Neurons

The Molecular Basis of their Electrical Excitability

Viva La Complexity!

Consider,

- The human brain contains $>10^{11}$ neurons!
- Each neuron makes 10^3 (average) synaptic contacts on up to 10^3 other neurons, and receives up to 10^5 (typically 10^4) synaptic inputs!

Conclusion: the computational power of the nervous system is based on ***sheer numbers of, and connections between, individual elements, as well as in the computational powers of the elements***. Adding modulation and plasticity to each of these connections makes it even more impressive.

Support Staff

CNS: brain and spinal cord **PNS:** nerves (what are they?)

neurons:glia # 1:9 volume 1:1

In central nervous system (*CNS*)

oligodendrocytes: myelinate (up to 40 different) axons

astroglia: regulates extracellular fluid (K^+, neurotransmitters, glucose, NH_3, guidance)

microglia: immune-like macrophagish cells

In peripheral nervous system (*PNS*)

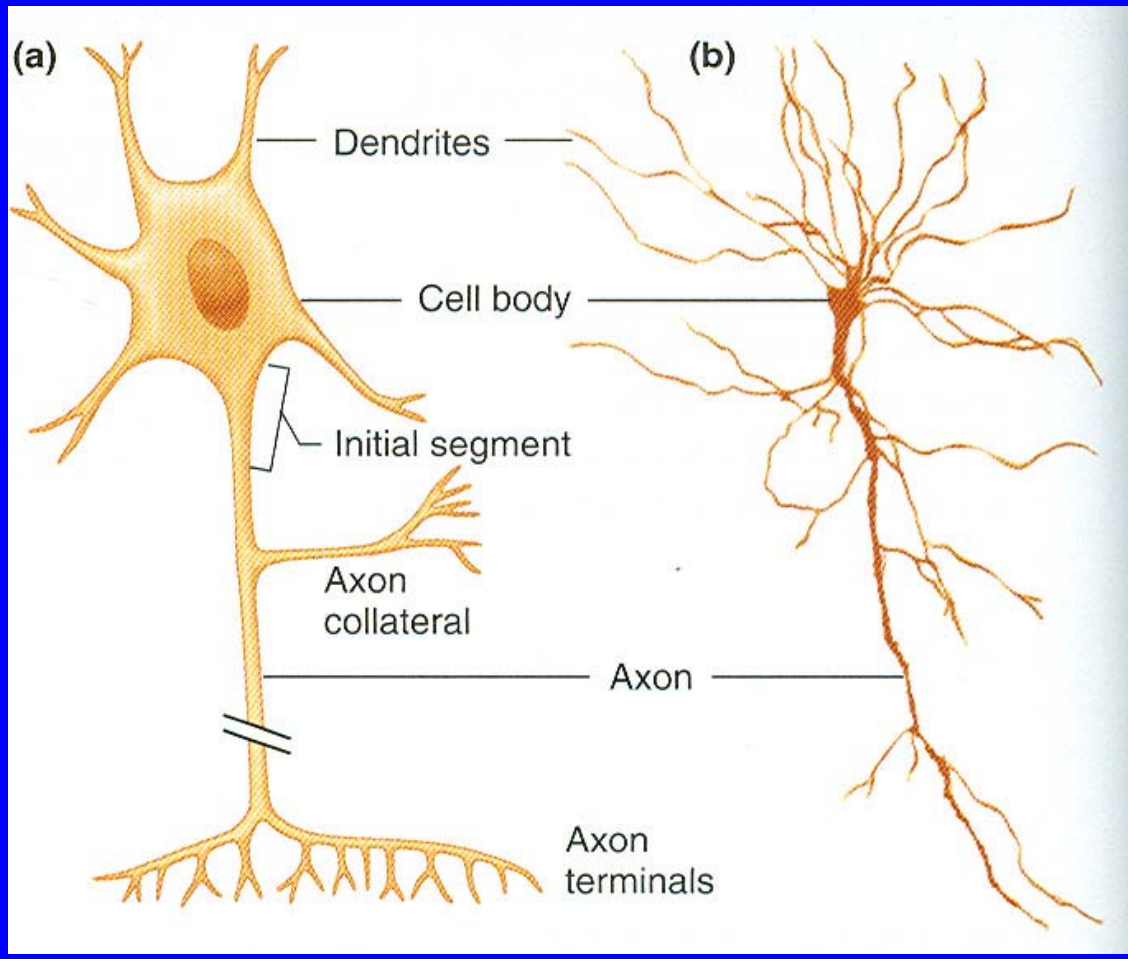
Schwann cells: myelinate single axons

nodes of Ranvier: bare axons between myelination

Axons may be 1 m long! nutrients? axonal transport via microtubular "railways", consuming ATP

Neurons Are Cells

- cell body
- organelles
  - nucleus
  - cytoplasm
  - mitochondria
  - endoplasmic reticulum
  - golgi apparatus
- cell processes
  - axon
  - dendrites
- cell membrane: phospholipid bilayer



Neuron Parts by Function

- "Input": chemoelectrical reception; in dendrites (soma, axon)
- "Metabolic Center" soma (axons, dendrites):
  - nucleus
  - protein synthesis
  - ATP production
- "Trigger" axon hillock: digital output of spatiotemporal integration
- "Transmission" axon, terminals: transmit information to other cells via action potentials

Distinctive Feature

- In addition to all the genetic and biochemical complexities that all cells possess, neurons have the added feature of having ***electrically excitable membranes***, a trait they share with certain other cell types (e.g., myocytes).
- Electrical excitability results from maintenance of membrane potential and differential distribution of many voltage- and ligand-sensitive ion channels in the membrane.
- Communication between cells requires electrical responsivity

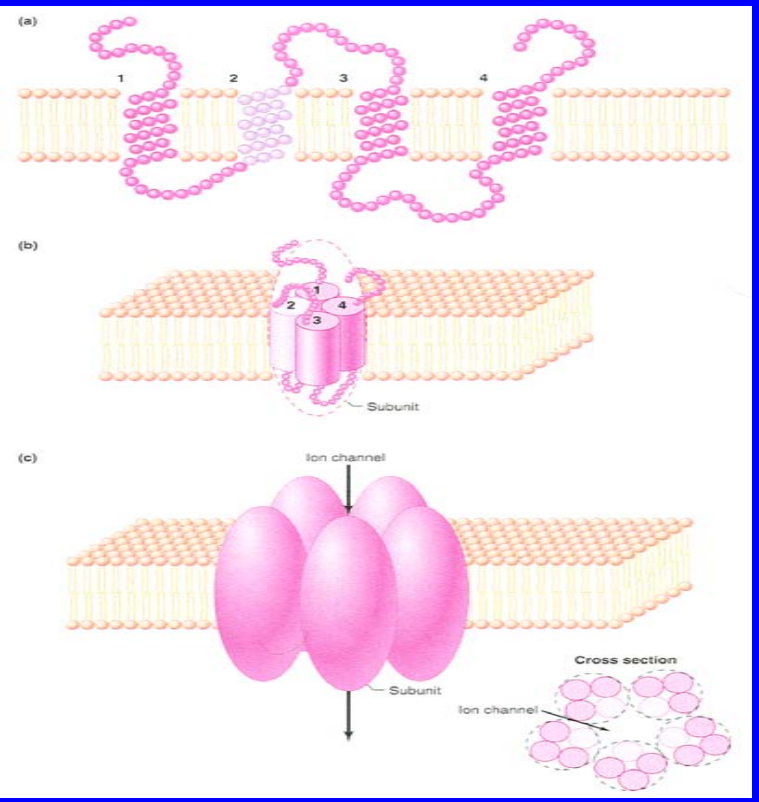
Membrane Function

- physical barrier: holds in contents
- chemical barrier: allows for selective passage of compounds, ions, water.
- amphipathic (polar & non-polar regions)
- composition:
  - phospholipids
  - cholesterol
  - integral membrane proteins
- capacitor: 1 $\mu F/cm^2$
- membrane potential, typically ~ -65 mV, ~7nm
- Integral membrane proteins: receptors; ion channels;

Ion Channels

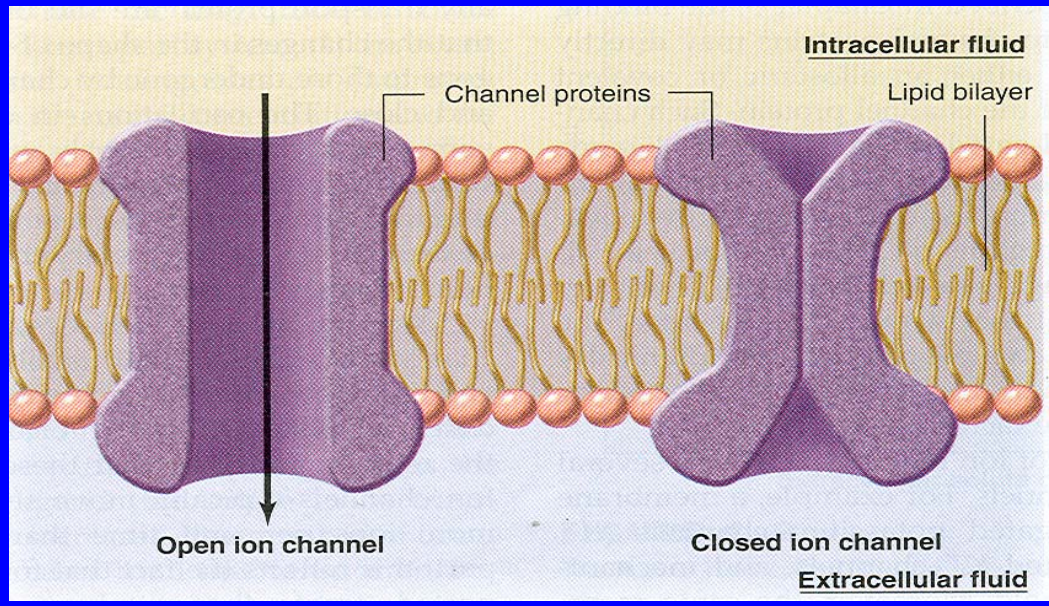
- Na^+, K^+, Cl^-, Ca^{2+} diffuse across membranes at high rates, despite their ionic nature. How?
- Integral membrane proteins form channels through which ions may pass through membranes
- May be single proteins or protein complexes
- Different channels are selective for different ions
- Pore is v. small: ions in single file

Ion Channels



consist of single proteins or protein complexes

open or close via conformational changes



Ion Flux: Electrical Forces

- electrical potential exists across cell membrane (inside negative relative to outside)
- ions are charged, and thus are influenced by electric field
- consider, if no Δ [in] vs. [out], still have electrical driving force
  - cations into the cell, anions out of the cell
- *electrochemical* gradient takes into account concentration gradient *and* electrical potential
- forces may act in concert *or* oppose each other

A little more complex…

- Ion channels may be open or closed, based on conformational change of the protein
- Process may be very rapid: $\tau < 0.5$ ms
- At a given EC gradient and time period, total ion flow depends on the frequency and duration of it being open (i.e., it's probability of being open) x driving force
- Probability depends on:
  - allosteric/covalent forces for ***ligand-gated*** channels
  - membrane potential in ***voltage-gated*** channels
  - physical deformation in ***mechanically-gated*** channels
  - a combination of the above

Biophysics: Resting E_m

- cells maintain negative intracellular potential via ion pumping
- membrane has conductive ion channels
- membrane also acts as capacitor
- ion separation = electrochemical gradient:

$$E = [RT/(z_sF)]\ln([out]/[in])$$ *Nernst, 1888*

R, gas constant; F, faraday; T, temp; z_s, valence

$$E \sim 61.54\log([out]/[in])$$ (@body temp, 1 atm)

Ion	**[in]** (mM)	**[out]**(mM)	E_{Nernst} (mV)	**EG** (-60mV)	**CG**	**Net**
Na^+	**15**	**150**	**+62**	**+122 in**	**in**	**in**
K^+	**150**	**5.5**	**-89**	**-29 in**	**out**	**out**
Cl^-	**9**	**125**	**-71**	**-11 out**	**in**	**0**
Ca^{2+}	**.0001**	**1.5**	**+129**	**+189 in**	**in**	**in**

must then multiply Net by conductance to get flow

Goldman Equation

$$V_m = \frac{RT}{F} \ln \left\{ \frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o} \right\}$$

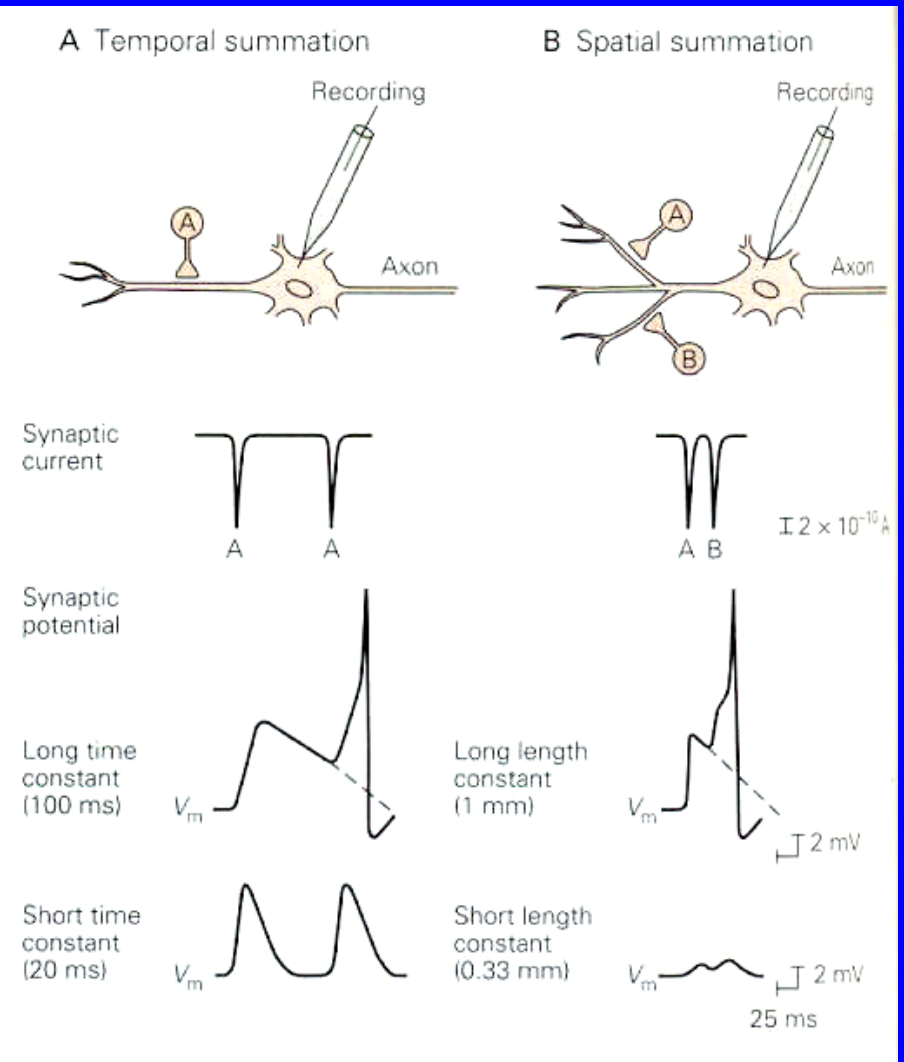
- Based on ***electrochemical gradient***
- generalizes to Nernst Eq. for single species
- small effect of pump on V_m, except to establish/maintain
- Na^+/K^+-ATPase "pump" is ***electrogenic*** since it moves net charge across the membrane ($3Na^+/2K^+$)
- Ion exchangers (Na^+/Ca^{2+}) use potential energy of one species to move the other species uphill

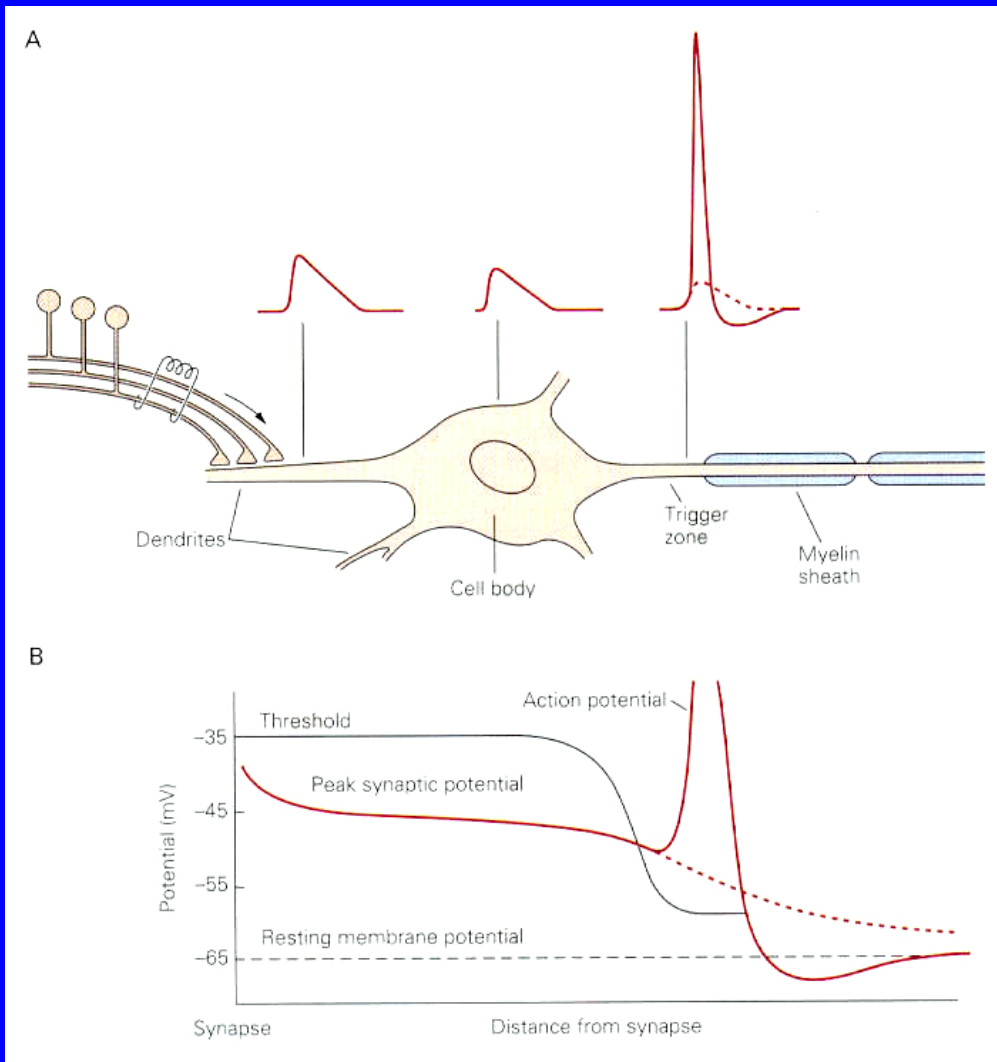
Changes in V_m

- terms:
  - ***de***polarizing: V_m from rest towards 0
  - ***hyper***polarizing: V_m more negative than rest
  - ***re***polarizing: return to from V_m depolarization
  - overshoot: V_m positive
  - graded potential (changes) because charge moves (e.g., ions flow) across the membrane, due to changes in g. Decay is according to length constant
  - ***synaptic potentials***
  - ***generator potentials*** (sensory neurons)
  - ***action potentials***
- ***Spatial Integration*** of synaptic activity from different sites of the postsynaptic neurons (long vs. short space constants)
- ***Temporal Integration*** of same at different times (long vs. short time constants)

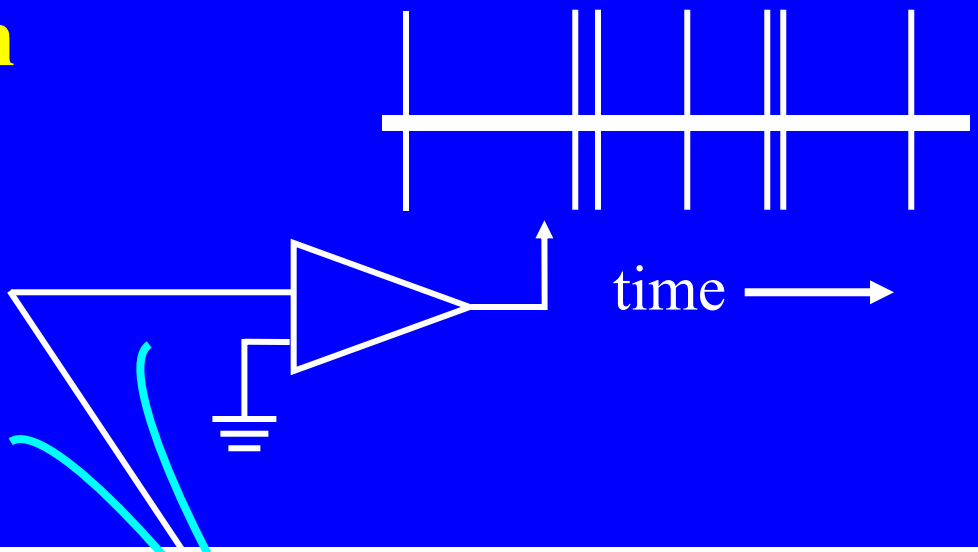
Length & Space Constants

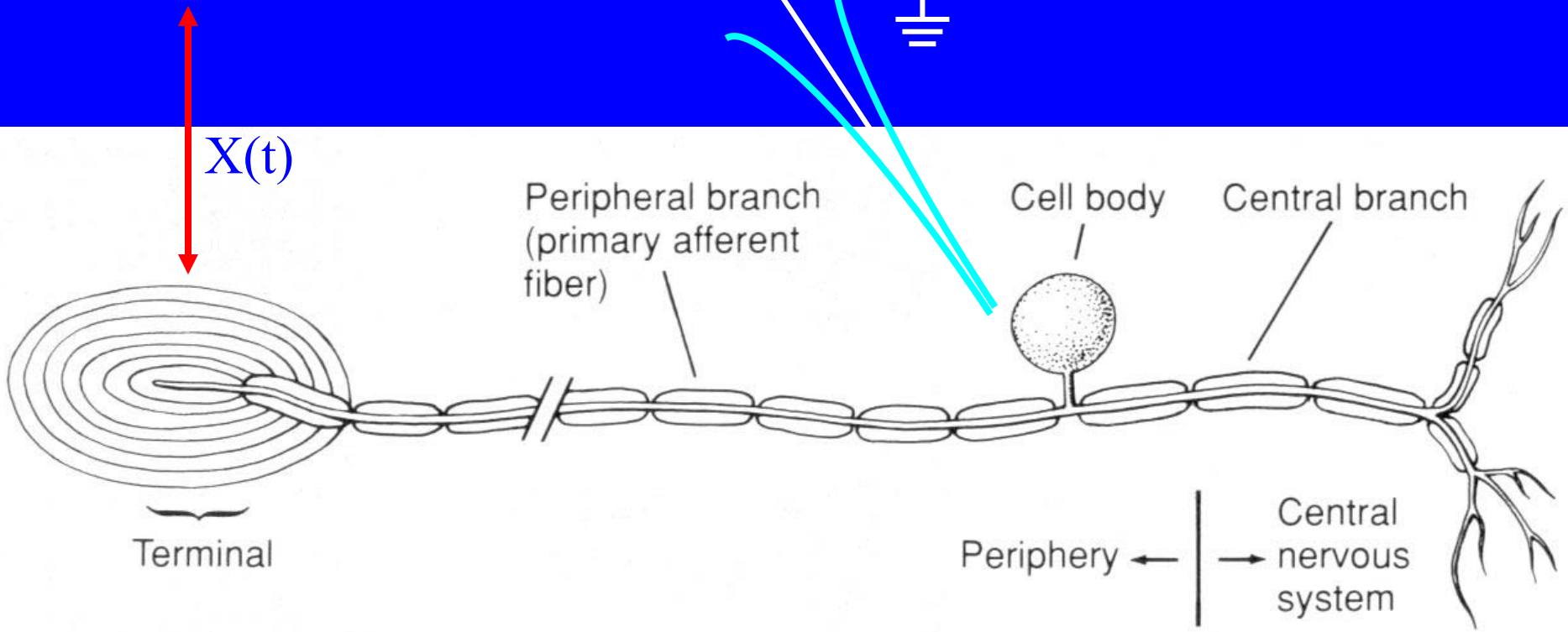
$\tau = R_m C_m$ $\lambda = (r_m/r_a)^{1/2}$



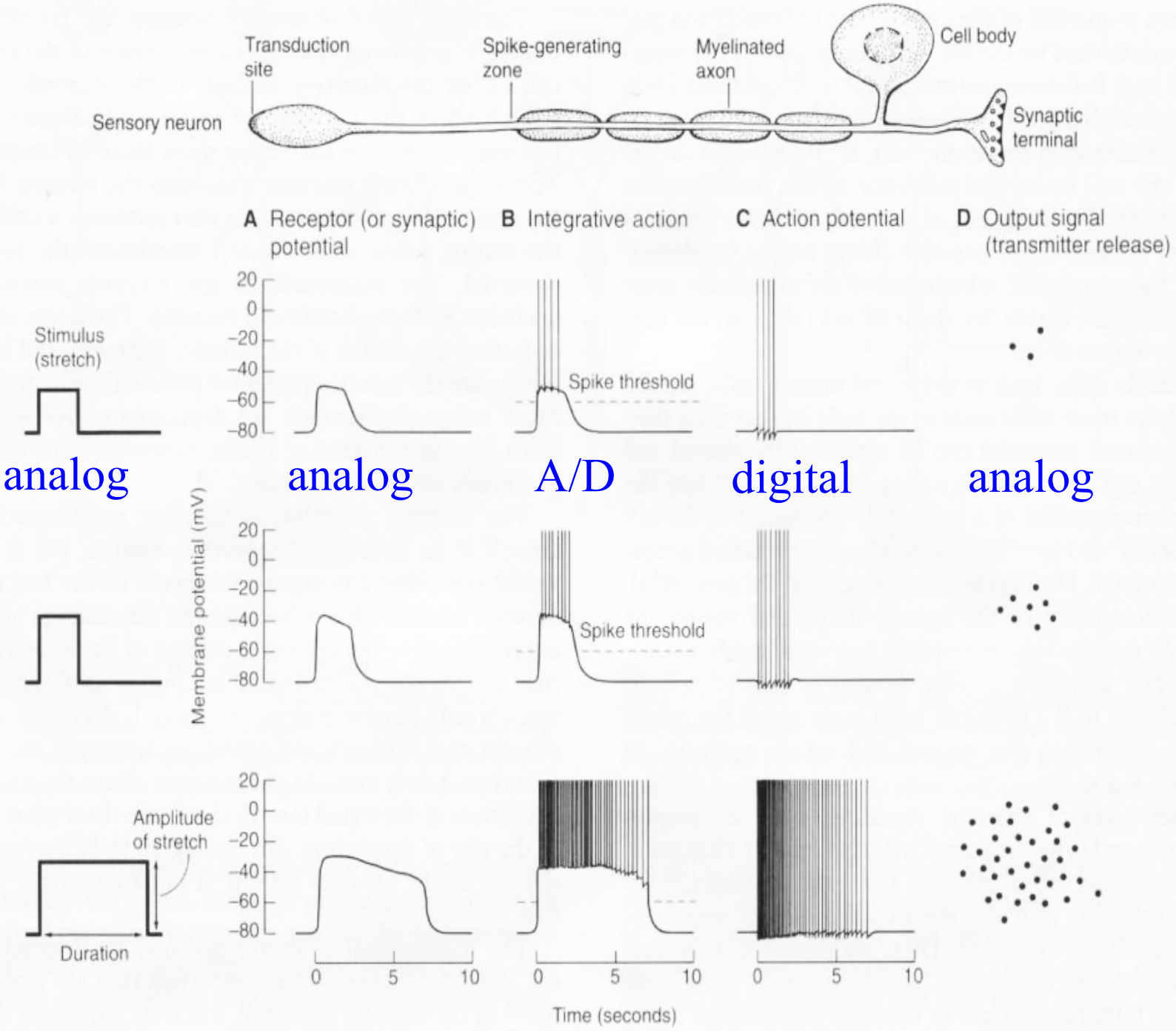


Stimulus Transduction and Sensory Encoding





Thus, analog (continuous)-to-digital (discrete) conversion

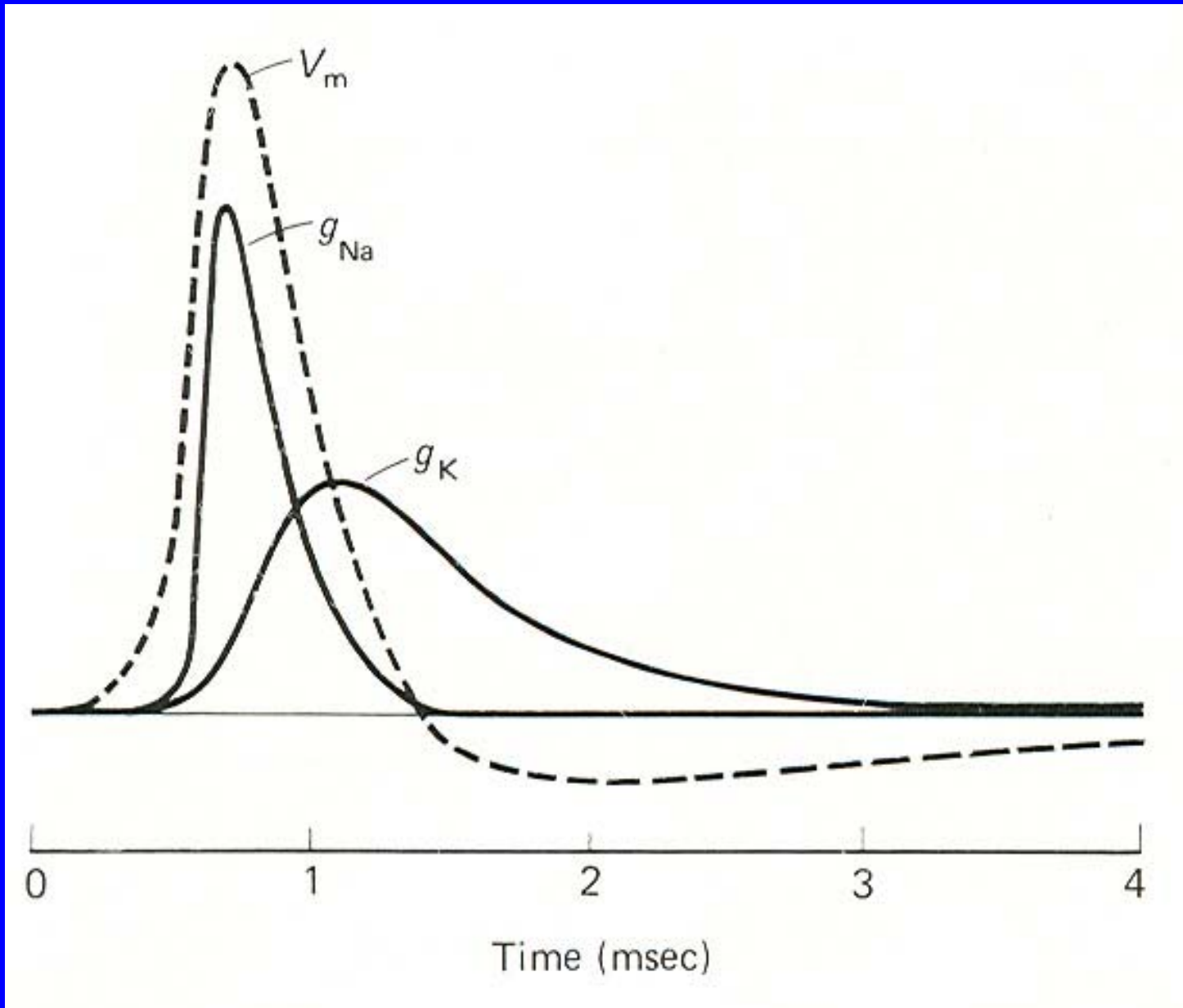

Transduction site
Spike-generating zone
Myelinated axon
Cell body
Sensory neuron
Synaptic terminal
A Receptor (or synaptic) potential
B Integrative action
C Action potential
D Output signal (transmitter release)
Stimulus (stretch)
Membrane potential (mV)
Spike threshold
Amplitude of stretch
Duration
Time (seconds)
analog
analog
A/D
digital
analog

Action Potential

- Na: $g_{Na} = I_{Na}/(E-E_{Na})$; $E_{Na} \sim +67$ mV
  - opens fast, positive feedback mechanism
  - closes fast, negative feedback mechanism
  - inactivates spontaneously
- K: $g_K = I_K/(E-E_K)$; $E_K \sim -90$ mV
  - opens slowly
  - closes v. slowly
  - inactivates from polarization only

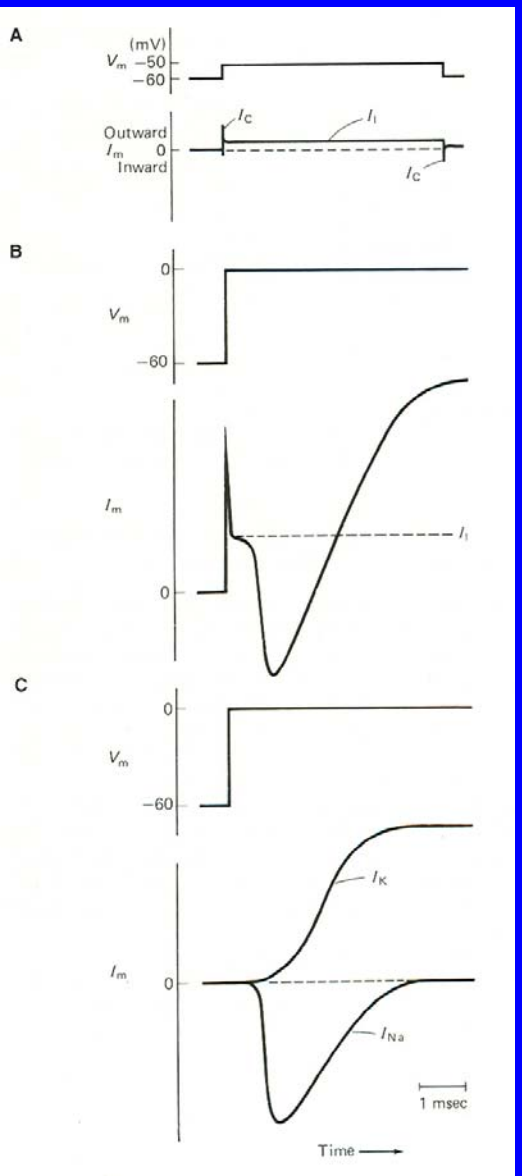
Action Potential Currents

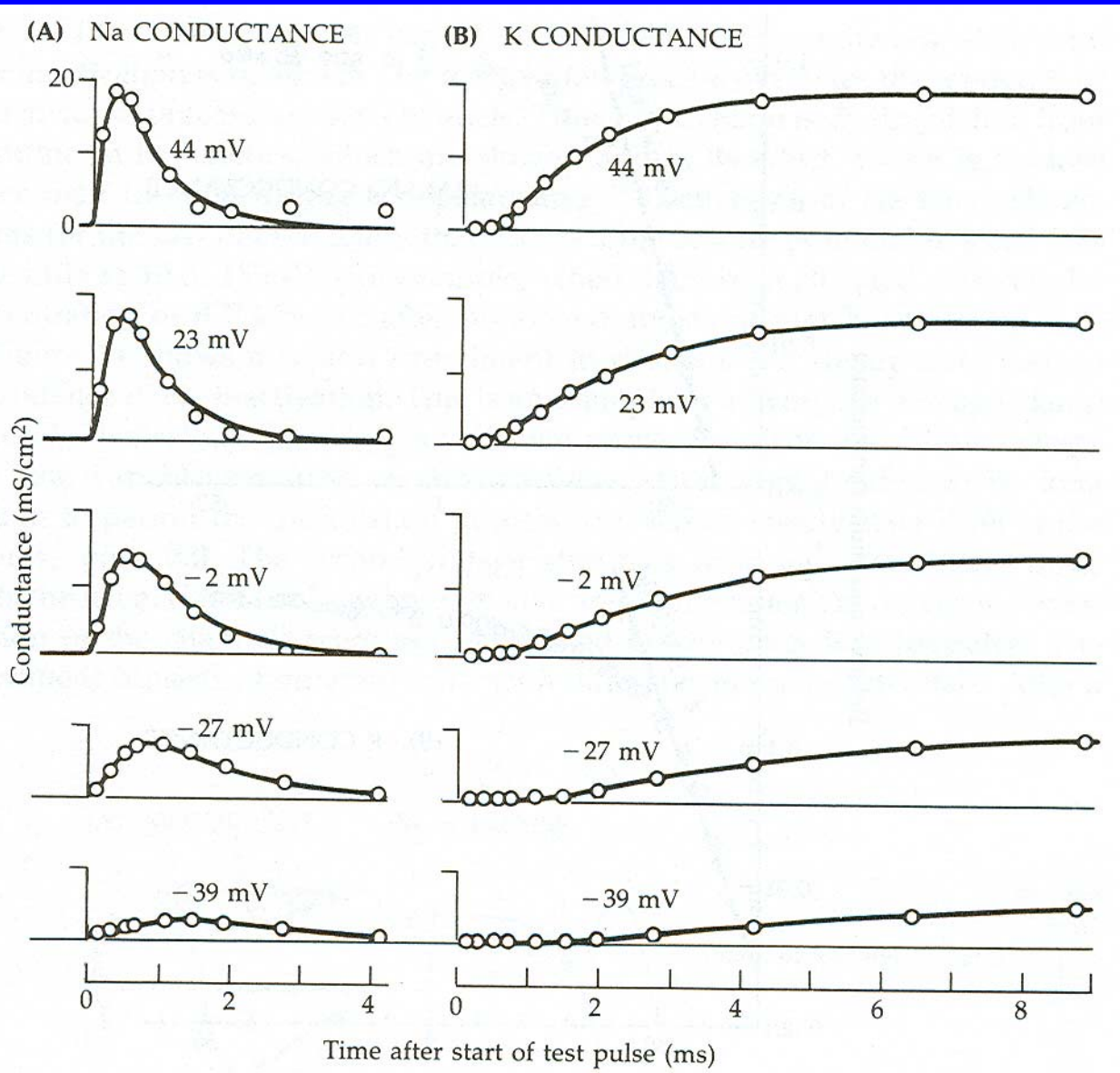
How do we know this?

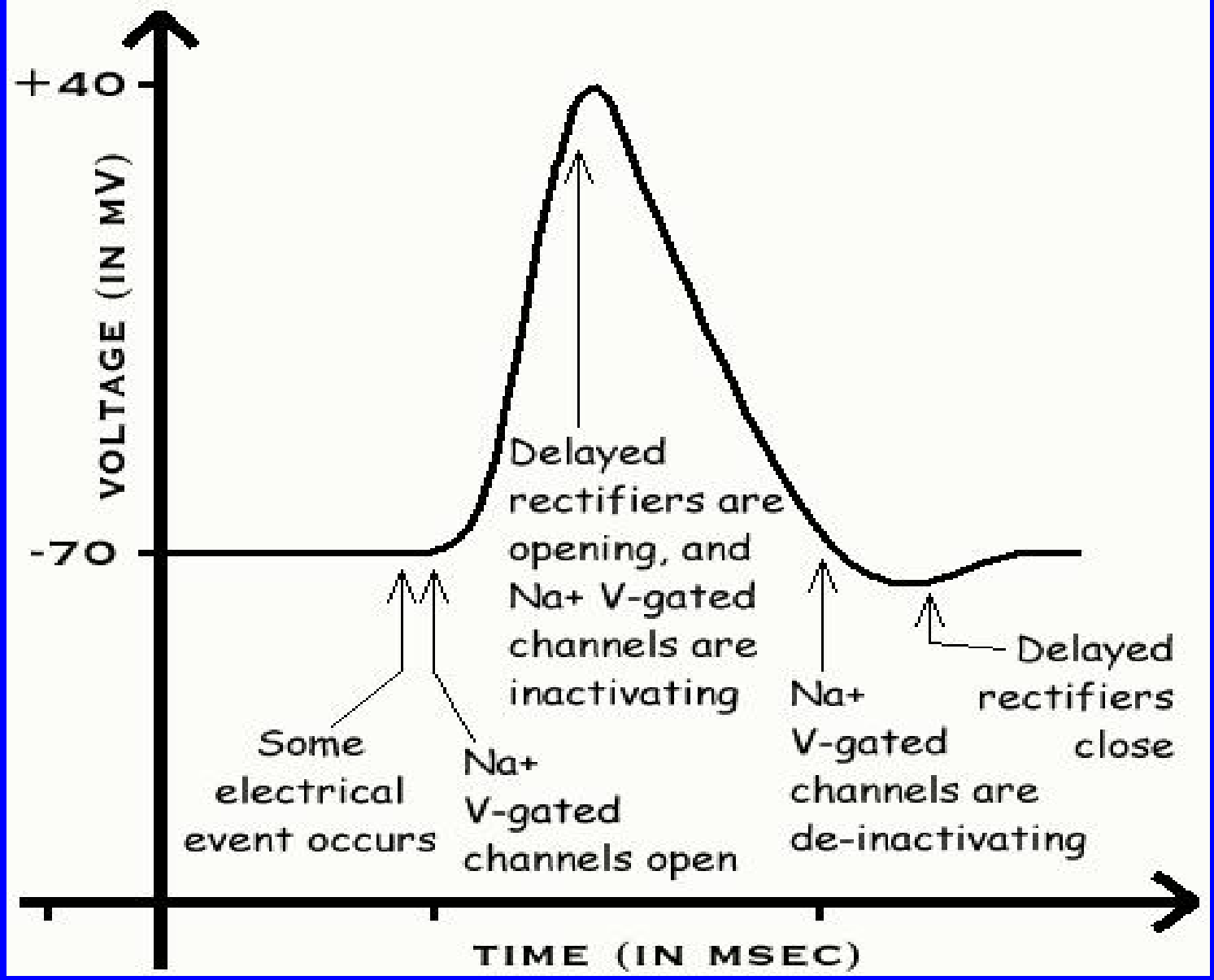


Voltage Clamp Experiments

Hodgkin & Huxley (1950s)



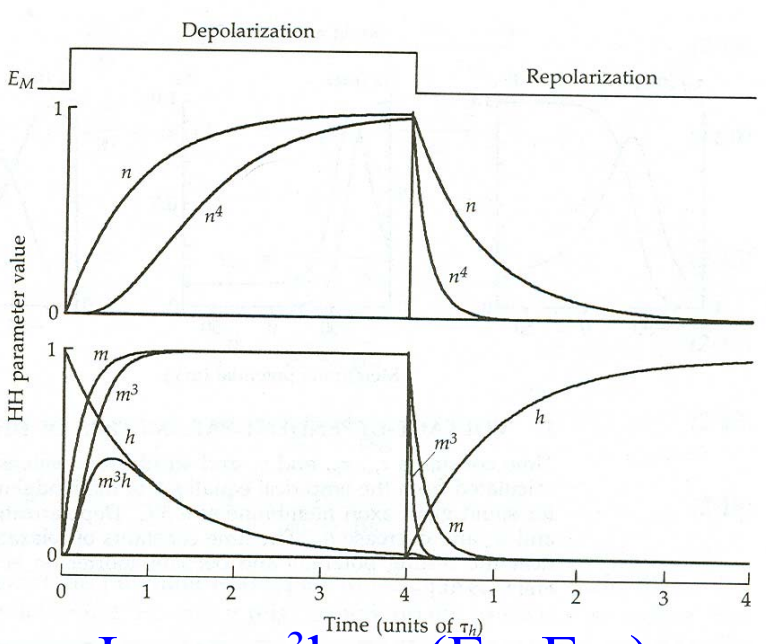




Absolute Refractory Period: **due to Na^+ wide open or inactivated**
Relative RP: **most Na^+ not deinactivated; K^+ channels mostly open**

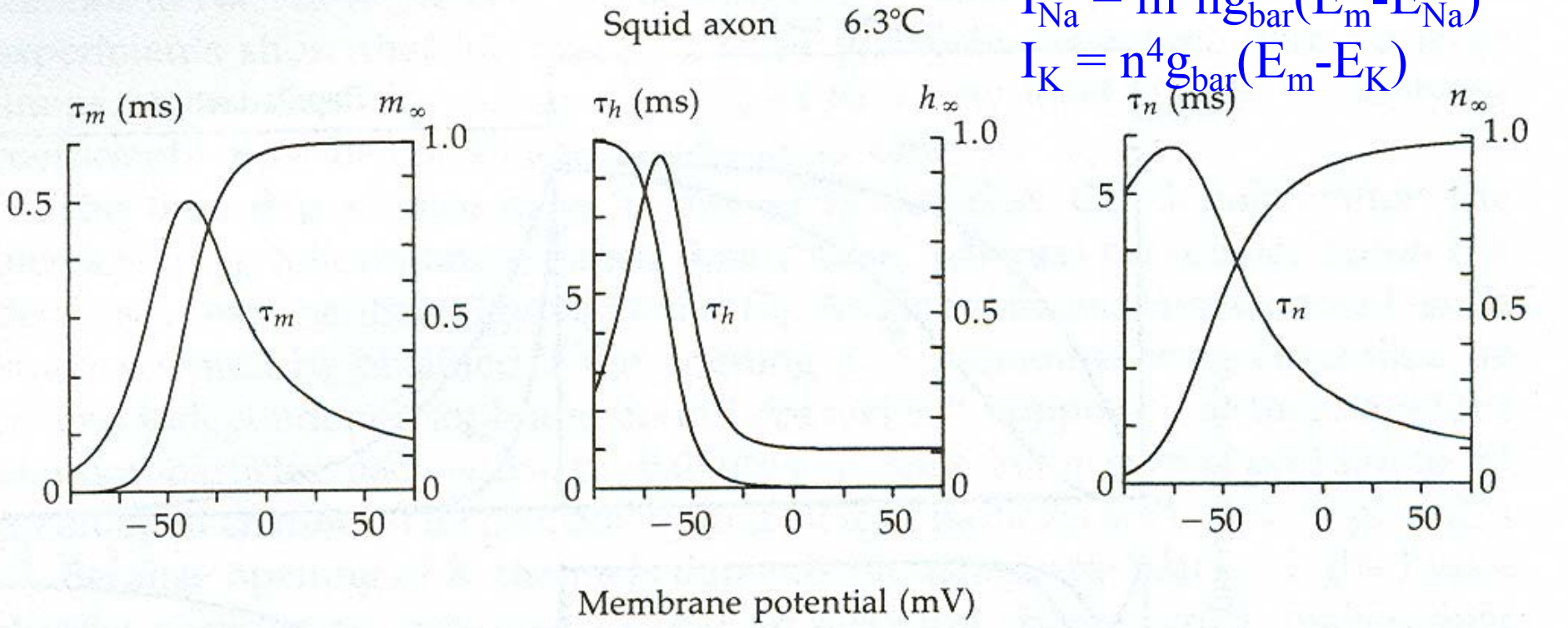
Model

- Na activation and inactivation modeled as separate processes.
- K activation only.
- Basis of Na pos. feedbk

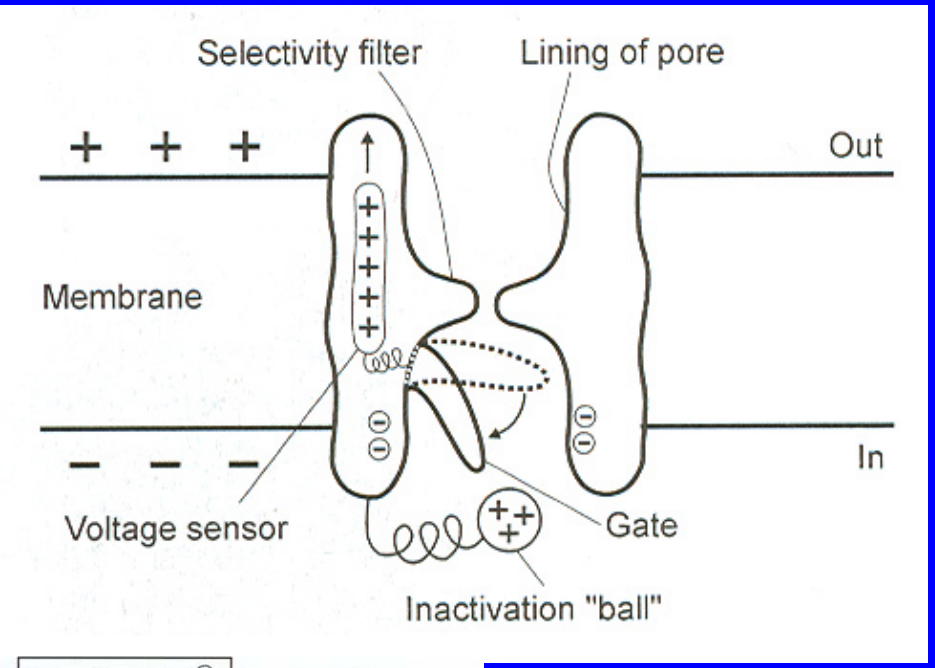


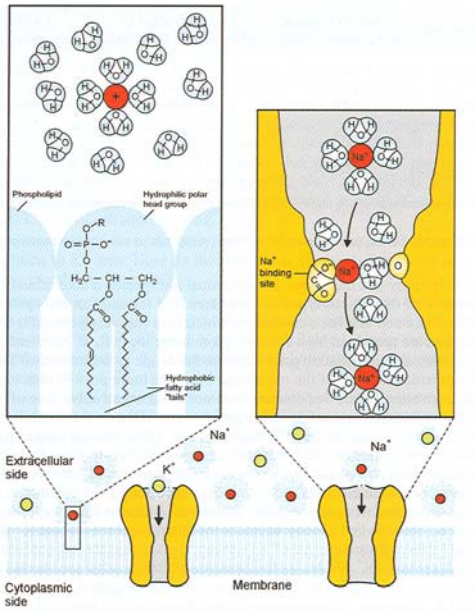
$$I_{Na} = m^3 h g_{bar}(E_m - E_{Na})$$

$$I_K = n^4 g_{bar}(E_m - E_K)$$



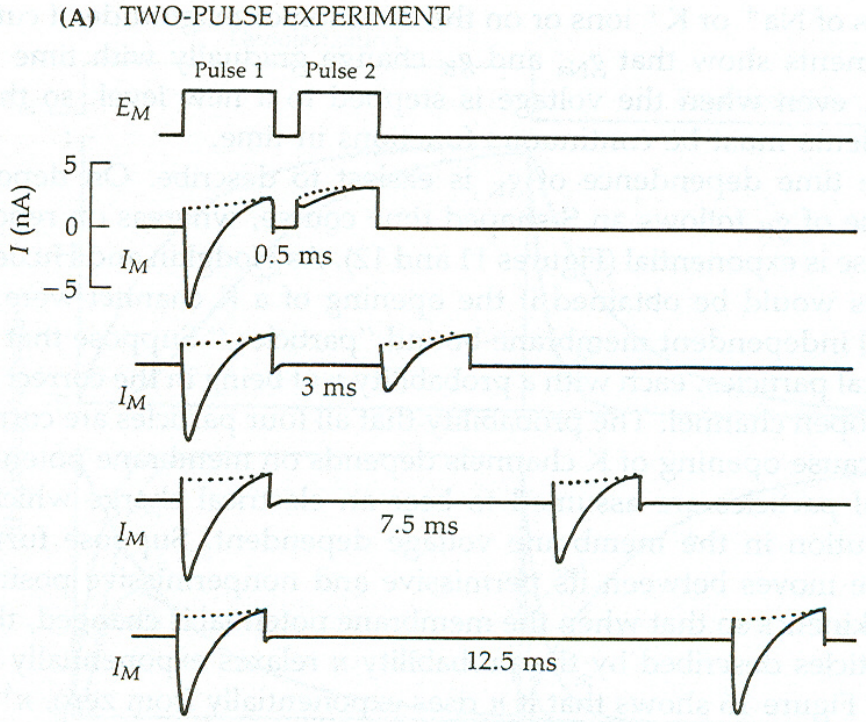
Na^+ Channel Models

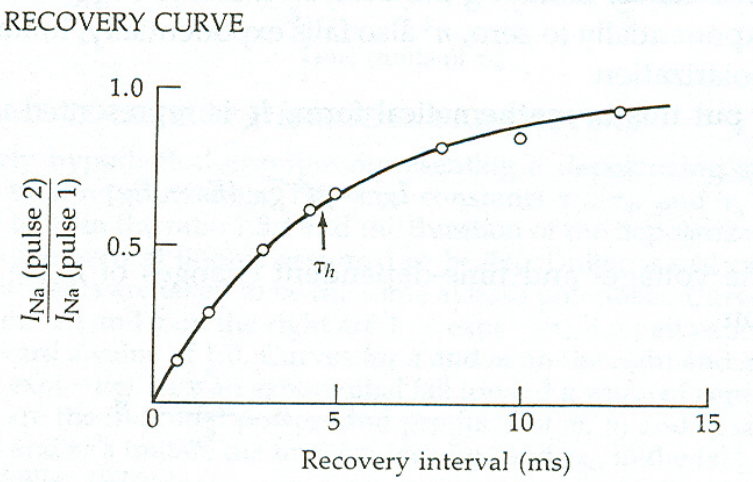




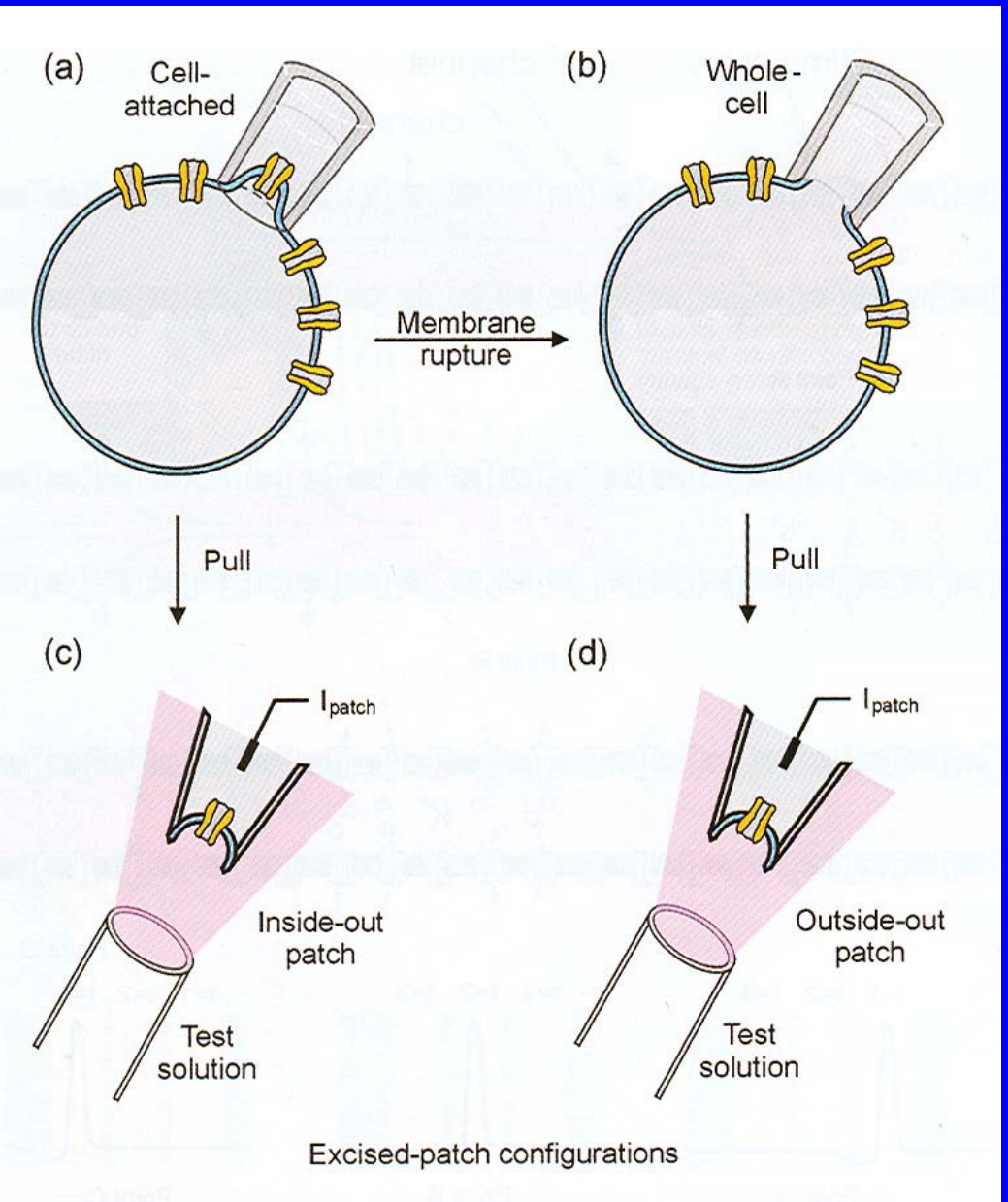
- "ball & chain" inactivation
- activation gate charged R groups

Inactivation



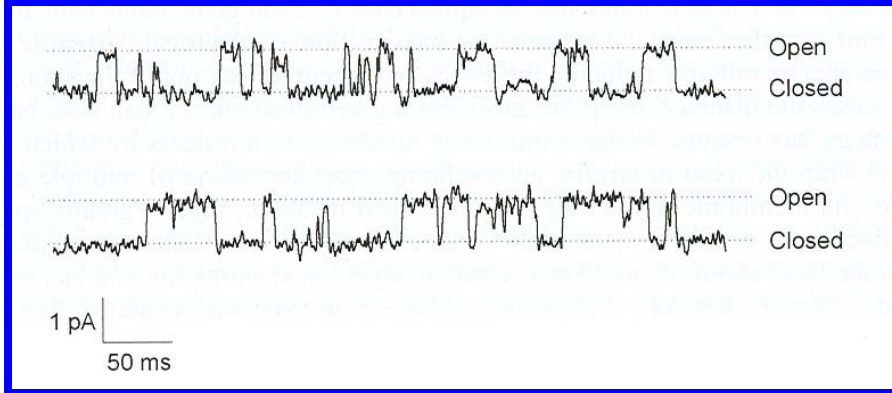


Patch Clamp Method

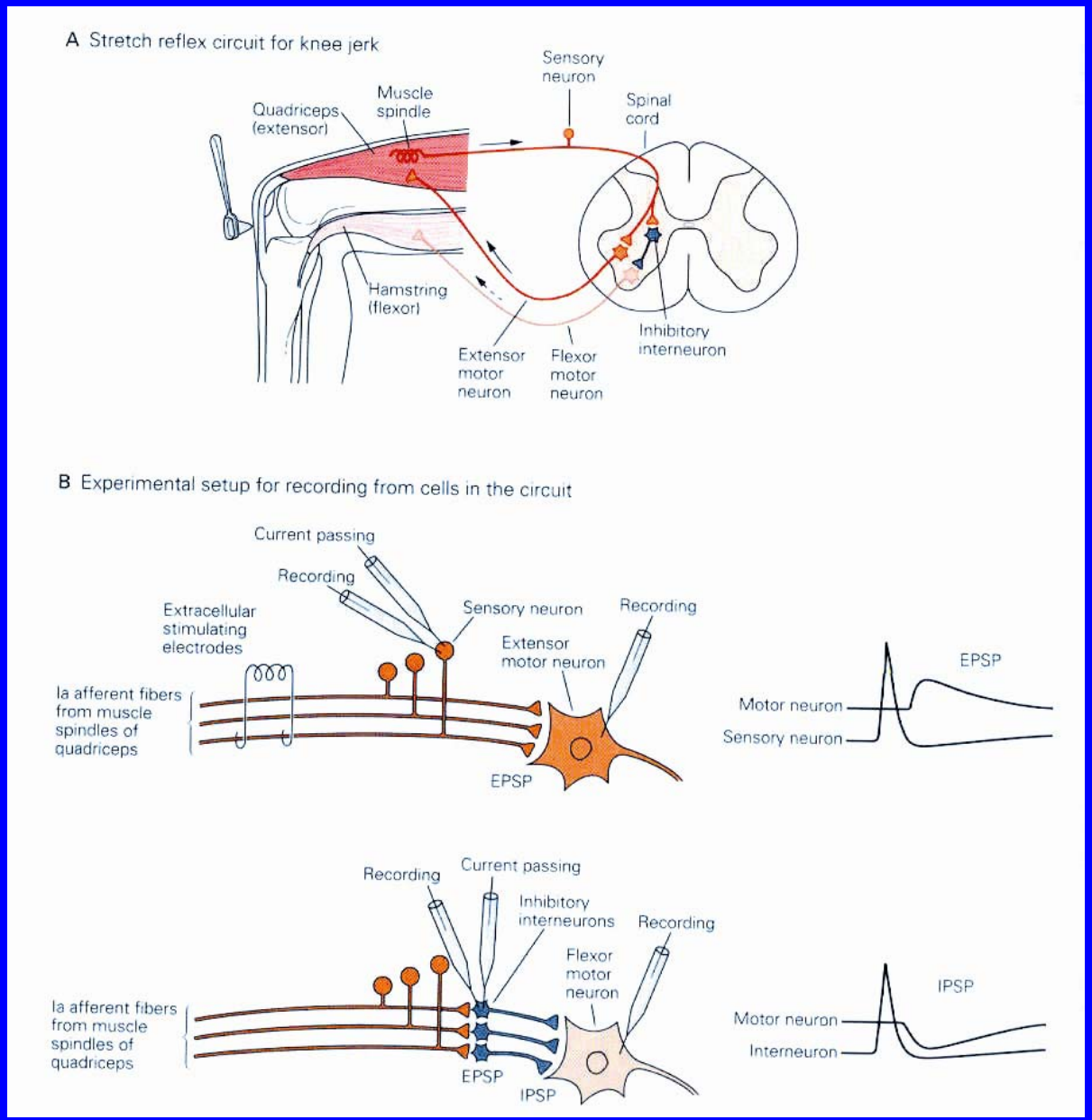


Excised-patch configurations

- allows for single channel recordings!
- single currents add up to whole cell currents



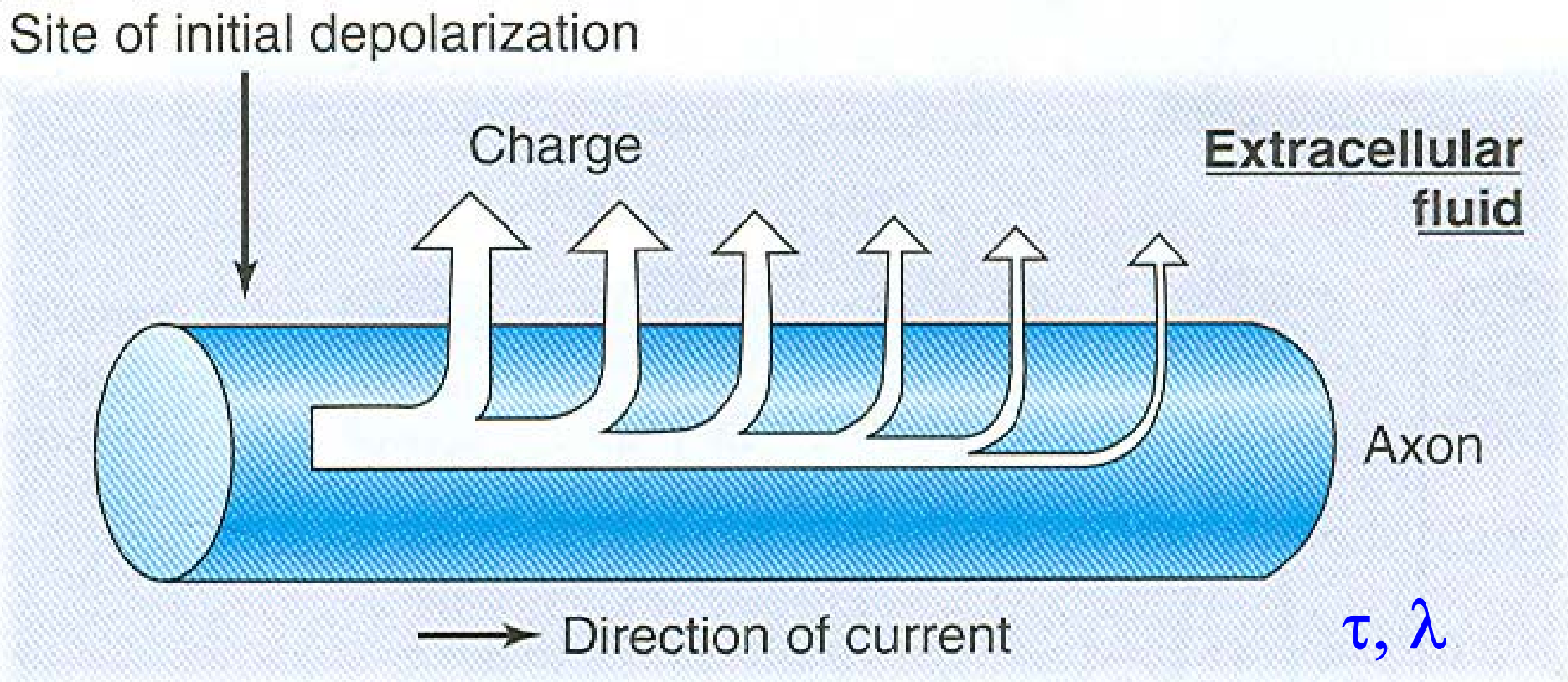
Synaptic Transmission



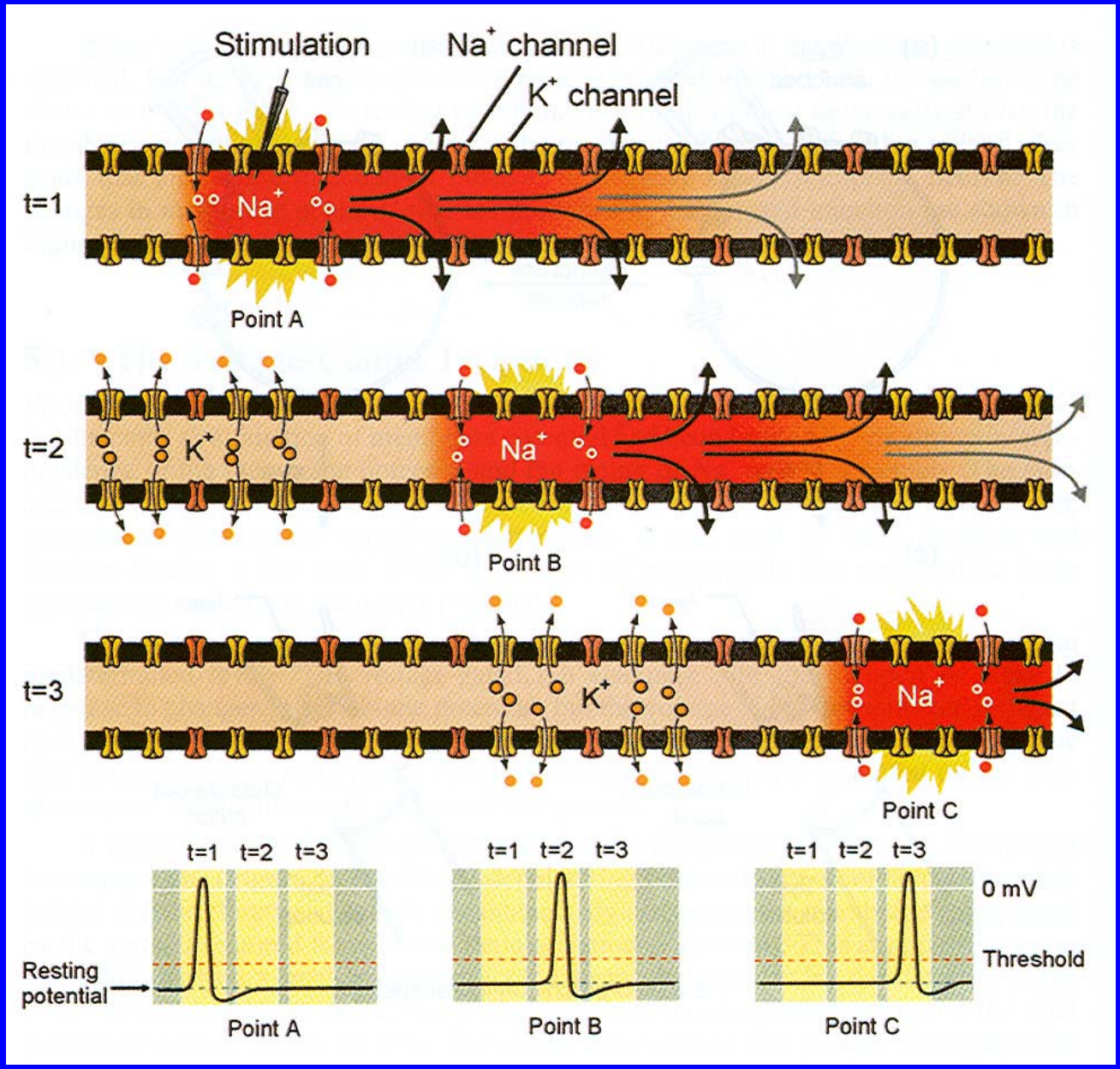
AP Propagation

- AP depolarization acts to open neighboring Na^+ channels, but not ones that are inactivated.
- Thus, ***directional*** propagation of AP occurs in axon
- APs are regenerative, not degenerative (like graded pots.).
- In myelinated axons, APs leap from one NoR to the next
  - Na^+ chs only at NoR
  - myelin prevents leak through memb
- ↑mylen → ↑conduction velocity
- ↑diam → ↑conduction velocity

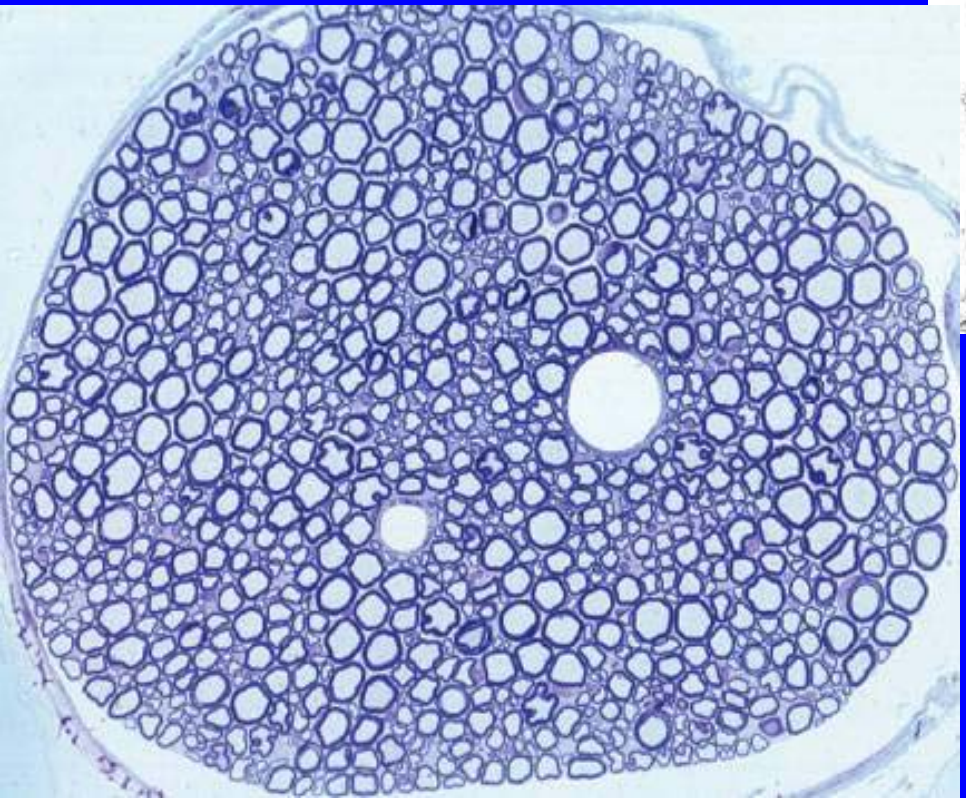
Passive Spread



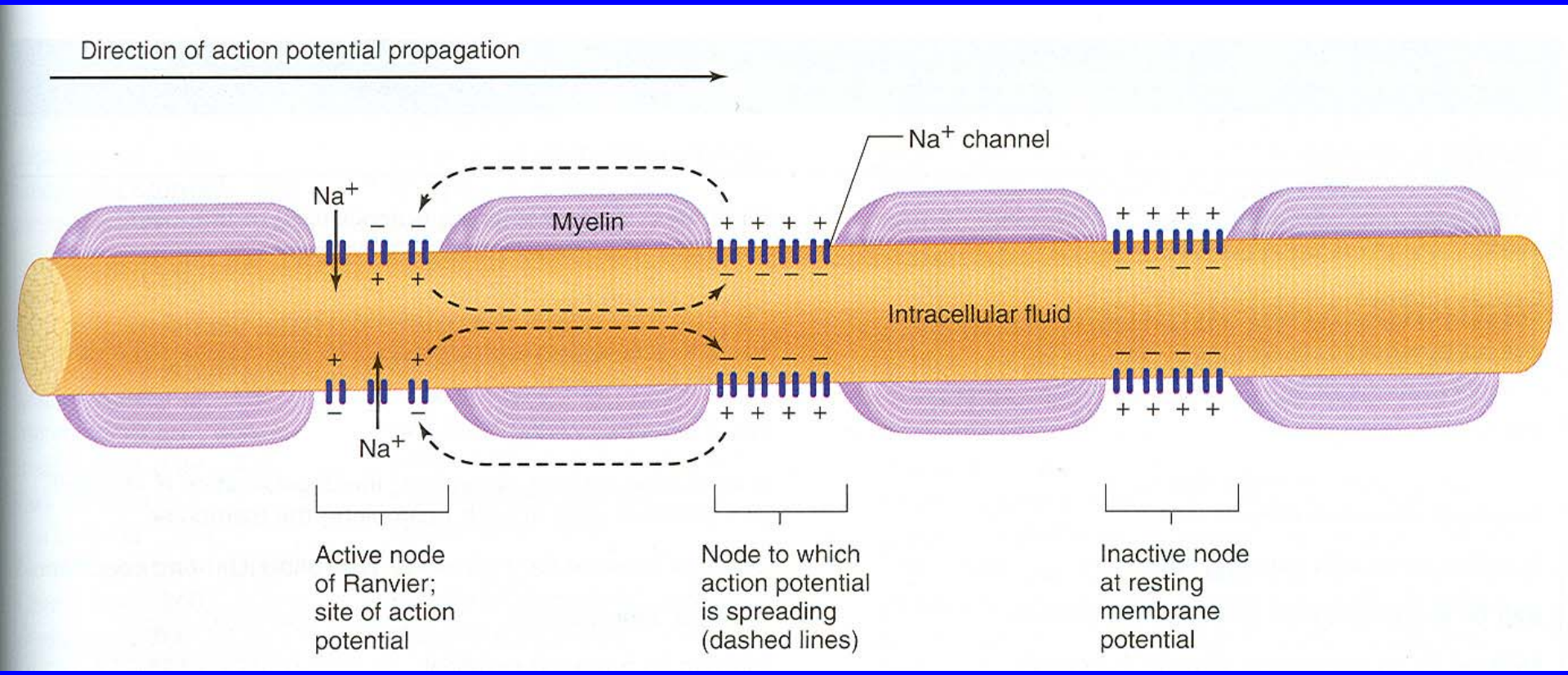
Active AP Propagation



Myelination



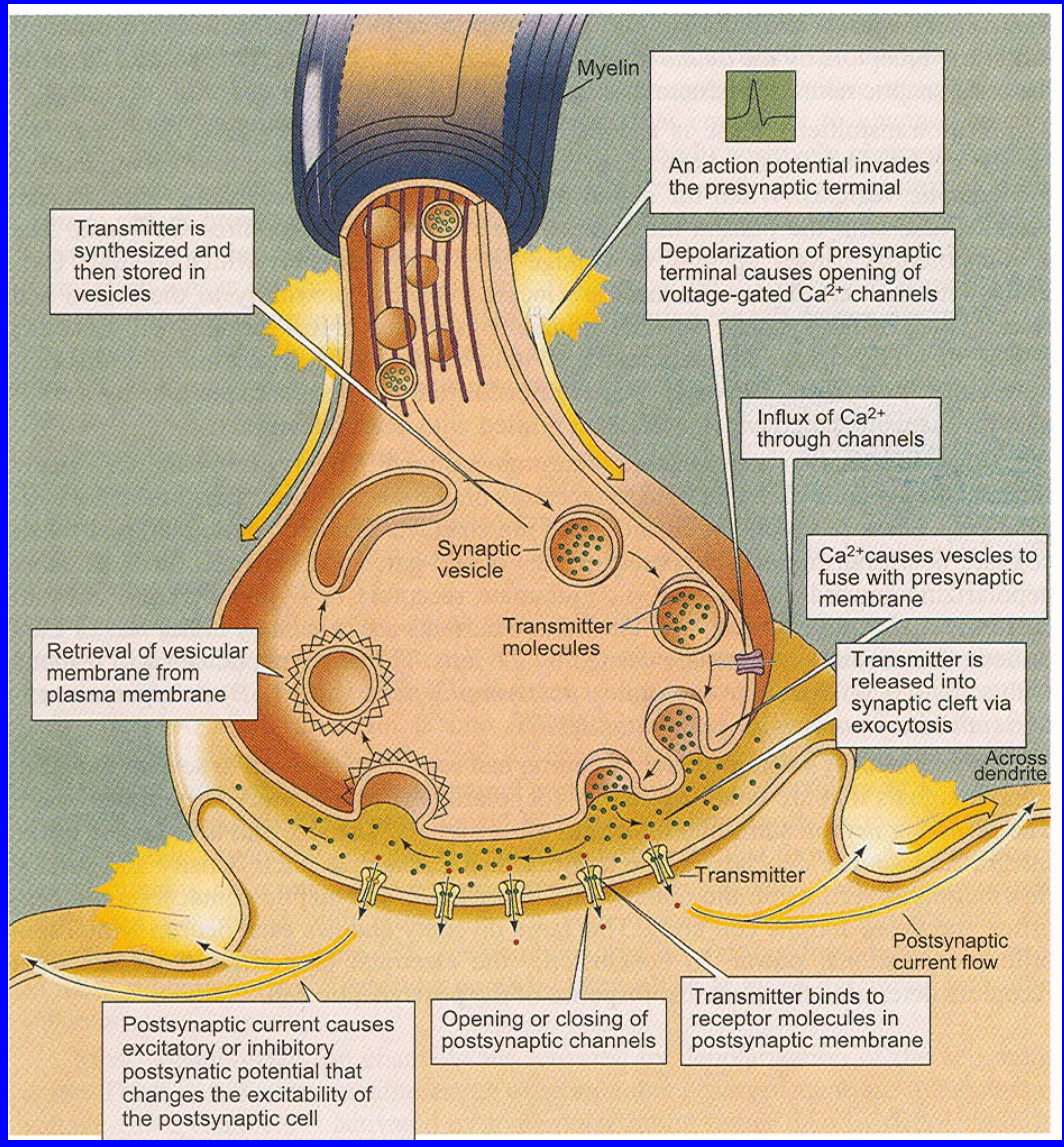
Saltatory Conduction



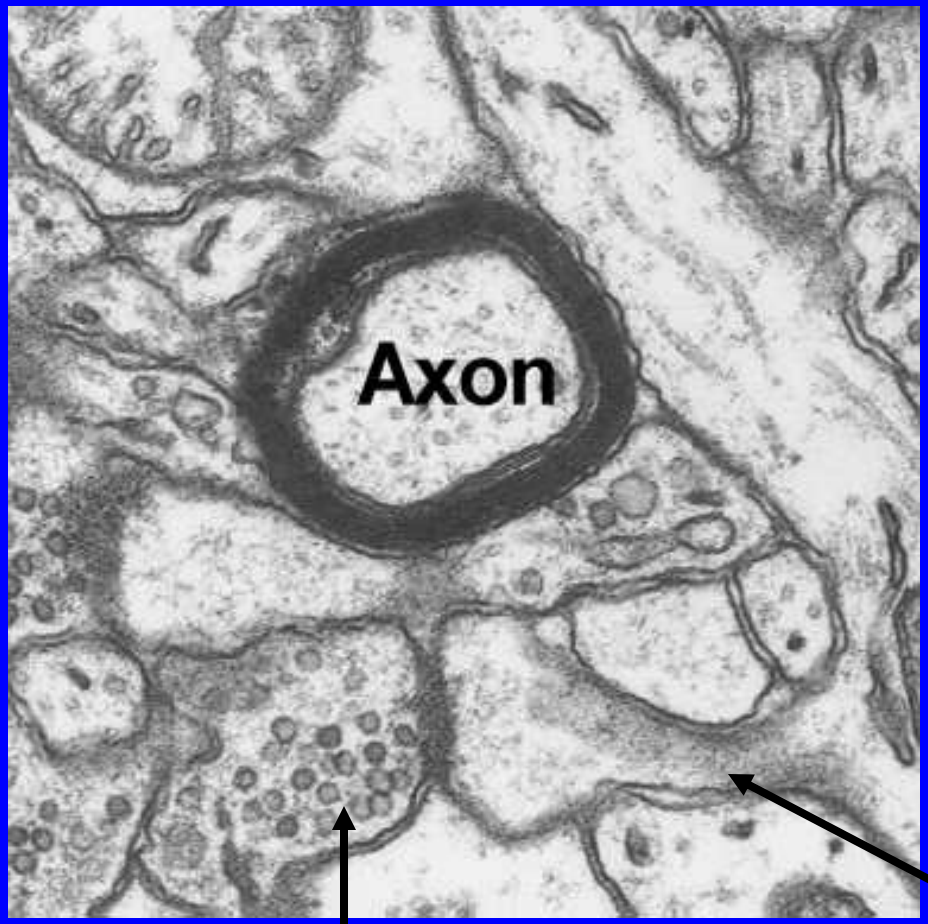
Synaptic Transmission

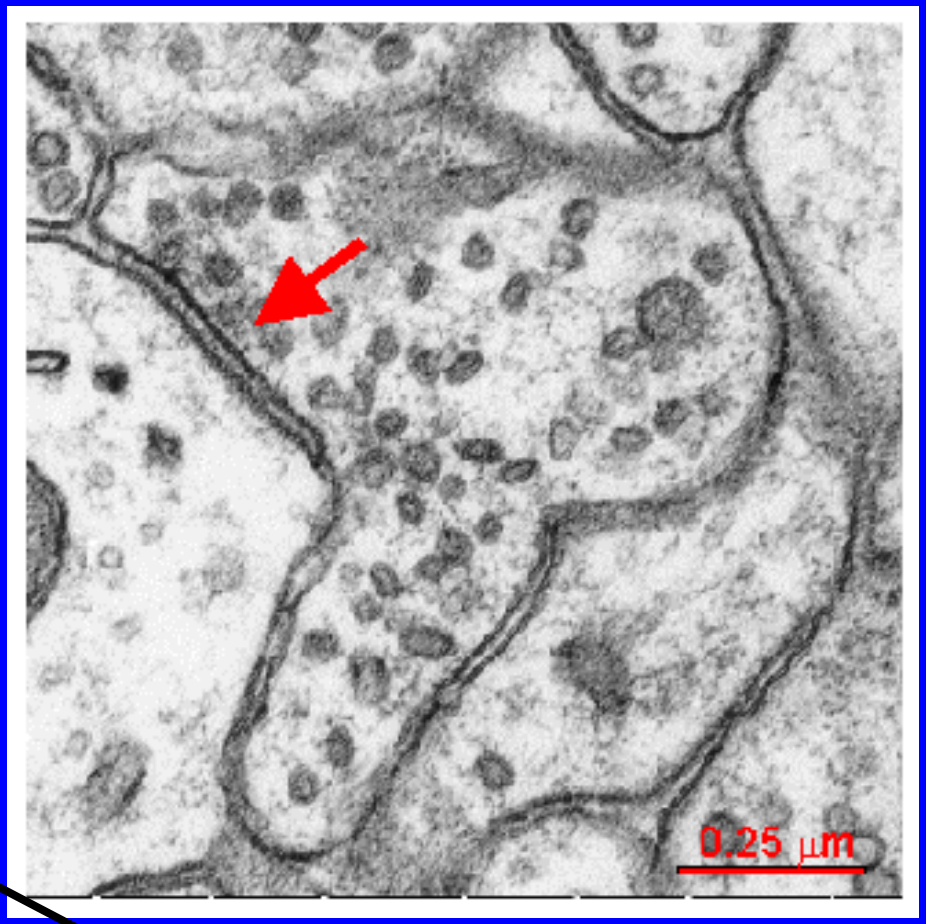
1. AP invades axon terminals
2. Vm-dep Ca2+ Chs open
3. [Ca2+]in rises
4. s. vesicles fuse to plasma m.
5. neurotransmitter released into s. cleft
6. NT binds to postsynaptic Rs, opening them
7. Cations or anions flow in

Thus, electrochemical communication



Synapses





presynaptic vesicles

dendritic spine

What Do I Do?

- record the electrical activity of individual neurons in context, while system is functioning
- perturb systemic variables, analyze neural/network computations
- quantify information in spike trains using information theory
- record network/systemic activity using optical imaging techniques

What Can YOU Do?

- design/manufacture microrecording electrodes, arrays
- signal processing of optical imaging data
- signal processing of spike train data\
- design/manufacture microchannel devices for chronic implantable devices for integration with the nervous system