Structure and Measurement of the brain lecture notes

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Based on slides from Flavia Filimon, 2008

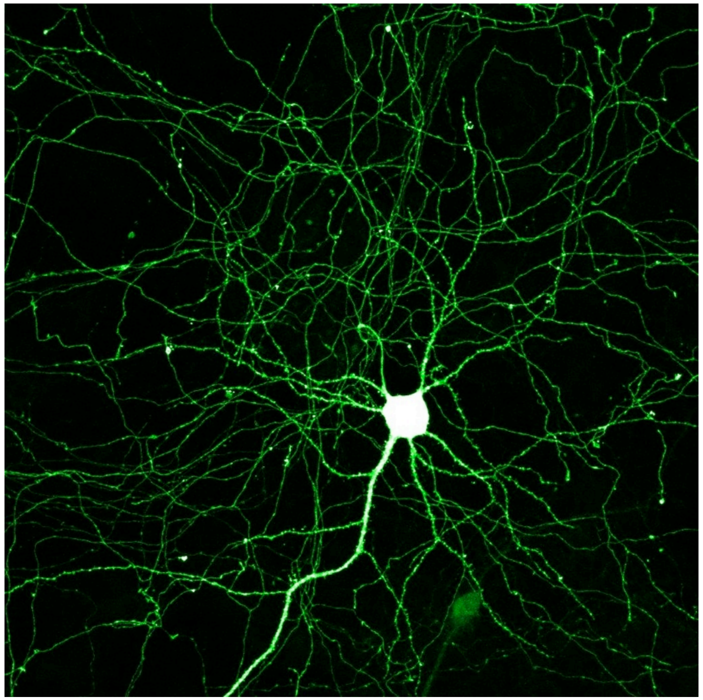
Neurons and Models

Lecture 1

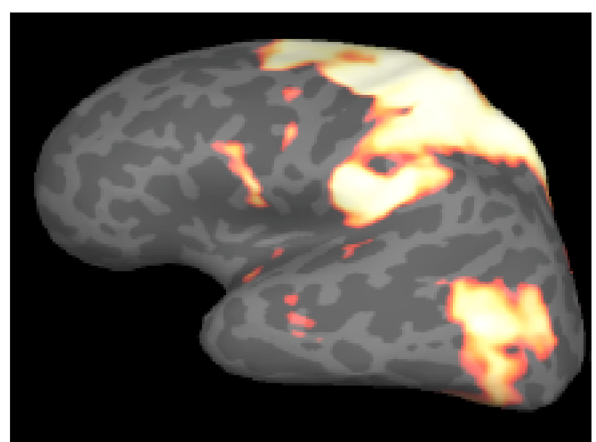
Topics

- Membrane (Nernst) Potential
- Action potential/Voltage-gated channels
- Post-synaptic potentials, ligand gated channels
- Dendritic propagation equivalent circuits
- NMDA channels and synaptic plasticity
- Spike timing dependent plasticity (STDP)

How does the brain work?

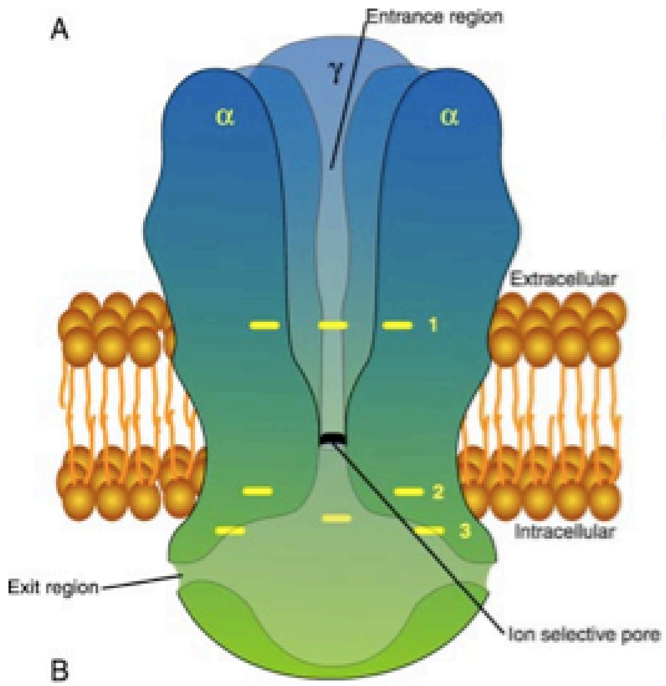


- 100 billion neurons in the human brain
- 10^{14} synapses (1000-5000 per neuron)



from molecular level
to systems level

Ion channels

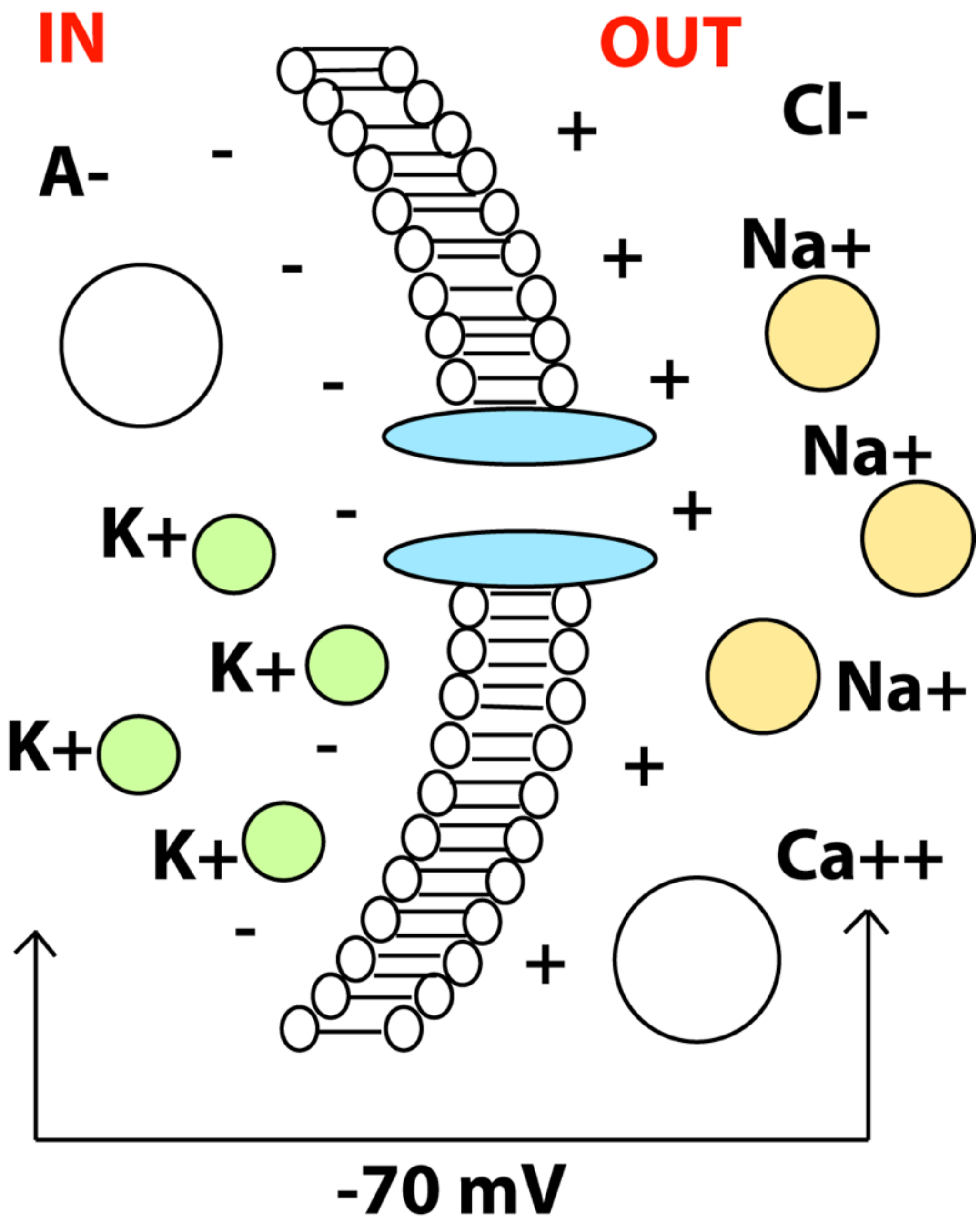


- resting (permanently open at rest)
- gated (require ligand, voltage, or mechanical stretch, to open)

Membrane Potential

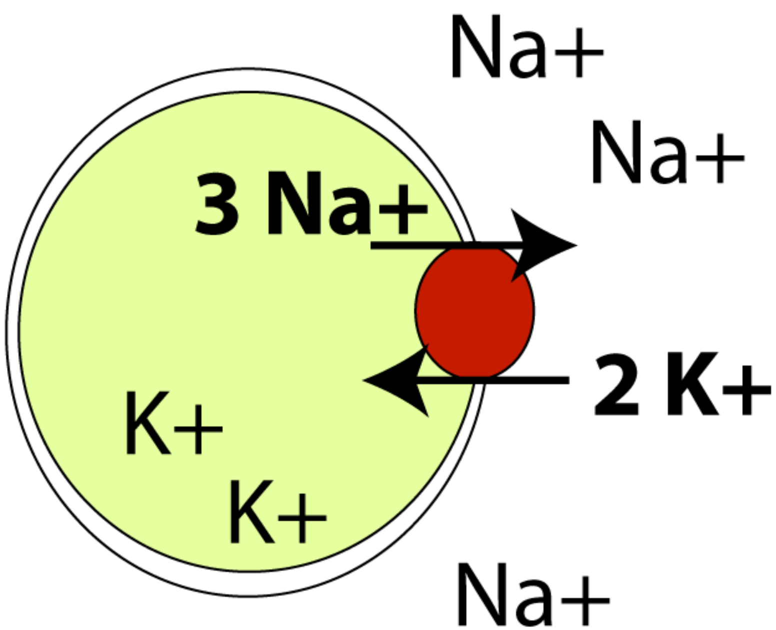
- Vm (membrane pot.) due to *resting* channels
- = voltage difference across the membrane
- I. different ions have different concentration gradients across the membrane
- ion species: K+, Na+, Cl-, Ca++
- II. membrane is semi-permeable - most resting channels are K+ (leaky) channels

Membrane Potential (Vm)



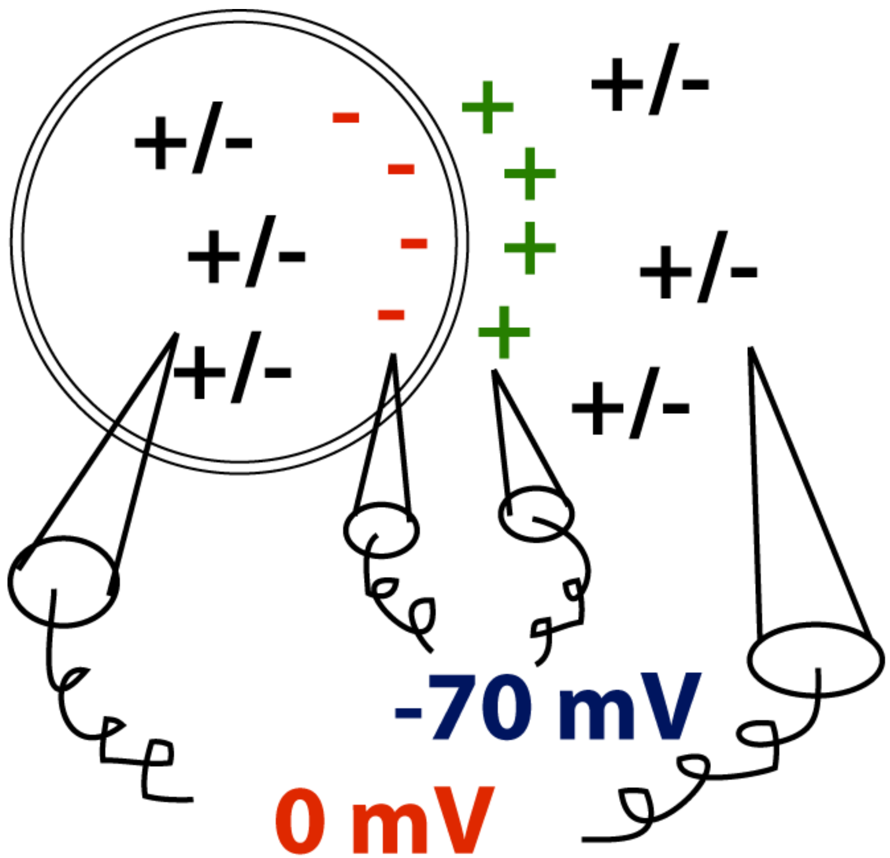
- ~ -70 mV (depends on cell type)
- semi-permeable membrane: K+
- differential concentration gradients of K+, Na+, Cl-, Ca++

Na+ - K+ pump



- 3 Na+ out, 2 K+ in
- moves ions against their concentration gradient
- re-establishes concentration gradients

note:

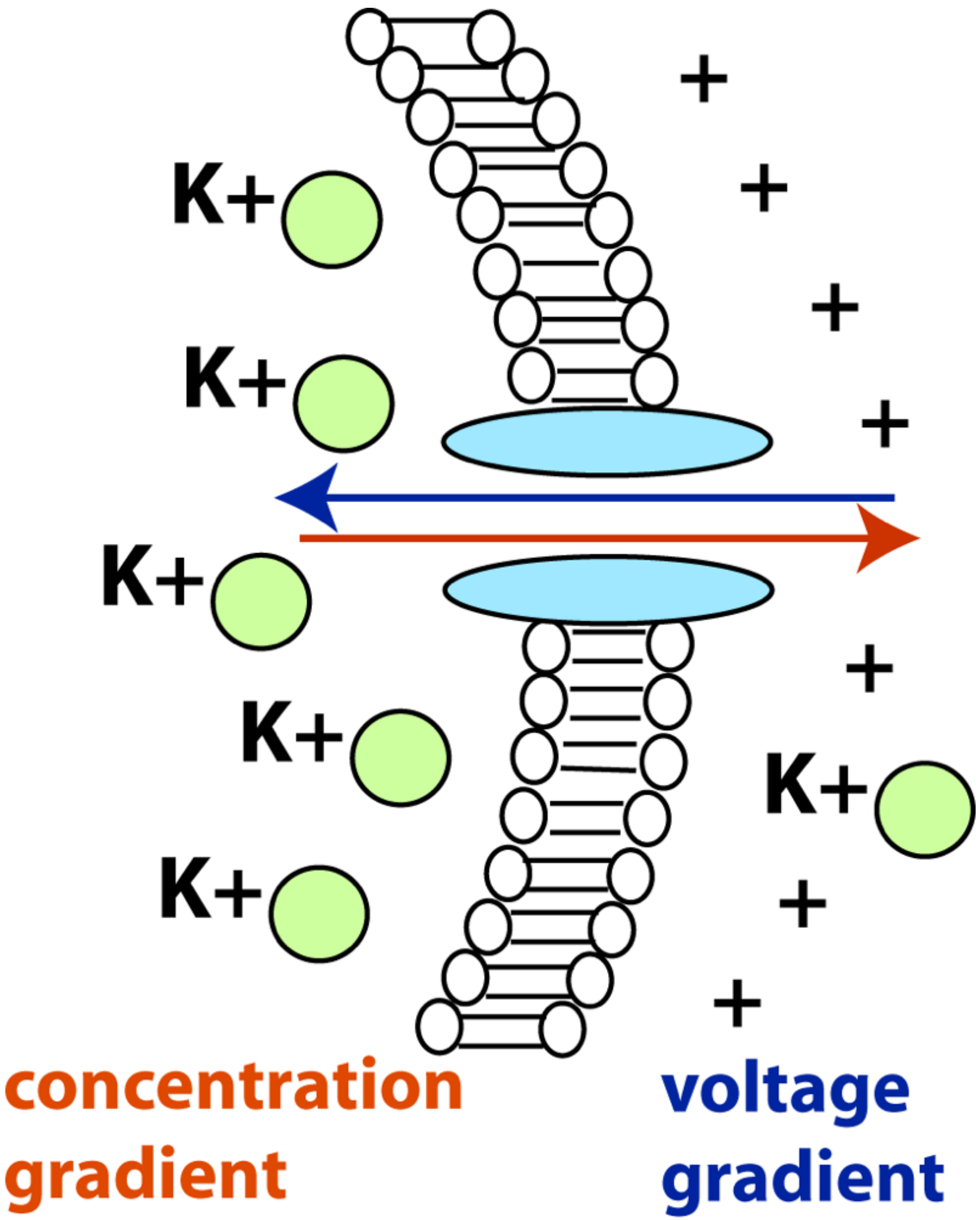


- voltage & concentration difference only immediately across membrane

Purpose of resting potential?

- signaling is a brief deviation from the resting potential;
- to signal information, must have a baseline/ resting state so incoming information isn't drowned in noise

Nernst Potential



- equilibrium potential for one ion
- = reversal potential
- when concentration gradient force balances out electrical force

Nernst values for different ions (in mammalian neurons)

	$[ion]_i$ (mM)	$[ion]_o$ (mM)	E_{ion} (mV)
K^+	135	3	-102
Na^+	18	150	+56
Cl^-	7	120	-76
Ca^{++}	0.1 μM	1.2	+125

Nernst potential

- NERNST EQUATION - target potential for one ion that must be distributed both inside and outside the cell
- reversal potential: Vm above or below Nernst: ion current reverses direction
- equilibrium potential = Nernst potential if channel permeable to only 1 ion (note: a channel can also have a Nernst potential)

Nernst questions

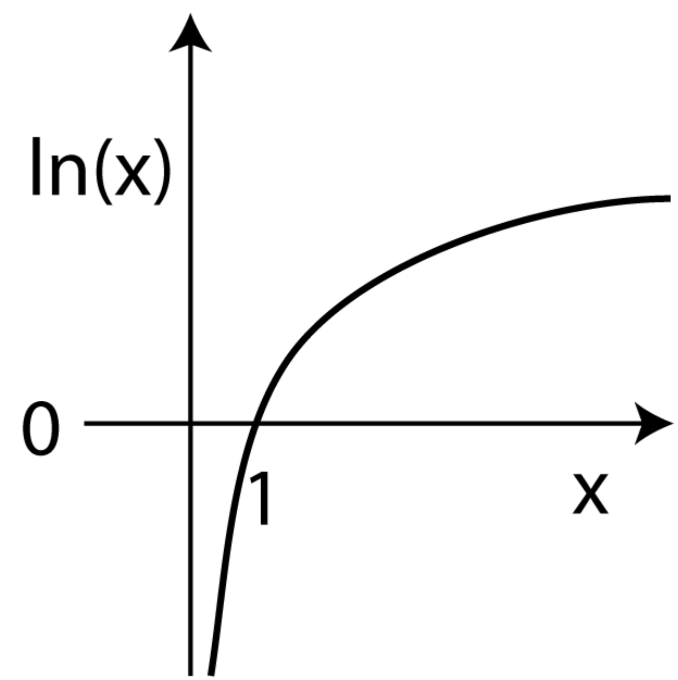
- Q: what happens to K+ if Vm is lowered to -130 mV? What about if it is raised to -50 mV?
- → K+ moves in; 2) K+ leaves cell
- Q: What happens to Na+ if channels are closed, and membrane potential is raised to -40 mV? (Nothing: channels are closed, can't get in). How about: raising Vm to +65 mV? →if channels open, Na+ will leave the cell

Nernst Equation

- allows to calculate Nernst potential for one ion

$$E_{ion} = RT/zF * \ln([ion]_o/[ion]_i)$$

- z = valence (+/- 1 or for Ca++: +2)
- ln(>1) = +ve number; ln(<1) = -ve number
- ln(1) = 0 --> Nernst will be zero.



Equilibrium potential continued

- +ve ion more concentrated outside → +ve E_{ion}
- +ve ion more concentrated inside → -ve E_{ion}
- -ve ion more concentrated outside → -ve E_{ion}
- -ve ion more concentrated inside → +ve E_{ion}
- Question: Suppose you have a species of ion called Flavium which is +ve, and has a -ve Nernst potential. Are there more Flavium ions inside or outside the cell?
- (→ inside)

GOLDMAN EQUATION

$$V_m = \frac{RT}{F} \cdot \ln\left[\frac{(p_K[K^+]_o + p_{Na}[Na^+]_o + p_{Cl}[Cl^-]_i)}{(p_K[K^+]_i + p_{Na}[Na^+]_i + p_{Cl}[Cl^-]_o)}\right]$$

- calculates Vm for multiple ions
- permeability of membrane to ions and concentration (inside vs. outside) of ions
- K+, Cl-, and Na+ all contribute to the resting membrane potential; but membrane more permeable to K+

Questions

- What happens if you tear a hole in the cell membrane?

→Vm goes to zero, cell dies (after spiking a lot due to depolarization)

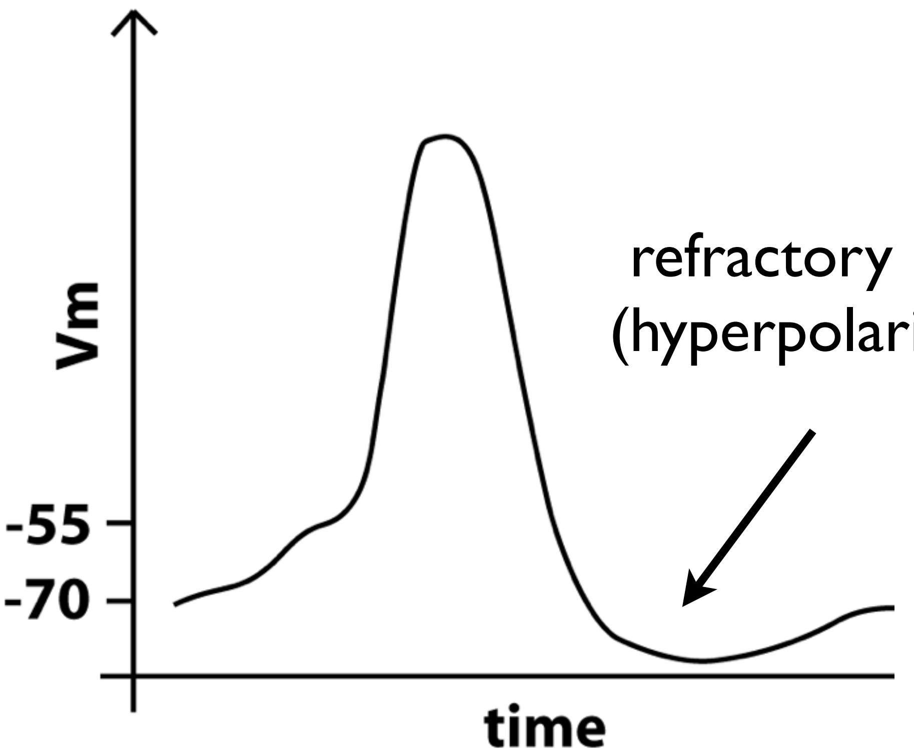
- What happens if you add K+ (K+Cl-)outside the cell at rest?

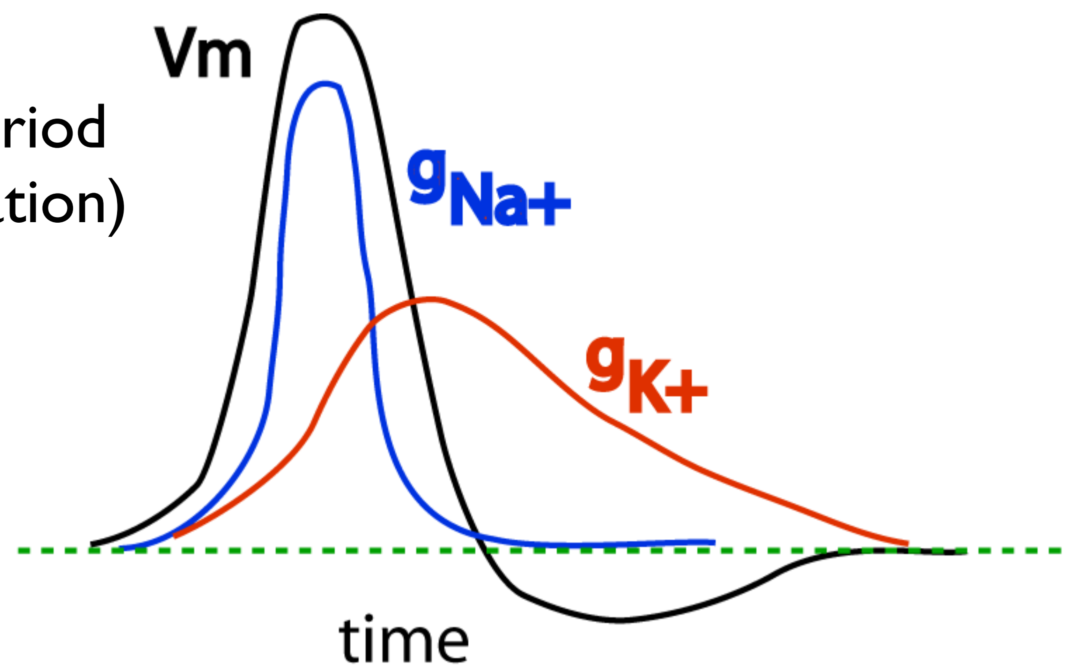
→ K+ enters cell, depolarizes it

Action Potential

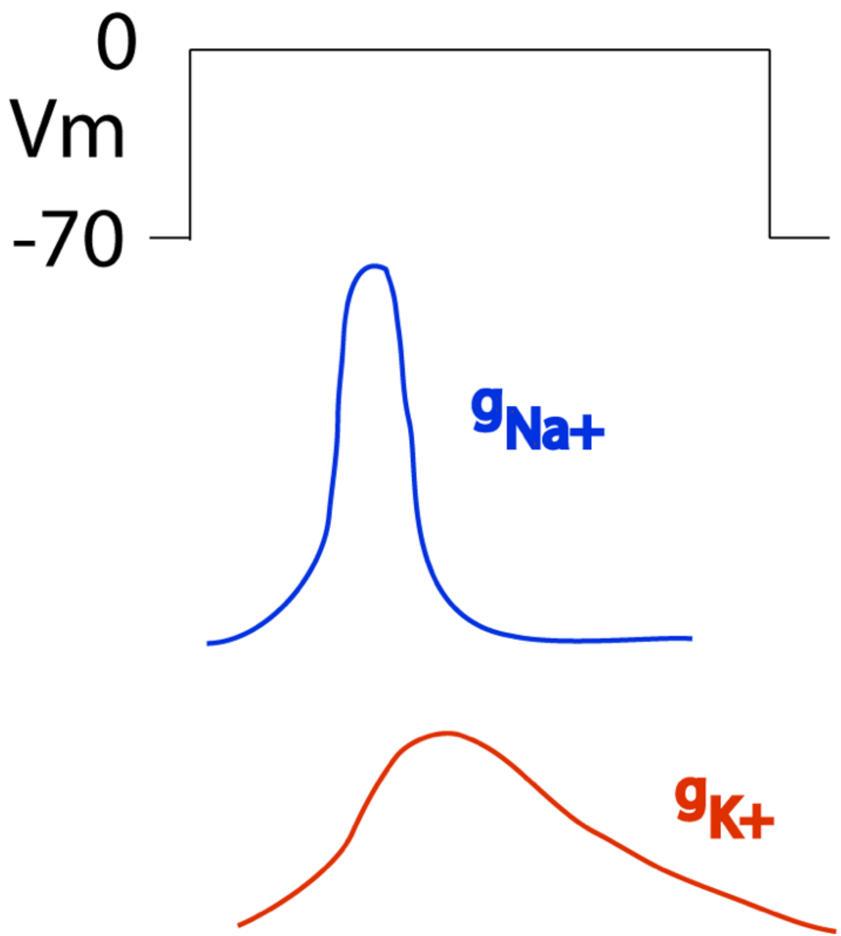
- Purpose: long-distance communication; e.g. photoreceptor cells in retina don't need to spike, b/c other cells are close-by
- depends on voltage-gated Na+ and K+ channels
- Hodgkin-Huxley equation

Action Potential





Voltage-gated Na+ and K+ conductances

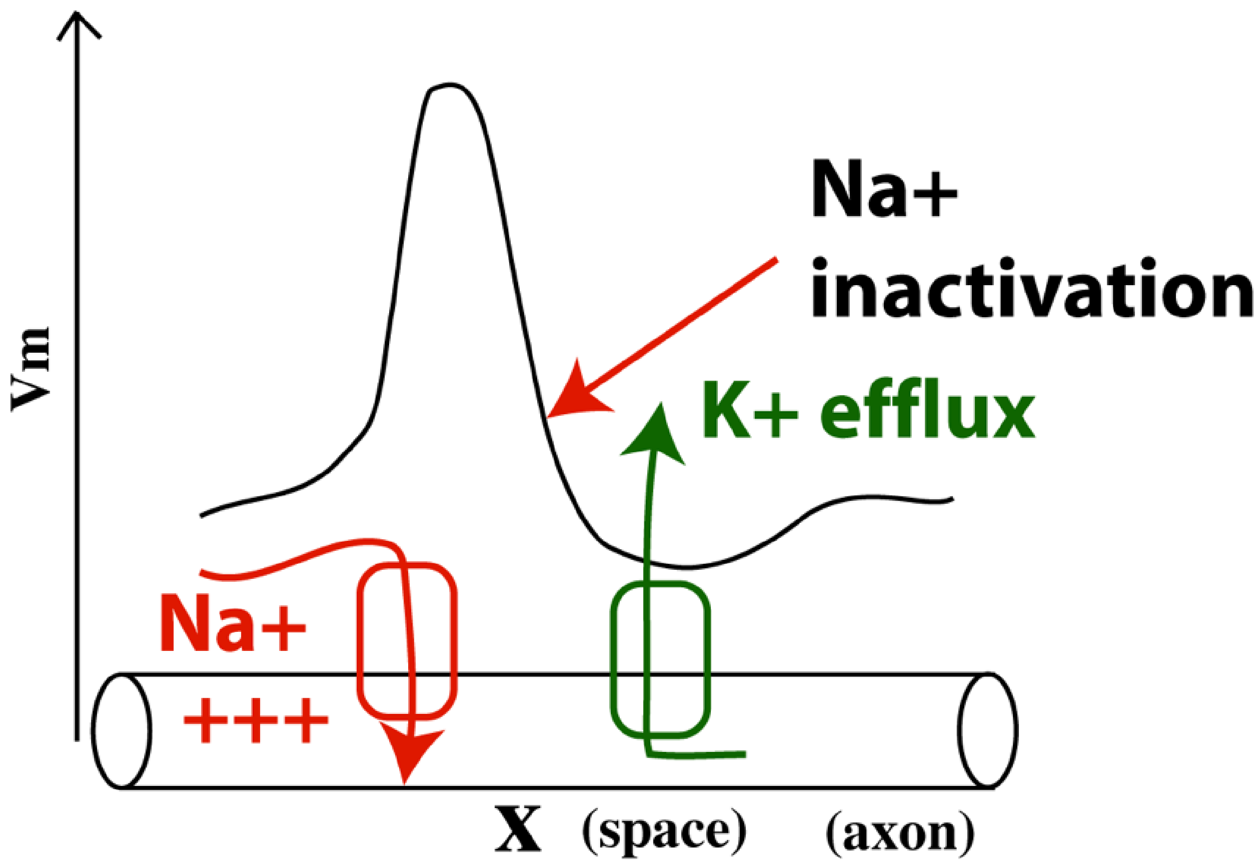


- Na+: fast, transient, inactivating
- K+: slow/ delayed, long-lasting, non-inactivating

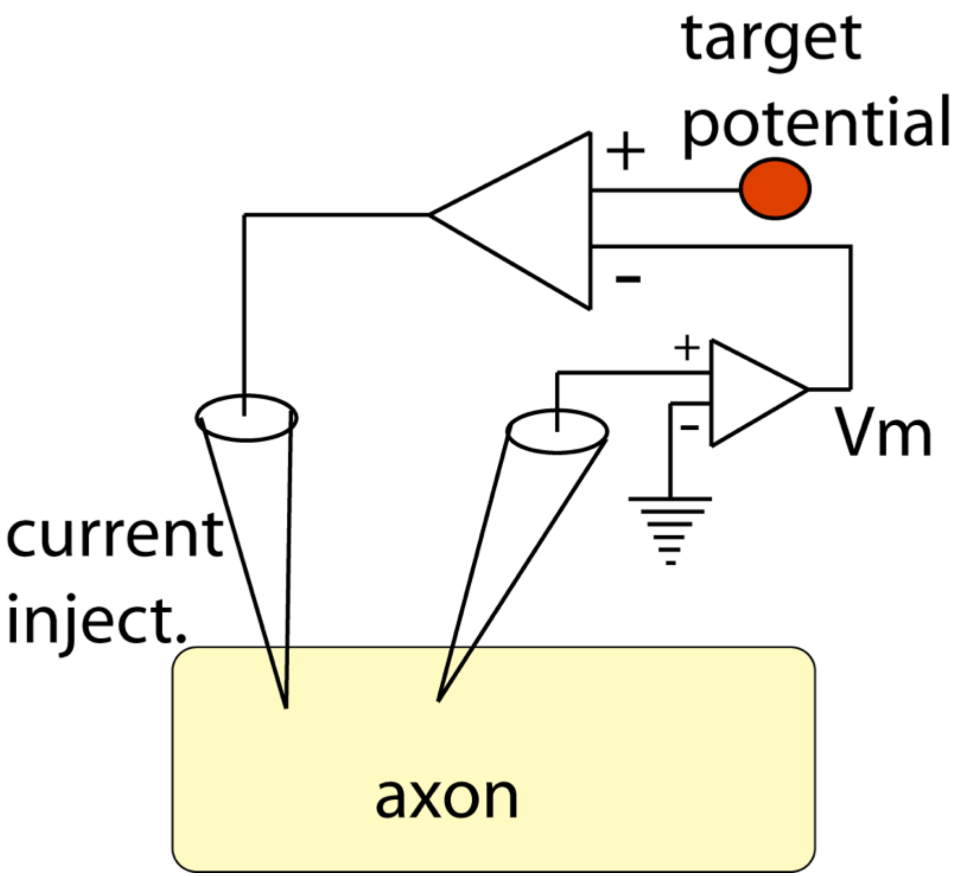
Action Potential

- fast voltage-gated inward Na+ current that inactivates: transient
- slow long-lasting voltage-gated outward K+ current that does not inactivate, only deactivates: sustained
- purpose of Na+ inactivation: prevent reverberation; cell can't spike during absolute refractory period no matter what the voltage - not due to negative voltage, but due to inactivation of Na+ channels

Hyperpolarization is caused by K+ efflux and Na+ inactivation

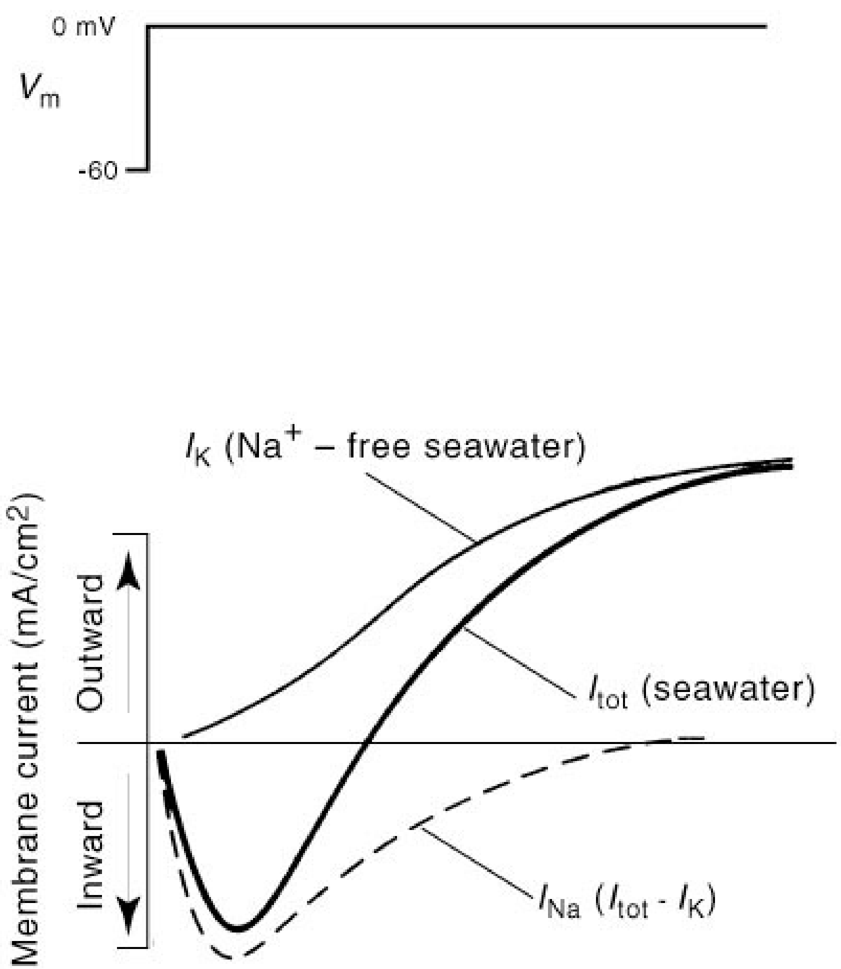


Voltage clamp



- two electrodes: voltage electrode + current electrode
- compare desired Vm to actual Vm, inject +ve or -ve current

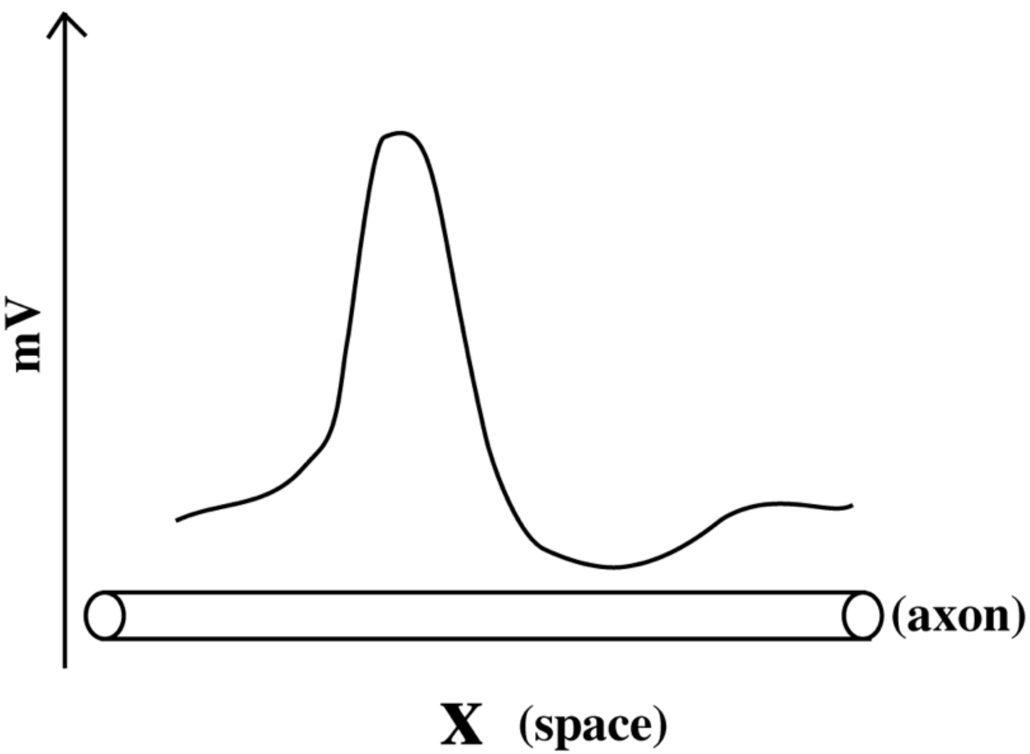
Characterizing time course and amplitude of ionic currents during Action Potential



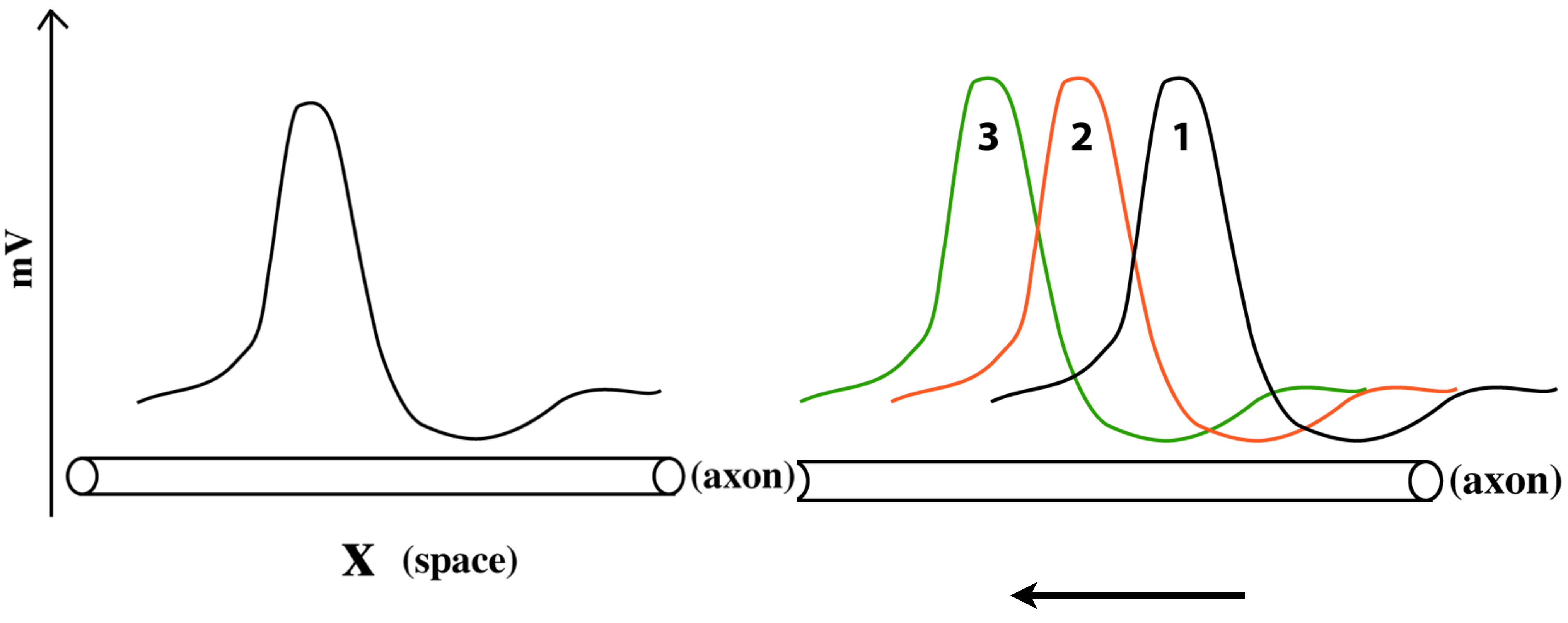
- voltage-clamp technique and selective removal of ions allows us to determine which ionic currents contribute to the AP (action pot.)

From: Fundamental Neuroscience, Squire et al. 2003

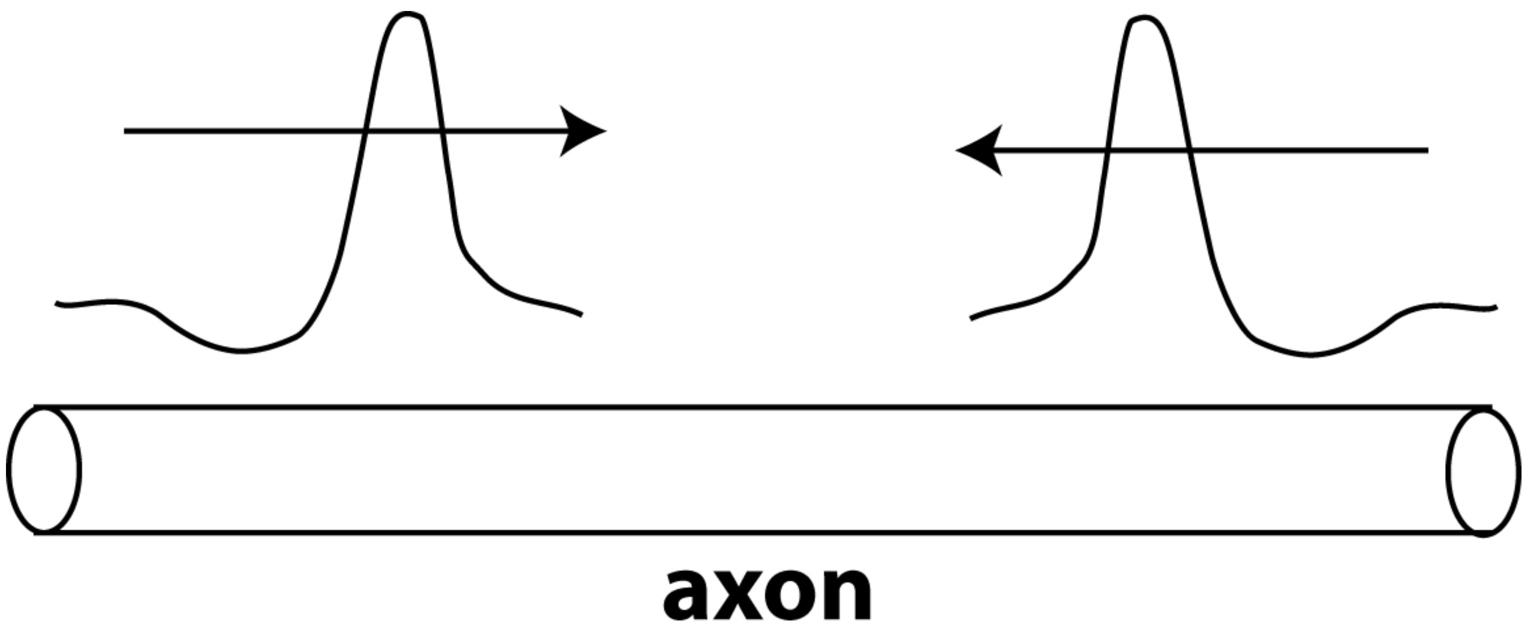
Which way is this AP traveling?



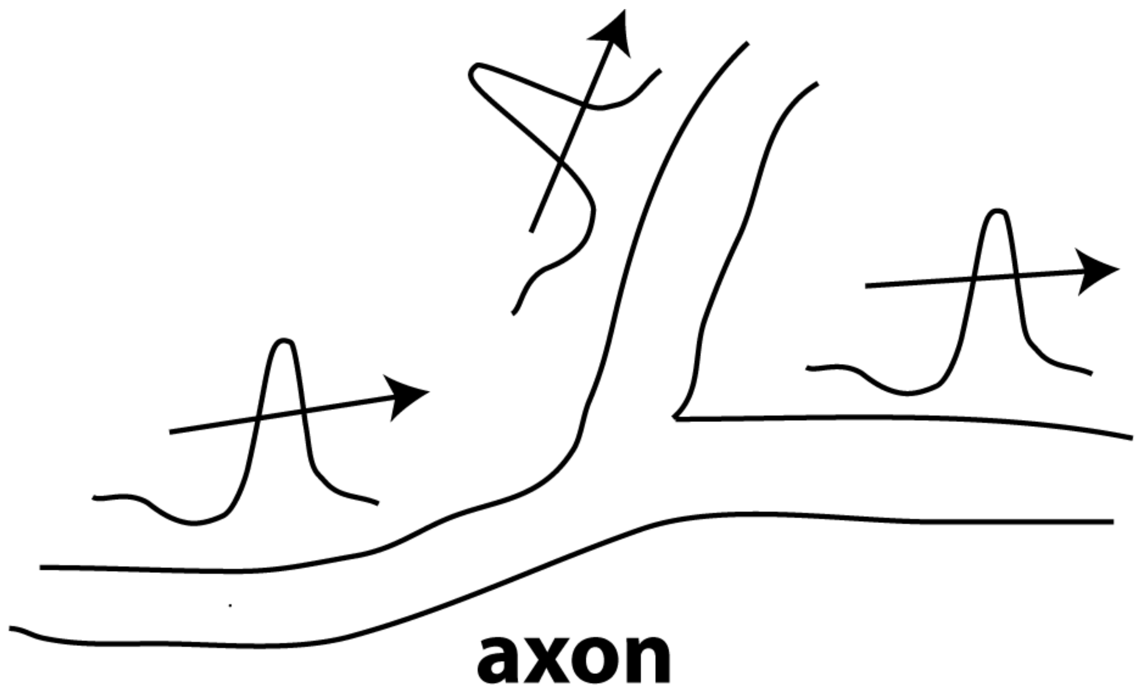
Which way is this AP traveling?



What happens when two APs collide?



What happens to AP when axon splits in two?

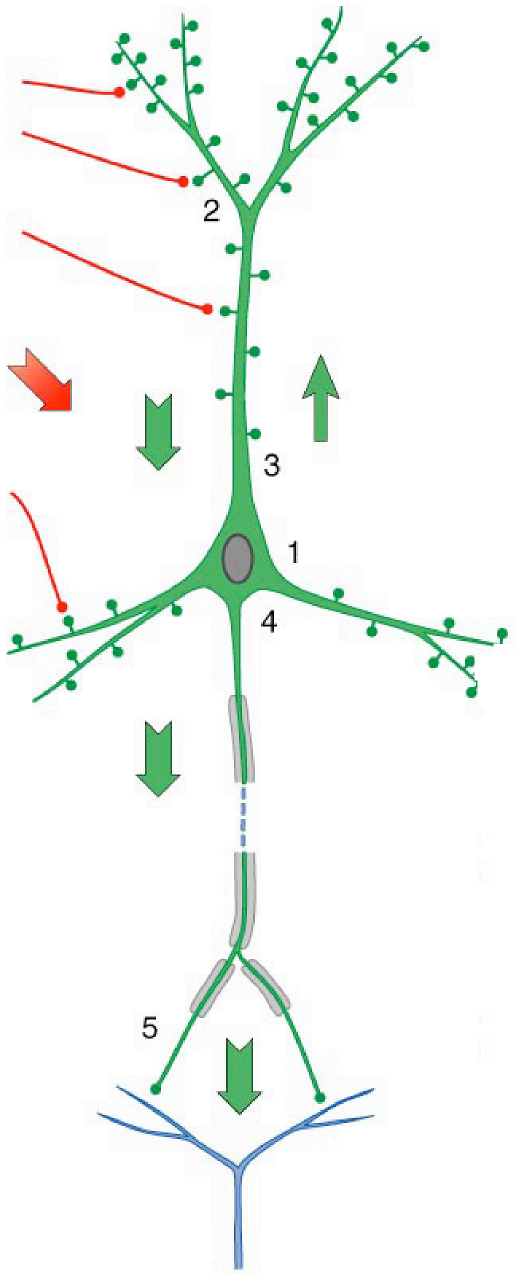


AP amplitude does not halve

- Action Potentials are actively regenerated; i.e. same amplitude; they're "all or none" - can't have just 1/2 an action potential
- therefore: if an AP hits a branch in an axon, it will either die, or go down each branch with the same amplitude; it won't halve. It might die down one branch rather than the other, but it won't halve its amplitude
- contrast with "electrotonic" or "graded" potentials (passively spread).

Electrotonic Potentials/ graded potentials

- passively spreading electric current
- (as opposed to actively *propagated* action potentials)
- usually from dendritic inputs; or current injection via electrode



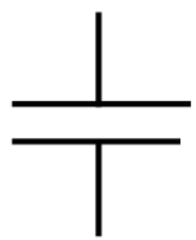
Basic concepts

- R = resistance (difficulty of spreading; e.g. Library Walk)
- I = current (amount of flow) (I = Q/t)
- V = voltage (e.g. "water pressure")
- C = capacitance (how much charge you can hold); C $\propto$ area/distance betw. plates (e.g. 5 nm)
- g = conductance = 1/R
- Q = charge = C*V

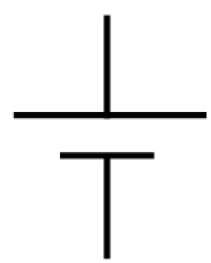
Symbols

- resistor

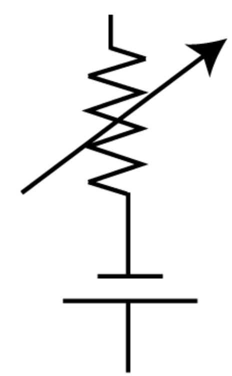
- capacitor



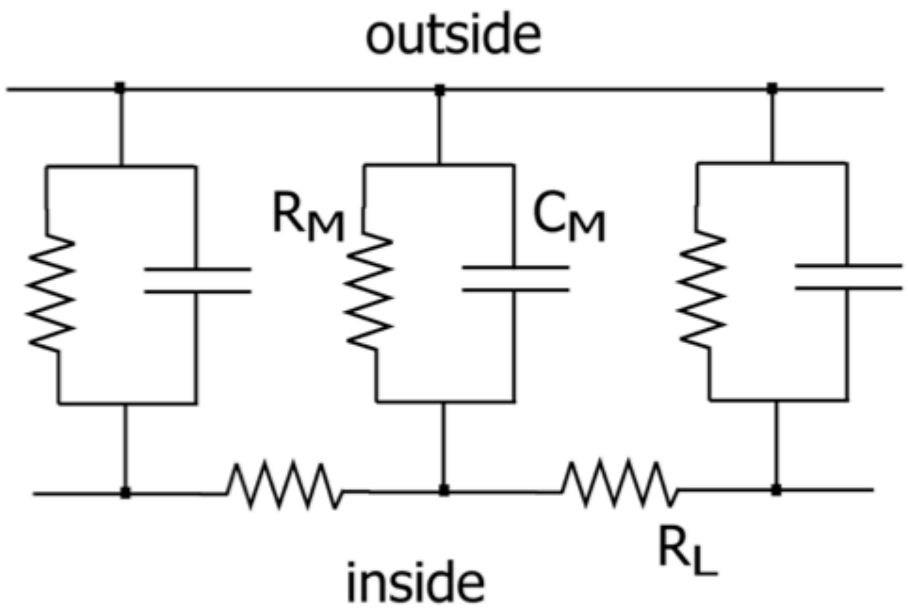
- battery

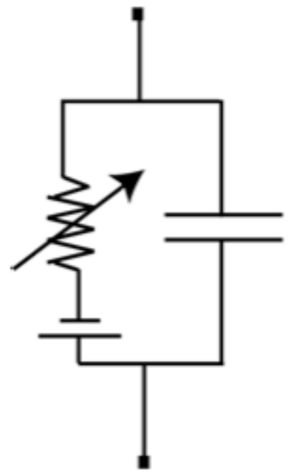


- Nernst potential across channel



Equivalent Electrical Model of Dendrite

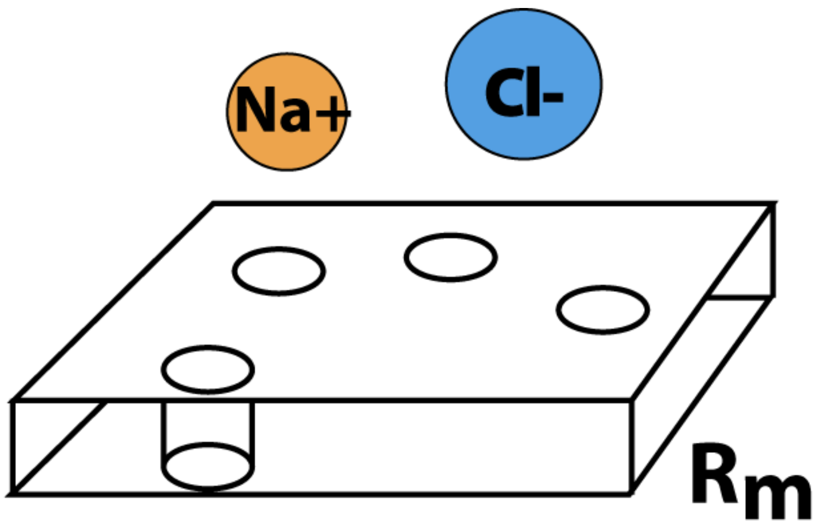




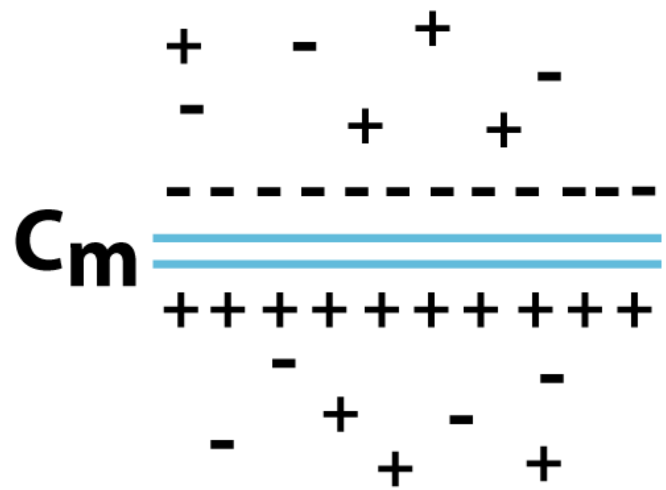
In membrane, C_m and R_m are in parallel; R_L are in series; R_L is much larger than R_m

Patch of membrane with Nernst potential across channel (serves as battery)

Rm and Cm

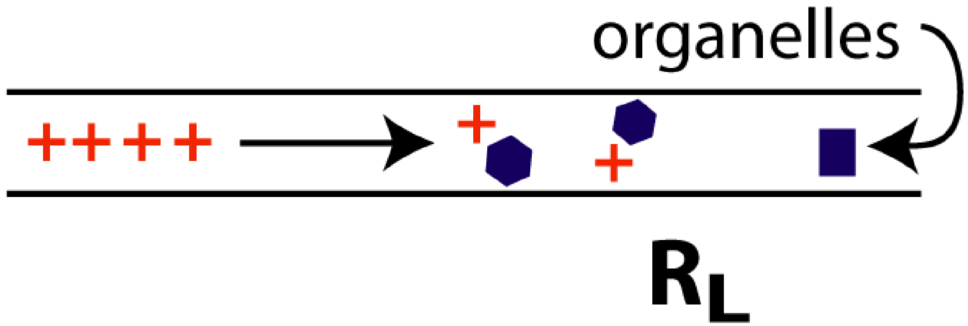


membrane has resistance (Rm)



membrane has capacitance (Cm)

R_L

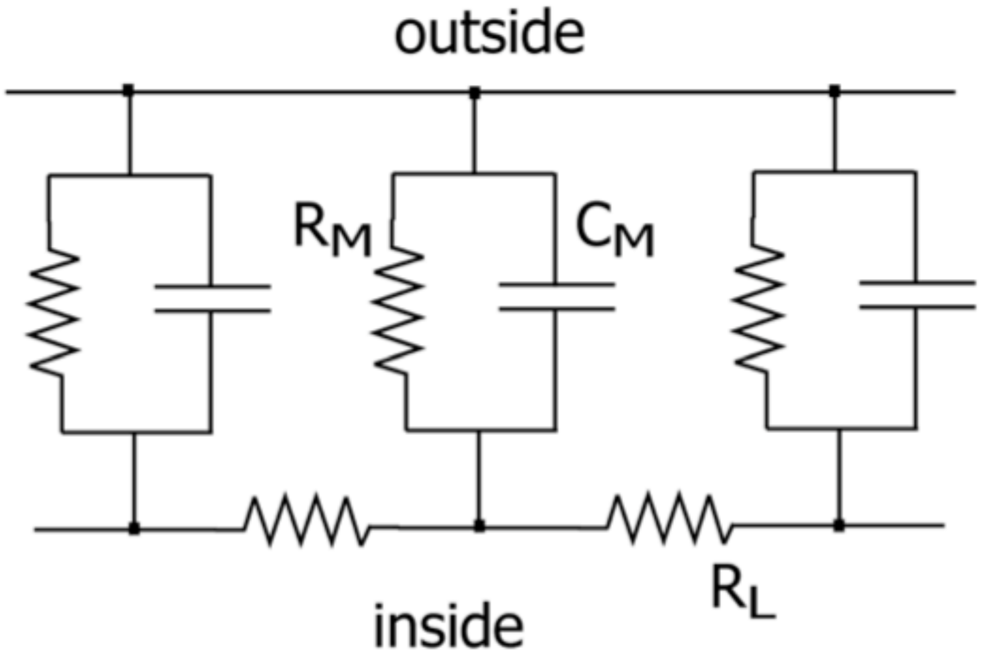


- axons/dendrites have internal/axial/longitudinal resistance (R_L)
- NOTE: outside resistance negligible (zero)

Laws

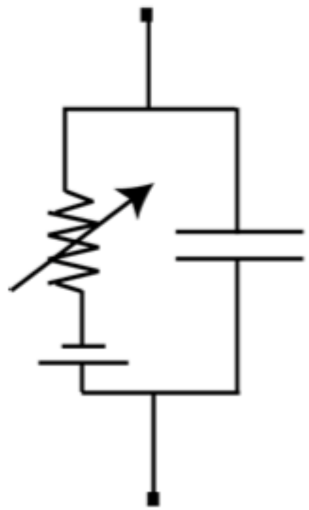
- uncharged capacitor = zero resistance
- charged capacitor = infinite resistance
- it takes time to charge a capacitor
- current follows the path of least resistance

Equivalent Electrical Model of Dendrite



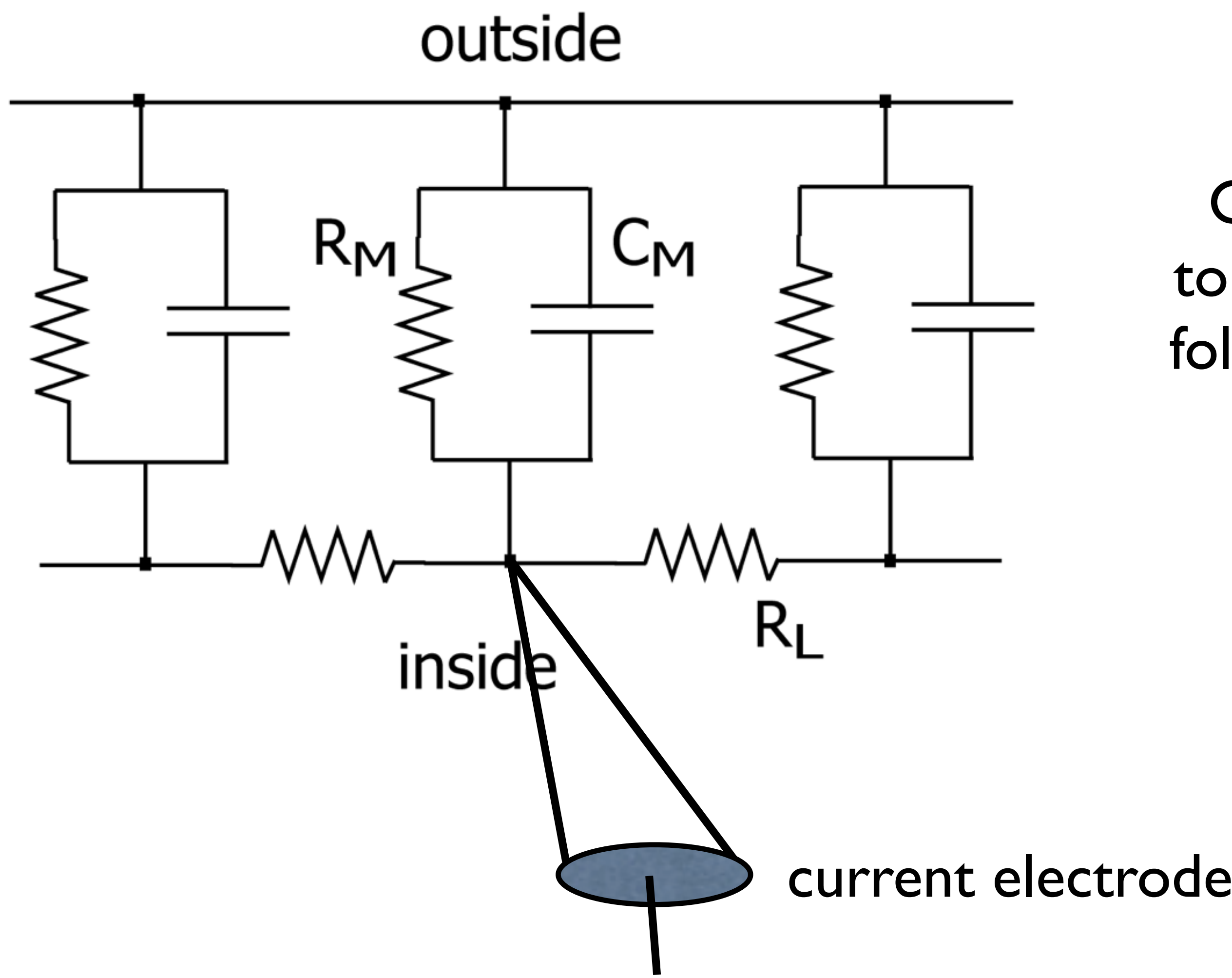
In membrane, Cm and Rm are in parallel; R_L are in series

R_L is much ~~larger~~ than R_m
smaller!



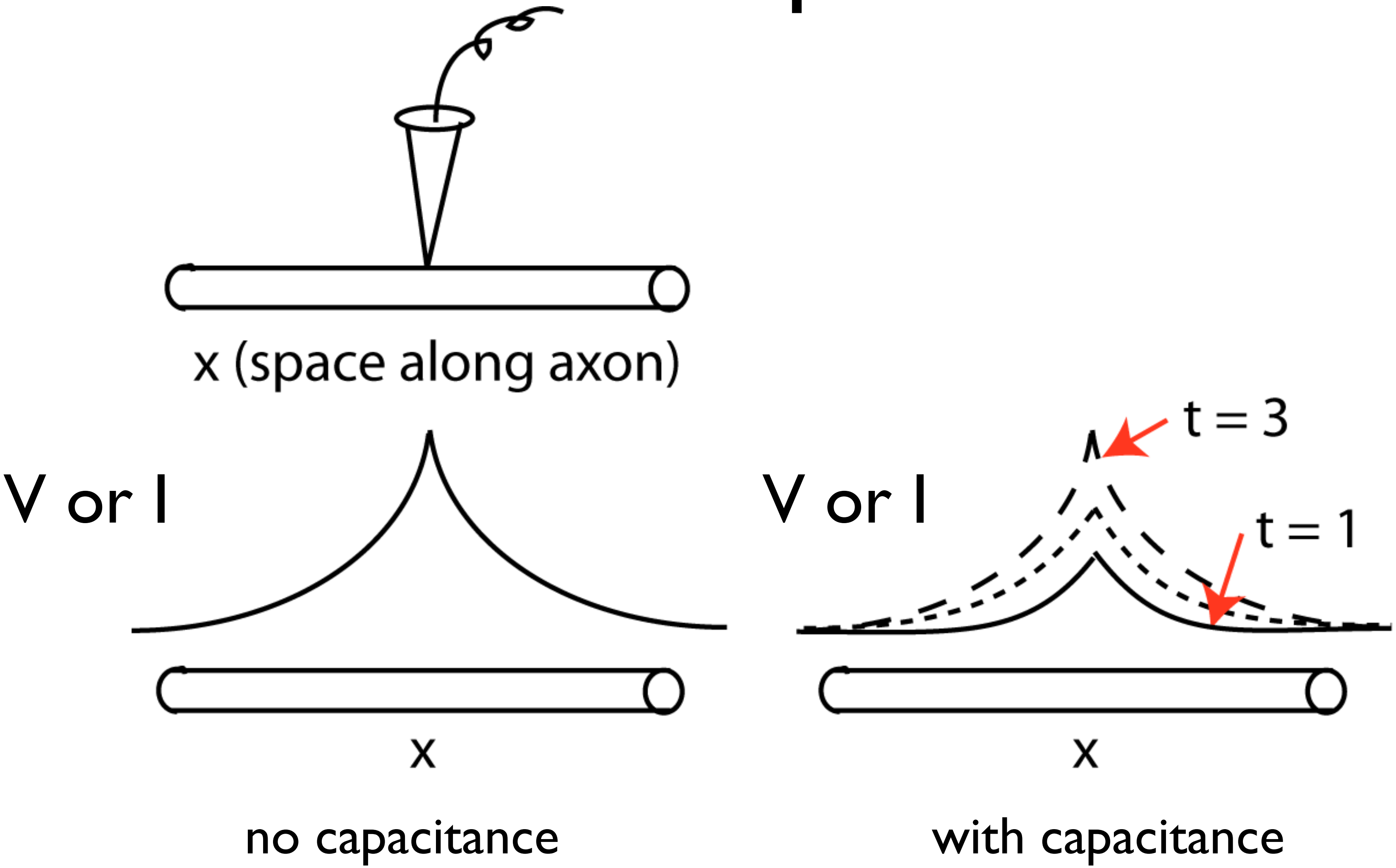
patch of membrane with Nernst potential across channel - battery

What happens if we inject current into dendrite?

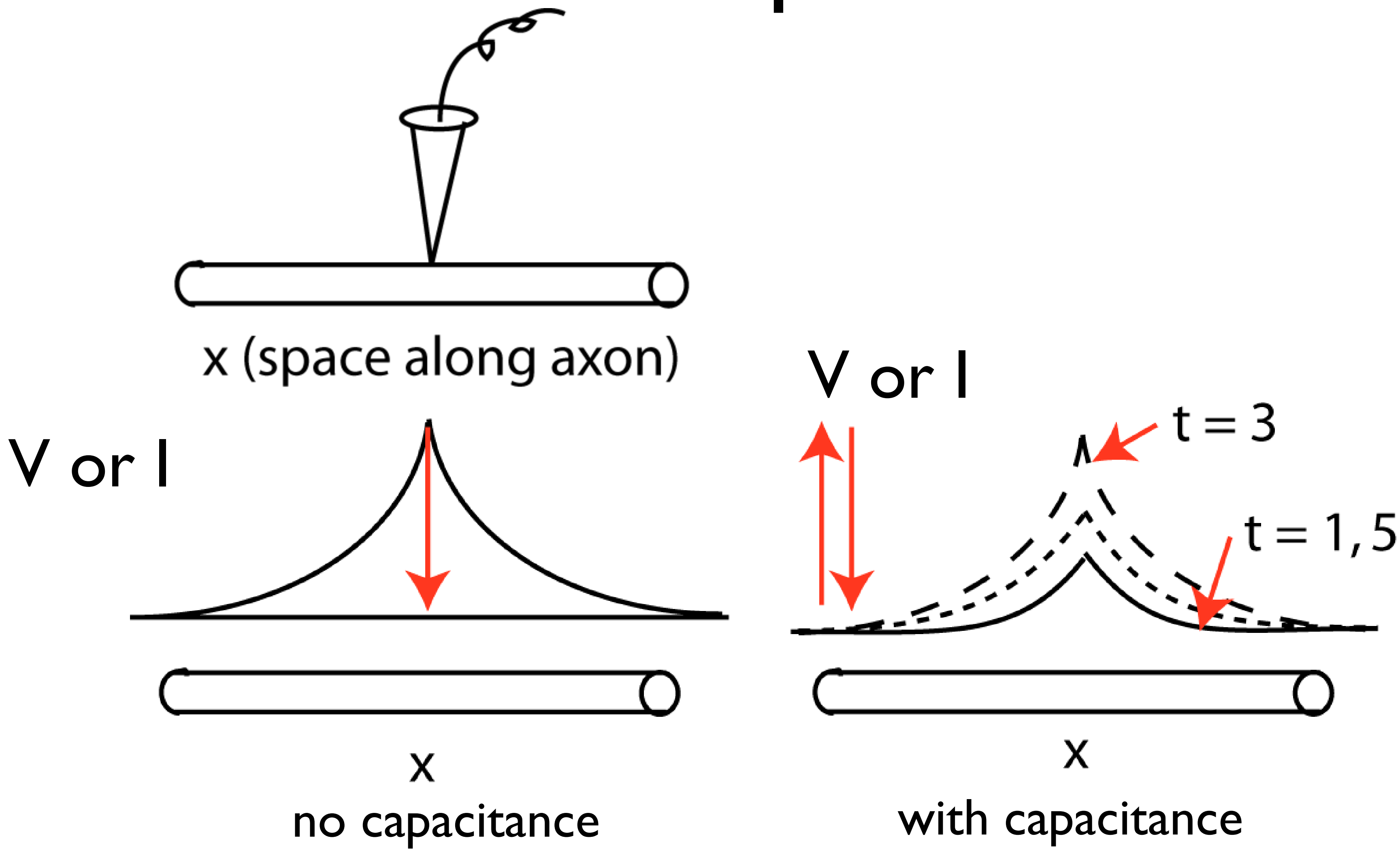


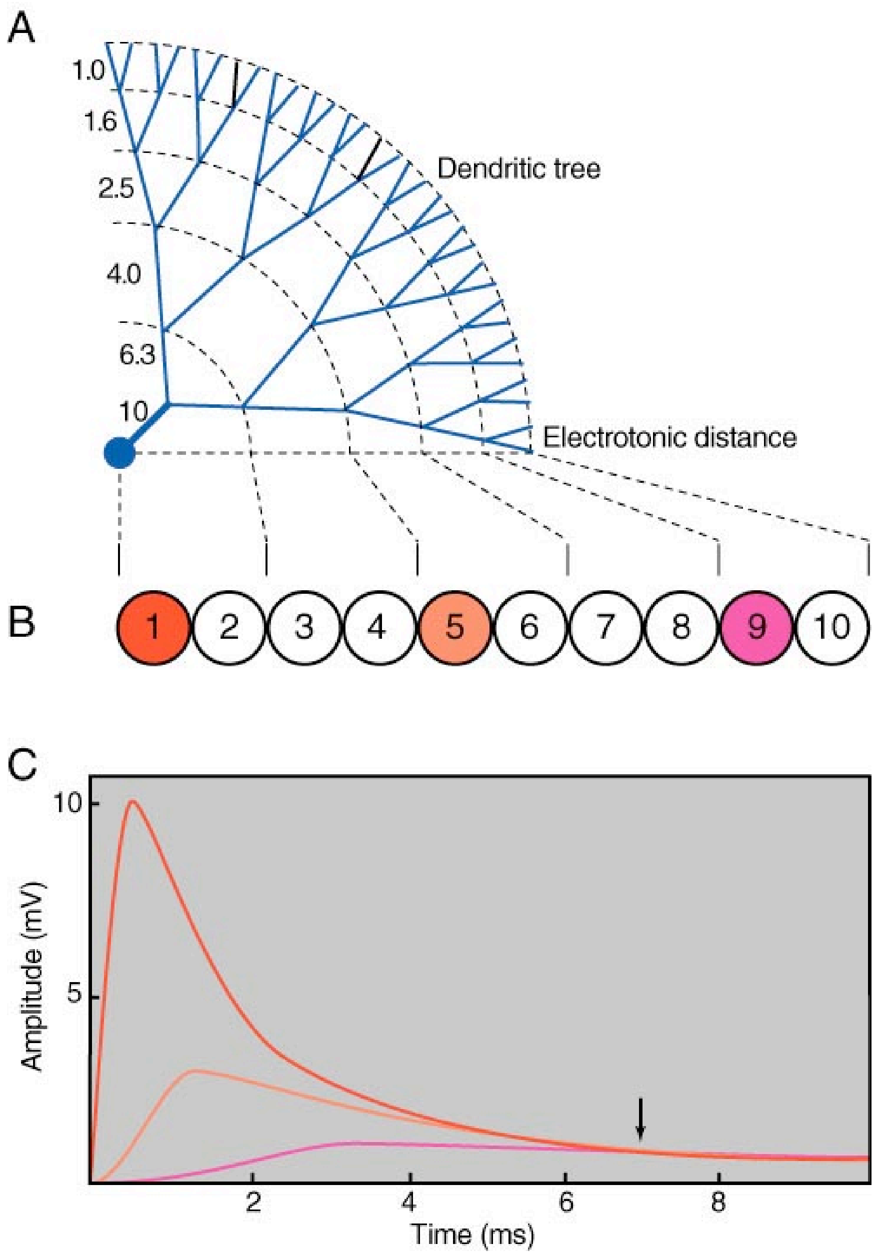
Current will start to flow everywhere, following the path of least resistance

Steady-state current: with and without capacitance



Transient impulse: with and without capacitance

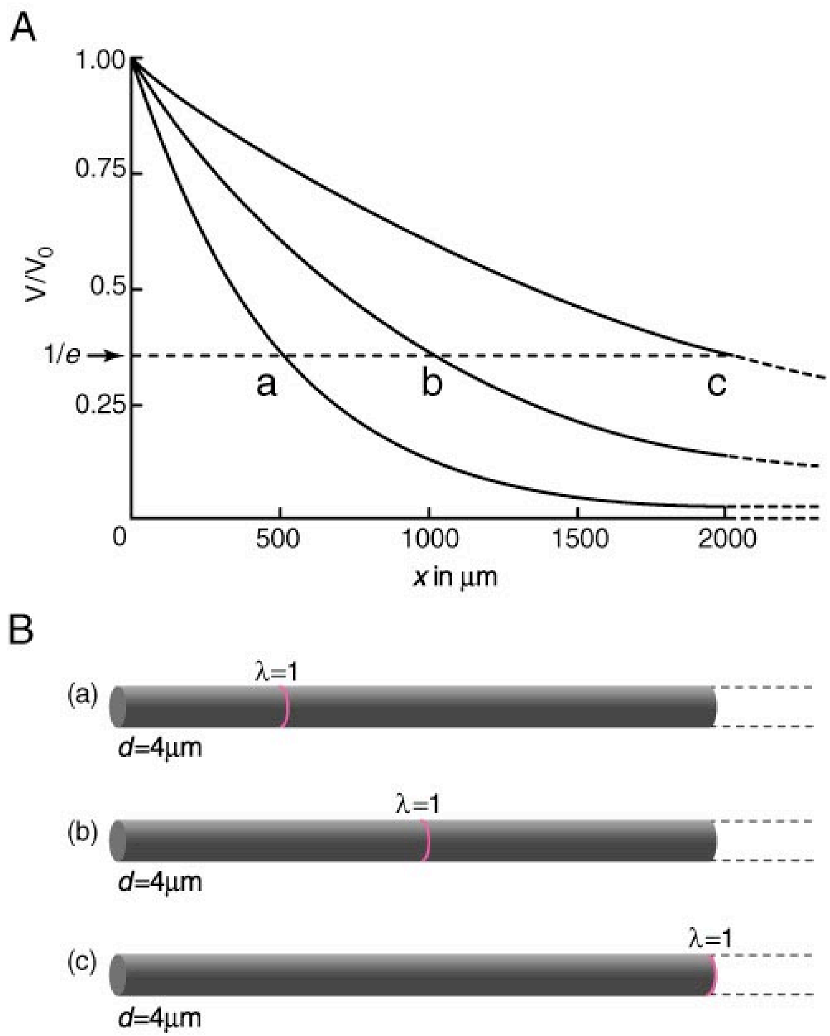




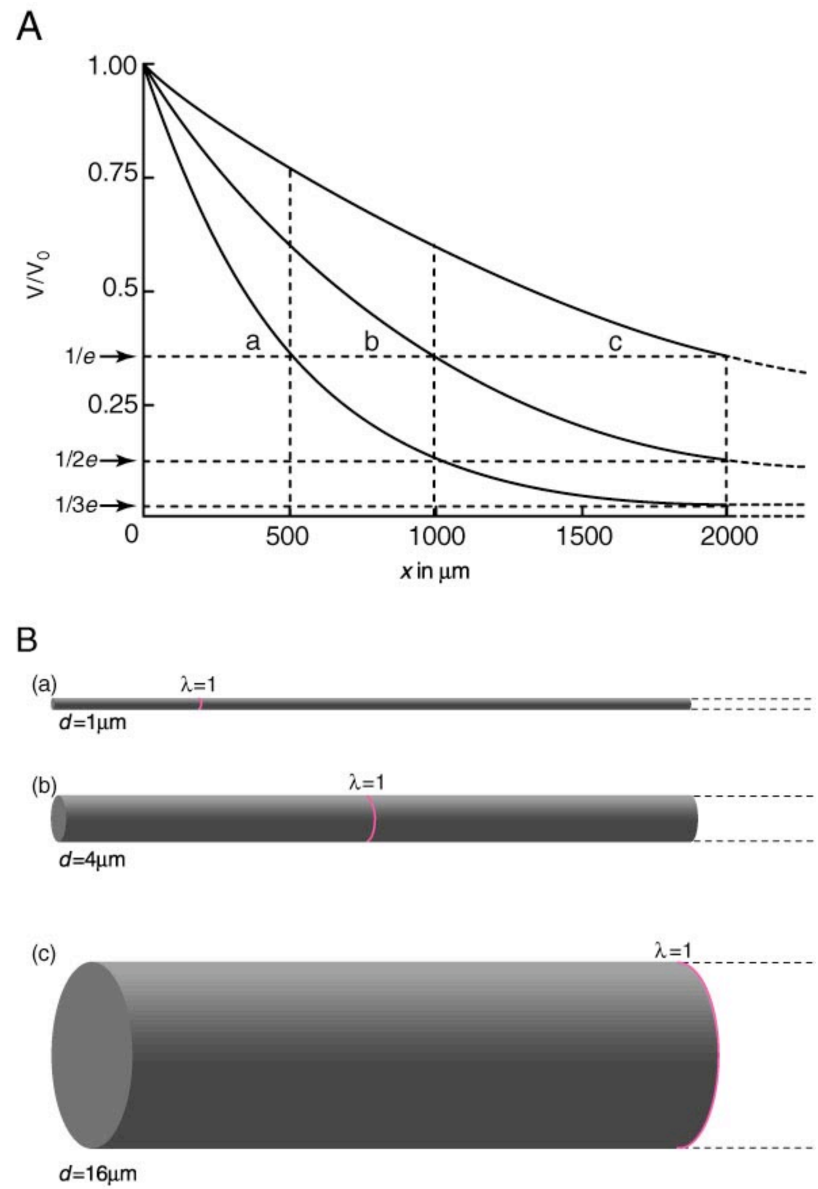
- spread of electrotonic potentials is delayed and of smaller amplitude the farther away from injection site

Length constant

- characteristic length (membrane space constant) λ (lambda) - depends on Rm and R_L (also on diameter of process - big diameter, low R_L)
- the length of dendrite over which the electrotonic potential decays to a value of 0.37 of value at injection site



high Rm and low R_L
increase λ

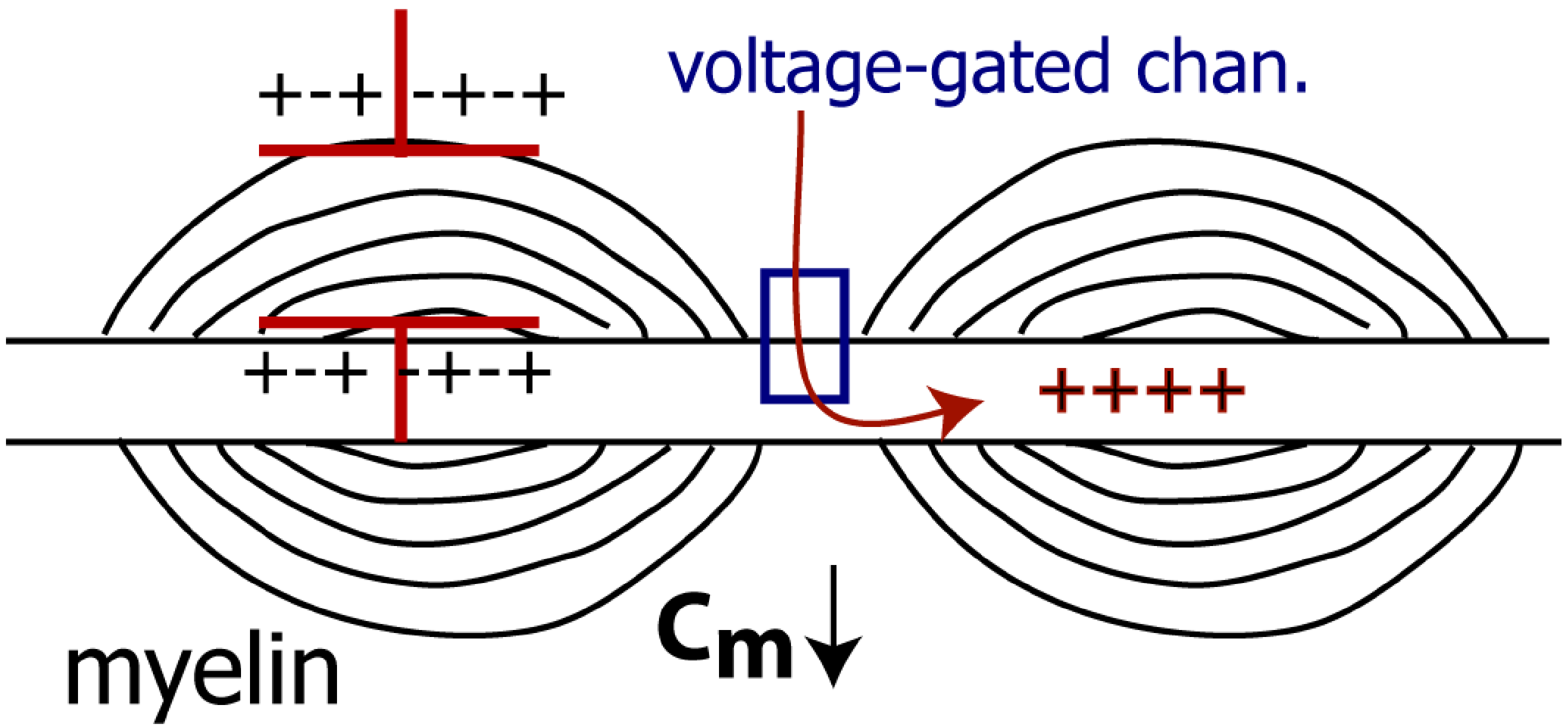


big diameter
increases λ

Time constant τ

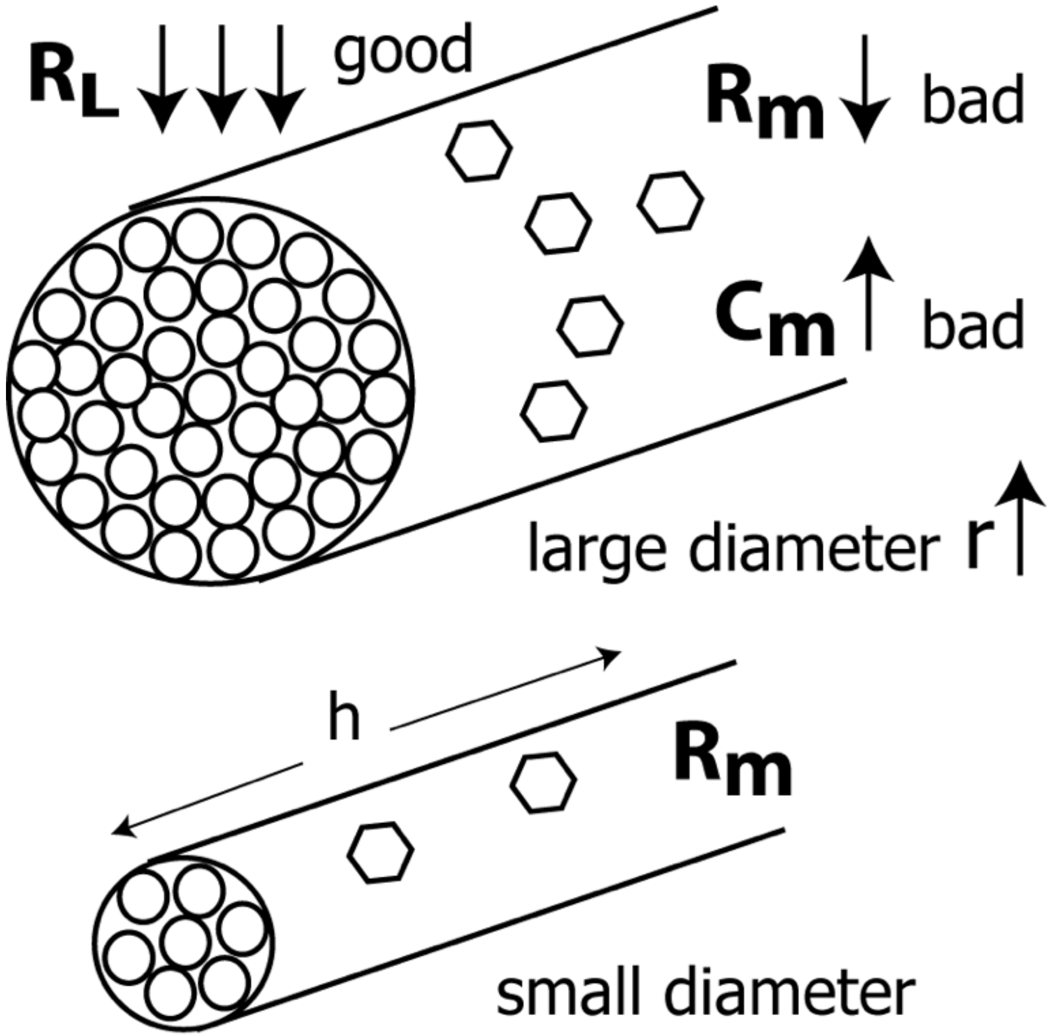
- membrane time constant τ (tau) depends on Cm
- the time required for voltage change across membrane to reach 0.37 of its final value (i.e. of maximally charged capacitor)
- the greater the capacitance, the greater τ is

Myelin decreases capacitance



* Myelin separates the plates of the capacitor - current won't get wasted charging up the capacitor
* (myelin also INcreases Rm - less leakage)

Increasing diameter of axon



volume = $\pi r^2 * h$

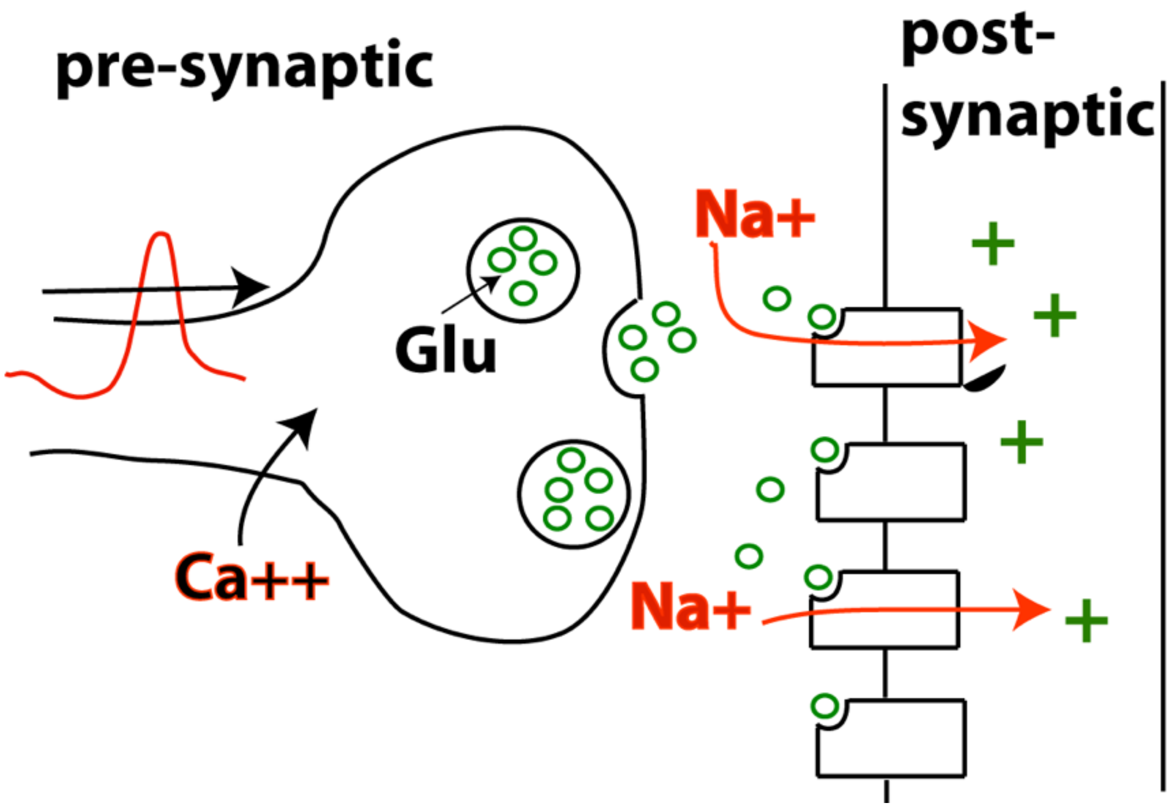
surf. area = $2 \pi r * h$

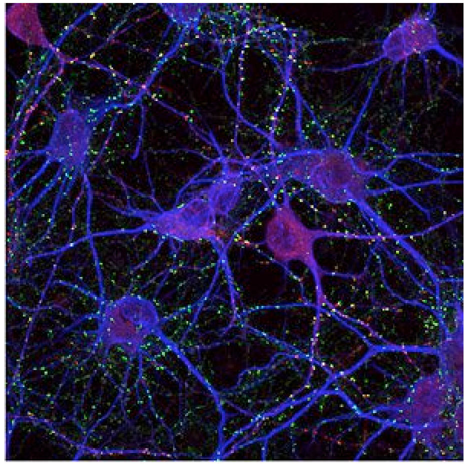
→ volume goes up faster than membrane surface area with increased diameter

→ decrease in longitudinal resistance greater than increase in C_m or decrease in R_m

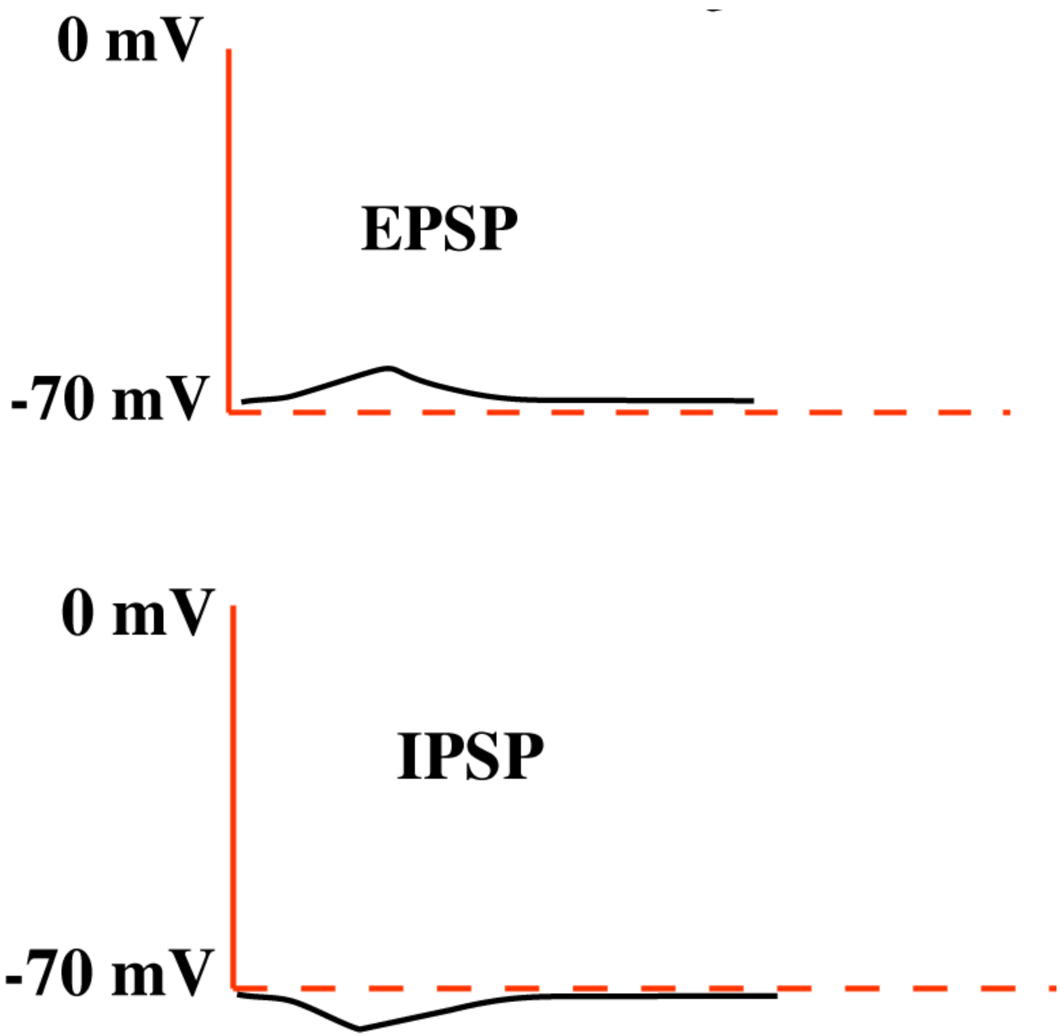
- in order to spread electrotonic potentials as far as possible, we want:
  - high membrane resistance (myelin)
  - low membrane capacitance (myelin)
  - low internal resistance (large diameter)

Synaptic Transmission





EPSP and IPSP

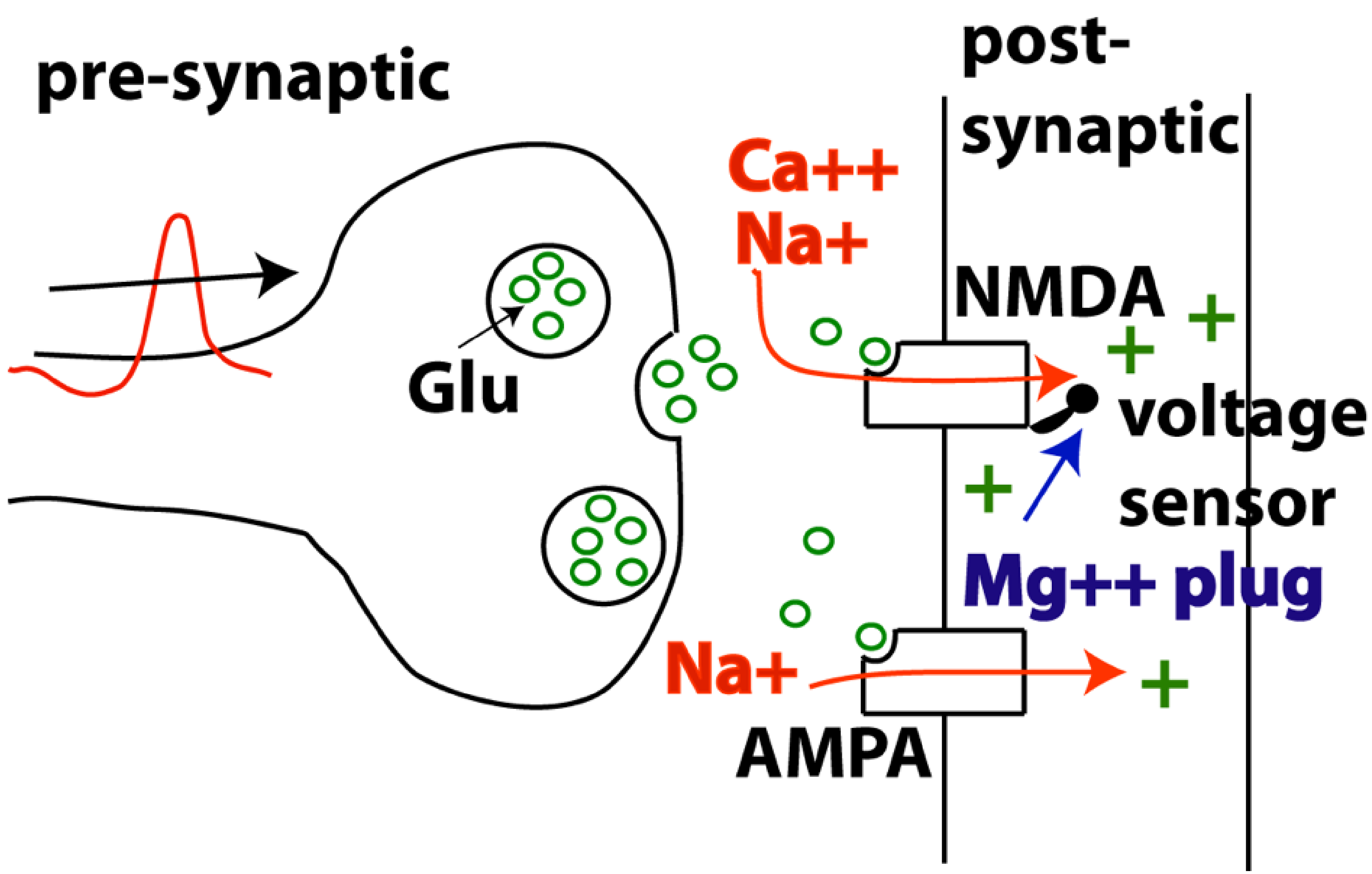


- excitatory post-synaptic pot. (EPSP)
- inhibitory post-synaptic pot. (IPSP)
- one input not enough

Receptor channels (examples)

- AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid) - **excitatory**; E_{AMPA} = ~ -10 mV; NT = Glu; conducts Na+, Ca++
- NMDA (N-methyl-D-aspartic acid) - **excitatory**; NT = Glu, voltage-sensitive; E_{NMDA} = 0 mV; conducts Na+, Ca++, K+
- $GABA_A$ (Gamma-aminobutyric acid): - **inhibitory**; NT = GABA; E_{GABAA} = -70 mV; conducts Cl-
- $GABA_B$: - **inhibitory**; NT = GABA, E_{GABAB} = ~-80 mV); conducts K+

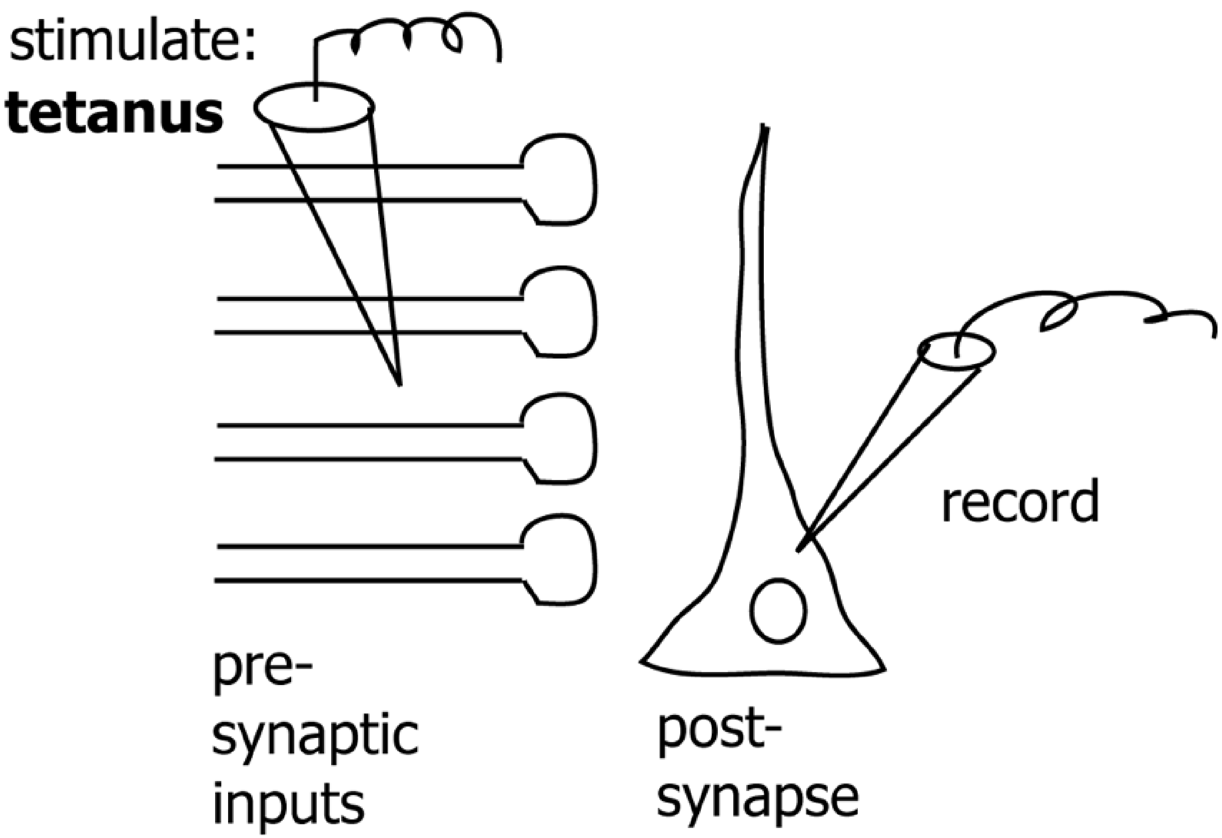
NMDA channels act as AND gates



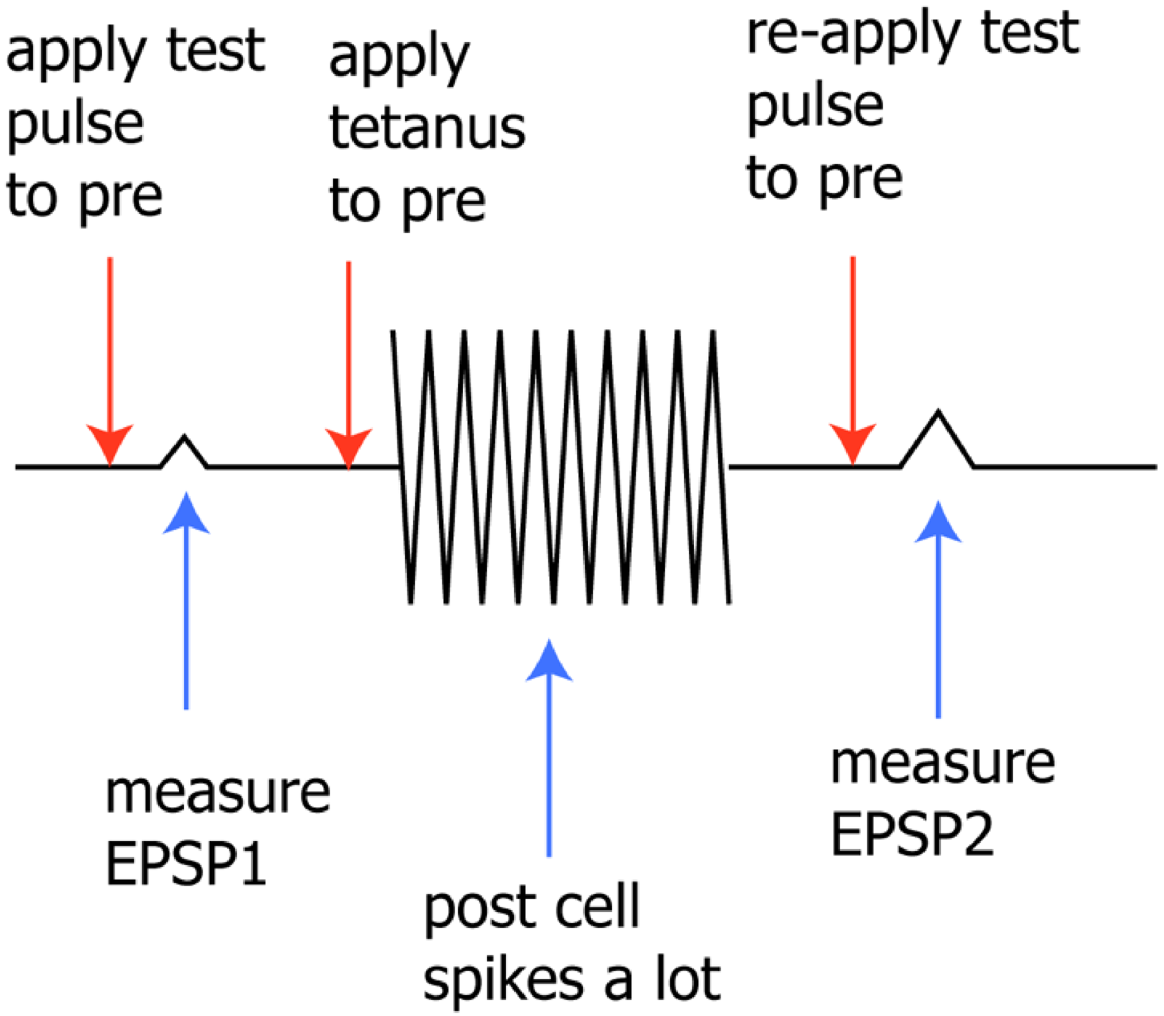
NMDA requires both depolarization AND glutamate

LTP

- long term potentiation

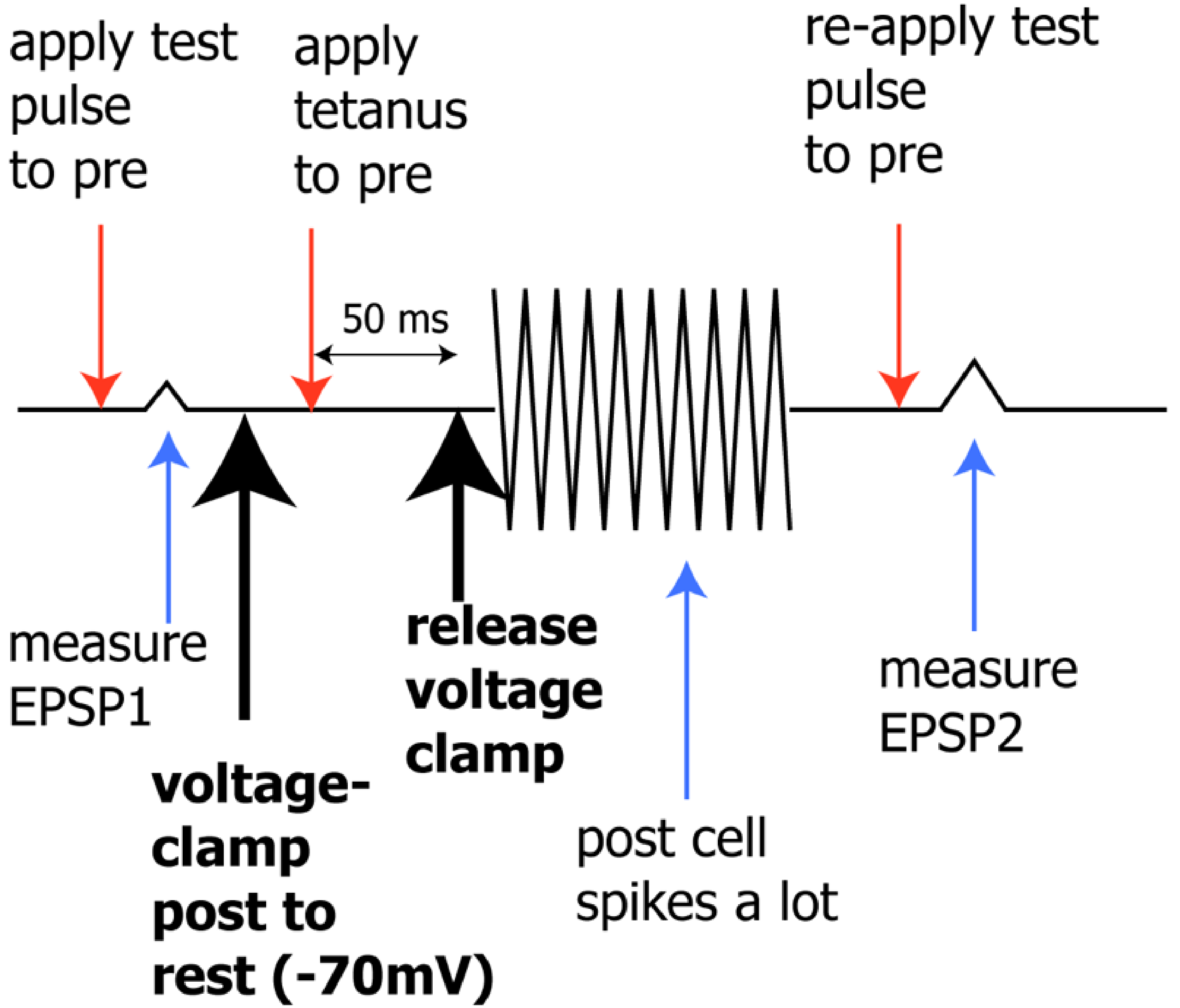


Inducing and measuring LTP

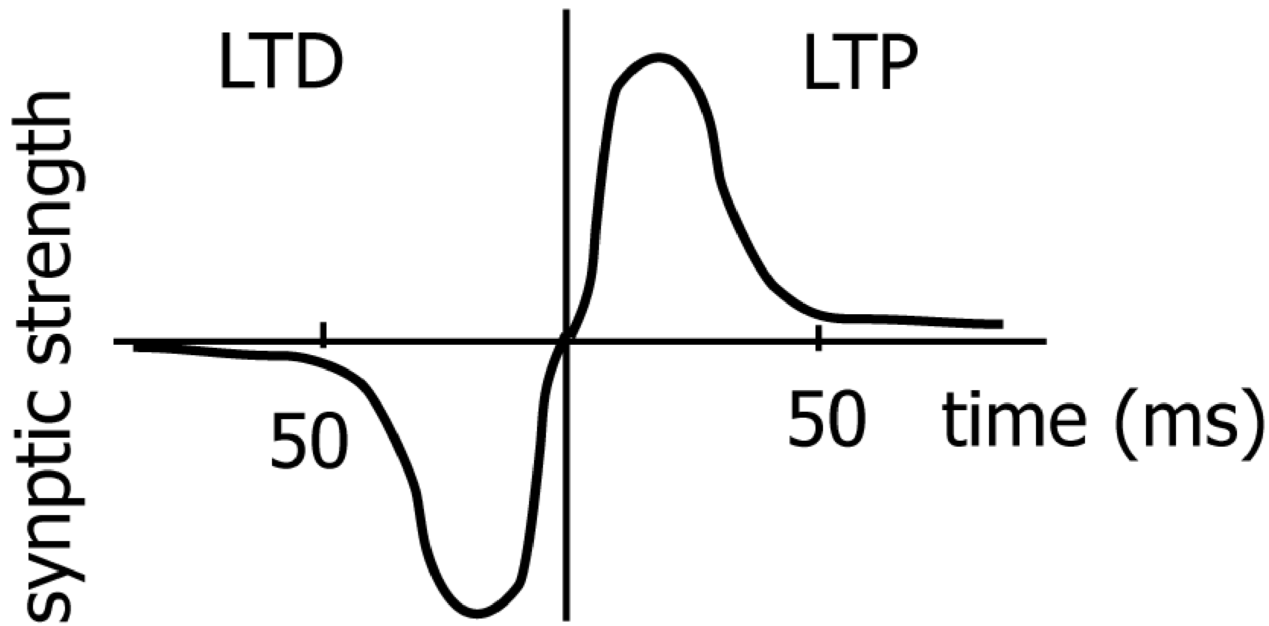


If EPSP2 > EPSP1, LTP has occurred

Timing of pre-synaptic stimulation and post-synaptic response matters



Spike-timing dependent plasticity (STDP)



Synaptic strength change

- if pre spikes within 50 ms before post: LTP
- if post spikes within 50 ms before pre: LTD
- if pre and post spike > 50 ms apart: no change

Possible LTP mechansims