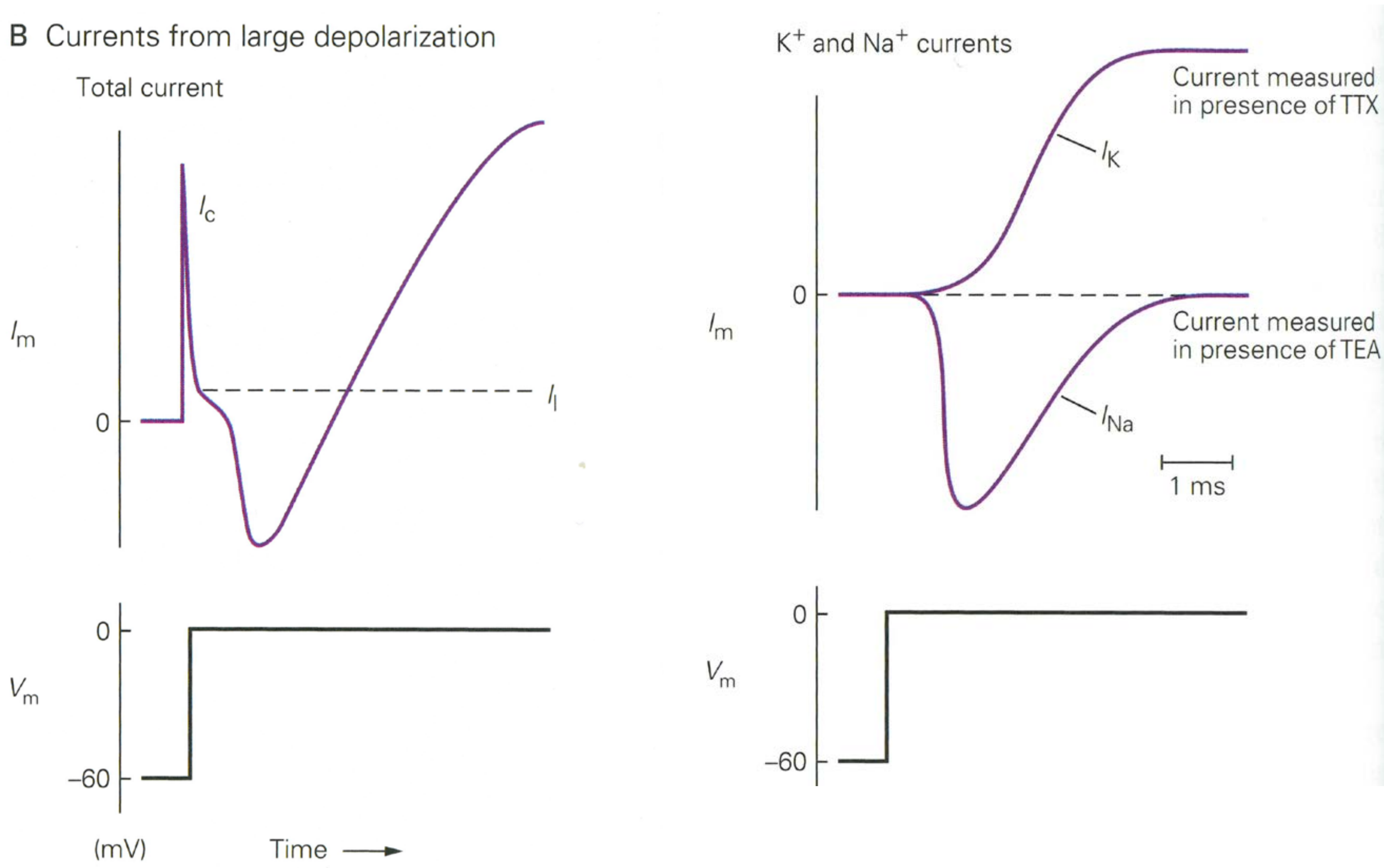
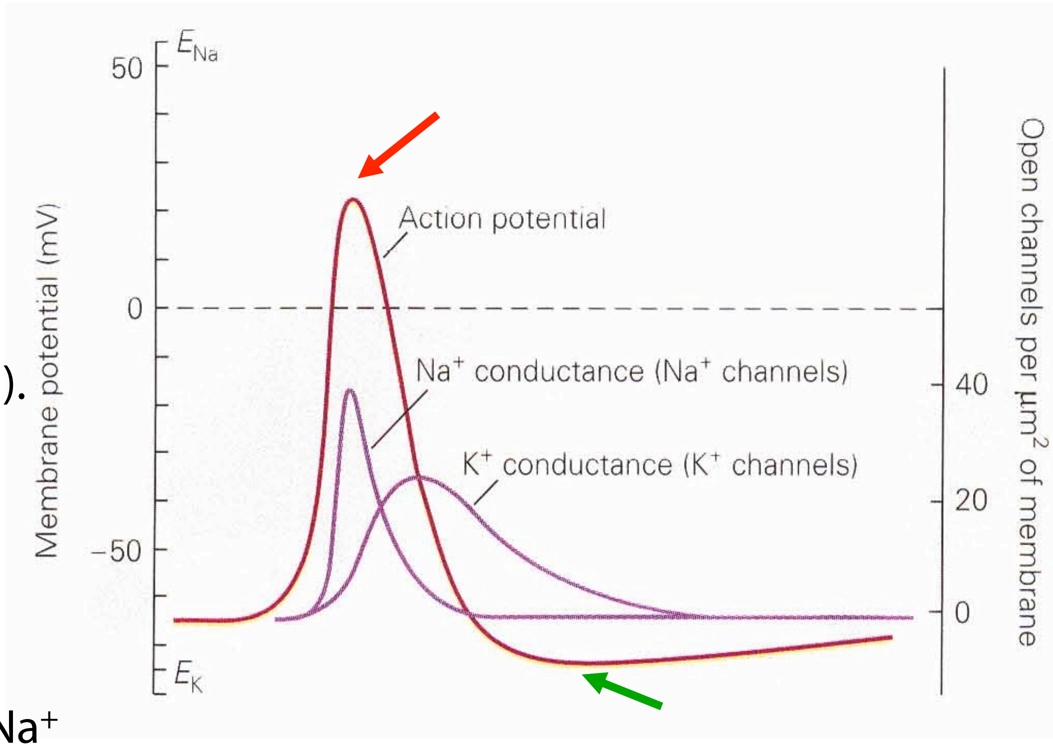
Propagated Signaling: Action Potential 2

Action Potential Currents

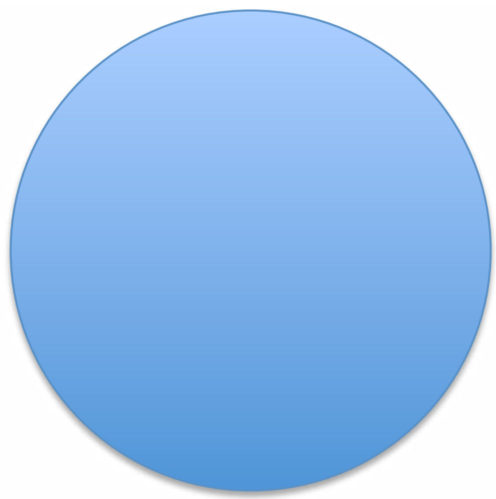


Hodgkin-Huxley Measurements & Model Explain APs

1) Depolarization event.
2) Na^+ channels open fast (g_{Na} **UP**).
3) Inward Na^+ current.
4) Further depolarization.
5) Further Na^+ channels open.
6) Positive feedback continues…
7) $V_m \Rightarrow E_{Na}$.
8) Na^+ channels inactivate (g_{Na} **DOWN**).
9) K^+ channels start opening (g_K **UP**).
10) Outward current decreases V_m.
11) $V_m \Rightarrow E_K$. Hyperpolarizes beyond resting potential (*after potential*).
12) Absolute refractory period (due to Na^+ inactivation).
13) Relative refractory period (due to increased opening of K^+).



How do APs change the concentration of ions?



- Membrane C = 1 μF/cm^2
- Charge of *e*=1.6e-19 Couloumbs
- Q=CV
- ions/mol= 6.02e23

Ionic species J	Outside (mM)	Inside (mM)	E_j (mV)
Na^+	145	12	+67
K^+	4	155	-98
Ca^{++}	1.5	10^{-4}	+129
Cl^-	123	4.2	-90

- Neuron volume = 7,000 μm^3
- Neuron surface area = 20,000 μm^2

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2775381

What about Ca^{++}

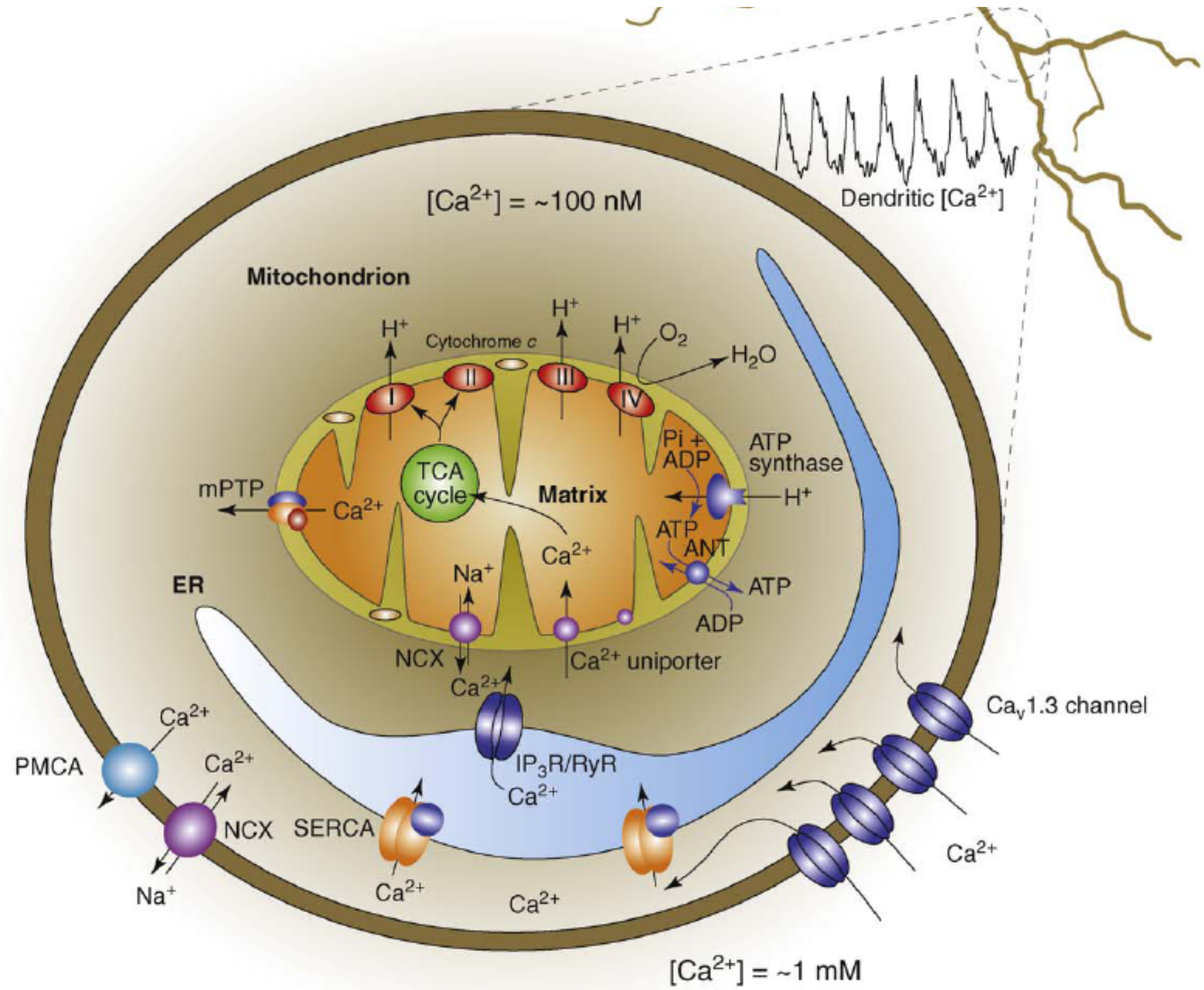
Ionic species J	Outside (mM)	Inside (mM)	E_j (mV)
Na^+	145	12	+67
K^+	4	155	-98
Ca^{++}	1.5	10^{-4}	+129
Cl^-	123	4.2	-90

- Ca^{++} inside the neuron is 4 orders of magnitude smaller than outside.
- Ca^{++} is important for intracellular signaling

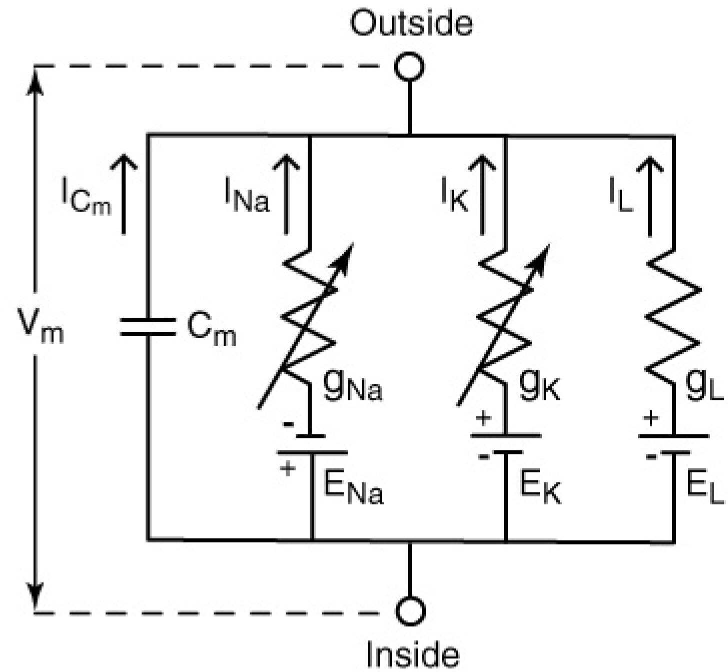
How do neurons regulate intracellular Ca^{++} concentrations?

Ca++ homeostasis

- When Ca++ enters the cell, *microdomains* occur near the membrane (important for signaling)
- The Ca++ rapidly binds to proteins (such as calmodulin) or is sequestered by the ER and mitochondria
- For every 100-1000 Ca++ ions entering the cell, on average one ion “remains free”
- Eventually the Ca++ is extruded by Ca++ ATPases (PMCA) or Na+/Ca+ countertransporters



Hodgkin-Huxley Equations



$$i_m = i_C + i_l + i_{Na} + i_K$$

where,

$$i_l = g_l(V_m - E_l)$$

$$i_{Na} = g_{Na}(V_m - E_{Na})$$

$$i_K = g_K(V_m - E_K)$$

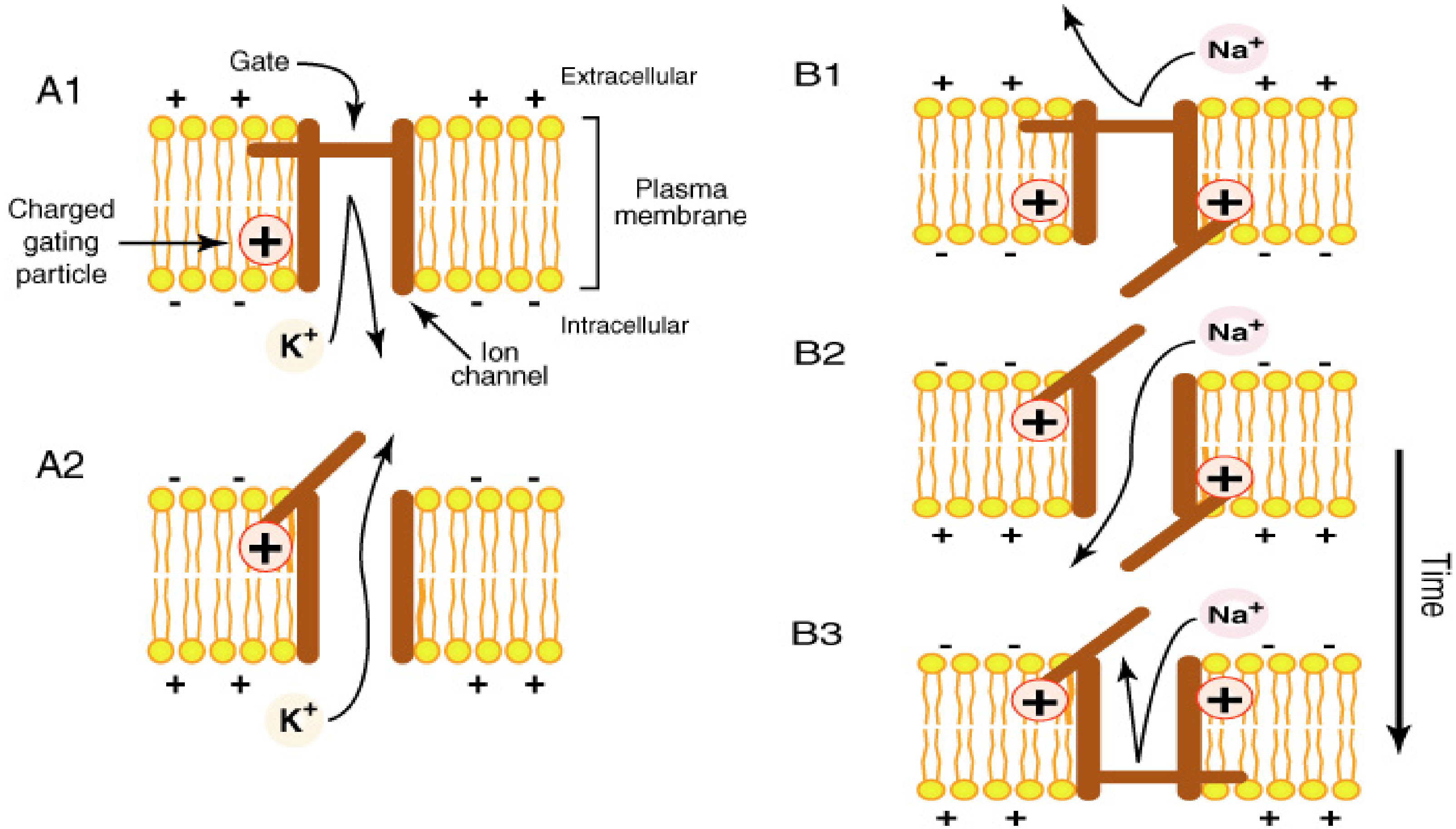
$$i_m = C_m \frac{dV_m}{dt} + g_l(V_m - E_l) + g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)$$

$$g_{Na} = \bar{g}_{Na} m^3 h$$

$$g_K = \bar{g}_K n^4$$

What are gating variables?

persistent *transient*



Modeling Gating Variables

Modeling Gating Variables

For K currents:

$$\underset{(1-n)}{\text{closed}} \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} \underset{n}{\text{open}}$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

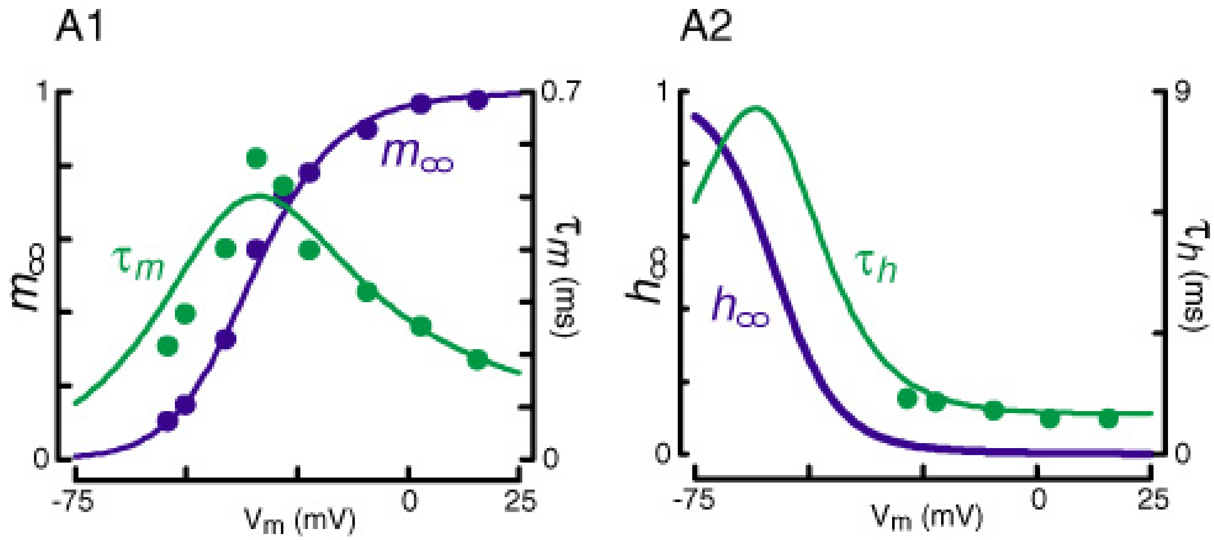
$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n \qquad \tau_n = \frac{1}{\alpha_n + \beta_n}$$

$$n = n_\infty - (n_\infty - n_0)^{e^{-t/\tau_n}} \qquad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$$

Refer to TCN Ch. 5

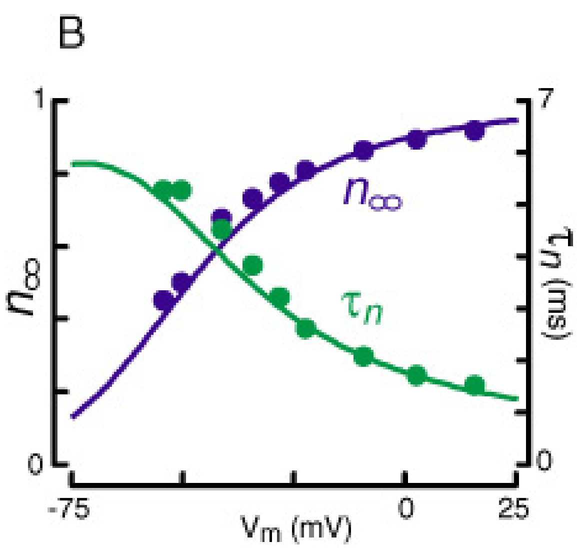
Voltage Dependence of Gates

Na current

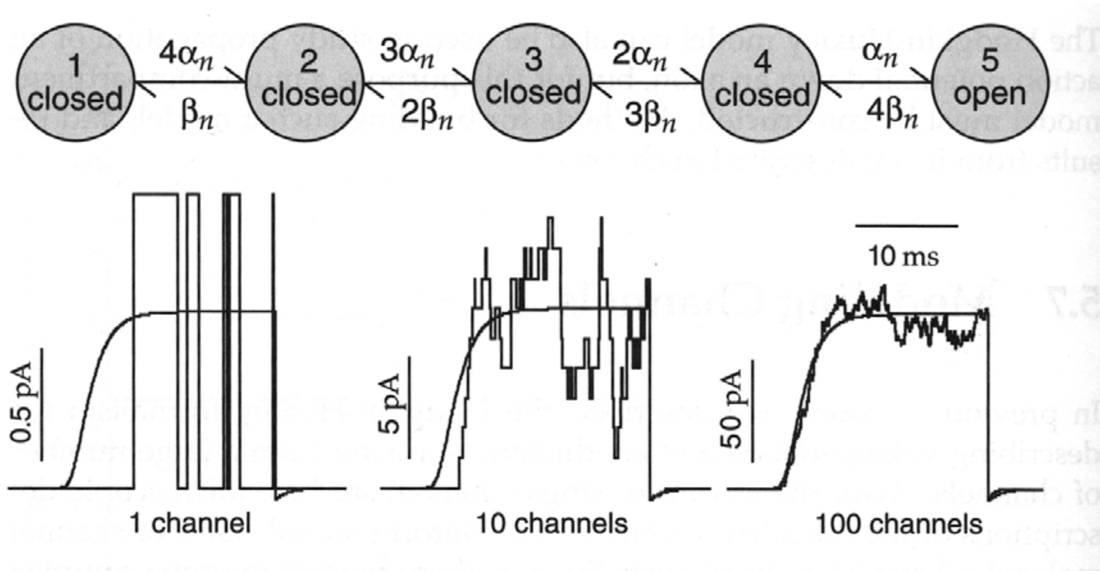


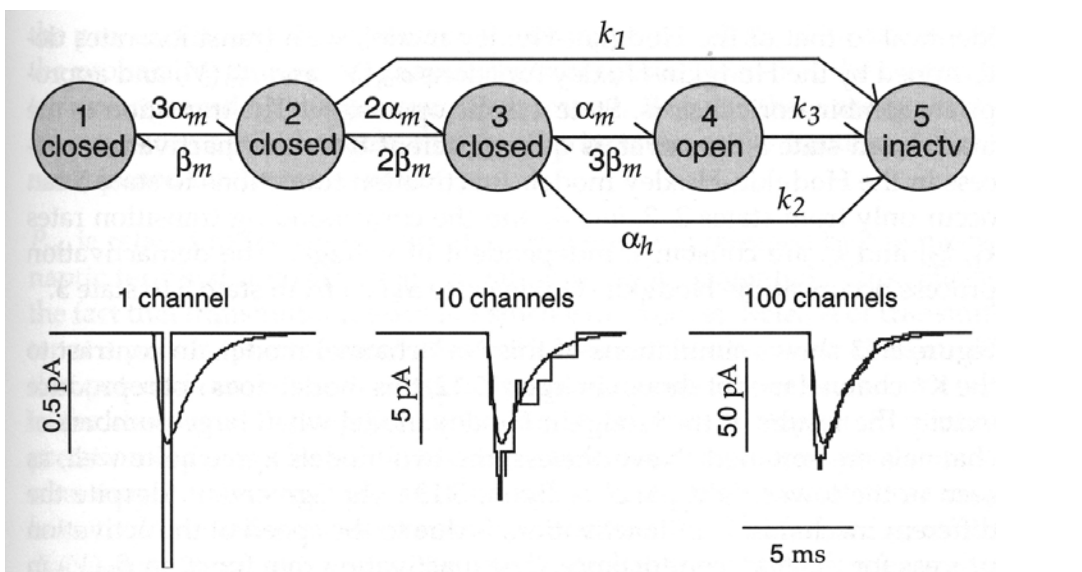
K current

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \qquad \tau_n = \frac{1}{\alpha_n + \beta_n}$$

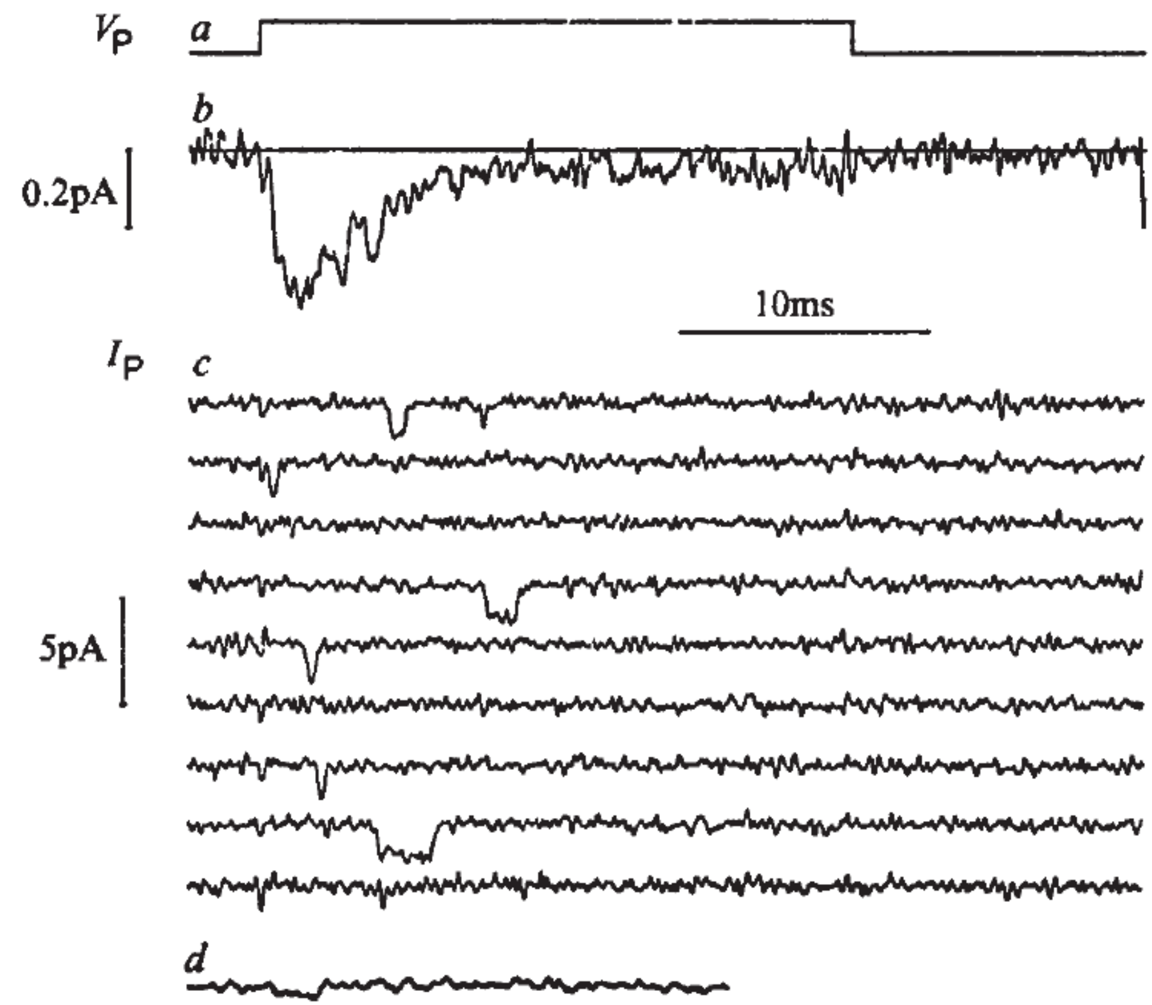


Markovian Single Channels





Markovian Single Channels



Modern models

- (Multi-compartment)
- Model reduction
- Integrate and fire (pasted spikes)
- Izhikevitch (dynamical system)

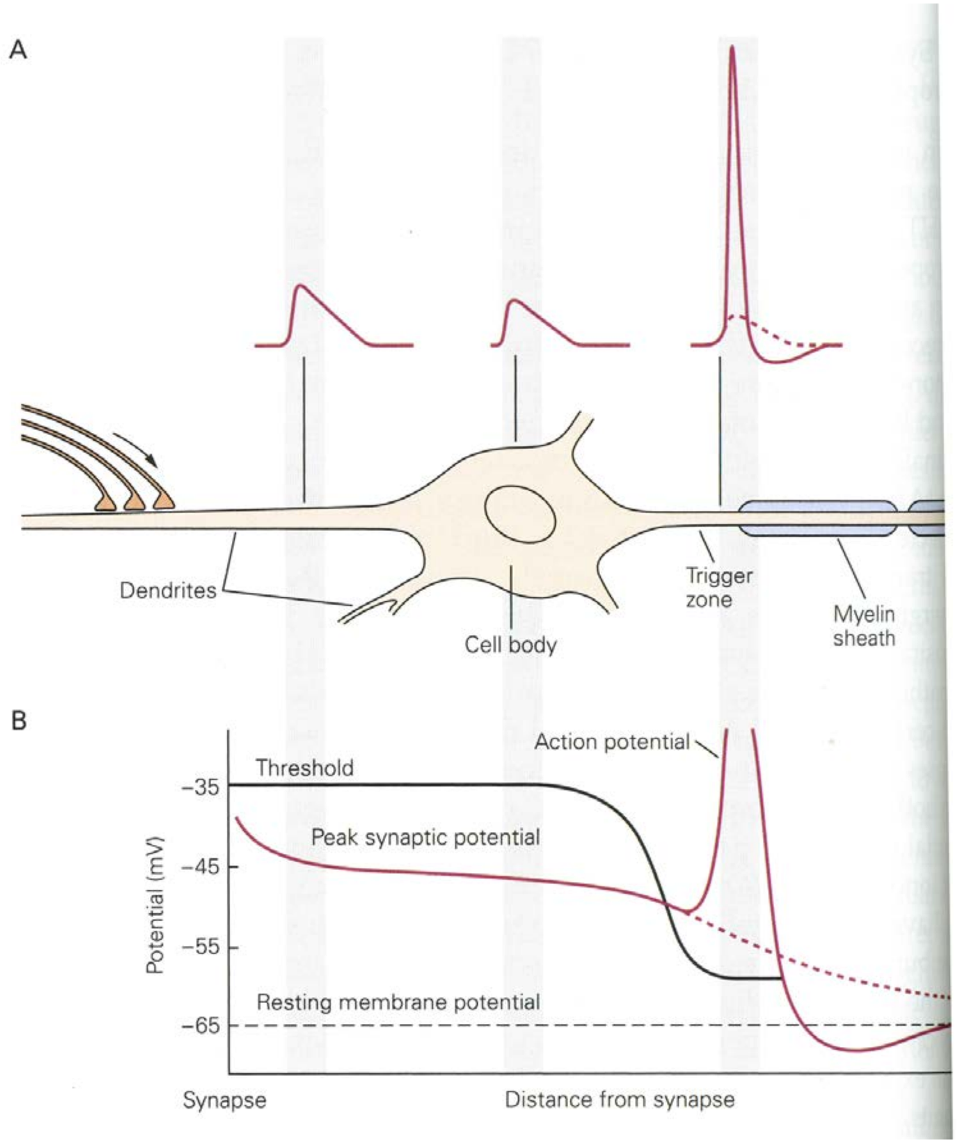
What triggers action potentials and how do they propagate?

Axon Hillock / Initial Segment

- What is the effect on the threshold of an increase in the density of voltage gated Na+ channels?

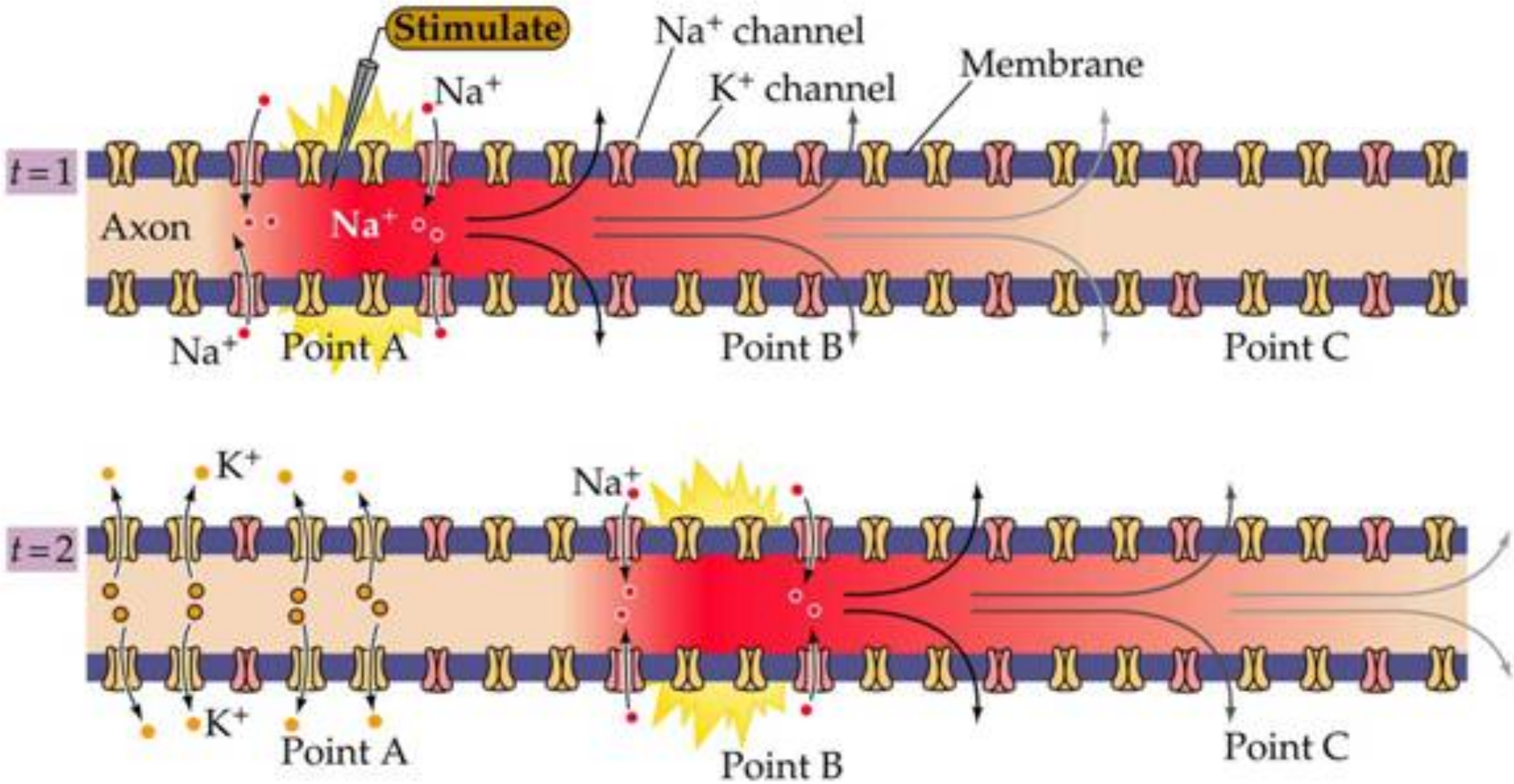
Axon Hillock / Initial Segment

- Has lower threshold, triggering AP propagation down axon.



How do APs move on axons?

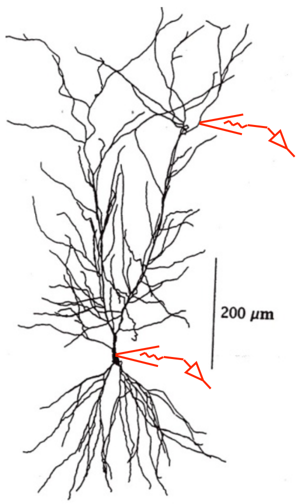
Action Potentials Propagate

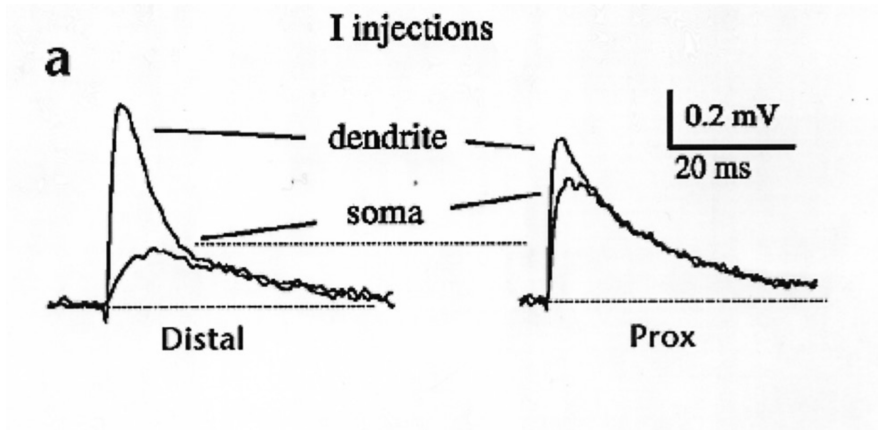


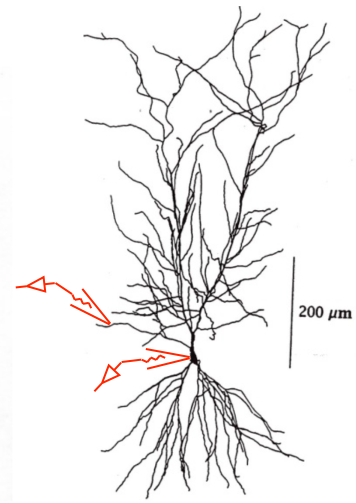
Synaptic Currents

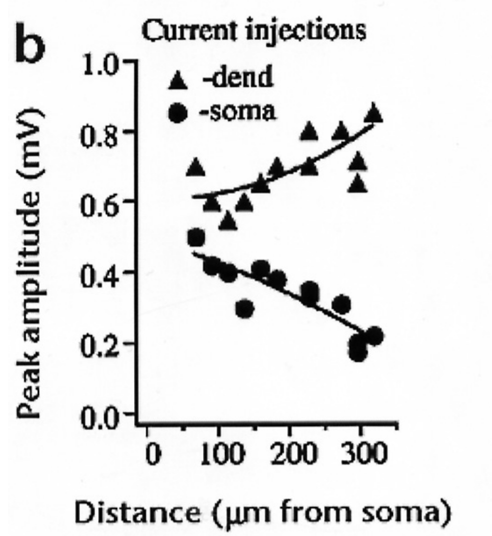
Effect of the Dendritic Cable

Neurons are not spherical nor just a single RC Compartment





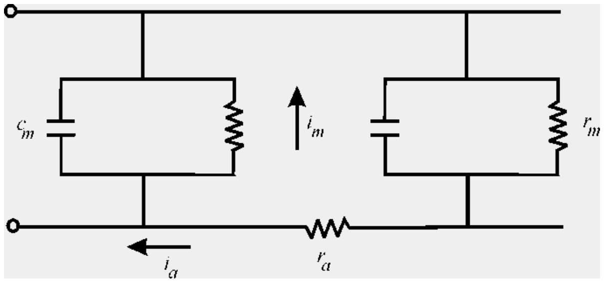


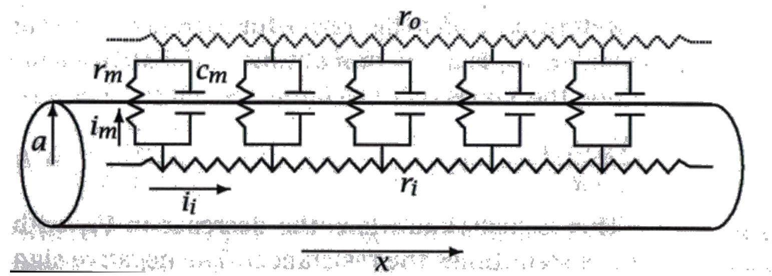


Nature Neurosci 3:895

Modeling Dendrites (Cable Equation)

The Cable Equation





r_a Axial resistance of unit length cable

r_m Membrane resistance of unit length cable

c_m Membrane capacitance of unit length cable

$$R_a = \pi a^2 r_a$$

$$R_m = 2\pi a r_m$$

$$C_m = \frac{c_m}{2\pi a}$$

Typical values for a neuron $R_a = 100\ \Omega\text{cm}$, $R_m = 10^4 \sim 10^5\ \Omega\text{cm}^2$, $C_m = 10^{-6}\ \text{F/cm}^2$

The Cable Equation

Assumptions:

1) The electrical components are assumed to be linear and constant throughout the length of the fiber
2) The voltage drop due to radial current flow within the axoplasm is negligible.
3) The extracellular resistance to current flow is 0

Axial $\Delta V = -i_a r_a \Delta x$ $\frac{\partial V}{\partial x} = -i_a r_a$

Radial $\Delta i_a = -i_m \Delta x$ $\frac{\partial i_a}{\partial x} = -i_m = -c_m \frac{\partial V}{\partial t} - \frac{V_m}{r_m}$ since $i_m = c_m \frac{\partial V}{\partial t} + \frac{V_m}{r_m}$

Plugging the axial equation into the radial one yields:

$$\frac{1}{r_a}\frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m}$$

Rearranging:

$$\frac{r_m}{r_a}\frac{\partial^2 V}{\partial x^2} - c_m r_m \frac{\partial V}{\partial t} - V = 0$$

Or:

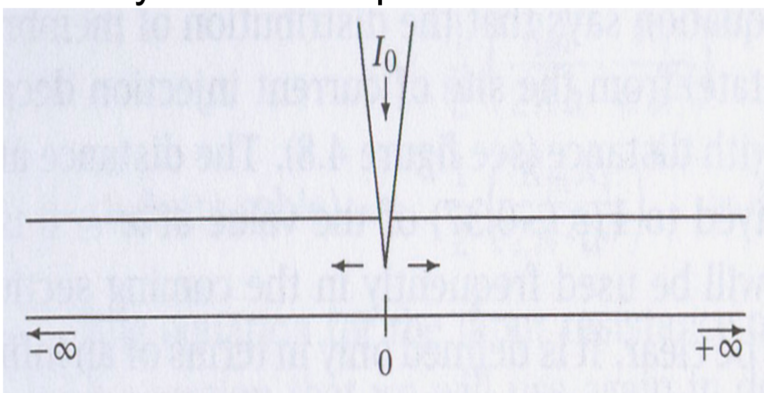
$$\lambda^2 \frac{\partial^2 V}{\partial x^2} - \tau_m \frac{\partial V}{\partial t} - V = 0$$

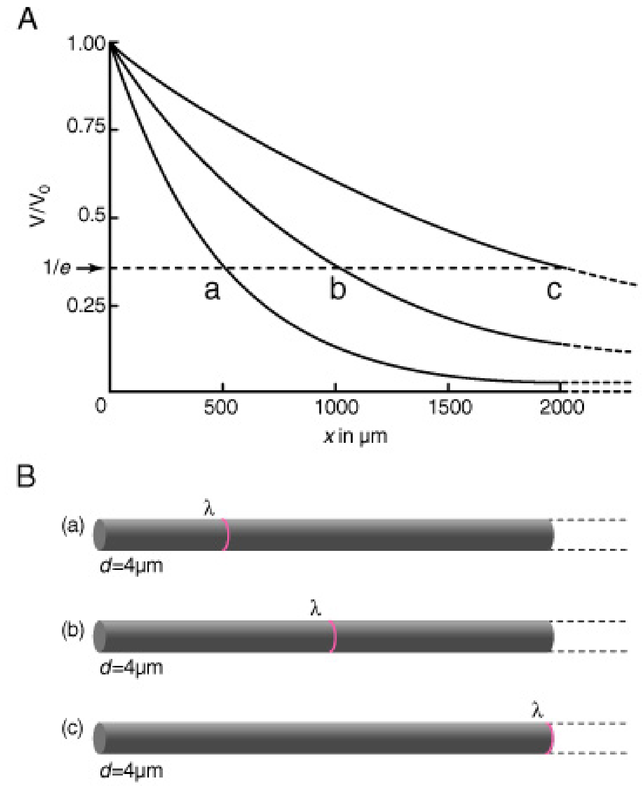
Where:

$$\tau_m = r_m c_m = R_m C_m \qquad \lambda = \sqrt{\frac{r_m}{r_a}} = \sqrt{\frac{R_m a}{2R_a}}$$

Solutions to the Cable Equation: Length Dependence

Steady State for a point current source I_0 applied to X=0 to an Infinite Length Cable





$$\lambda^2 \frac{\partial^2 V}{\partial x^2} - \tau_m \frac{\partial V}{\partial t} - V = 0$$

$$V(T,X) = \frac{\lambda r_a I_o}{4}\left[\exp(-X)\,erfc\left(\frac{X}{2\sqrt{T}} - \sqrt{T}\right) - \exp(X)\,erfc\left(\frac{X}{2\sqrt{T}} + \sqrt{T}\right)\right]$$

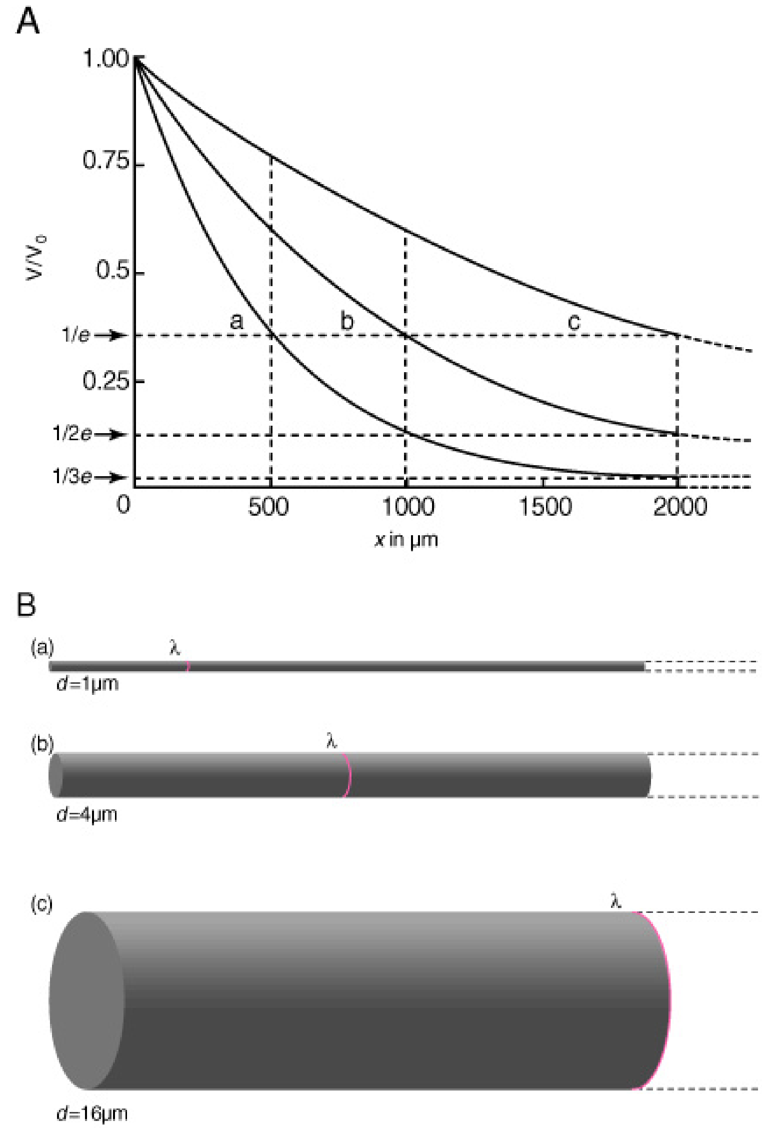
$$X \equiv \frac{x}{\lambda}; T \equiv \frac{t}{\tau}$$

at steady state the time derivative is 0

$$V = \frac{r_a I_0 \lambda}{2} e^{-\frac{x}{\lambda}}$$

Thickness Dependence

$$\lambda = \sqrt{\frac{r_m}{r_a}} = \sqrt{\frac{R_m a}{2R_a}}$$



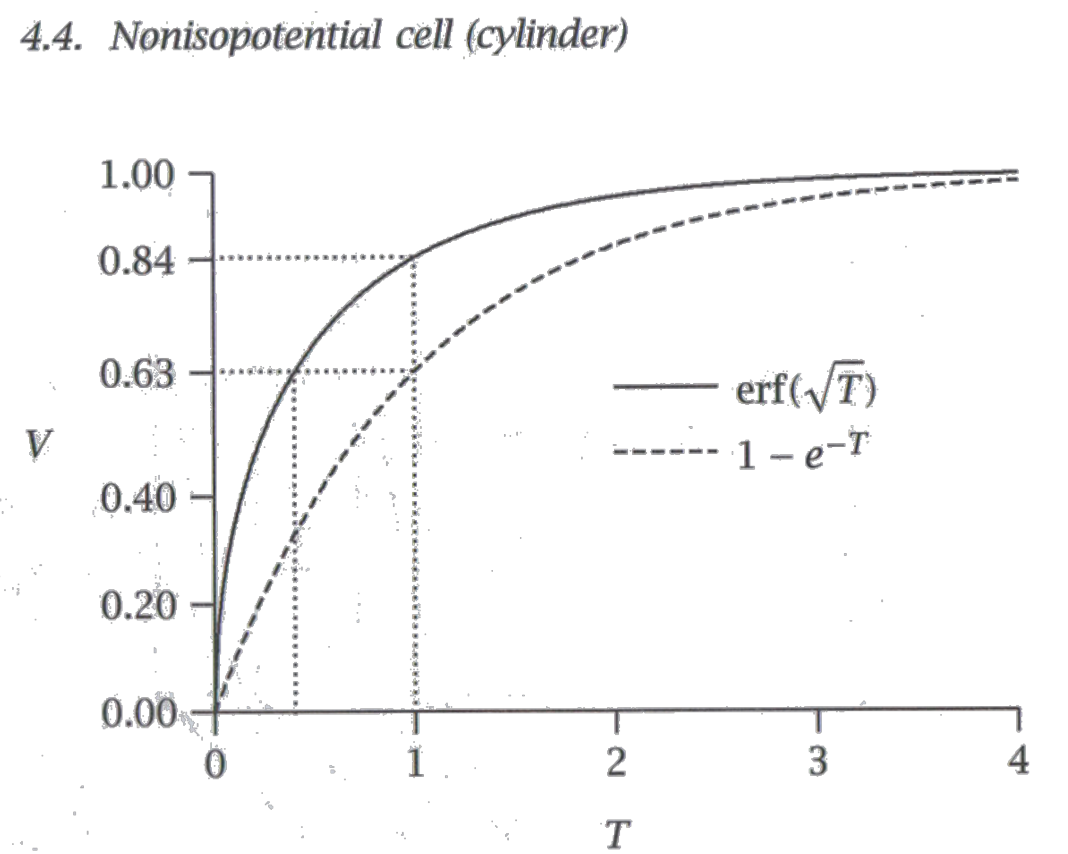
Characteristic length

Where a is the radius of the process, or d/2

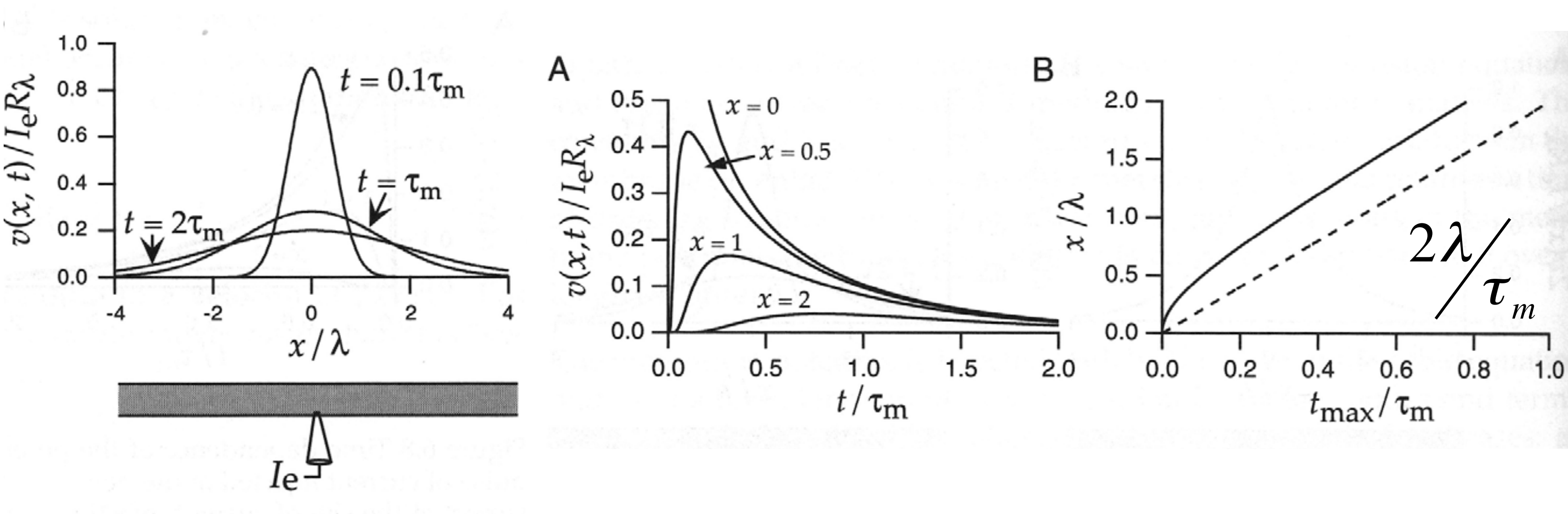
Time Dependence

$$V(T,0) = \frac{\lambda r_a I_o}{2} erf(\sqrt{T})$$

at X=0



Time and Space



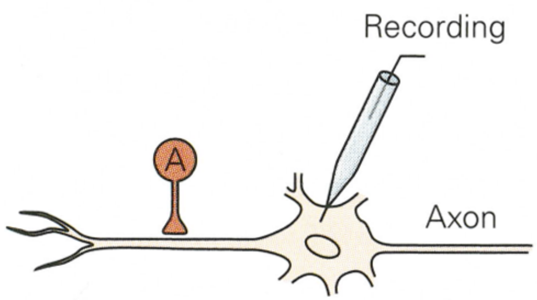
- How will the size of the dendritic process affect speed of conduction?

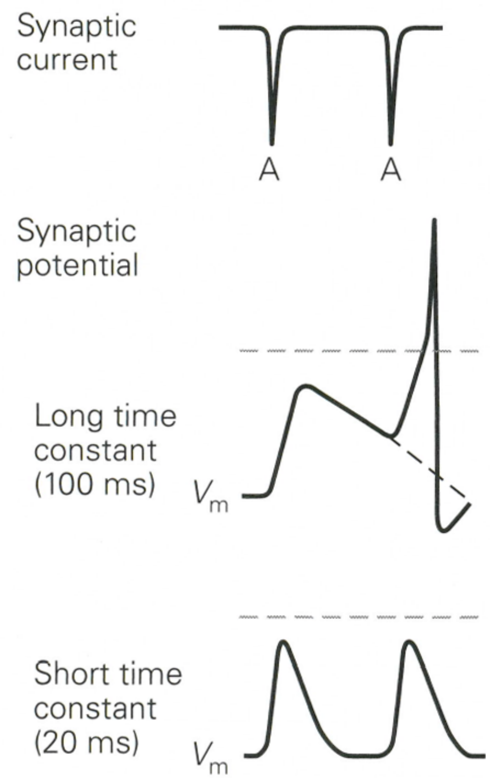
How do neurons actually compute?

- Temporal summation

- Spatial summation

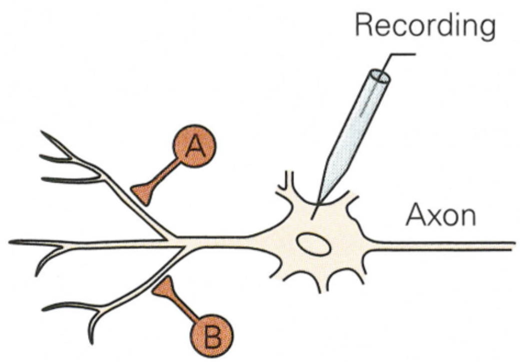
Temporal Summation

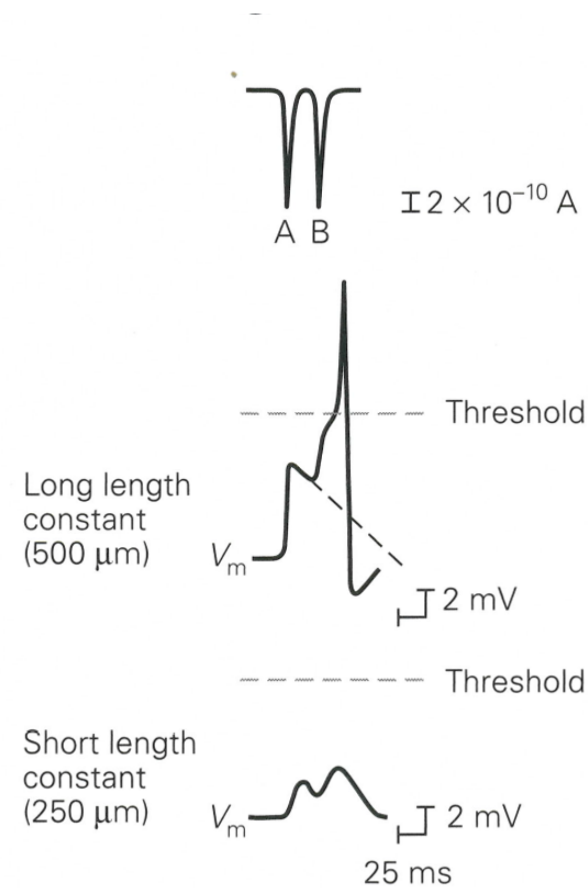




- Consecutive synaptic potentials are added together in the postsynaptic cell.
- Larger time constant => more likely that two consecutive inputs will summate to cross threshold.
- Time constant depends on density of resting ion channels, their conductance, membrane properties.

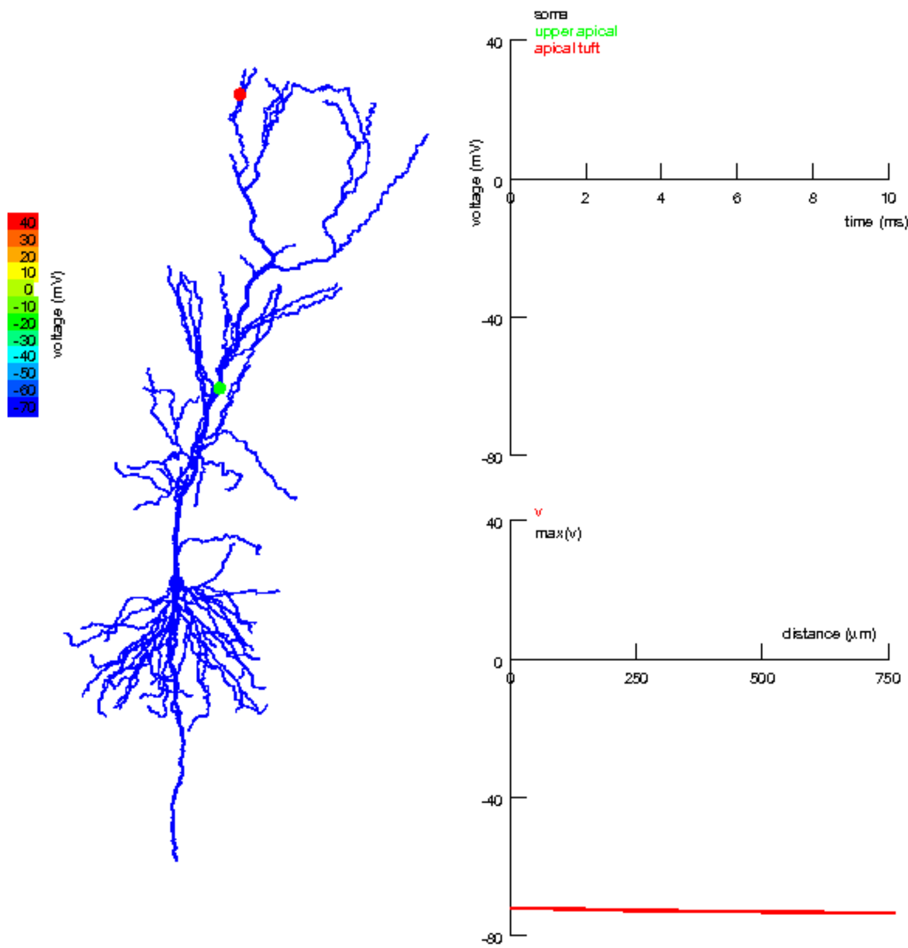
Spatial Summation





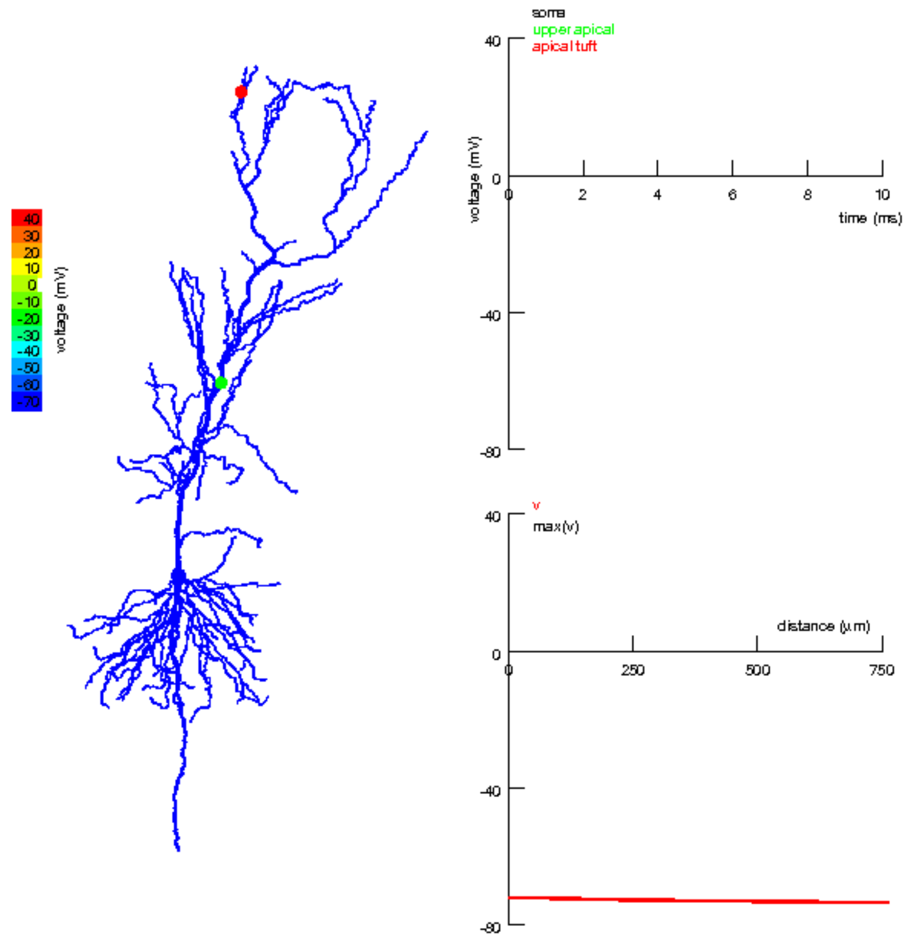
- Inputs from presynaptic neurons acting at different sites on postsynaptic neuron are added together.
- Larger length constant => signals do not rapidly decay with distance, thus 2 different inputs are more likely to bring postsynaptic neuron to threshold.
- Length constant depends on size of axons and dendrites, resistive properties of cytoplasm, density of resting ion channels, their conductance.

(No) Spatio/Temporal Summation

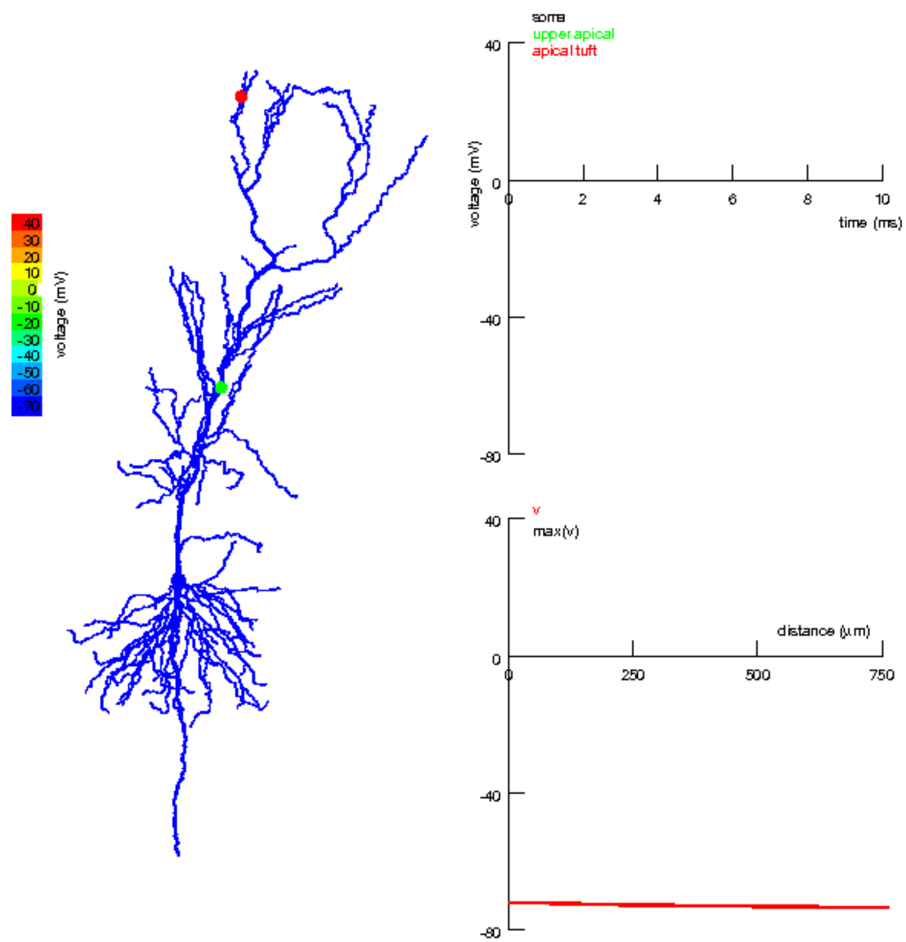


http://www.nature.com/neuro/journal/v8/n12/full/nn1599.html

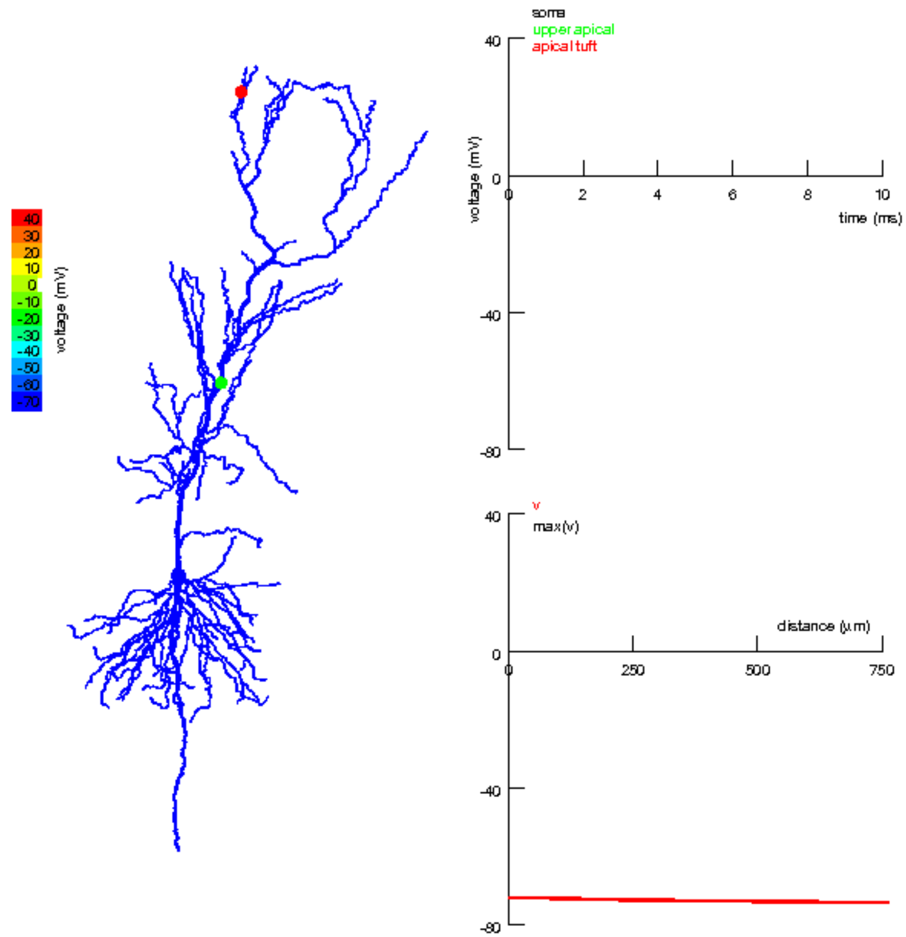
Spatio/Temporal Summation



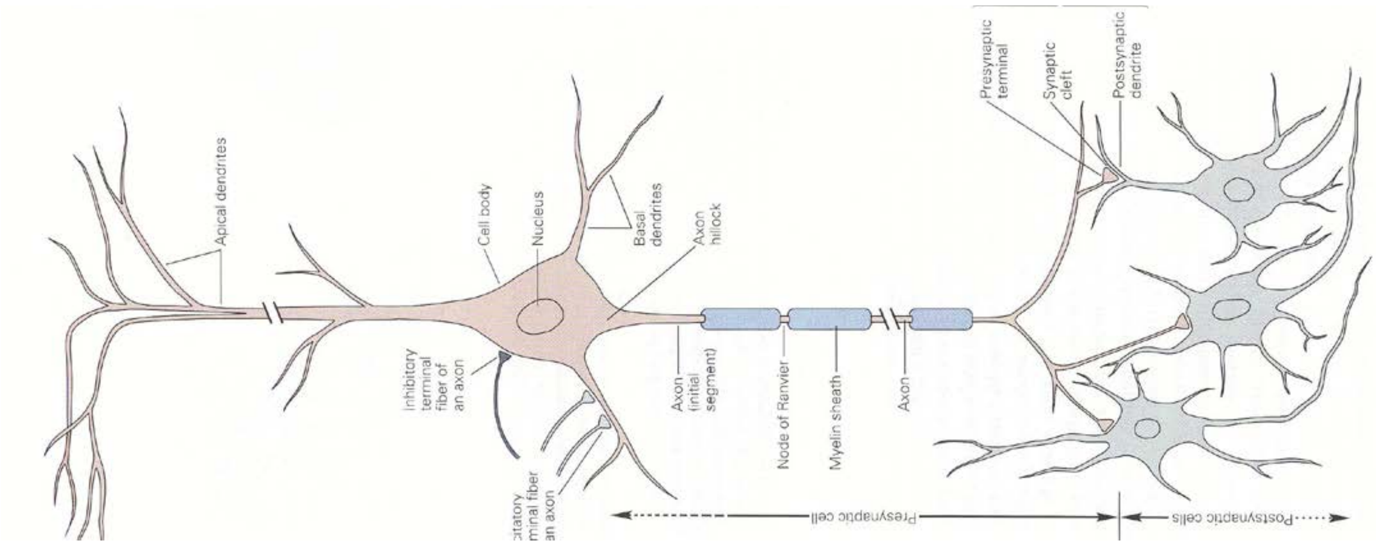
Spatio/Temporal Summation



Spatio/Temporal Summation



What happens at the other end?



Few voltage gated channels

Lots of voltage gated Na^+ channels

Lots of voltage gated Ca^{++} channels