

# Diffusion-activation model of CaMKII translocation waves in dendrites

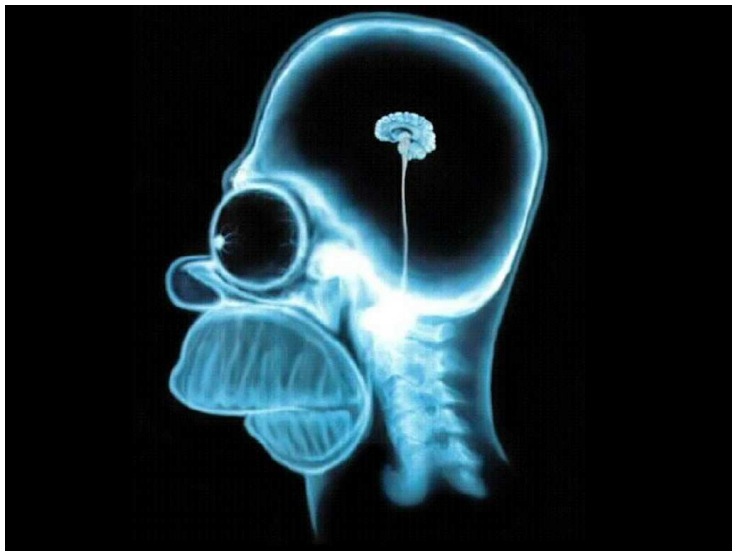
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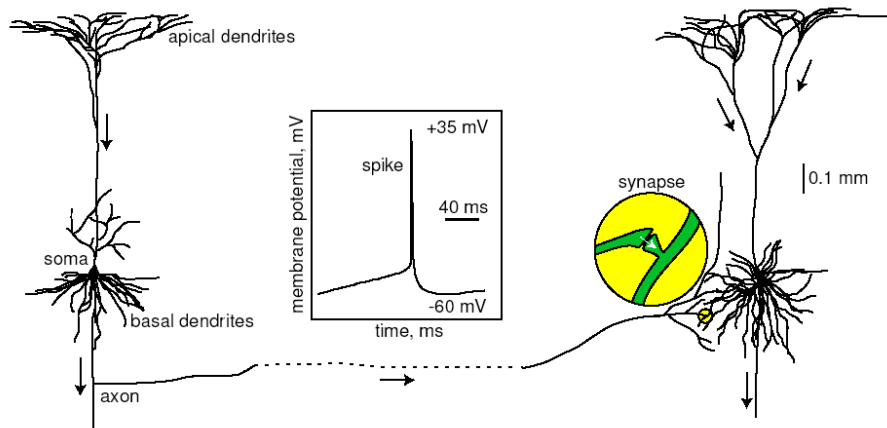
Mathematical Institute  
University of Oxford

August 25, 2009

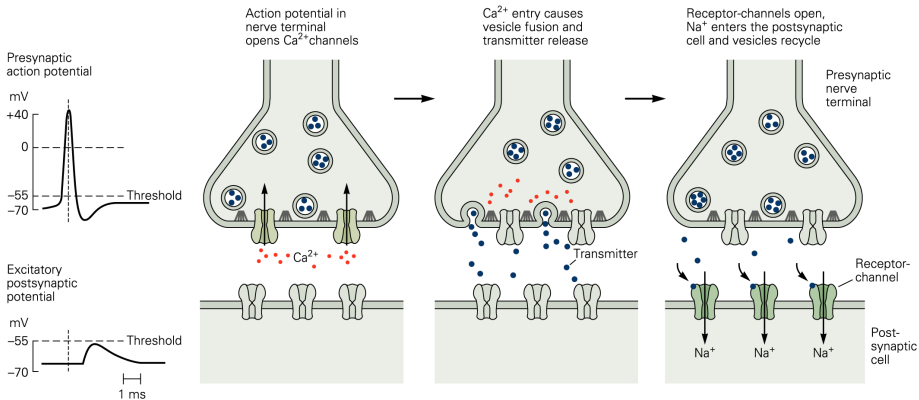
# The amazing brain



# Neurons communicate at synapses

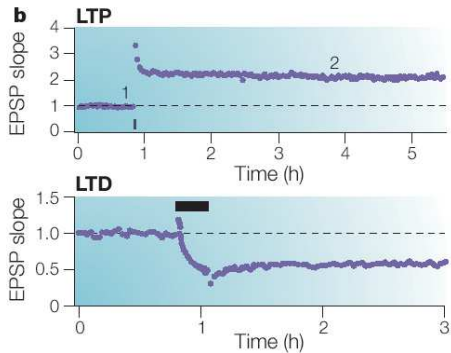
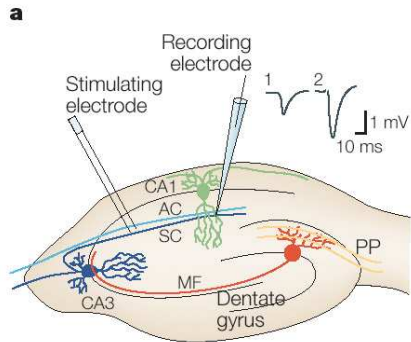


# Communication at a synapse



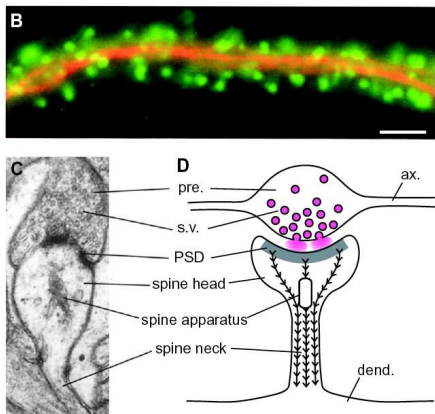
Kandel, Schwartz &amp; Jessel (2000)

# Synaptic plasticity



Collingridge et al., *Nat. Rev. Neurosci.* (2004)

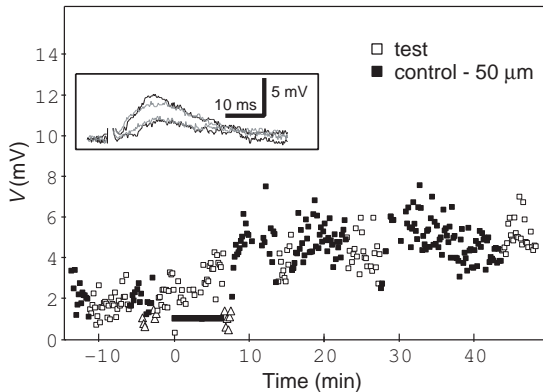
# Excitatory synapses and dendritic spines



Matus, *Science* (2000)

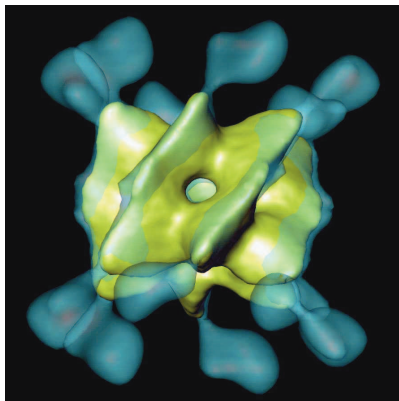
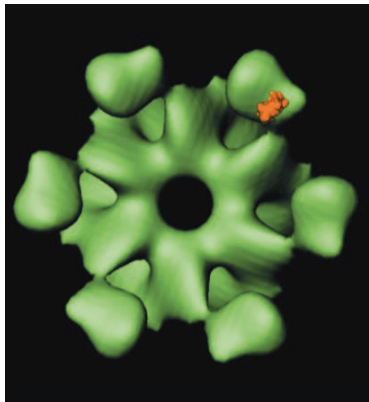
- Most excitatory synapses of CNS located in dendritic spines

# Heterosynaptic plasticity



Engert & Bonhoeffer, *Nature* (1997)

# CaMKII holoenzyme

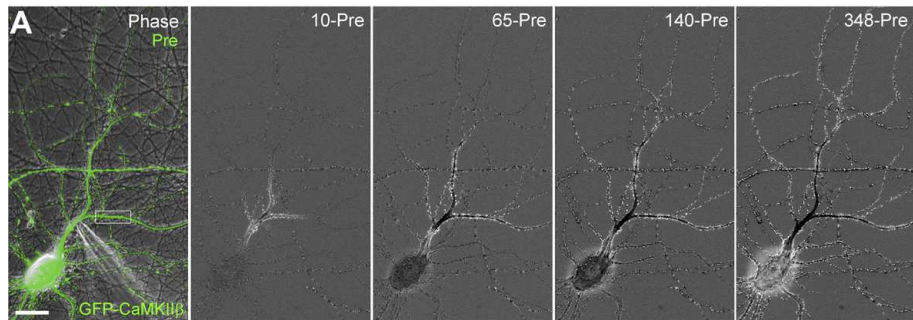


Kolodziej et al., *J Biol Chem* (2000)

- family of 28 isoforms derived from four genes ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ )
- holoenzyme formed from two hexameric rings
- targets substrates responsible for expression of LTP
- **necessary** and **sufficient** for LTP



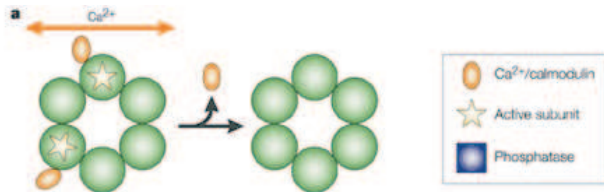
# CaMKII translocation waves



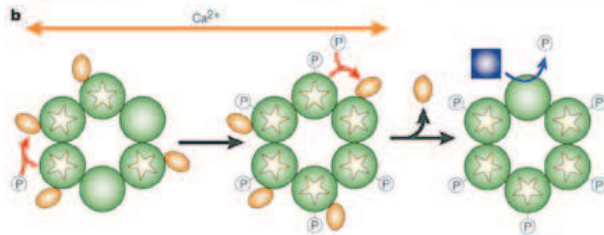
Rose et al., *Neuron* (2009)

# Activation states of CaMKII

"Primed"  
Ca/CaM dependent

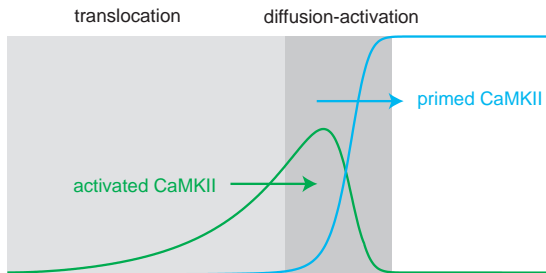
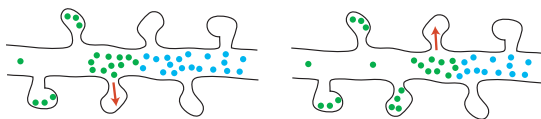
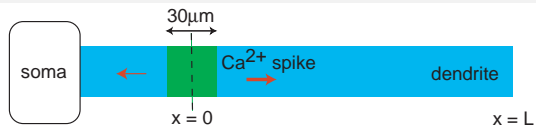


"Activated"  
Ca/CaM independent  
via autophosphorylation



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

# Diffusion-activation model of CaMKII translocation waves



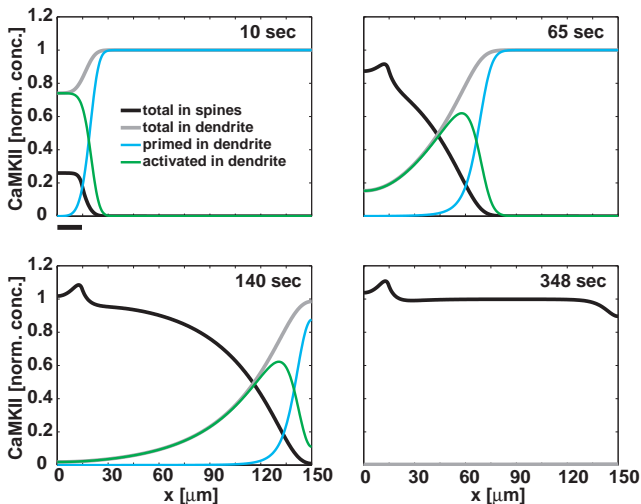
# Equations for diffusion-activation model

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

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

$$\frac{\partial s}{\partial t} = ha$$

- $p$  = 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 CaMKII $\alpha$ 

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

# 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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- 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

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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

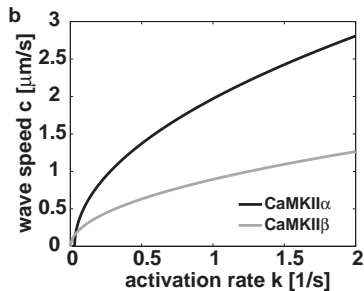
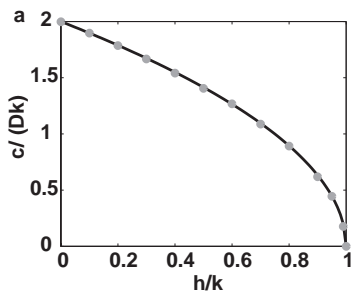
$$c = 2\sqrt{Dk}$$



# 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  $z = x - ct$

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

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

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

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

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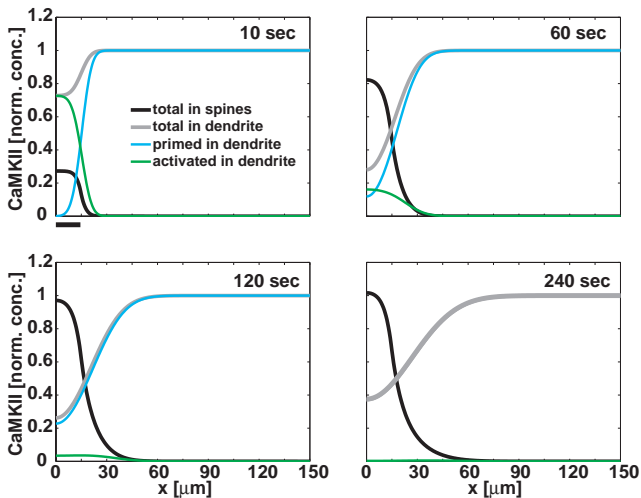
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- As with Fisher's equation, minimum wave speed is observed

# Wave propagation failure

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



# Conclusions and future directions

## Conclusions

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

## Future directions

- Heterosynaptic plasticity and synaptic tagging
  - Other diffusion-trapping models (e.g. AMPA receptor trafficking)
- Physiological dendrites (branching, discrete spines, heterogeneities)
- Threshold for wave initiation/propagation failure
  - modeling  $\text{Ca}^{2+}$  spike
  - stochastic effects of small numbers

# Thank you!

Thanks to

- Paul Bressloff
- University of Utah, NSF

