Diffusion-activation model of CaMKII translocation waves in dendrites

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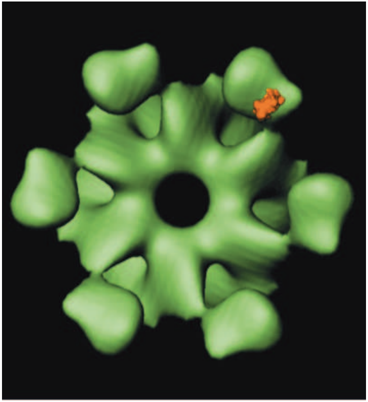
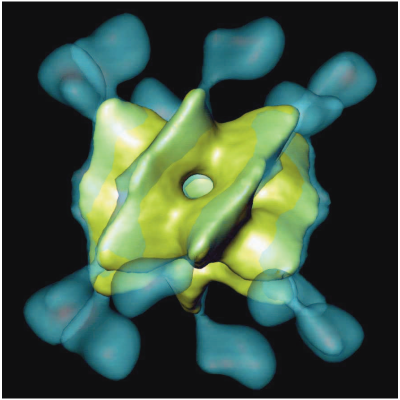
CaMKII holoenzyme

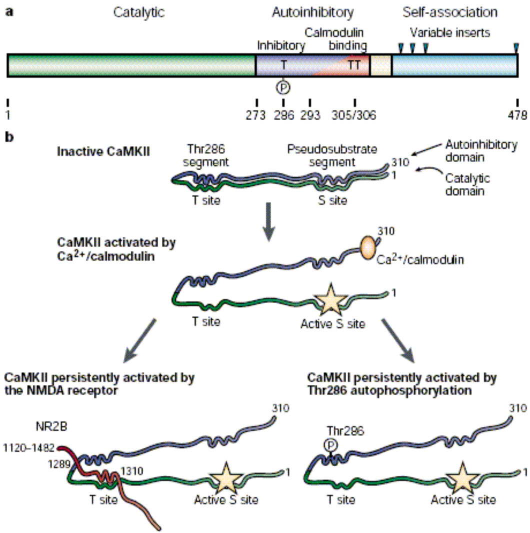




Kolodziej et al., *J Biol Chem* (2000)

- family of 28 isoforms derived from four genes (α, β, γ, δ)
- α-, β-subunits predominant
- holoenzyme formed from two hexameric rings

Kinetics of CaMKII subunit

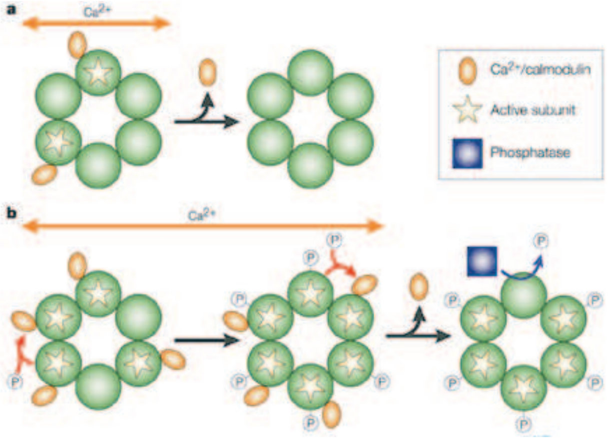


Lisman et al., *Nat Rev Neurosci* (2002)

Activation states of CaMKII

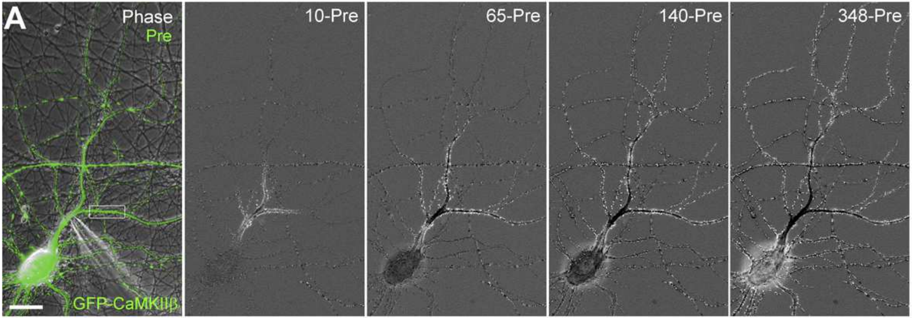
"Primed"
Ca/CaM dependent

"Activated"
Ca/CaM independent
via autophosphorylation



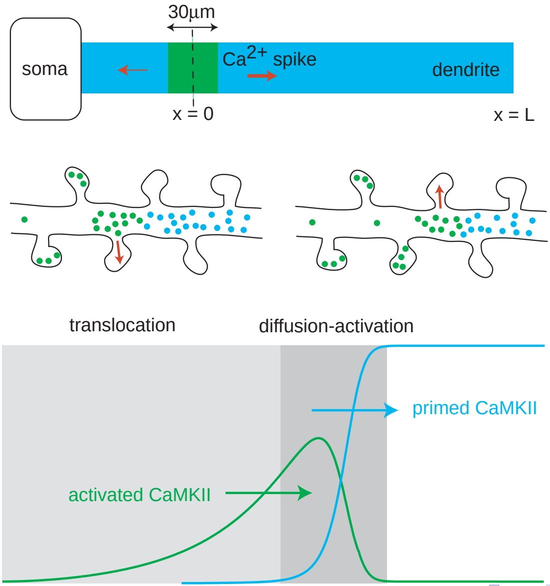
Lisman et al., *Nat Rev Neurosci* (2002)

CaMKII translocation waves



Rose et al., *Neuron* (2009)

Diffusion-activation model of CaMKII translocation waves

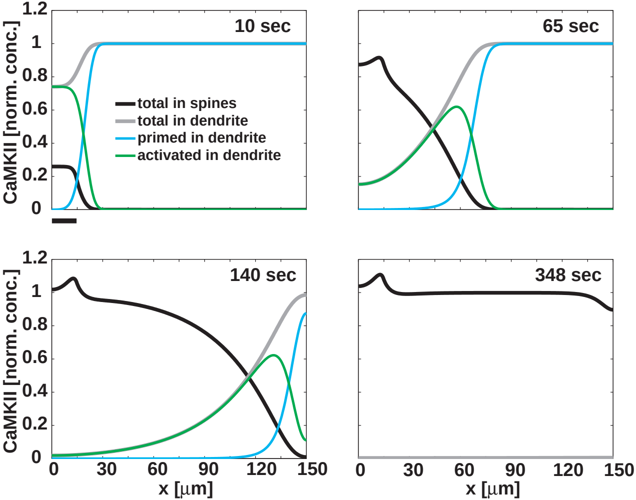


Equations for diffusion-activation model

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

- $p =$ 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 CaMKIIα



- $D = 1\mu\text{m}^2/\text{s},\ h = 0.03/\text{s},\ k = 0.28/\text{s} \Rightarrow c = 0.9\mu\text{m}/\text{s}$

Fisher's equation in absence of translocation

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} - kap$$
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- When $h = 0$, $p + a$ is constant (normalized to one).

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- Substituting $p = 1 - a$ into equation for a yields Fisher's equation

$$\frac{\partial a}{\partial t} = D\frac{\partial^2 a}{\partial x^2} + ka(1 - a)$$

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$$\frac{\partial a}{\partial t} = D\frac{\partial^2 a}{\partial x^2} + ka(1 - a)$$

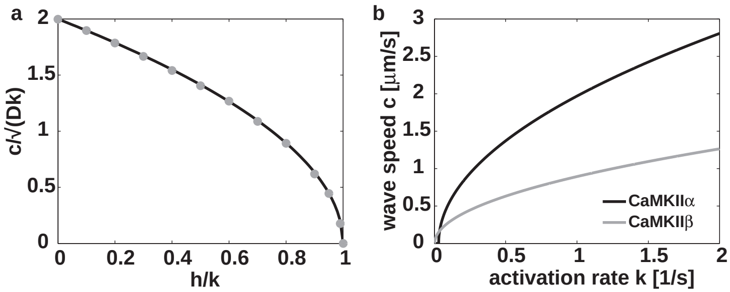
- Fisher's equation supports traveling fronts with speed

$$c = 2\sqrt{Dk}$$

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 $z = x - ct$

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

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

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

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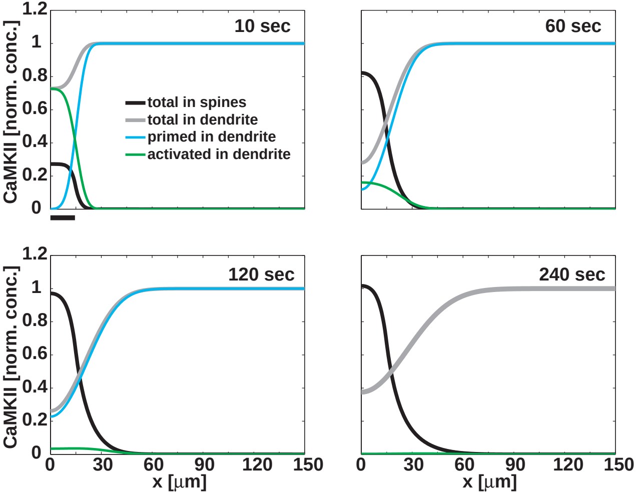
- As with Fisher's equation, minimum wave speed is observed

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!

Thanks to

- Paul Bressloff (Utah, Oxford)
- NSF