if $M(\mathbf{x}, t)$ is a solution of (2) then

$$\frac{1}{2}\|M(t)\|^2 + (D - \varepsilon) \int_0^t \|\nabla M\|^2 ds \leq$$

$$\frac{1}{2}\|m_0\|^2 + C \int_0^t \|M\|^2 ds + k_{-1}^2 t(1 + k_{-1}^2 t^2) \|A\|^2$$

$\|\cdot\|$ is the norm in $L^2(\Omega)$

Existence of solutions

Solving (2) via Schauder's Fixed Point Theorem

Define

$$\mathcal{K} := \left\{ M^\# \in L^2(0, T; L^2(\Omega)) : k_1 M^\# + k_{-1} \geq 0 \right\}$$

Fix $M^\# \in \mathcal{K}$ and solve

$$\partial_t U = -[k_1 M^\# + k_{-1}]U + k_{-1}A$$

With the solution U solve

$$\partial_t M = -\nabla \cdot \mathbf{J} - [k_1 M + k_{-1}]U + k_{-1}A$$

We have $M^\# \mapsto U \mapsto M$

Define $\mathcal{R}(M^\#) := M$

Lemma 1 *Fix a positive time $T > 0$. Then*

\mathcal{K} is a convex closed subset of $L^2(0, T; L^2(\Omega))$

$\mathcal{R} : \mathcal{K} \rightarrow \mathcal{K}$ (by Theorem 1)

\mathcal{R} is continuous (by Theorem 2)

*$\mathcal{R}(\mathcal{K})$ is relatively compact in $L^2(0, T; L^2(\Omega))$
(by Theorem 2)*

Theorem 3 *For any $T > 0$ the operator \mathcal{R} has a fixed point, i.e. the system (2) has a solution*

Summary of results

Existence of solutions $M(\boldsymbol{x}, t)$ and $U(\boldsymbol{x}, t)$ for any finite final time

Energy estimates for M and growth estimates for U

Positivity of U

“Almost positivity” of M . Positivity in particular cases