Neurons

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What makes neurons different from cardiomyocytes?

- Morphological polarity
- Transport systems
- Shape and function of action potentials
- Neuronal firing patterns
- Different roles of Ca^{2+}
- Methods of propagation
- Mechanisms of synaptic transmission
- Mechanisms of intracellular integration
- Glial support systems
- Synaptic plasticity
- Homeostatic plasticity

The father of modern neuroscience

Ramon y Cajal
1852-1934
Nobel prize 1906

Neuron doctrine: neurons are the basic structural and functional unit of the nervous system

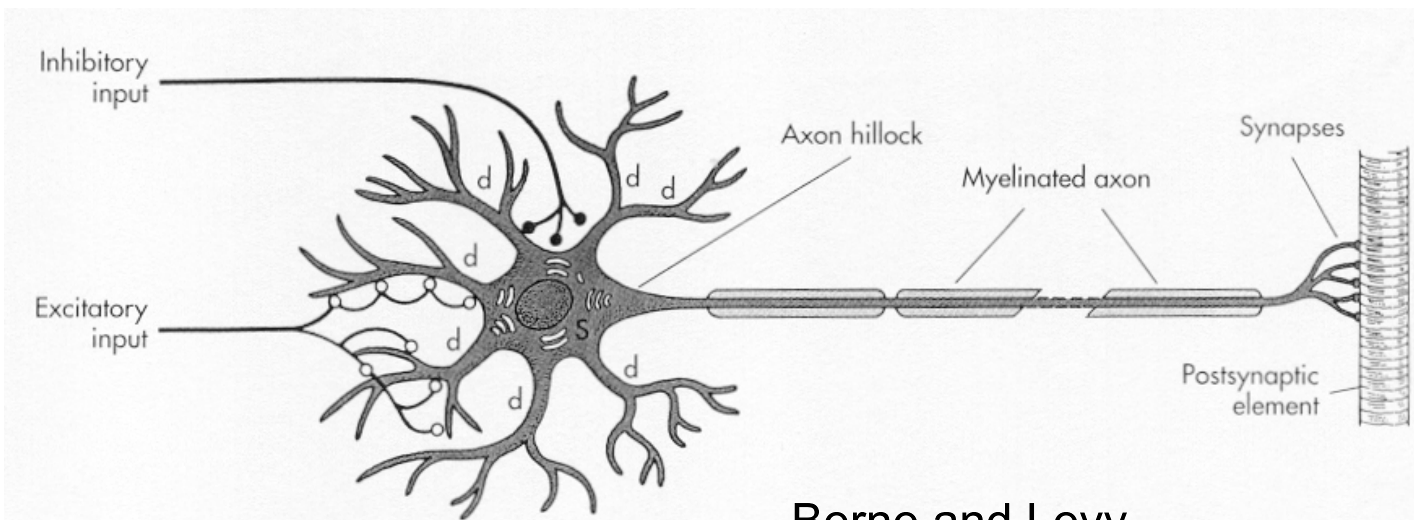
http://nobelprize.org

Morphological polarity

Ramon y Cajal
1852-1934

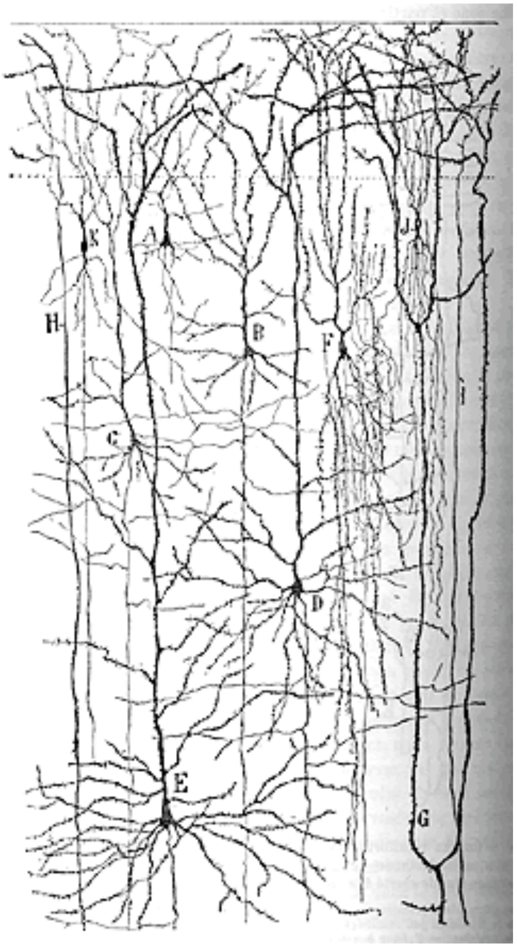
http://nobelprize.org

Law of dynamic polarization: nerve cells are *polarized*, receiving information on their cell bodies and dendrites, and conducting information to distant locations through axons



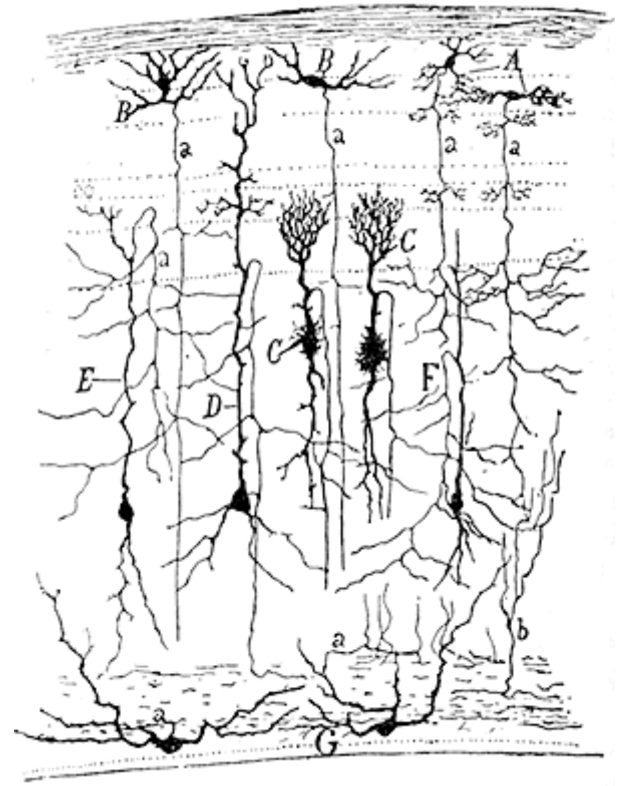
Berne and Levy

Cajal's art



Cerebral cortex

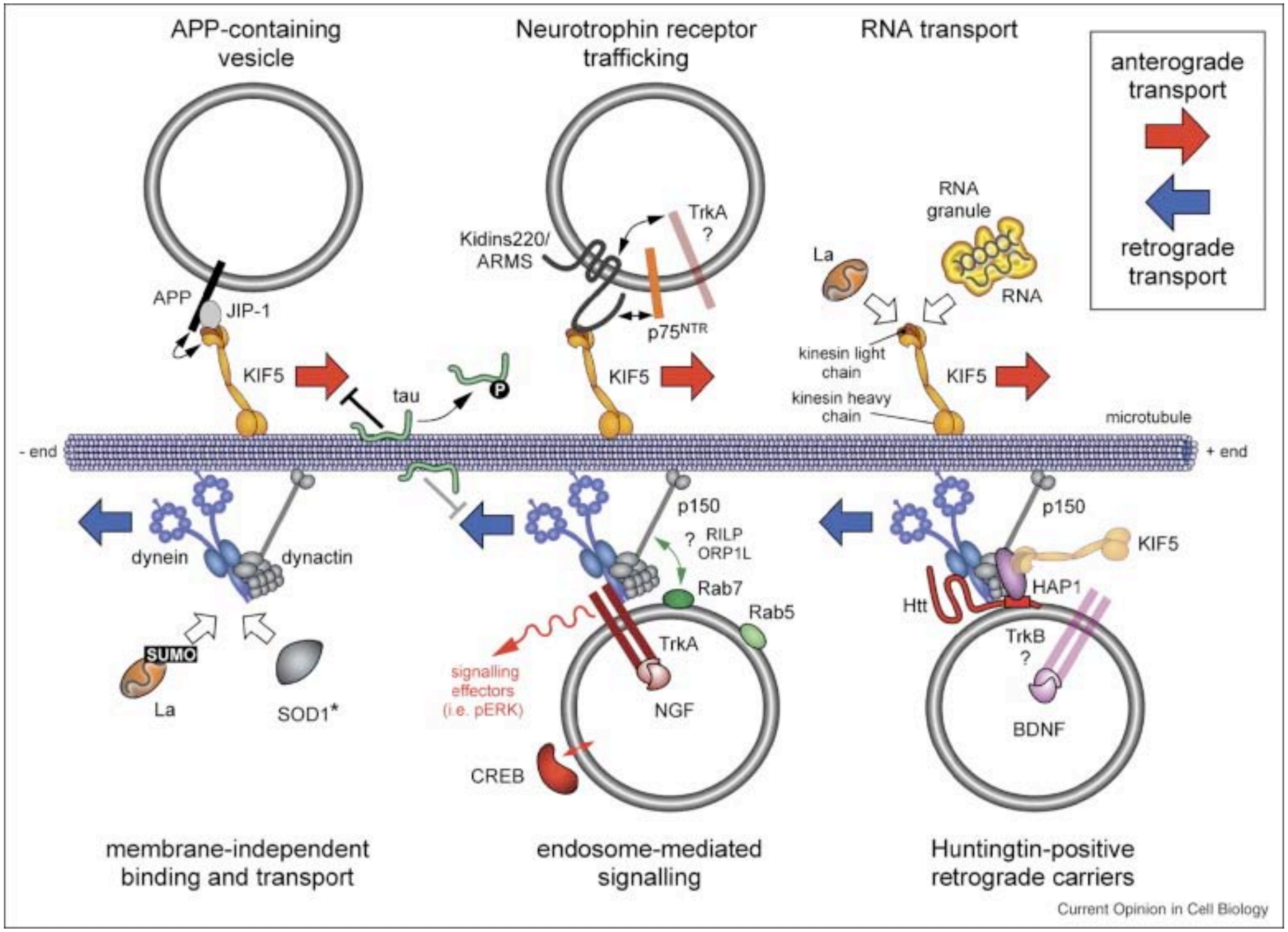
Cerebellum



Optic tectum

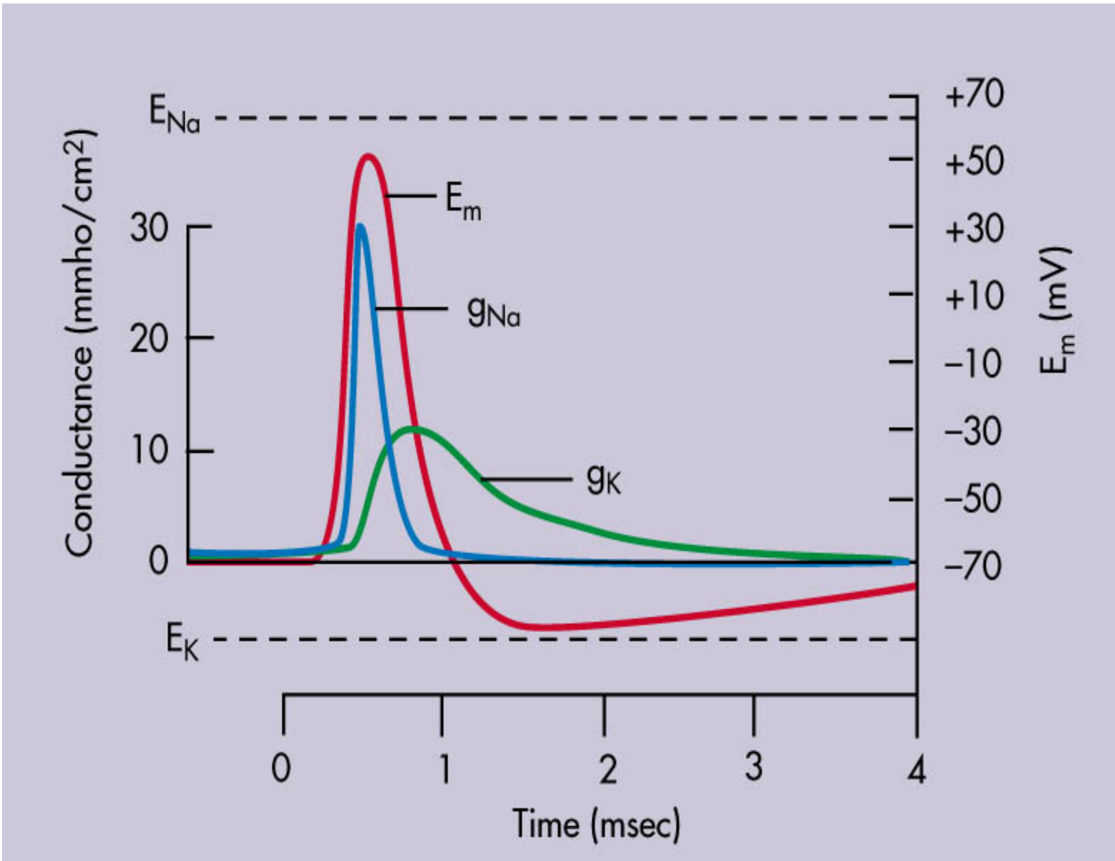
http://nobelprize.org

Microtubule-based transport



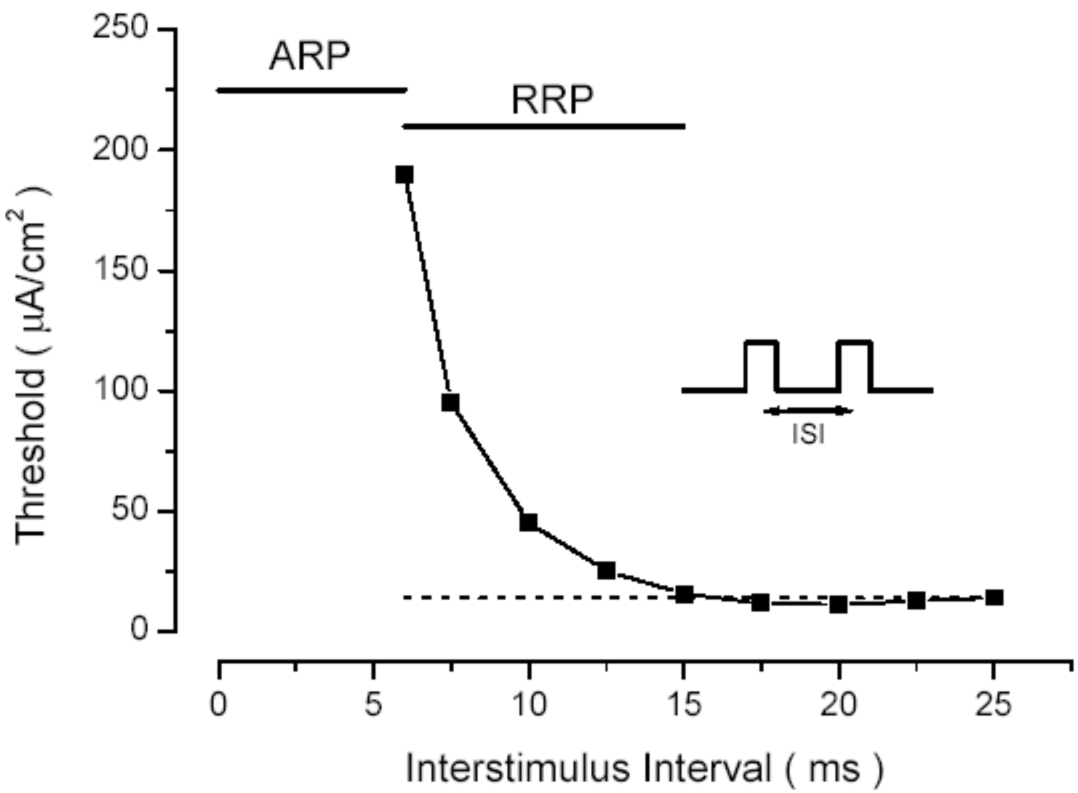
Salinas et al. (2008) *Curr Opin Cell Bio* 20: 445-453

Neuronal action potentials are Na^+ and K^+ dominated



Berne and Levy

Refractory periods are short



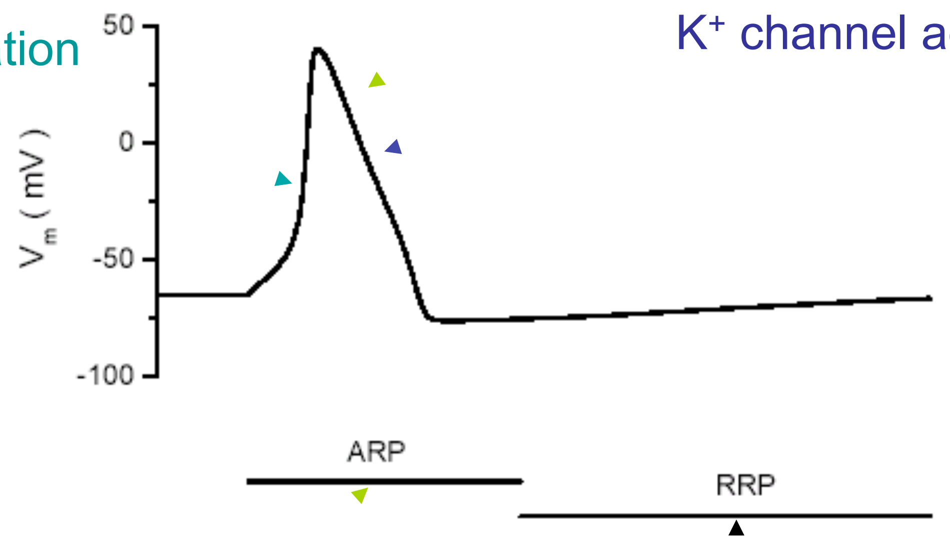
White (2000) *Encyclopedia of the Human Brain*

Crucial features of the neuronal action potential

Na⁺ channel inactivation

Na⁺ channel activation

K⁺ channel activation

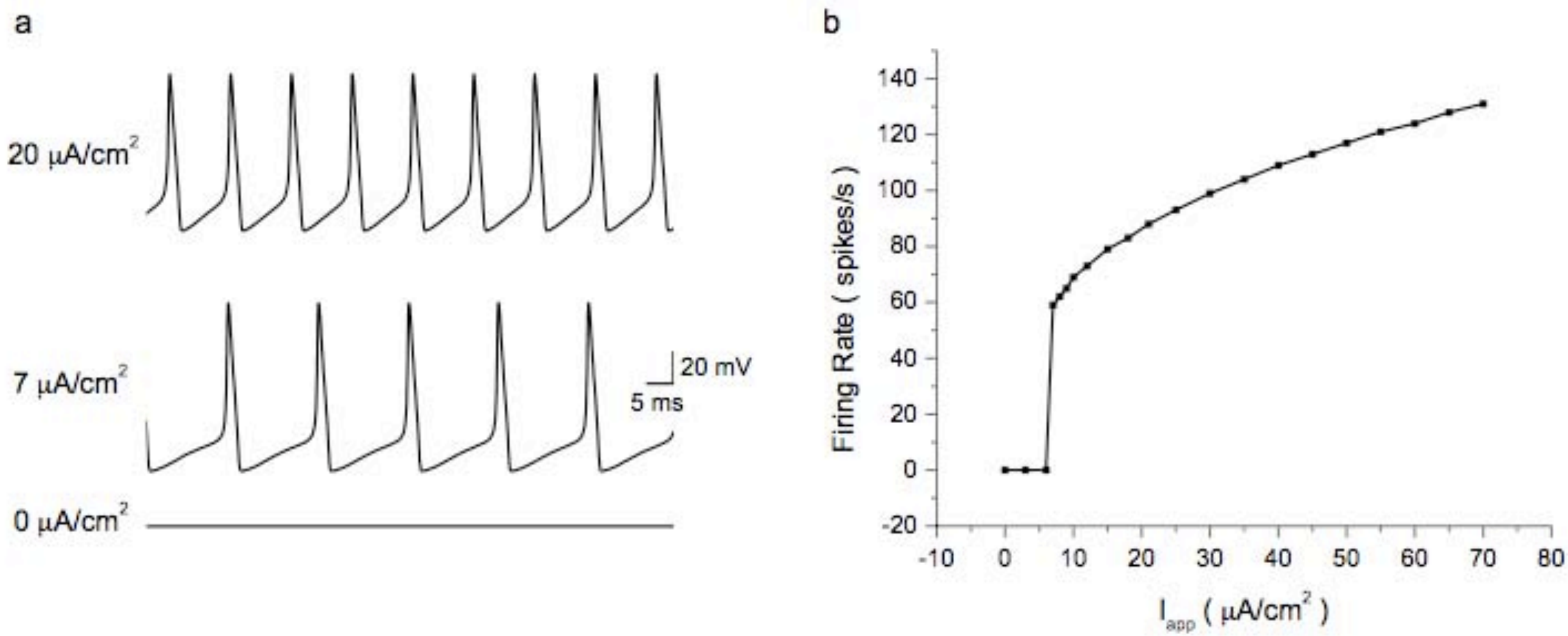


Na⁺ channels are inactivated
Impossible to generate another AP

Na⁺ channels still recovering from inactivation
K⁺ channels still recovering from activation
Possible, but more difficult, to generate AP

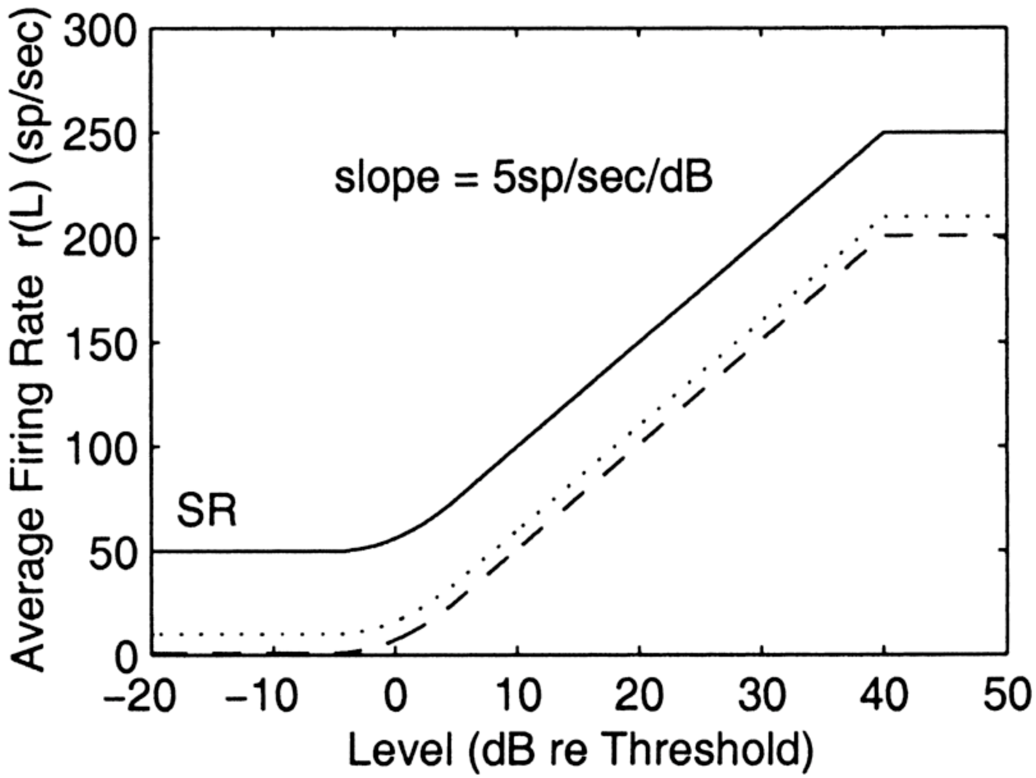
White (2000) *Encyclopedia of the Human Brain*

Neurons can fire at high rates



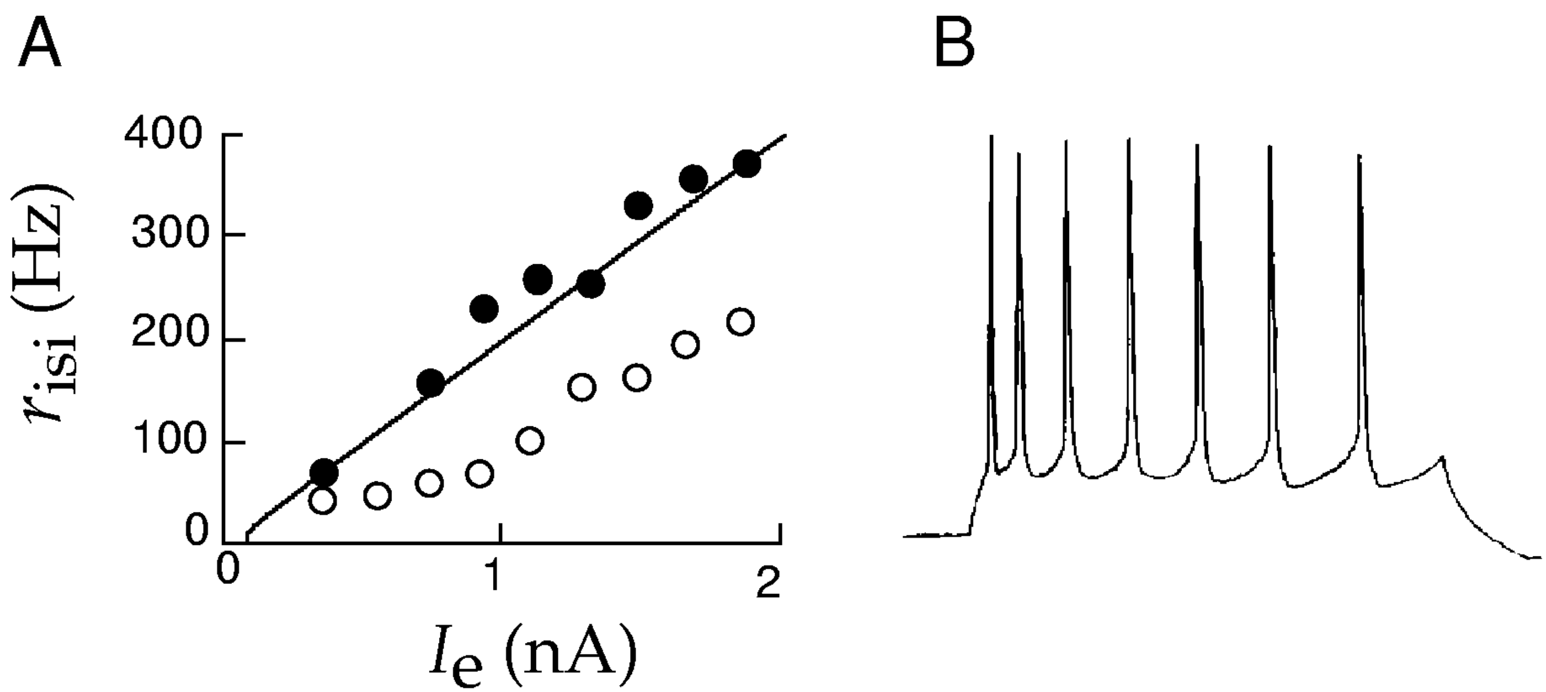
White (2000) *Encyclopedia of the Human Brain*

Neurons can fire at high rates



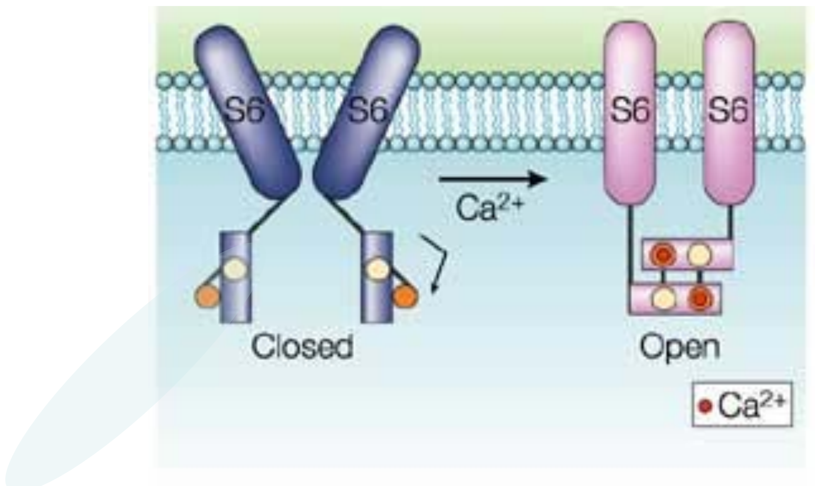
Colburn et al. (2003) *J Assoc Res Otol* 4: 294-311

Spike-rate adaptation is very common in neurons



Dayan and Abbott, Fig. 5.6

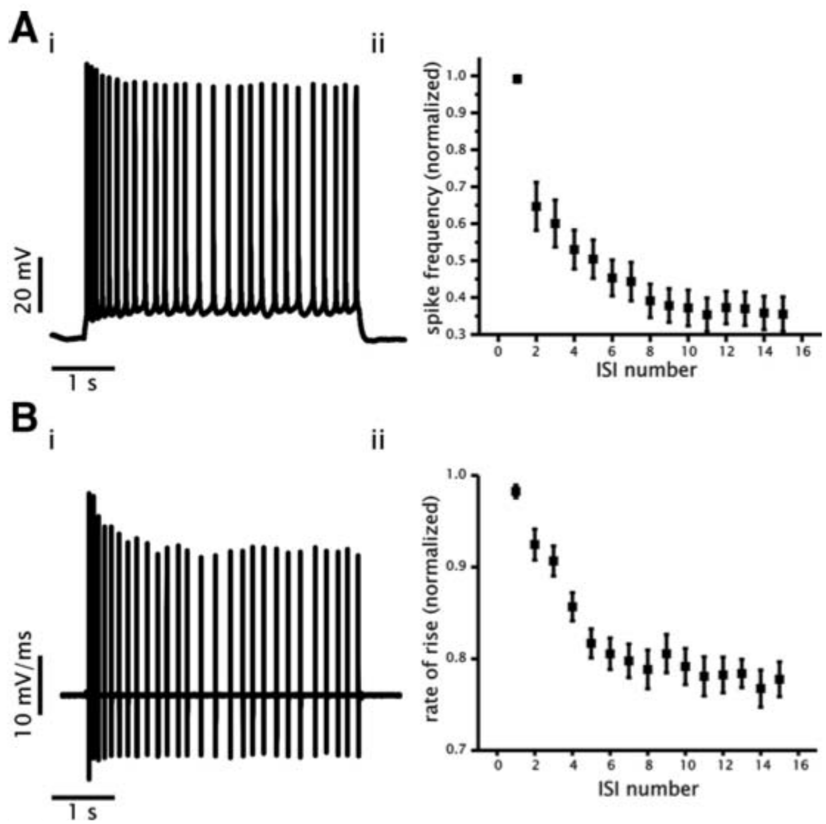
SK-type Ca^{2+}-activated K^{+} channels often play a role in adaptation



Calmodulin-binding domain

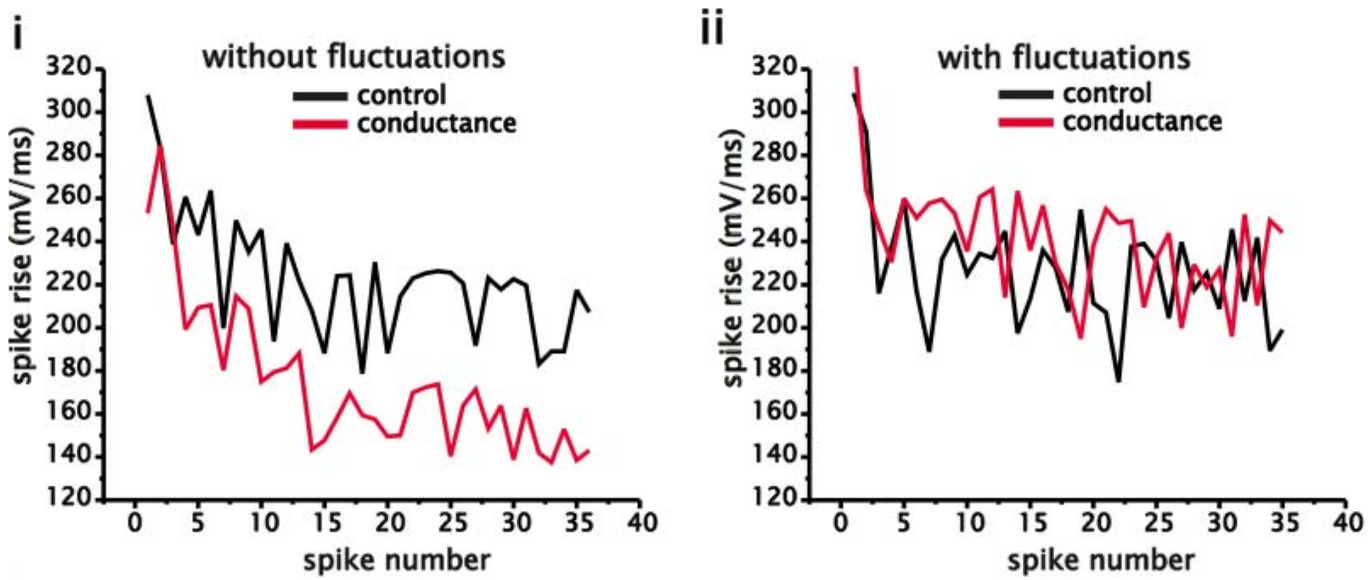
Stocker (2004) *Nature Reviews Neuroscience 5:* 758-770

Cumulative inactivation of Na^+ channels is a 2nd mechanism of adaptation



Fernandez and White (2010) *Journal of Neuroscience 5:* 758-770

Cumulative Na^+-channel inactivation is relieved by fluctuating inputs



Fernandez and White (2010) *Journal of Neuroscience 5:* 758-770

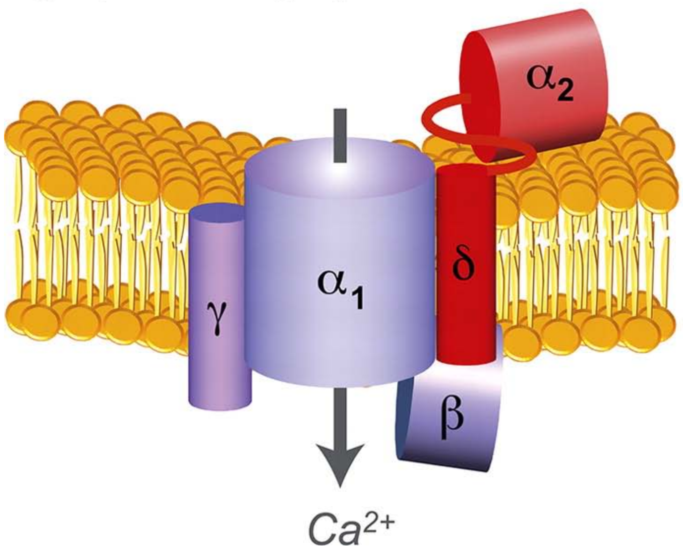
Neuronal calcium channels

Ancillary subunits

$\beta_1, \beta_2, \beta_3, \beta_4$

γ_1 through γ_8

$\alpha_2\text{-}\delta_1$ through $\alpha_2\text{-}\delta_4$



Neuronal α_1 subunits

HVA	$Ca_v1.2$	L-type
	$Ca_v1.3$	L-type
	$Ca_v1.4$	L-type
	$Ca_v2.1$	P/Q-type
	$Ca_v2.2$	N-type
	$Ca_v2.3$	R-type
LVA	$Ca_v3.1$	T-type
	$Ca_v3.2$	T-type
	$Ca_v3.3$	T-type

L: Slow, largely non-inactivating. Found in cell bodies, dendrites.

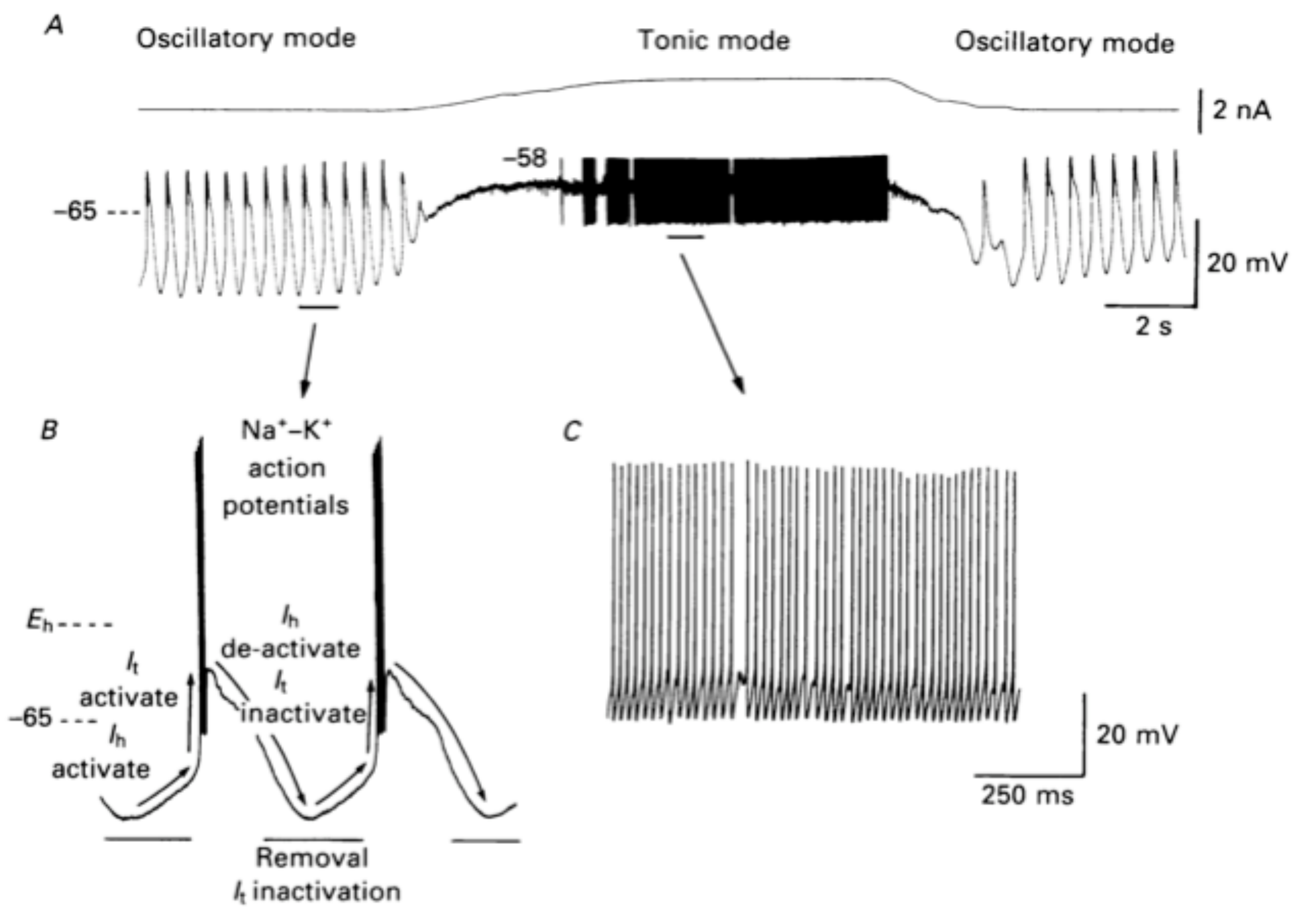
P/Q, N: Slowly inactivating, presynaptic terminals

R: More rapid inactivation than P/Q, N. Presynaptic terminals, proximal and distal dendrites.

T: Low-threshold, rapidly inactivating. Soma and (distal?) dendrites.

Khosravani and Zamponi (2006) *Physiol Rev* 86: 941-966

Multi-state activity in thalamocortical neurons

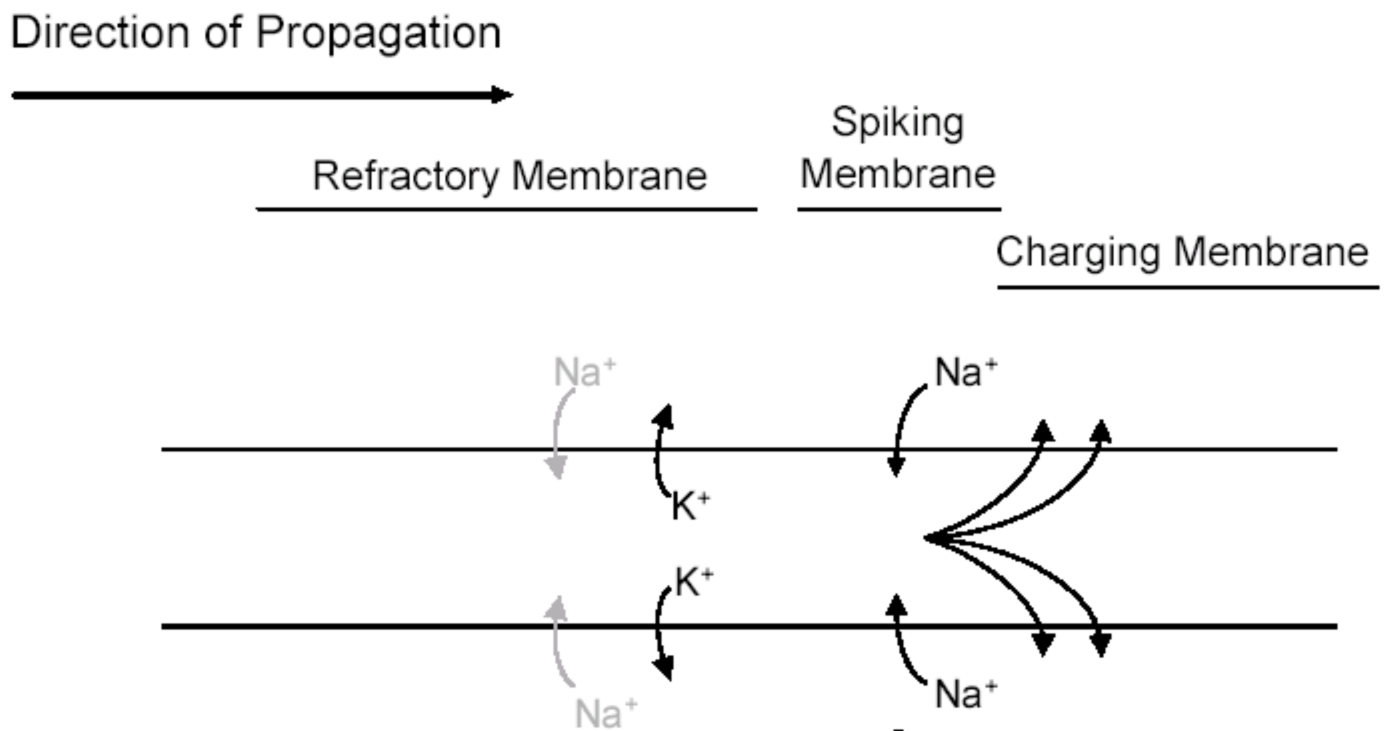


McCormick and Pape (1990) *J Physiol* 431: 291-318.

Major roles of Ca^{2+} in neurons

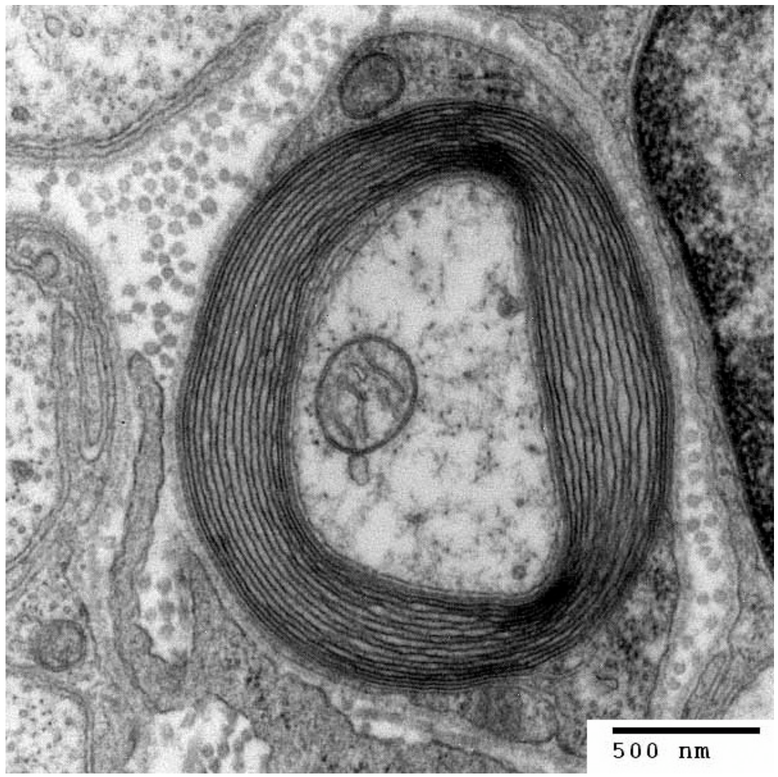
- Triggers spike-rate adaptation
- Involved in bursting
- Triggers exocytosis at chemical synapses
- Involved in dendritic processing
- Local signal for synaptic plasticity
- Control signal for cellular homeostasis

Propagation in unmyelinated axons



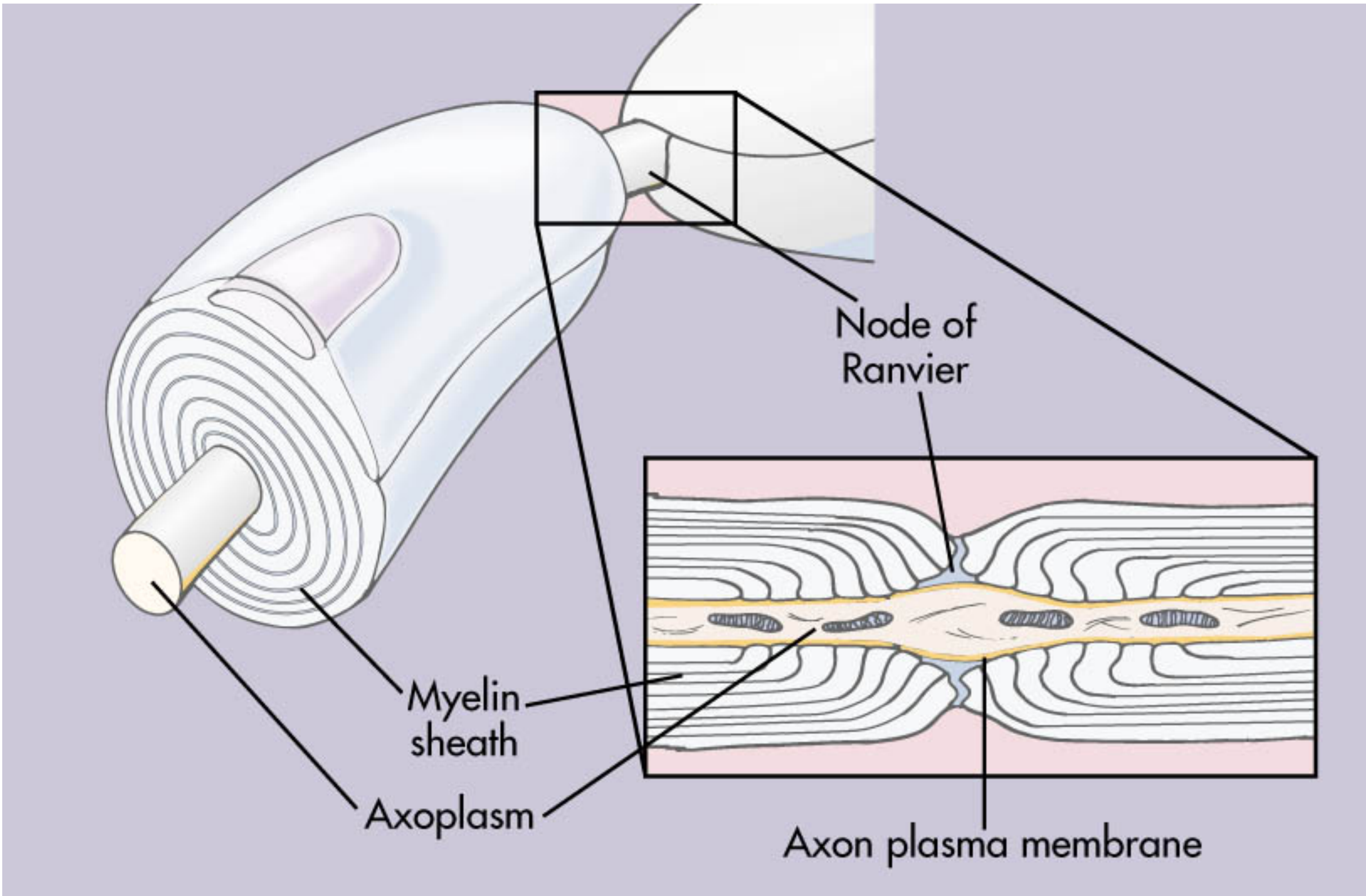
White (2000) *Encyclopedia of the Human Brain*

Myelination of axons



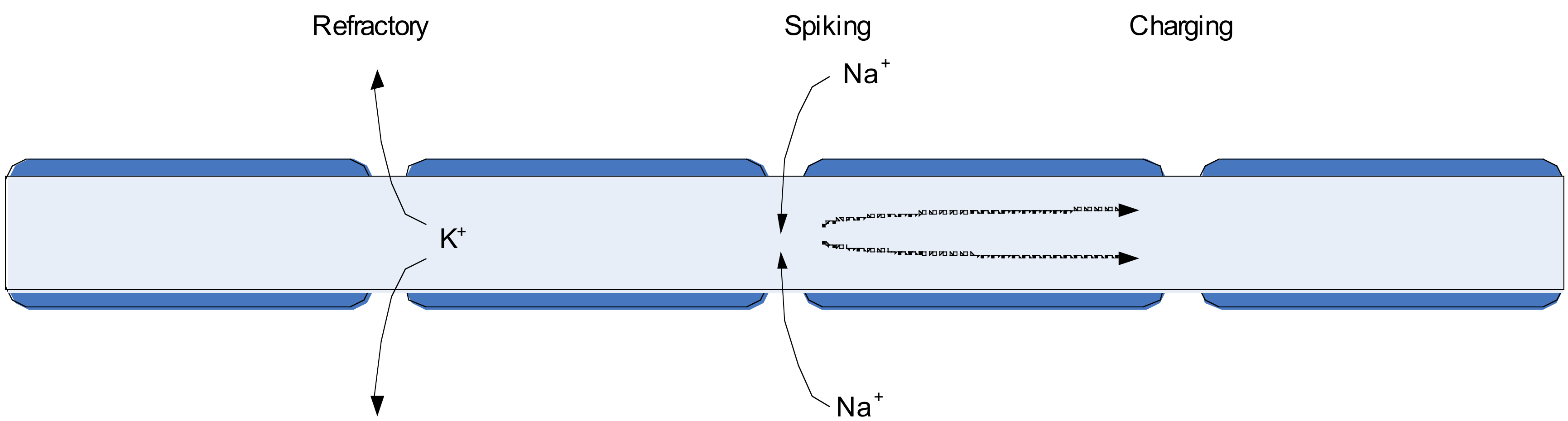
http://en.wikipedia.org/wiki/Myelin

Myelination of axons

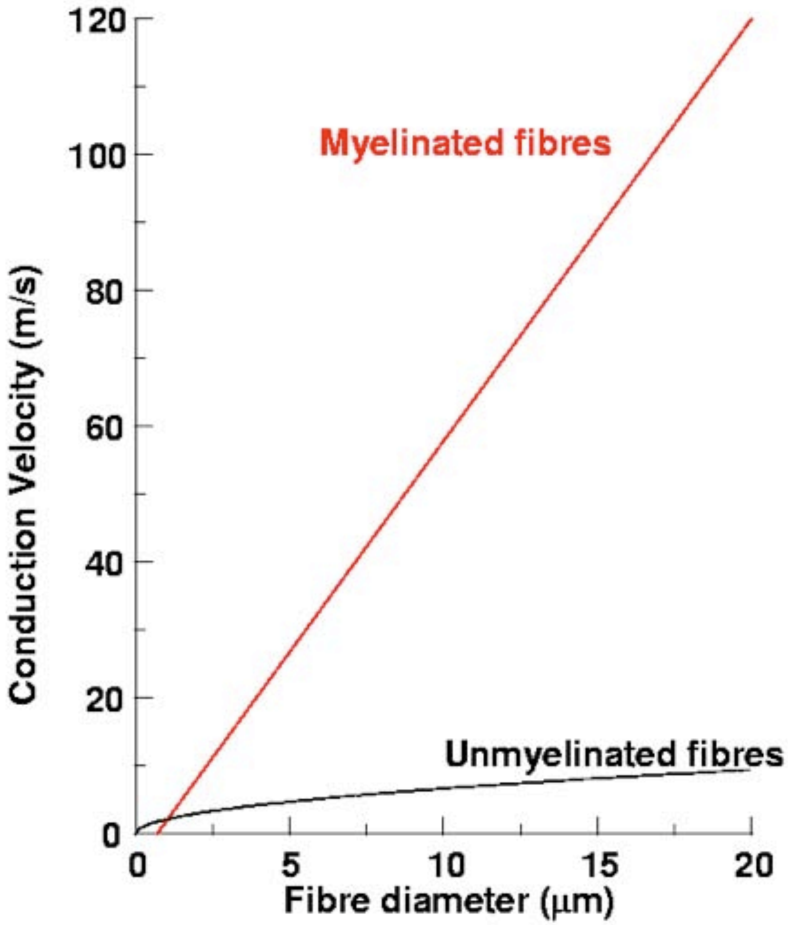


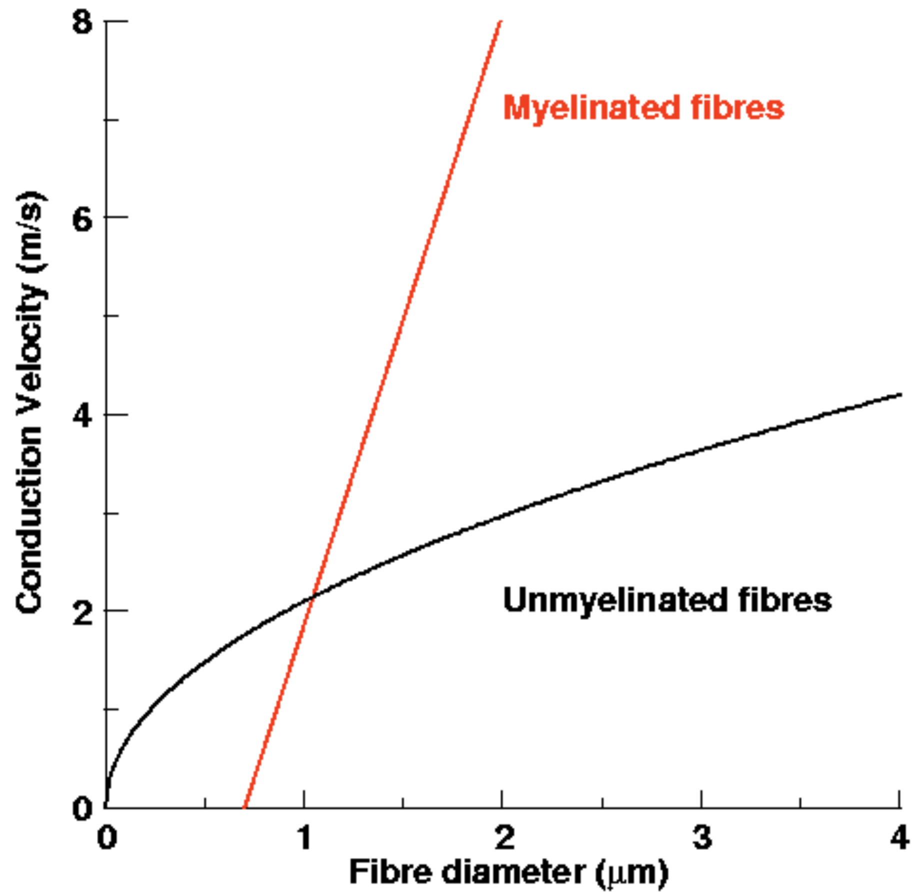
Berne and Levy

Propagation in myelinated axons



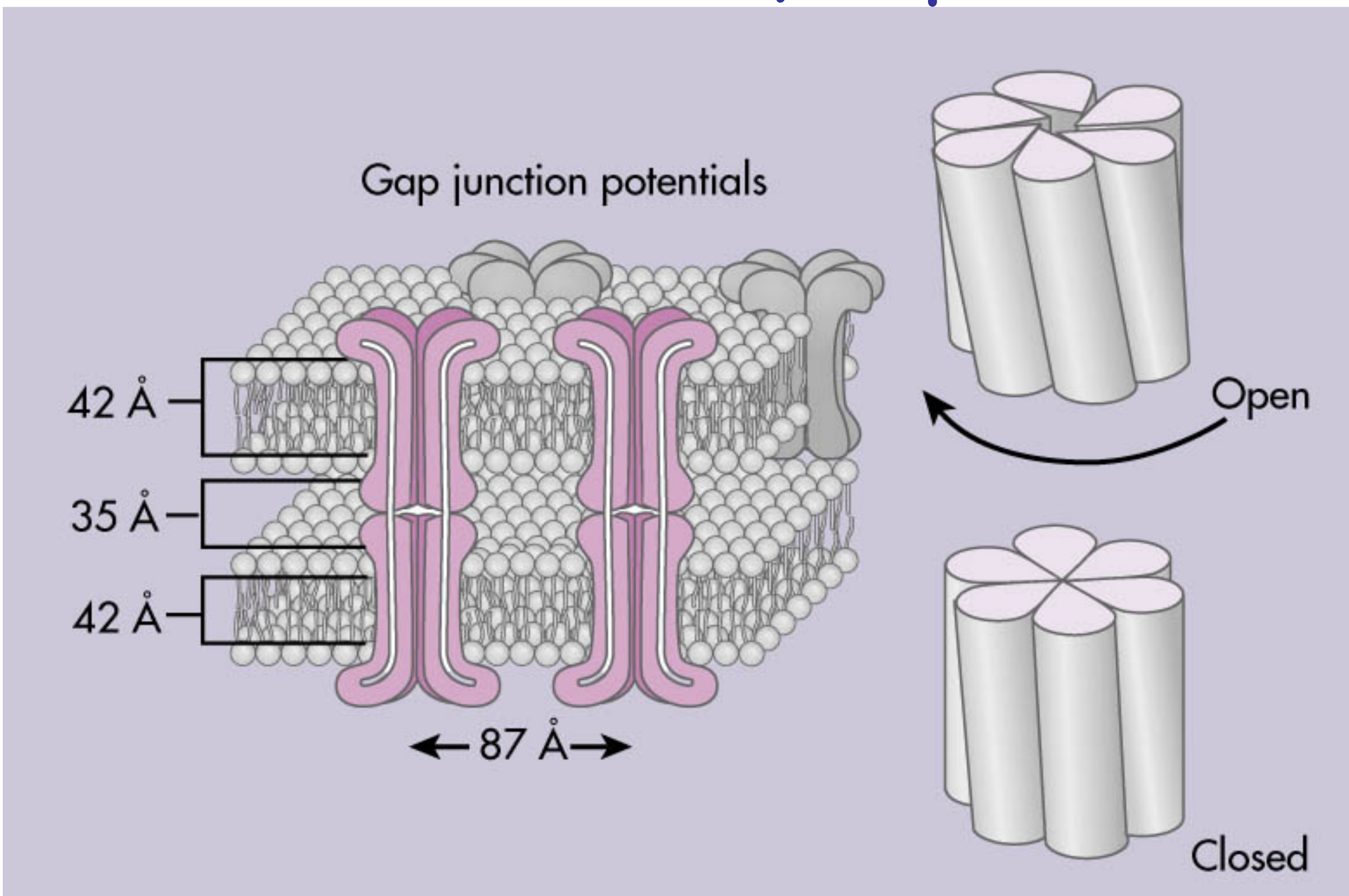
Myelinated axons have higher conduction velocities





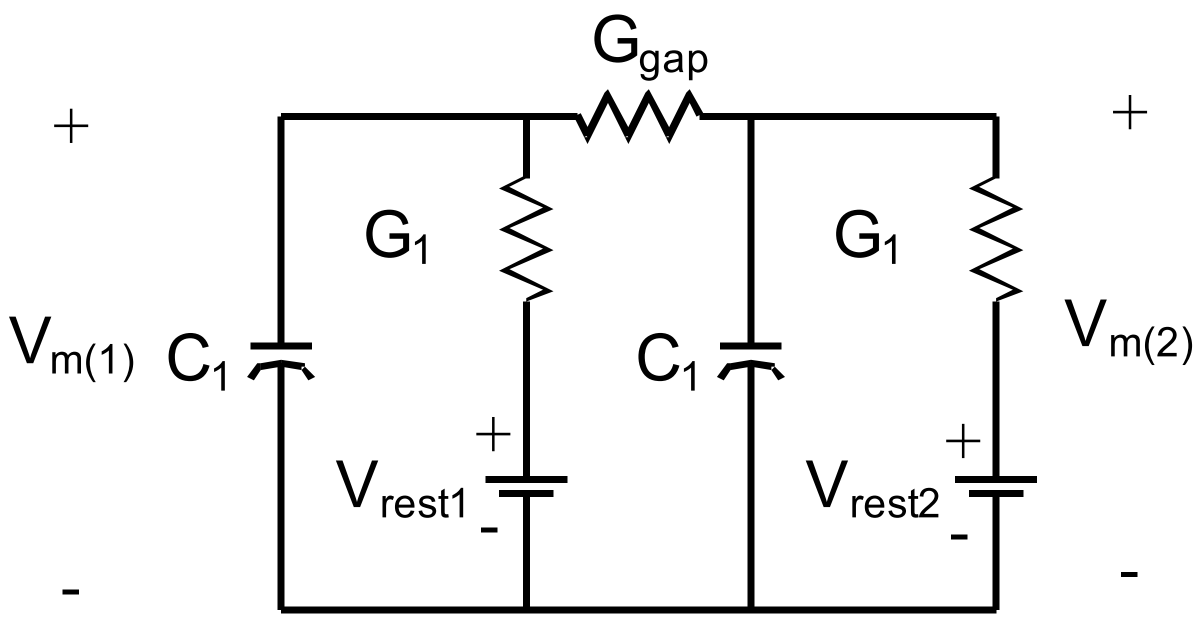
http://www.physiol.usyd.edu.au/daved/teaching/cv.html

Electrical synapses

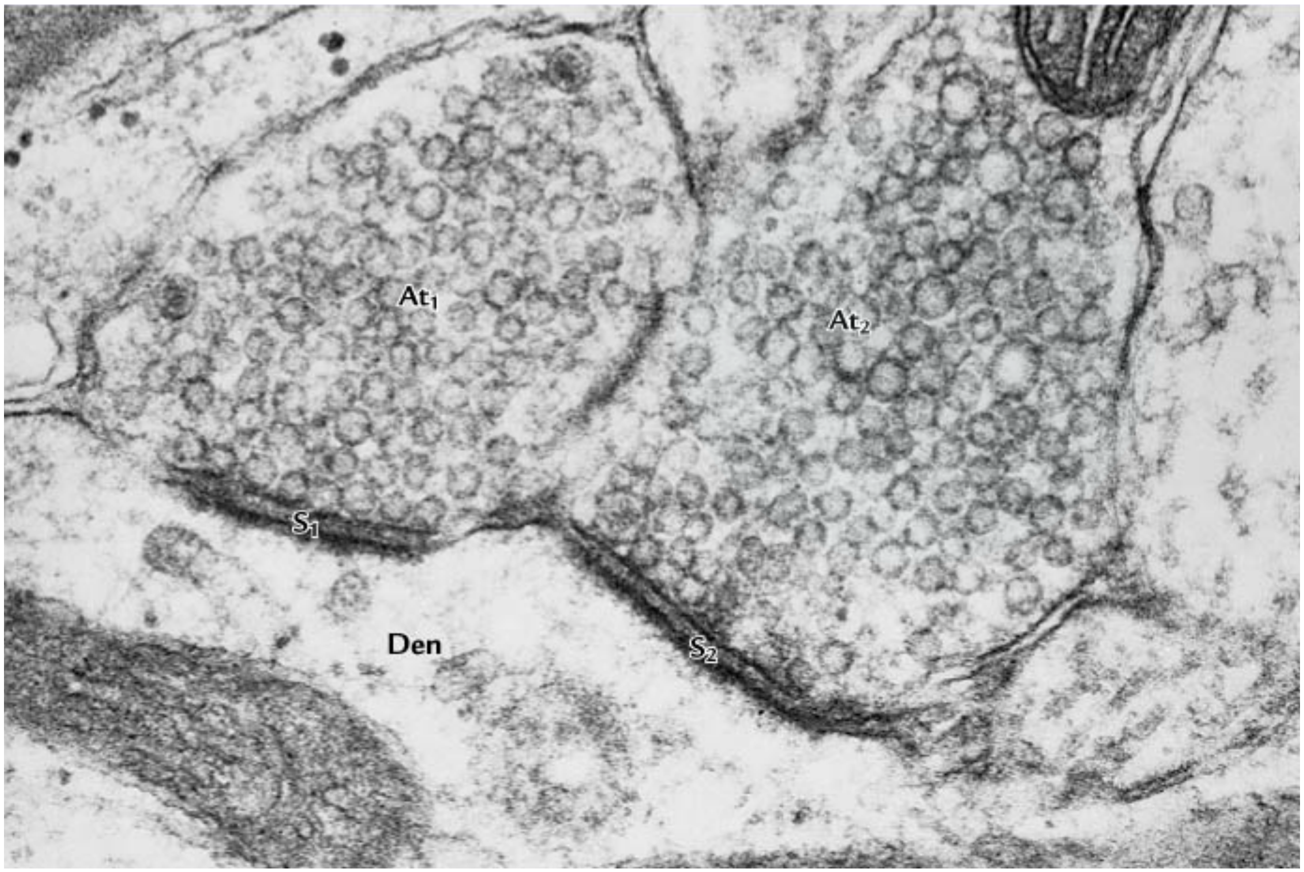


Berne and Levy

Electrical synapses are resistive and bidirectional



Chemical synapses



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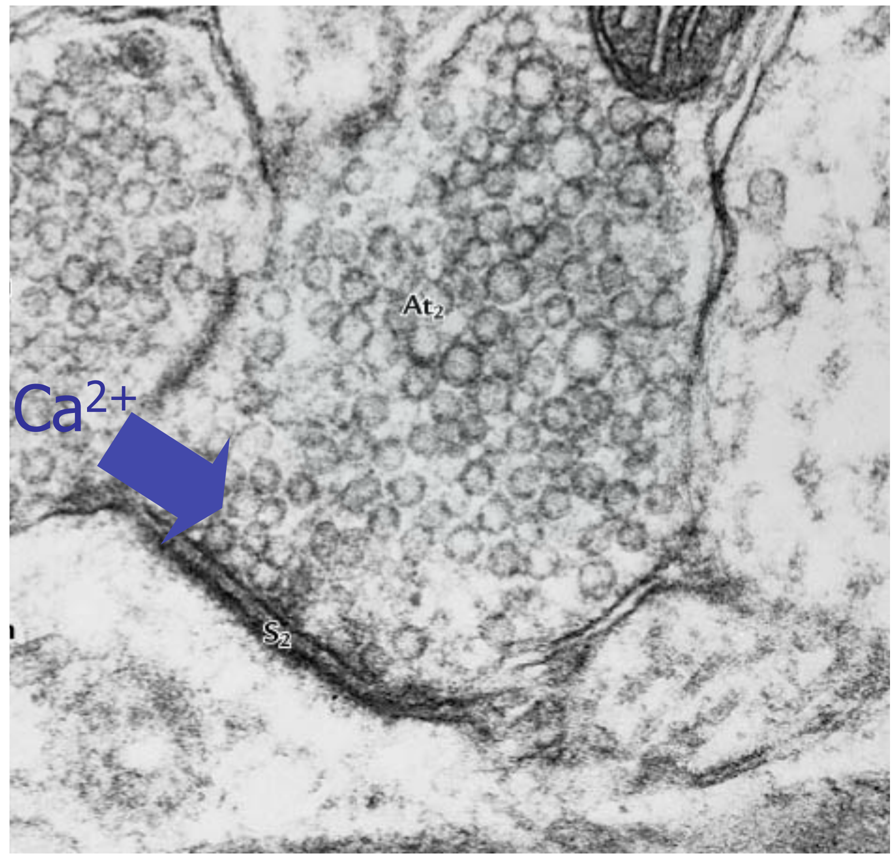
Chemical synapses

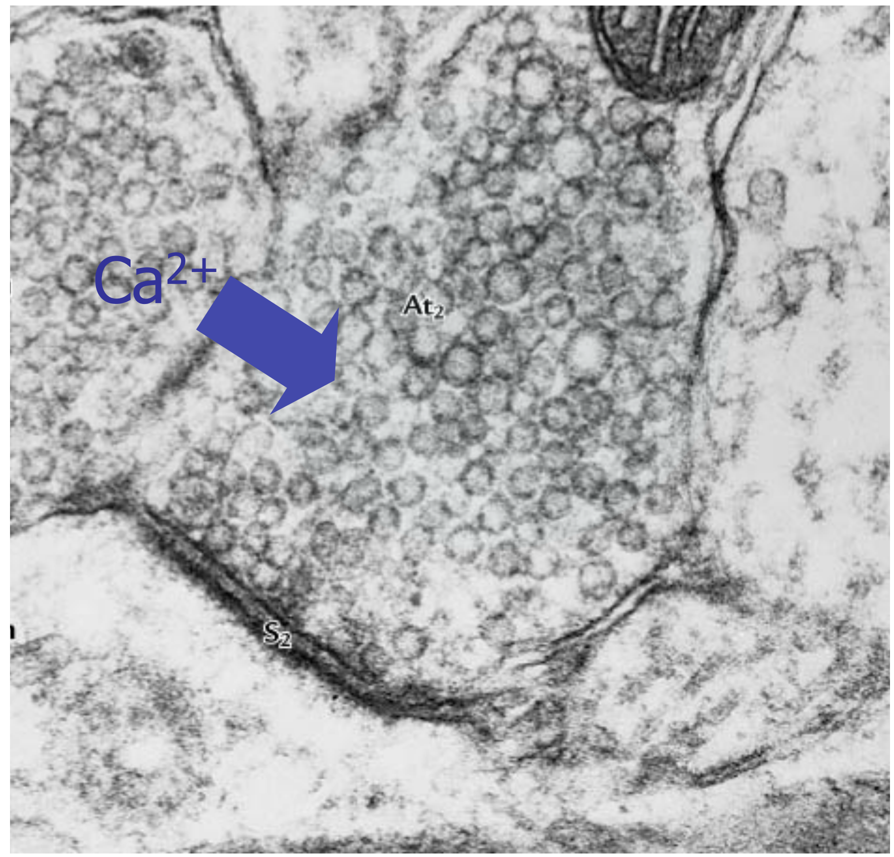
- Immediately releasable pool: vesicles held close to plasma membrane by SNAREs
- Depolarization of presynaptic terminal
- Ca^{2+} entry
- Fusion
- Diffusion of neurotransmitter across cleft
- Binding to postsynaptic receptor
- Recycling of neurotransmitter



Berne and Levy

Resupplying the immediately releasable pool

- Depol. of presyn. terminal
- Ca^{2+} entry
- Activation of CaMKII
- Phosphorylation of synapsin I
- Synapsin I frees vesicles
- SNAPs and SNAREs dock the vesicle



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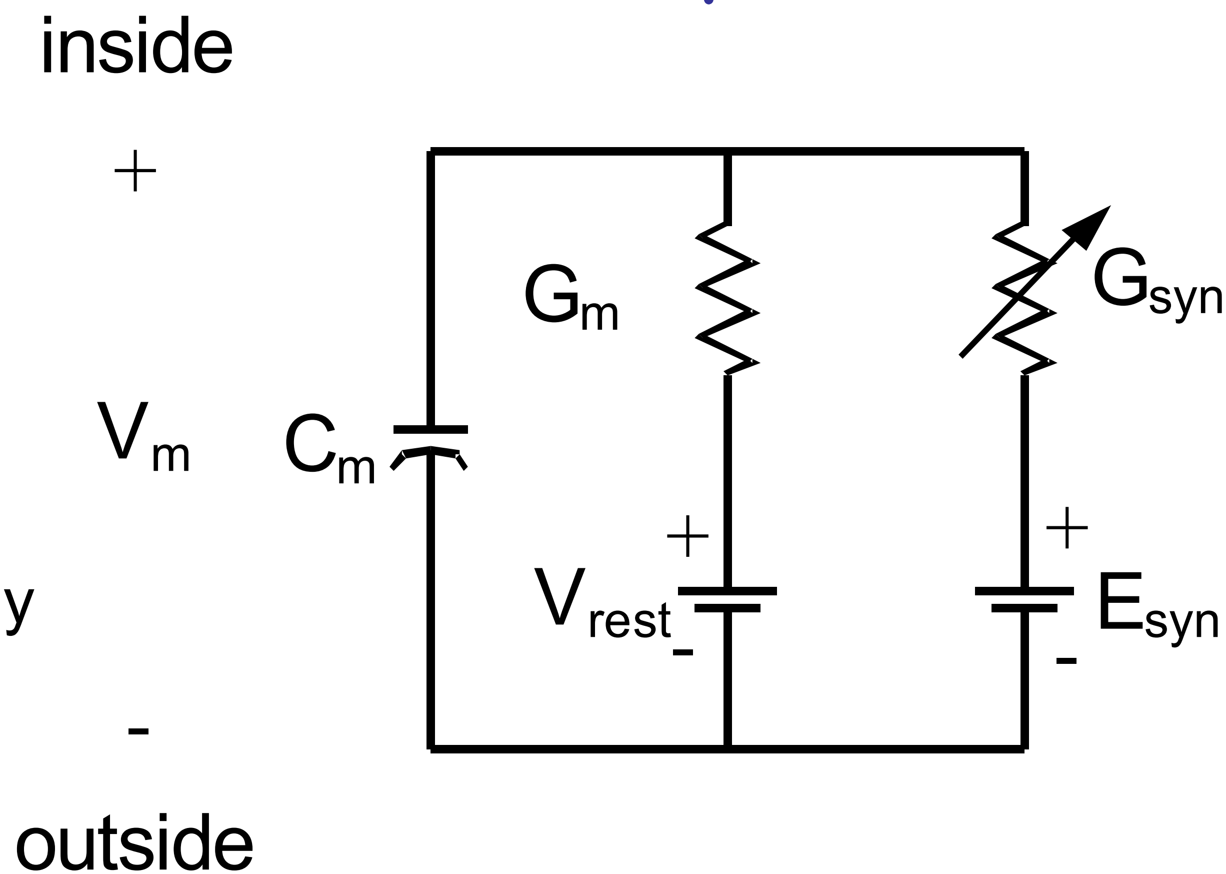
Distinguishing features of chemical synapses

Unidirectional

Induce post-synaptic conductance change (usually an increase)



Two distinct classes of chemical synaptic receptors

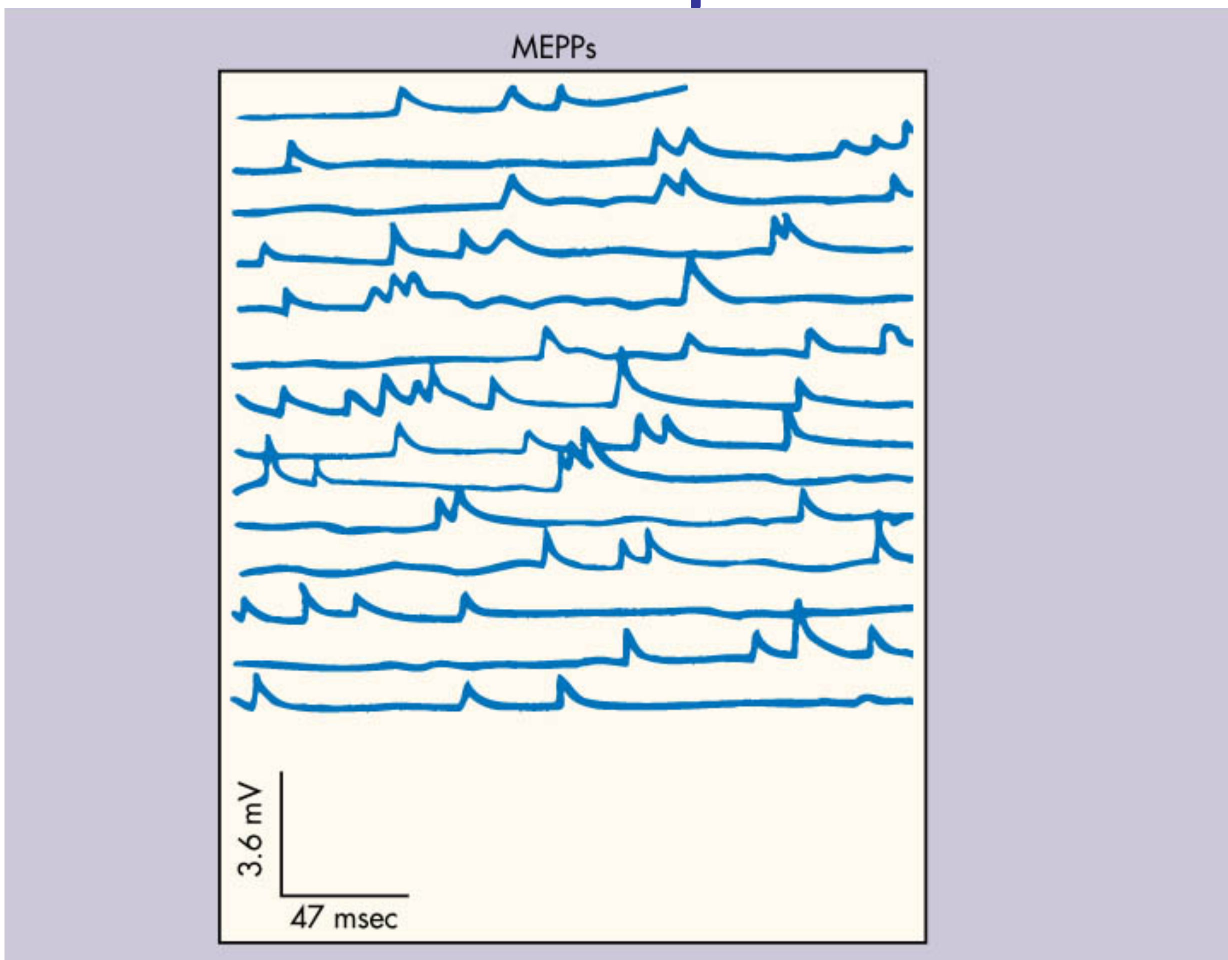
- Ionotropic
  - Postsynaptic receptor is an ion channel
  - Binding of ligand (neurotransmitter) changes P_{open}
  - Fast, transient, small gain

- Metabotropic
  - Postsynaptic receptor is tied to postsynaptic 2nd-messenger systems (usually G-protein-based)
  - Slow, long-lasting, enormous gain

Major neurotransmitters and neuromodulators

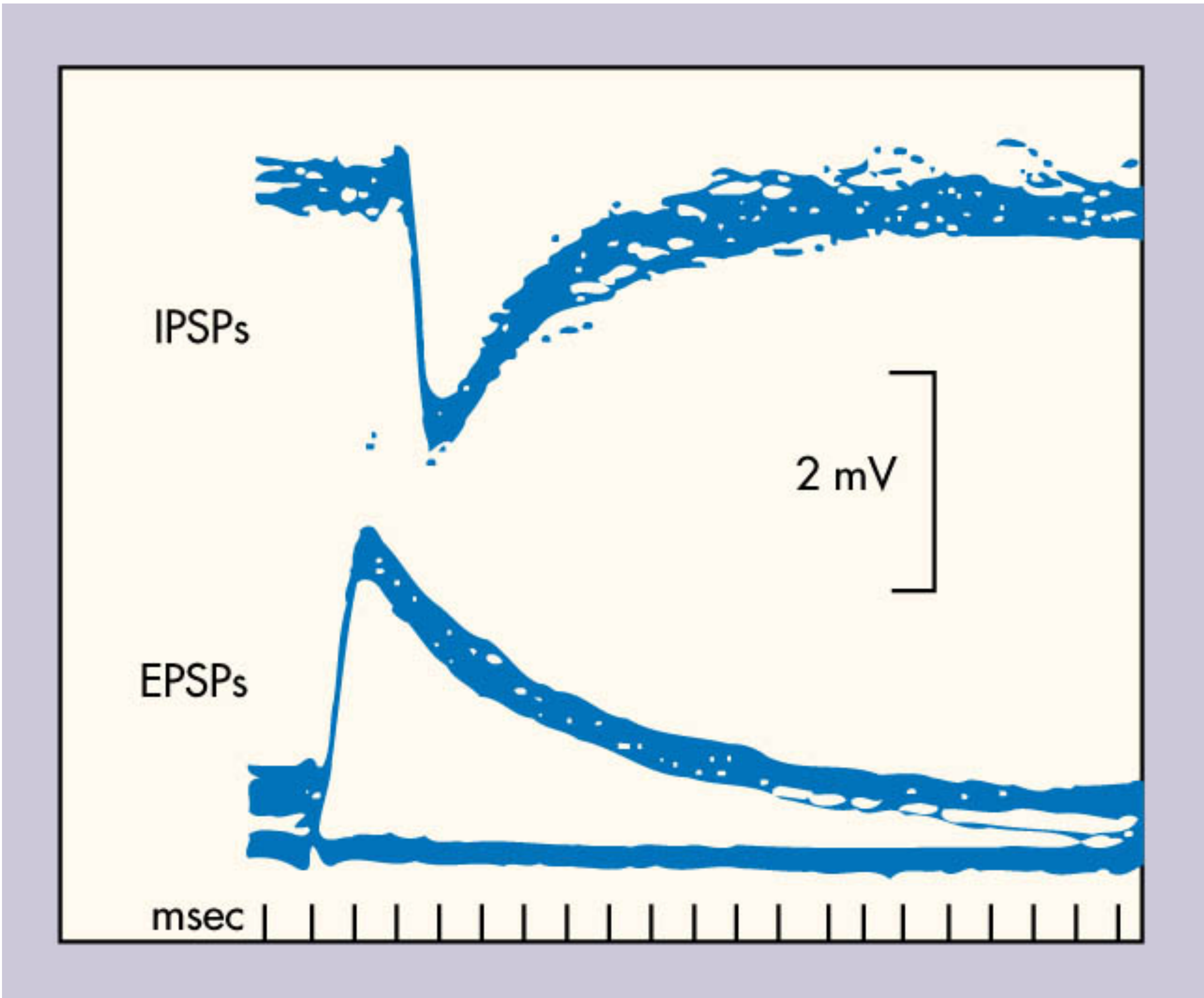
- Amino acids
  - Glutamate
  - GABA (gamma aminobutyric acid)
  - Glycine
- Acetylcholine
- Catecholamines
  - Norepinephrine
  - Dopamine
  - Serotonin
- Peptides
  - Opiods (endorphins, enkephalins, dynorphins)
  - Substance P
- Gases
  - Nitric oxide
  - CO

Spontaneous release of single vesicles (quanta)



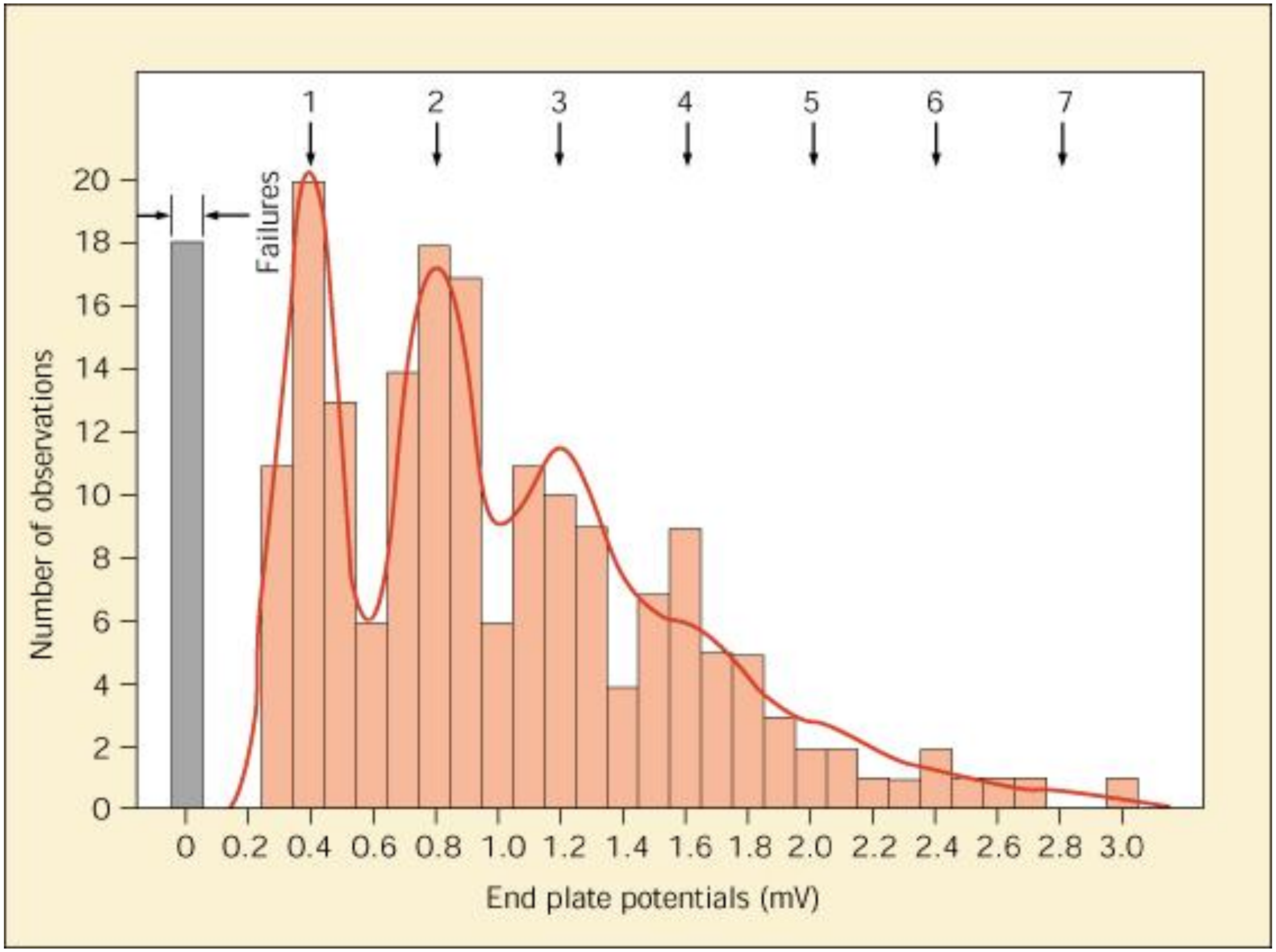
Berne and Levy

Ionotropic EPSPs and IPSPs



Berne and Levy

Quantal release



Berne and Levy

Binomial model

$$P(q=k)=\frac{N!}{k!(N-k)!}p^k(1-p)^{n-k}$$

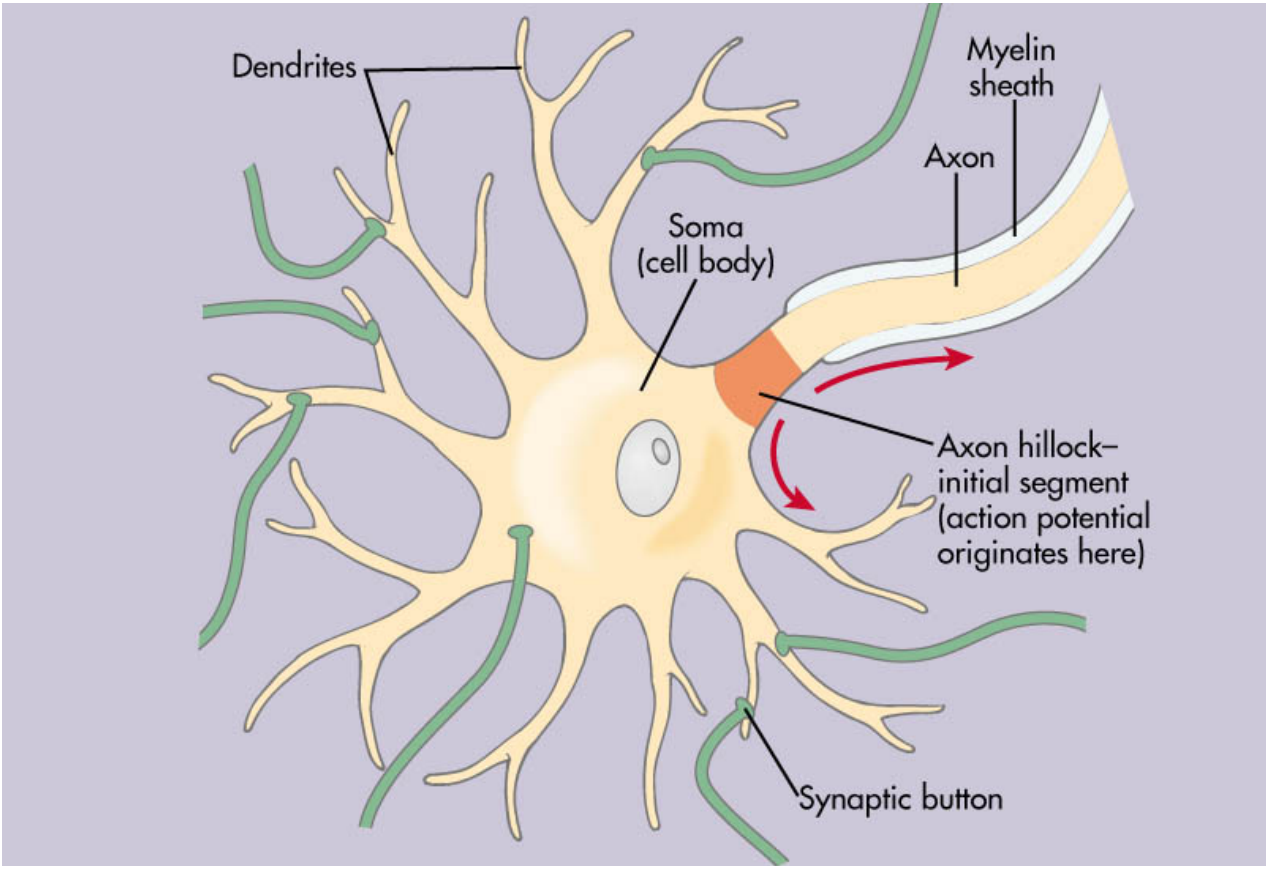
$$E[q]=Np$$

$$\sigma^2=Np(1-p)$$

Classical model of neuronal integration of inputs

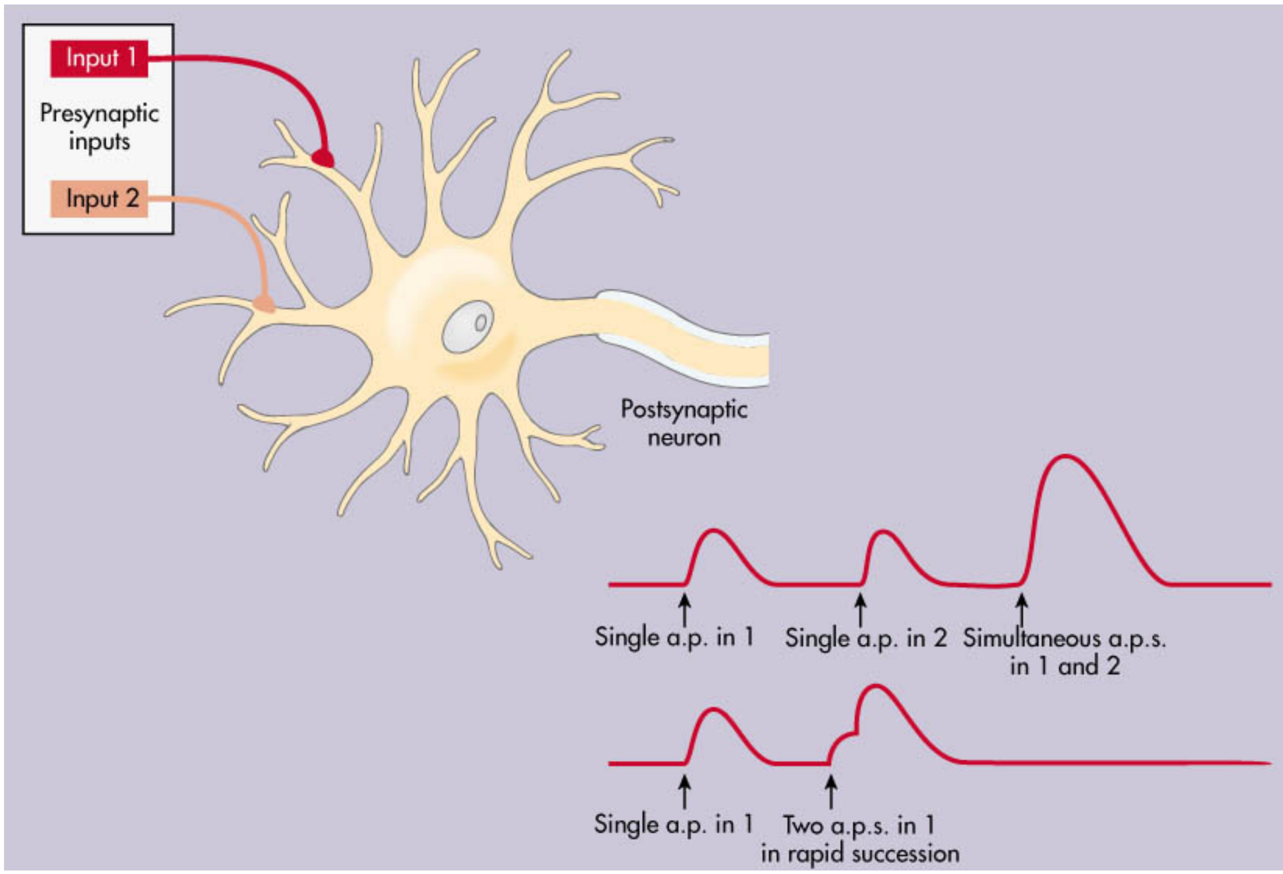
Excitatory inputs tend to innervate dendrites

Inhibitory inputs tend to innervate cell bodies



Berne and Levy

Spatial and temporal summation



Berne and Levy

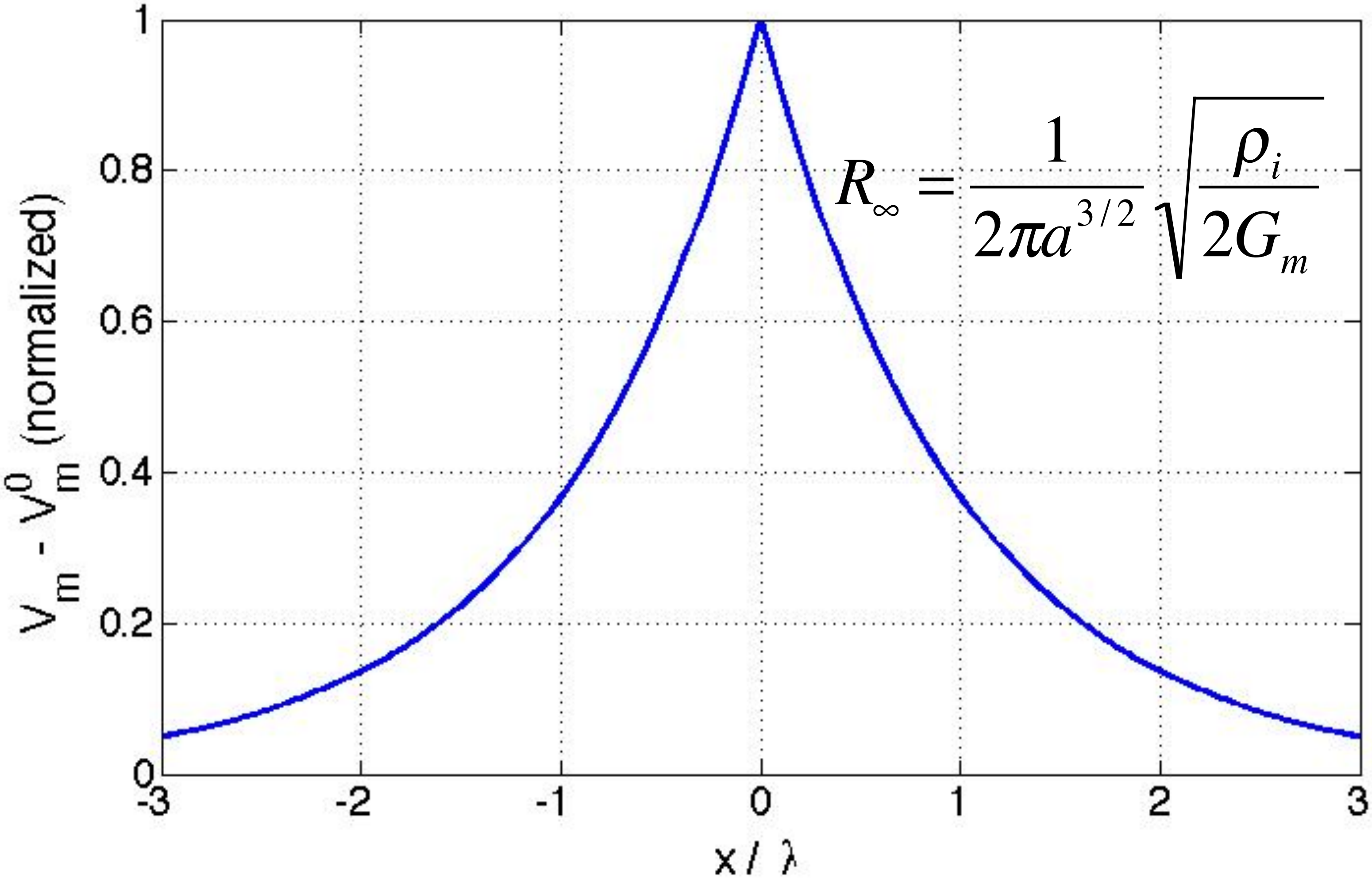
Cable theory

$$\lambda^2 \frac{\partial^2 V_m}{\partial x^2} = \tau_m \frac{\partial V_m}{\partial t} + V_m(x,t) - V_m{}^0$$

$$\lambda = \sqrt{\frac{a}{2\rho_i G_m}} \ [=] \ \mathrm{mm}$$

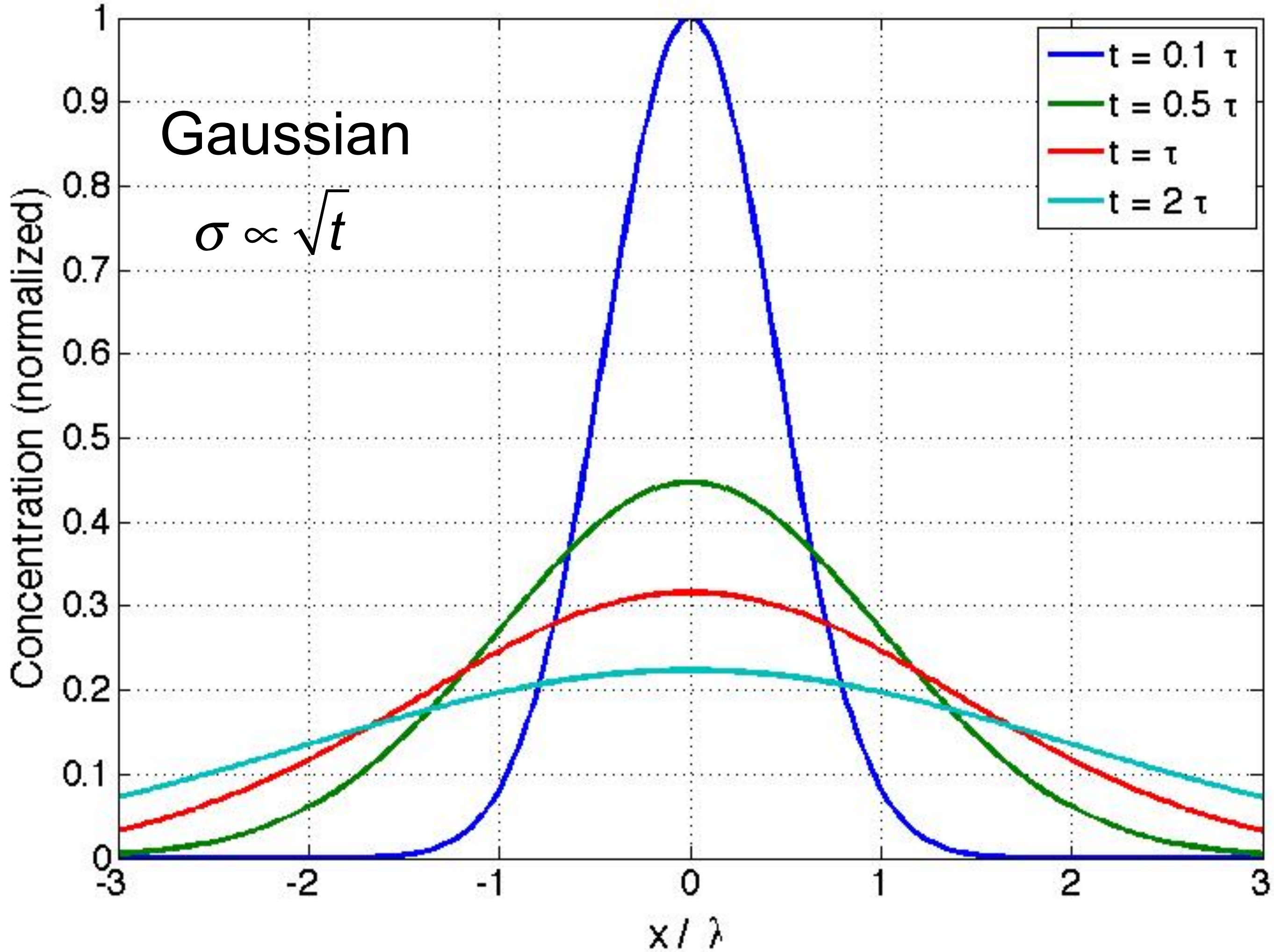
$$\tau_M = C_m / G_m \ [=] \ \mathrm{ms}$$

DC response of infinite cable

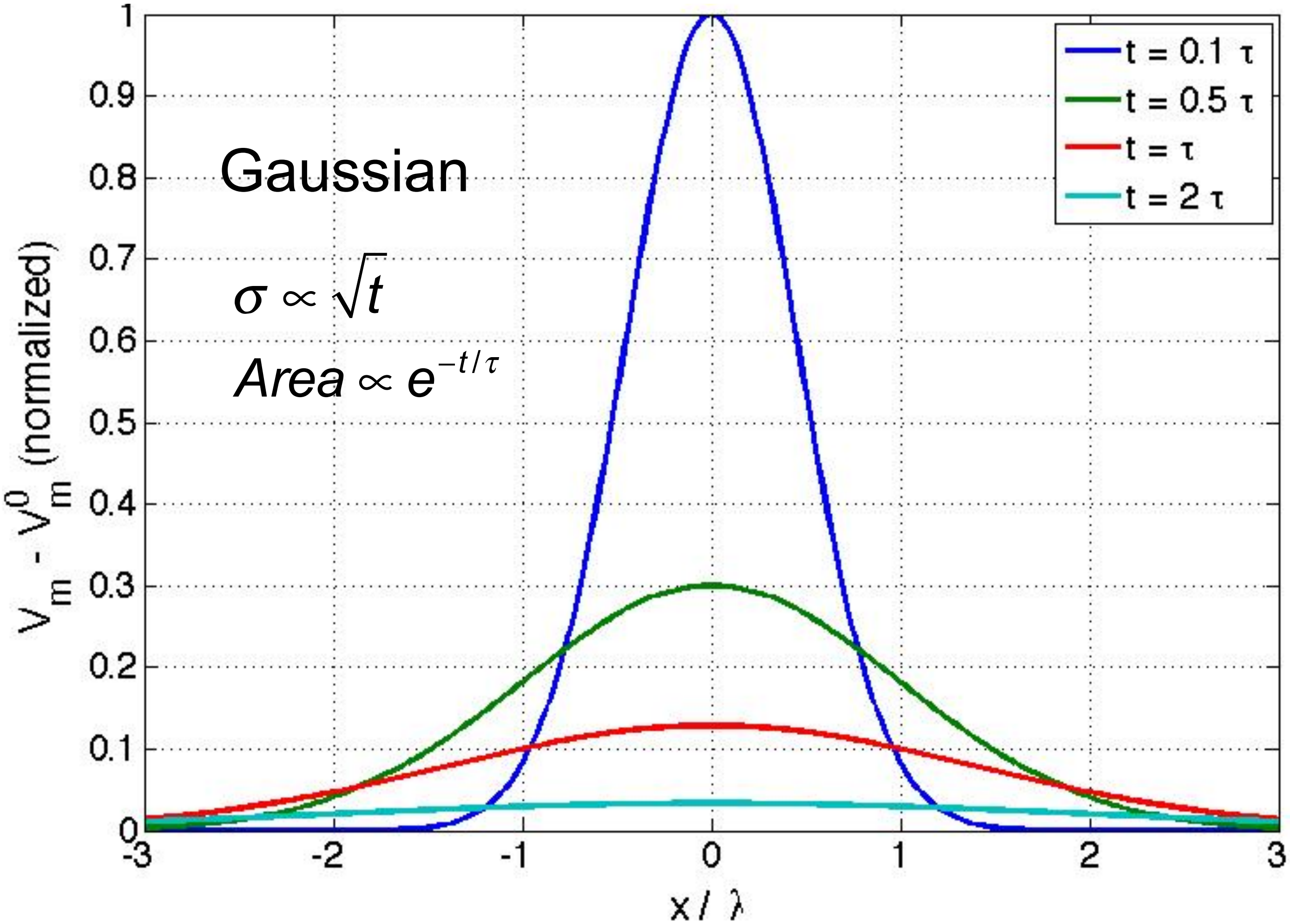


$$R_\infty = \frac{1}{2\pi a^{3/2}} \sqrt{\frac{\rho_i}{2G_m}}$$

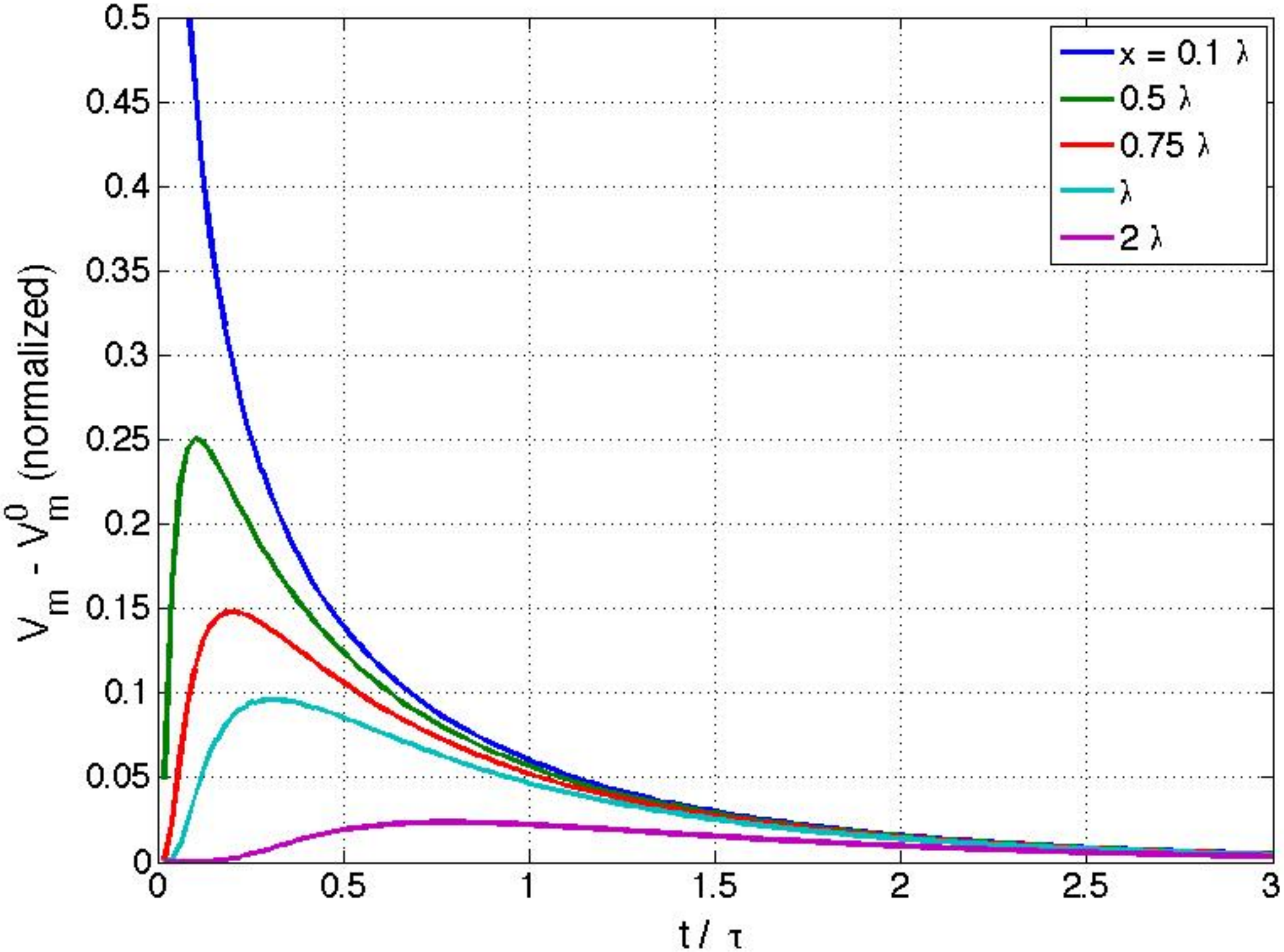
Impulse response of diffusion equation



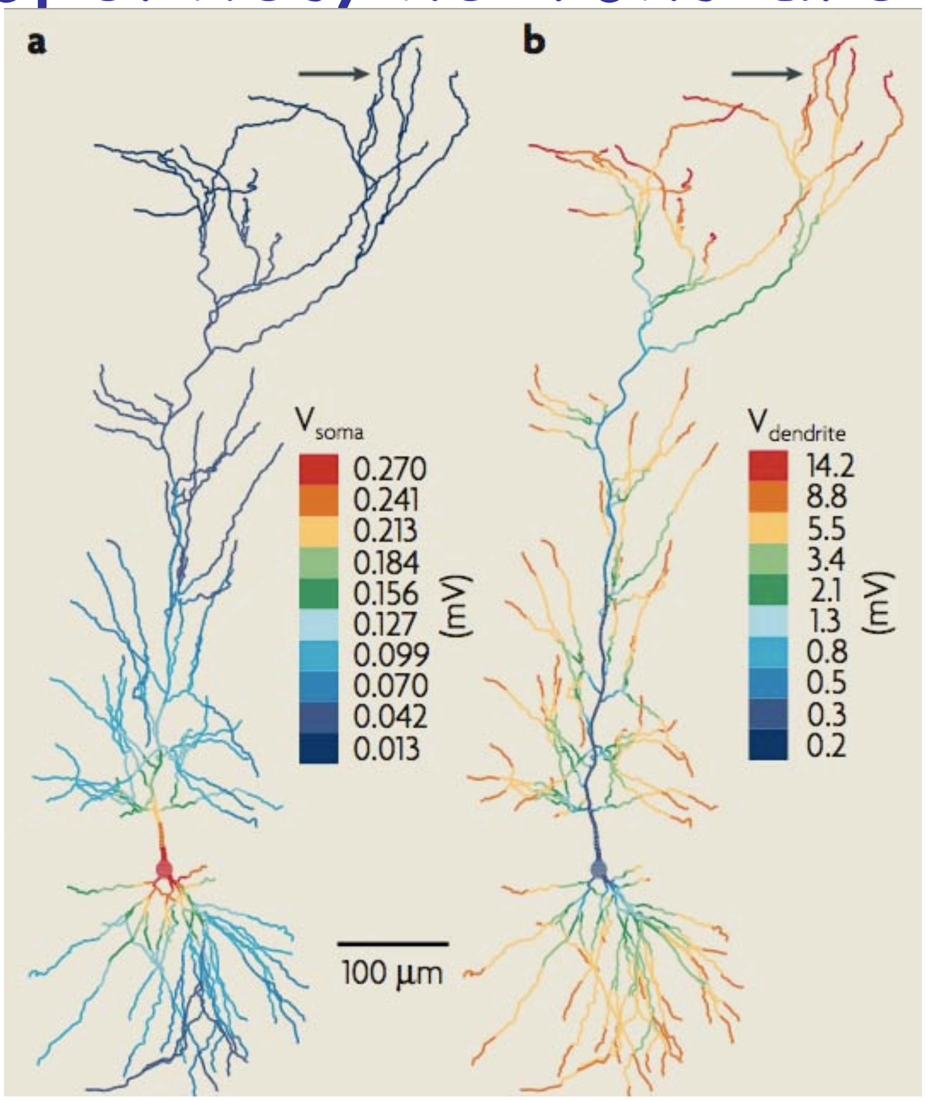
Impulse response of infinite cable



Impulse response of infinite cable

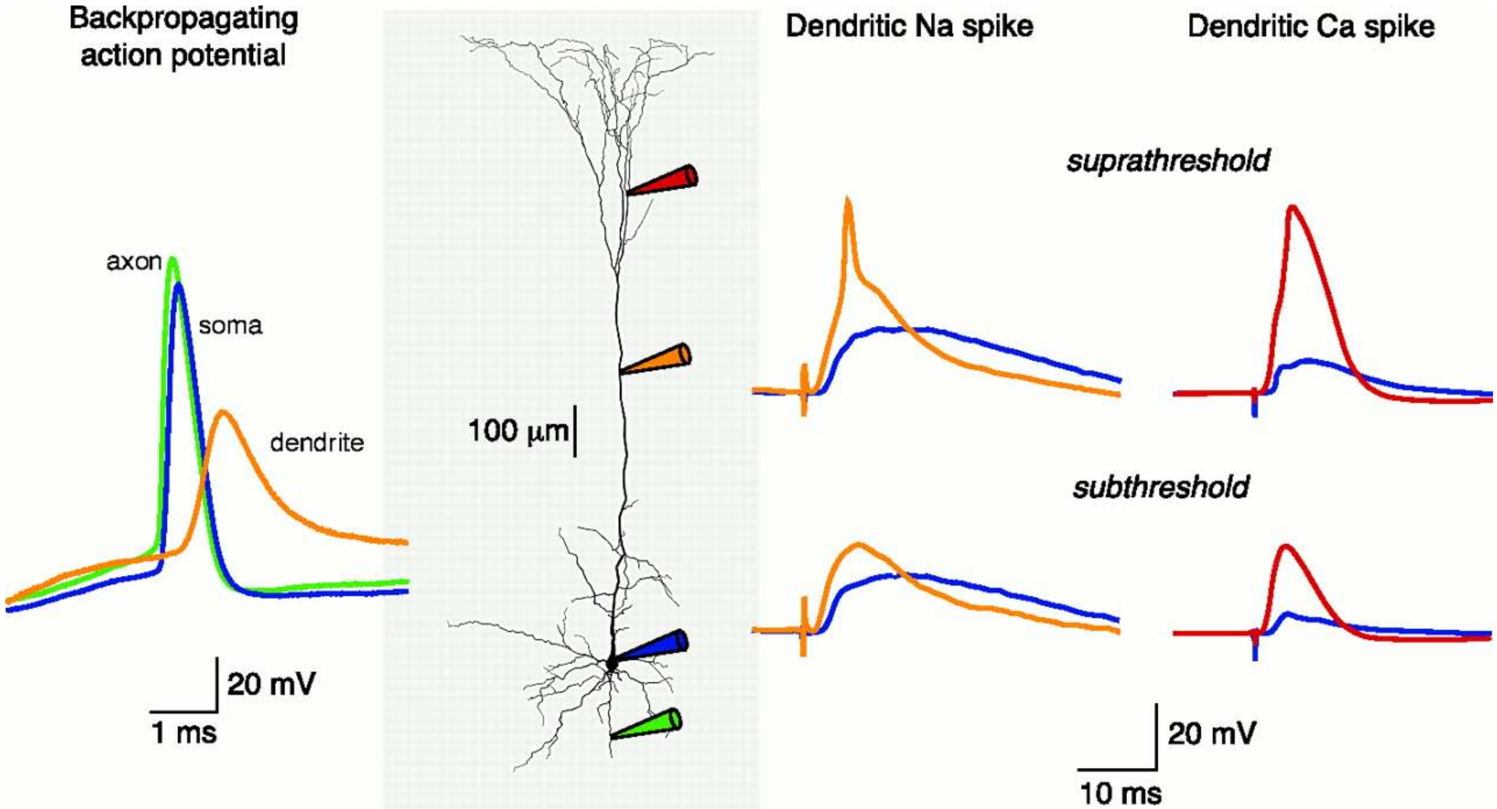


Assuming linear (passive) cable properties, neurons are very "long"



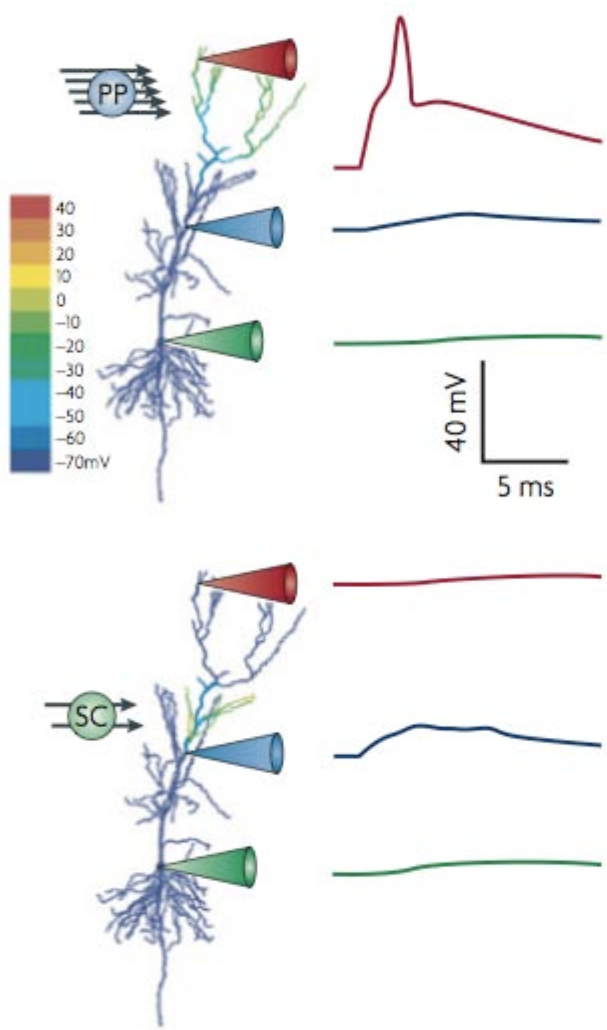
Spruston (2008) *Nature Rev Neurosci* 9: 206-221

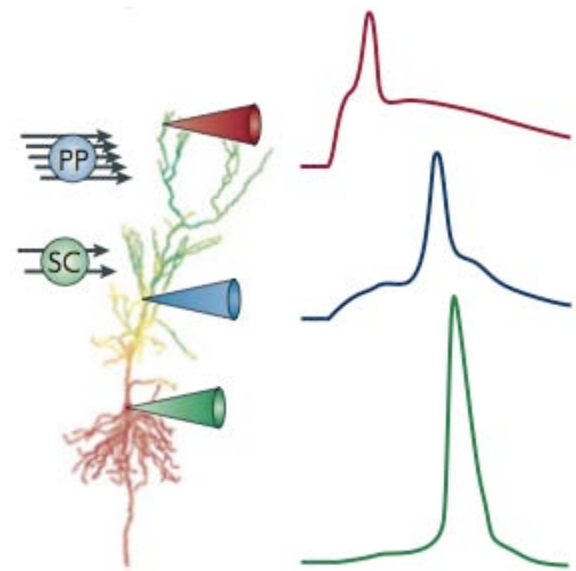
Dendrites are highly nonlinear



Häusser, Spruston, Stuart (2000) *Science* 290: 739-744

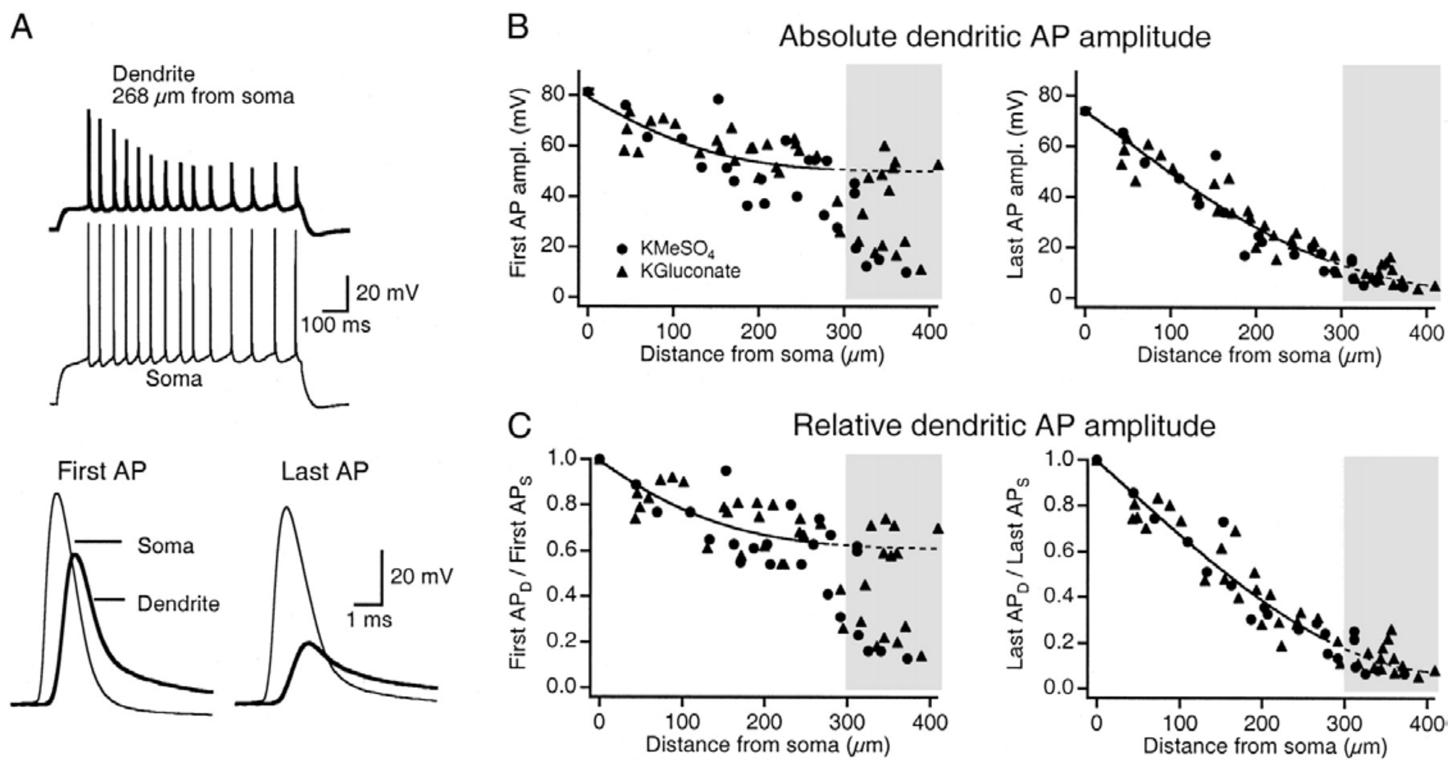
Dendritic spikes may propagate only when coincident with more proximal inputs





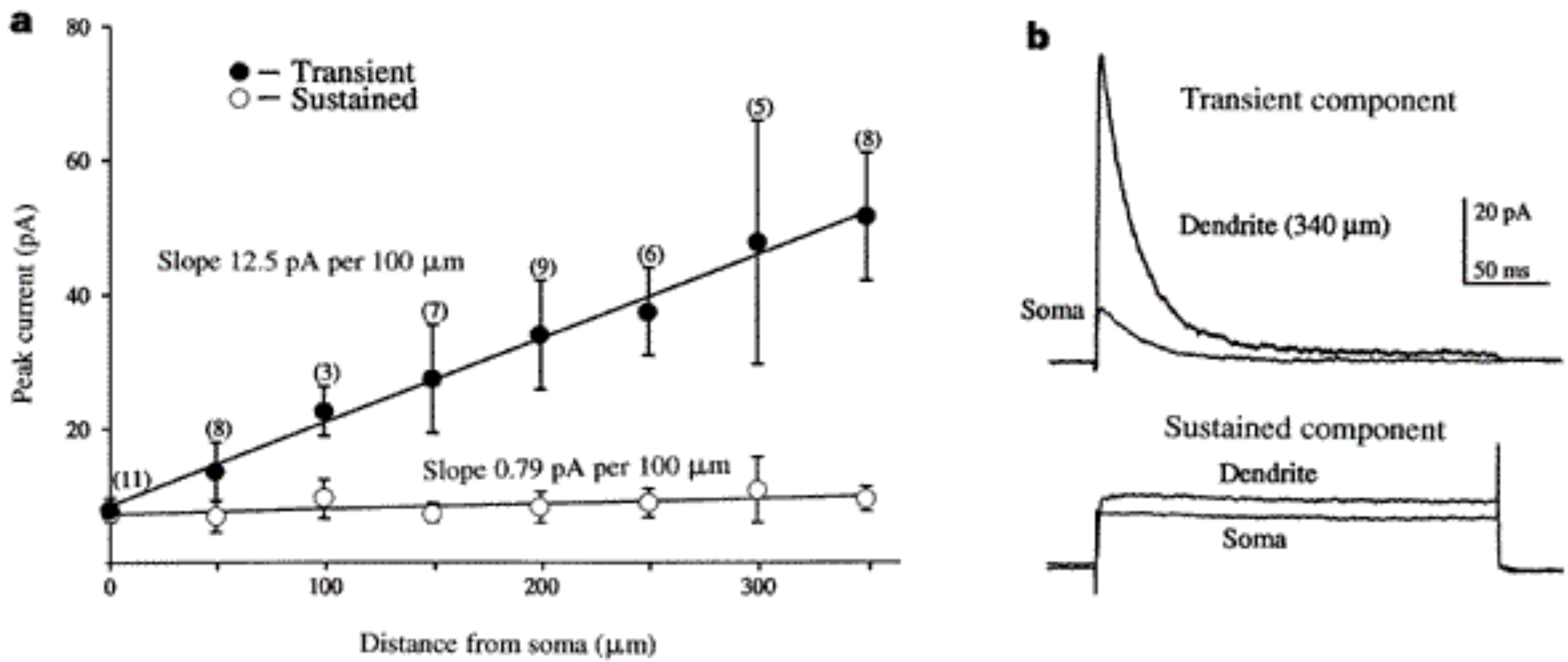
Spruston (2008)
Nature Rev Neurosci 9: 206-221

Back-propagating APs



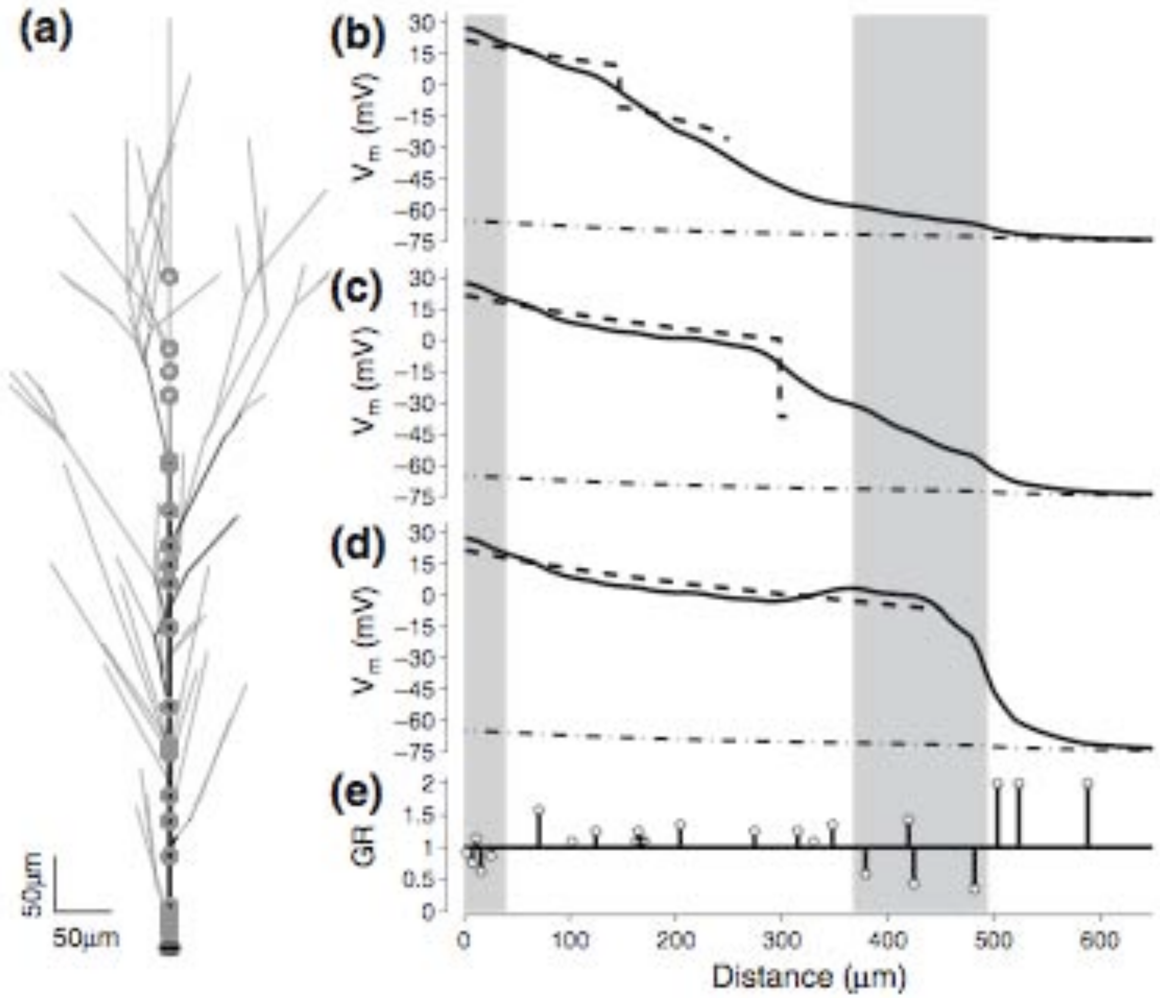
Golding et al.(2001) *J Neurophysiol* 86: 2998-3010

K^+ channel density grows with distance from the soma



Hoffman et al. (2001) *J Neurophysiol* 86: 2998-3010

Modeling bAPs



Acker and White (2007) *J Comput Neurosci* 23: 201-216