Diffusion-activation model of CaMKII translocation waves in dendrites

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CaMKII holoenzyme

- family of 28 isoforms derived from four genes ($\alpha$, $\beta$, $\gamma$, $\delta$)
- $\alpha$, $\beta$-subunits predominant
- holoenzyme formed from two hexameric rings
Kinetics of CaMKII subunit

Lisman et al., Nat Rev Neurosci (2002)
Activation states of CaMKII

"Primed"
Ca/CaM dependent

"Activated"
Ca/CaM independent via autophosphorylation

Lisman et al., Nat Rev Neurosci (2002)
CaMKII translocation waves

Rose et al., *Neuron* (2009)
Diffusion-activation model of CaMKII translocation waves

Bressloff, Earnshaw (Utah)  
Diffusion-activation model of CaMKII waves  
May 19, 2009  
6 / 15
Equations for diffusion-activation model

\[
\begin{align*}
\frac{\partial p}{\partial t} &= D \frac{\partial^2 p}{\partial x^2} - kap \\
\frac{\partial a}{\partial t} &= D \frac{\partial^2 a}{\partial x^2} + kap - ha \\
\frac{\partial s}{\partial t} &= ha
\end{align*}
\]

- \( p \) = concentration of primed CaMKII in shaft
- \( a \) = concentration of activated CaMKII in shaft
- \( s \) = concentration of activated CaMKII in spines
- \( k \) = activation rate
- \( h \) = translocation rate
Simulation of model for CaMKII$\alpha$

- $D = 1 \mu m^2/s$, $h = 0.03/s$, $k = 0.28/s \Rightarrow c = 0.9 \mu m/s$
Fisher’s equation in absence of translocation

\[ \frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} - kap \]

\[ \frac{\partial a}{\partial t} = D \frac{\partial^2 a}{\partial x^2} + kap - ha \]

\[ \frac{\partial s}{\partial t} = ha \]

- When \( h = 0 \), \( p + a \) is constant (normalized to one).
Fisher’s equation in absence of translocation

\[
\begin{align*}
\frac{\partial p}{\partial t} &= D \frac{\partial^2 p}{\partial x^2} - kp \\
\frac{\partial a}{\partial t} &= D \frac{\partial^2 a}{\partial x^2} + kp - ha \\
\frac{\partial s}{\partial t} &= ha
\end{align*}
\]

- When \( h = 0 \), \( p + a \) is constant (normalized to one).
- Substituting \( p = 1 - a \) into equation for \( a \) yields Fisher’s equation

\[
\frac{\partial a}{\partial t} = D \frac{\partial^2 a}{\partial x^2} + ka(1 - a)
\]
Fisher’s equation in absence of translocation

\[ \frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} - kap \]
\[ \frac{\partial a}{\partial t} = D \frac{\partial^2 a}{\partial x^2} + kap - ha \]
\[ \frac{\partial s}{\partial t} = ha \]

- When \( h = 0 \), \( p + a \) is constant (normalized to one).
- Substituting \( p = 1 - a \) into equation for \( a \) yields Fisher’s equation
  \[ \frac{\partial a}{\partial t} = D \frac{\partial^2 a}{\partial x^2} + ka(1 - a) \]
- Fisher’s equation supports traveling fronts with speed
  \[ c = 2\sqrt{Dk} \]
Wave speed in presence of translocation

- When \( h \neq 0 \), wave speed is

\[
c = 2 \sqrt{D(k - h)}
\]
Calculating wave speed \( c = 2 \sqrt{D(k - h)} \)

- Can verify wave speed analytically by
  1. changing into traveling wave coordinates \( z = x - ct \)

\[
-c \frac{dp}{dz} = D \frac{d^2 p}{dz^2} - kap
\]

\[
-c \frac{da}{dz} = D \frac{d^2 a}{dz^2} + kap - ha
\]

- linearizing about the invaded state \((p, a) = (1, 0)\)
- calculating eigenvalues

\[
0, \frac{c}{d}, \frac{c \pm \sqrt{c^2 - 4D(k - h)}}{2D}
\]
Calculating wave speed \( c = 2\sqrt{D(k - h)} \)

- Can verify wave speed analytically by
  1. changing into traveling wave coordinates \( z = x - ct \)

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\]

  2. linearizing about the invaded state \((p, a) = (1, 0)\)
  3. calculating eigenvalues

\[
0, \quad \frac{c \pm \sqrt{c^2 - 4D(k - h)}}{2D}
\]

- If last eigenvalues are complex, \( a \) oscillates about zero as \( z \to \infty \), so

\[
c^2 - 4D(k - h) \geq 0 \Rightarrow c \geq 2\sqrt{D(k - h)}
\]
Calculating wave speed $c = 2\sqrt{D(k - h)}$

- Can verify wave speed analytically by
  1. changing into traveling wave coordinates $z = x - ct$

$$
-c \frac{dp}{dz} = D \frac{d^2 p}{dz^2} - kap \\
-c \frac{da}{dz} = D \frac{d^2 a}{dz^2} + kap - ha
$$

  2. linearizing about the invaded state $(p, a) = (1, 0)$
  3. calculating eigenvalues

$$
0, \frac{c}{d}, \frac{c \pm \sqrt{c^2 - 4D(k - h)}}{2D}
$$

- If last eigenvalues are complex, $a$ oscillates about zero as $z \to \infty$, so

$$
c^2 - 4D(k - h) \geq 0 \Rightarrow c \geq 2\sqrt{D(k - h)}
$$

- As with Fisher’s equation, minimum wave speed is observed
Wave propagation failure

- Speed $c = 2\sqrt{D(k - h)} \Rightarrow$ propagation failure when $k < h$
Summary

• Minimal diffusion-activation model with translocation supports CaMKII translocation waves
• Formula for wave speed $c = 2\sqrt{D(k - h)}$
• Wave propagation failure when $k < h$
Discussion and future directions

- Heterosynaptic plasticity and synaptic tagging
- Comparison to other diffusion-trapping models (e.g. AMPA receptor trafficking)
- Threshold for wave initiation (modeling Ca\(^{2+}\) spike, stochastic effects)
- Physiological dendrites (branching, discrete spines, heterogeneities)
Thank you!

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