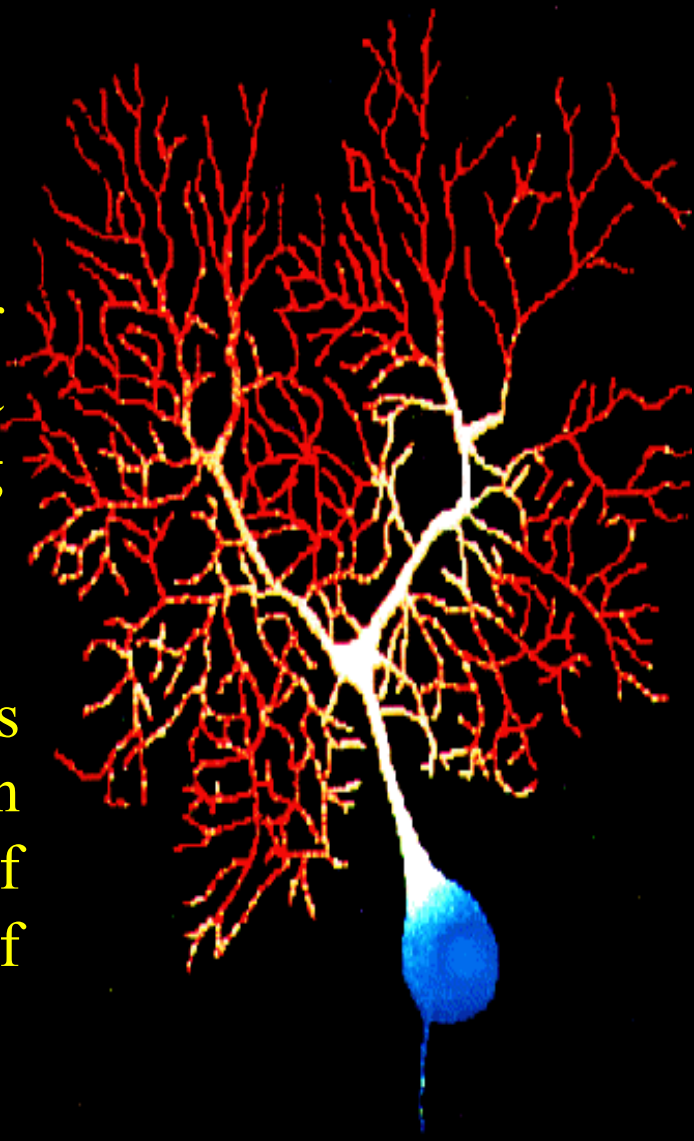
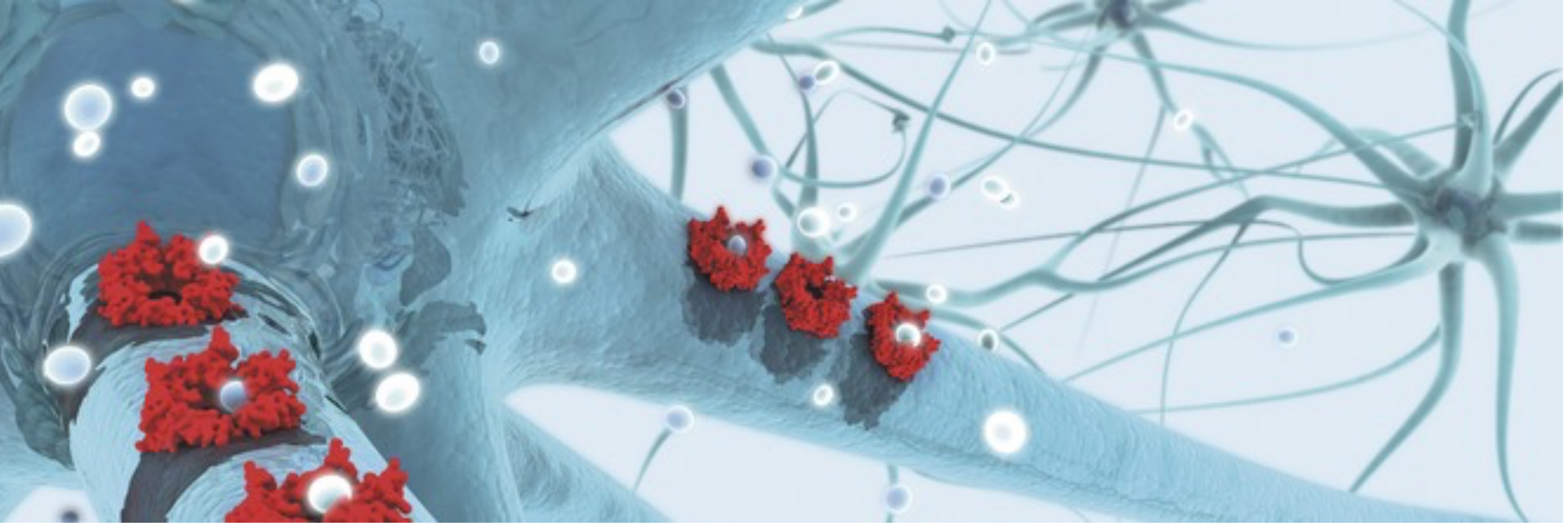
The membrane potential

- it vary rapidly over large distances

- controls a vast number of nonlinear gates – ionic channels – that provide a very rich substrate for implementing nonlinear operations.

- channels transduce stimuli into changes of the membrane potential and such voltage changes back into the release of neurotransmitter or the contraction of muscles.





Nerve and muscle are *excitable tissues* - they have the ability to generate and propagate electrical signals.

Membrane potential is influenced by:

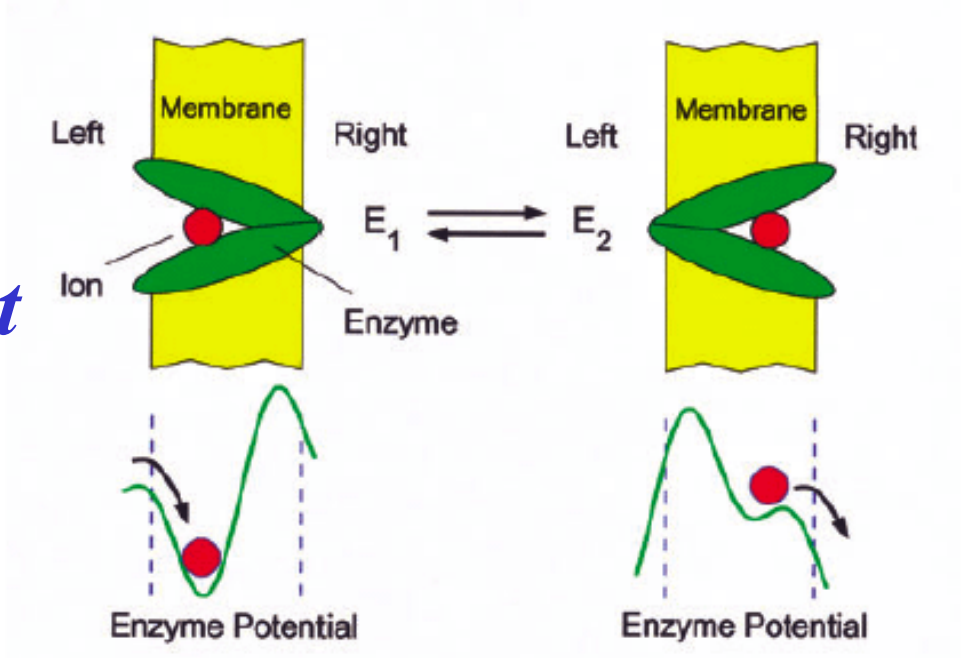
- Concentration gradients
- Permeability of the membrane to ions

$$\Delta\Psi = \frac{RT}{F} \ln \frac{P_K[K^+_{out}] + P_{Na}[Na^+_{out}] + P_{Cl}[Cl^-_{in}]}{P_K[K^+_{in}] + P_{Na}[Na^+_{in}] + P_{Cl}[Cl^-_{out}]}$$

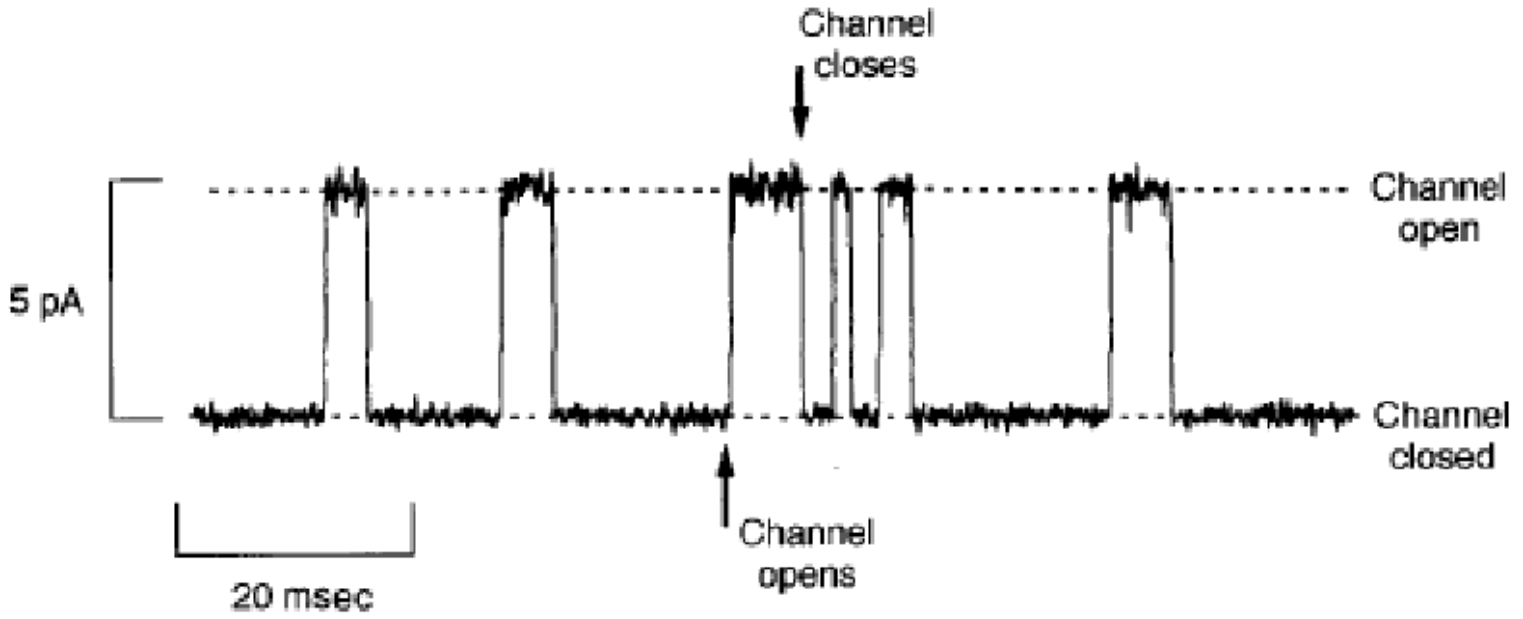
Channels

(gated pore)

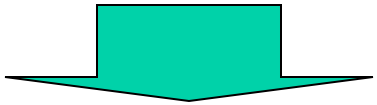
secondary active transport



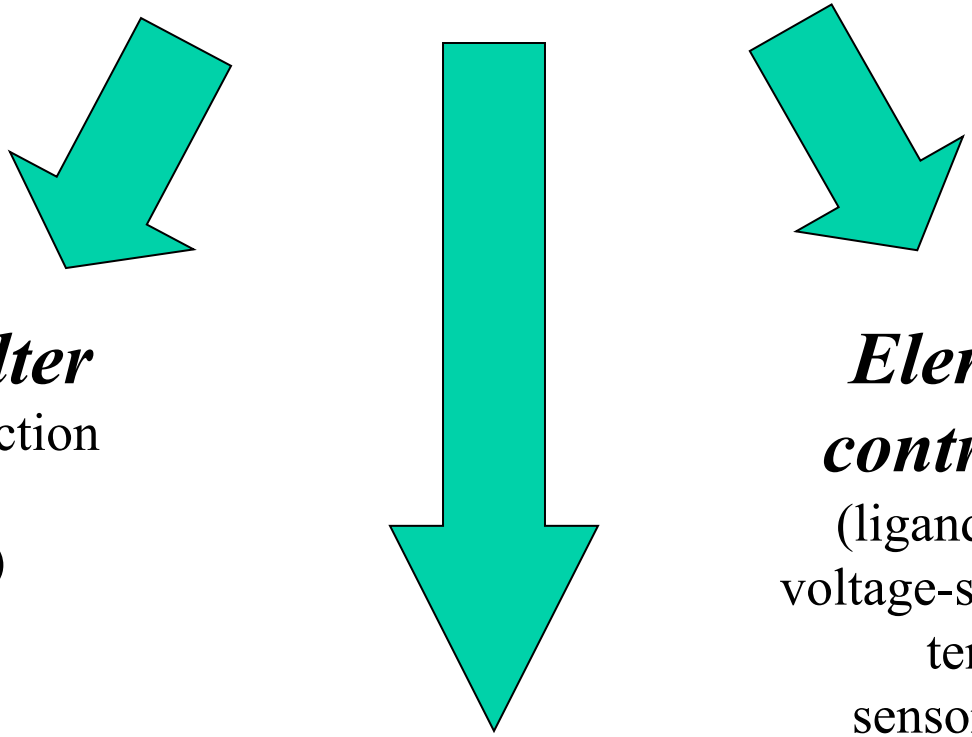
Single-channel currents



Ion channel



ion-permeation pathway through the membrane

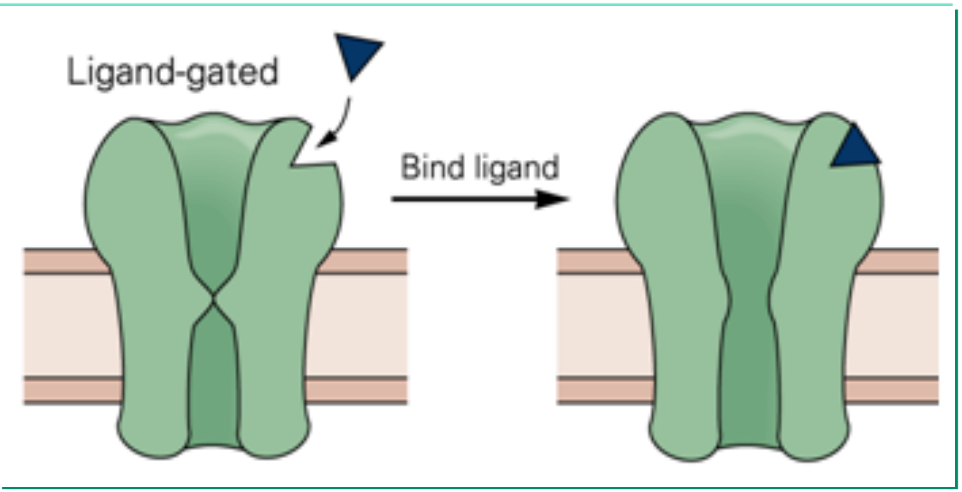


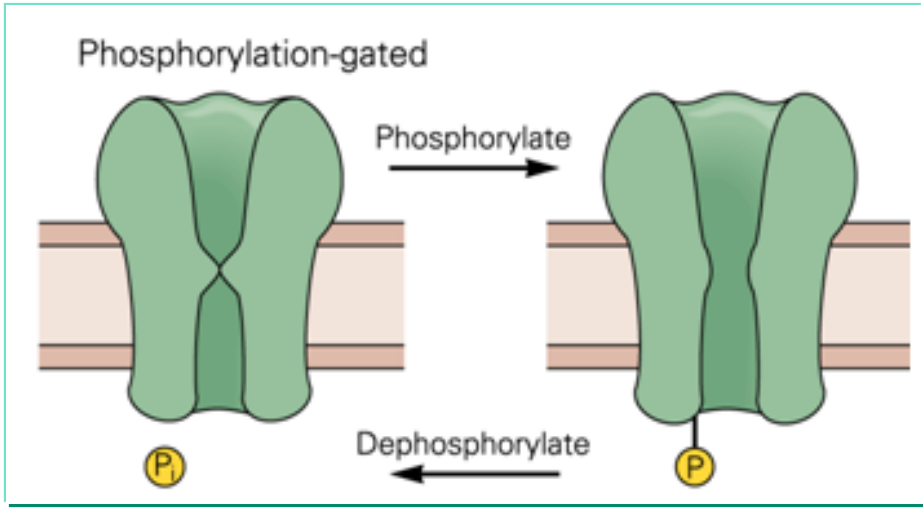
Selectivity filter
(narrowest constriction
in the 'open'
conformation)

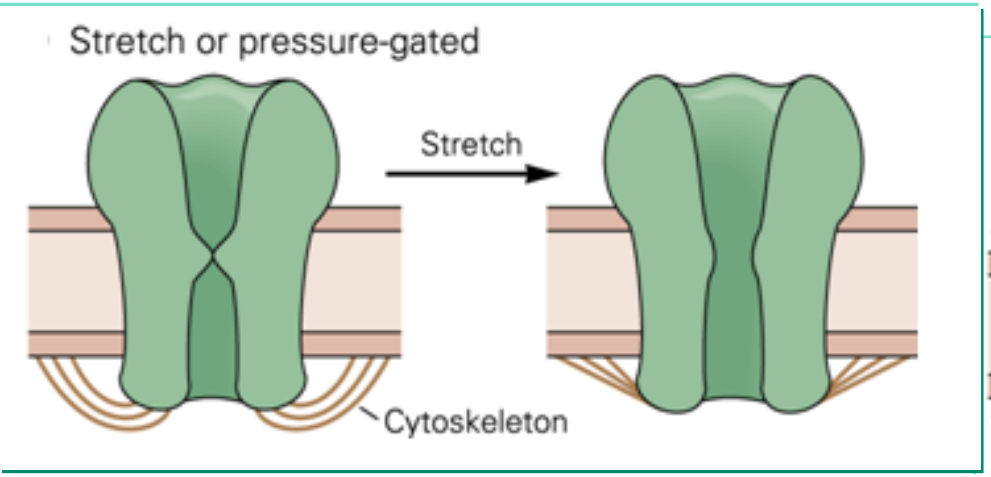
Gate
(narrowest constriction
in the 'closed' conformation)

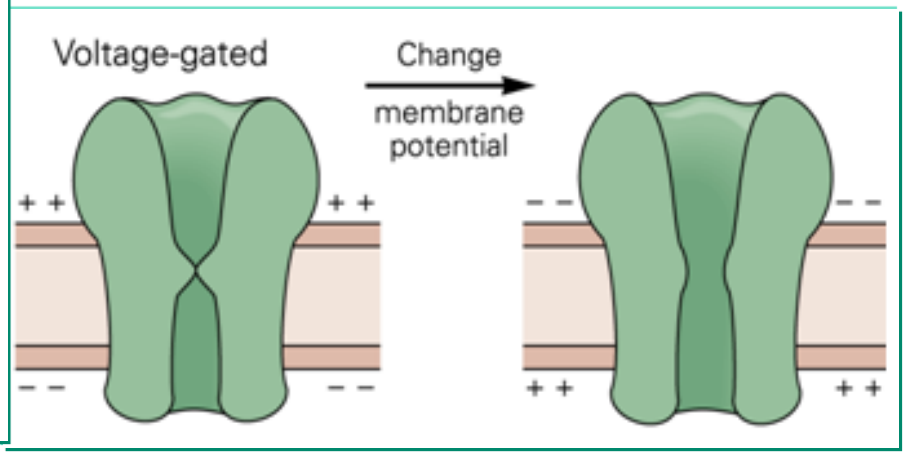
Elements that control the gate
(ligand-binding sites, voltage-sensor, pH-sensor, temperature-sensor, mechanical-deformation sensor)

Depending on the type of the channel, this gating process may be driven by:



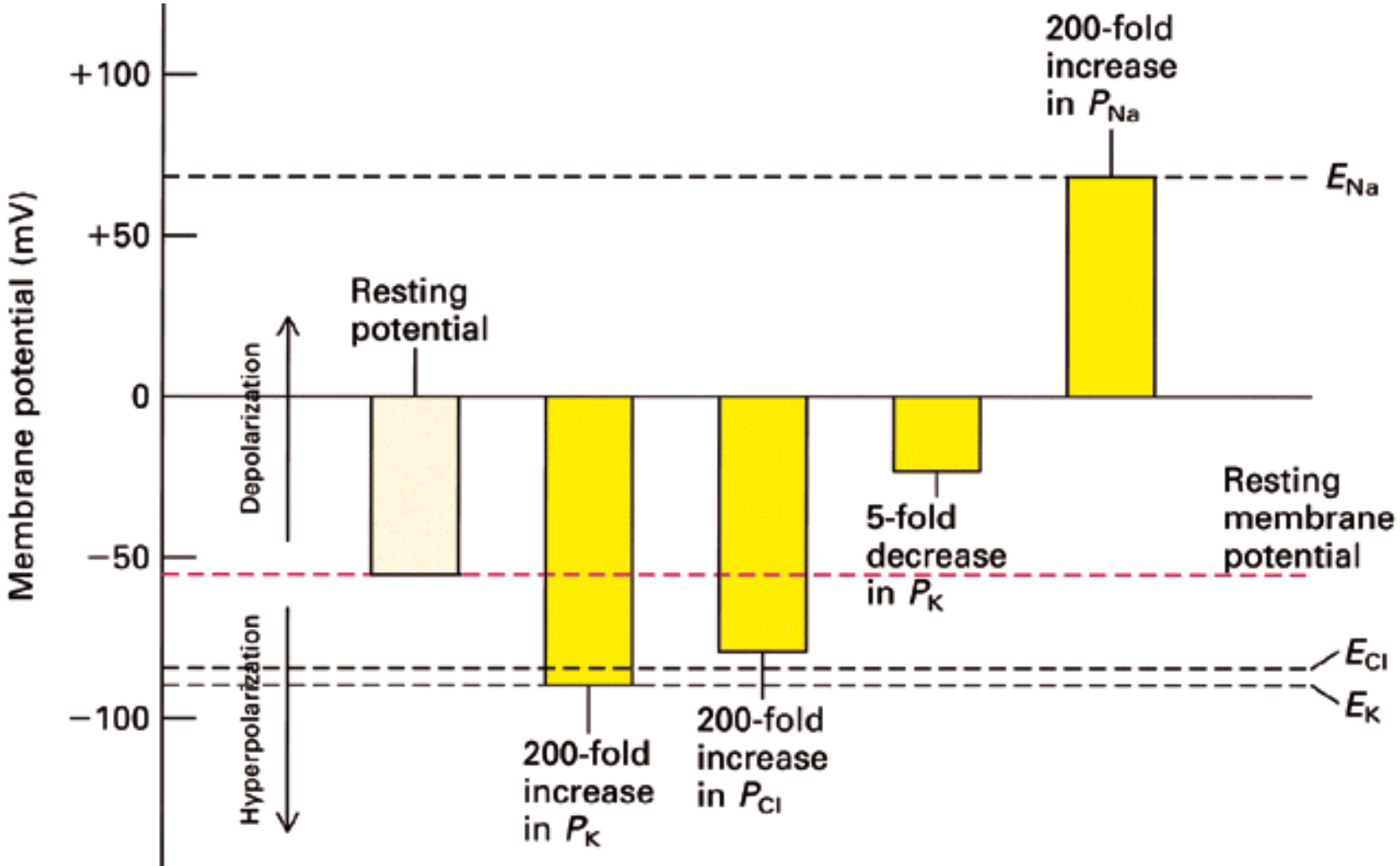




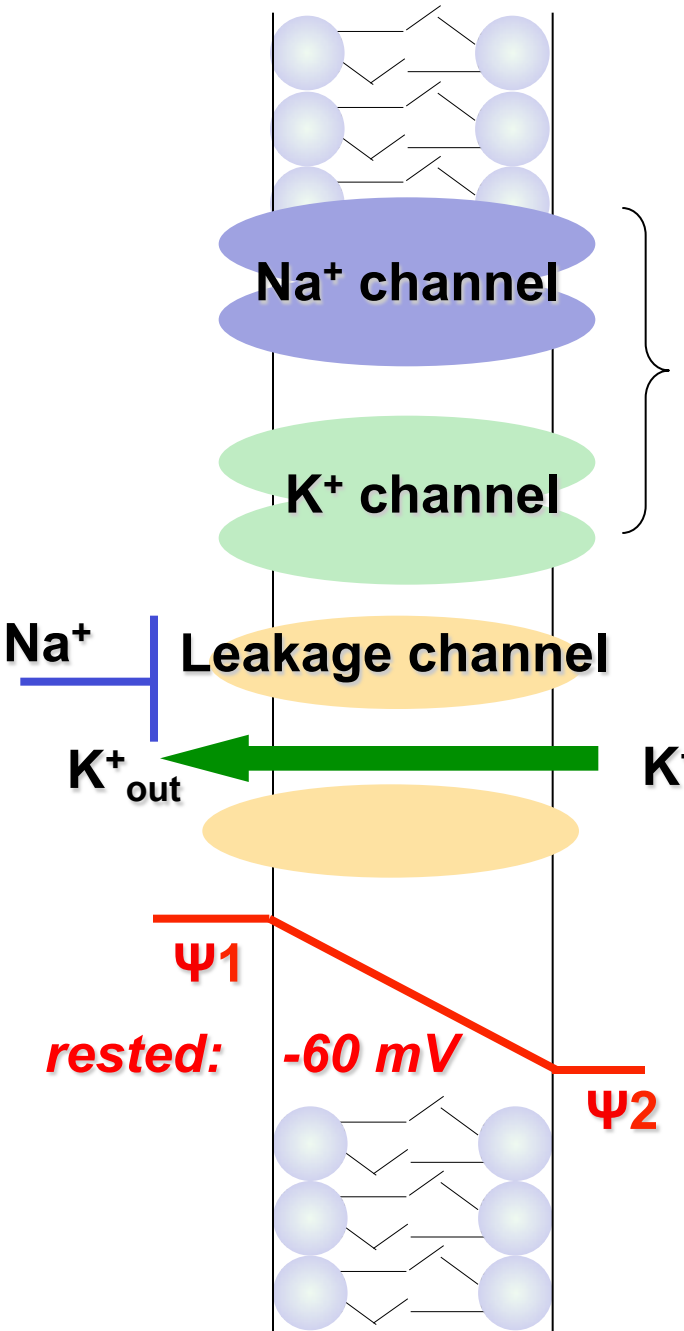


Membrane can be

- *Depolarized*
- *Hyperpolarized*
- *Repolarized*



Ion Channels at Resting State:



Voltage-gated
Generate action potential

Voltage-independent
Maintain resting potential

$$\Delta\Psi = \frac{RT}{F} \ln \frac{P_K[K^+_{out}] + P_{Na}[Na^+_{out}]}{P_K[K^+_{in}] + P_{Na}[Na^+_{in}]}$$

At rest:

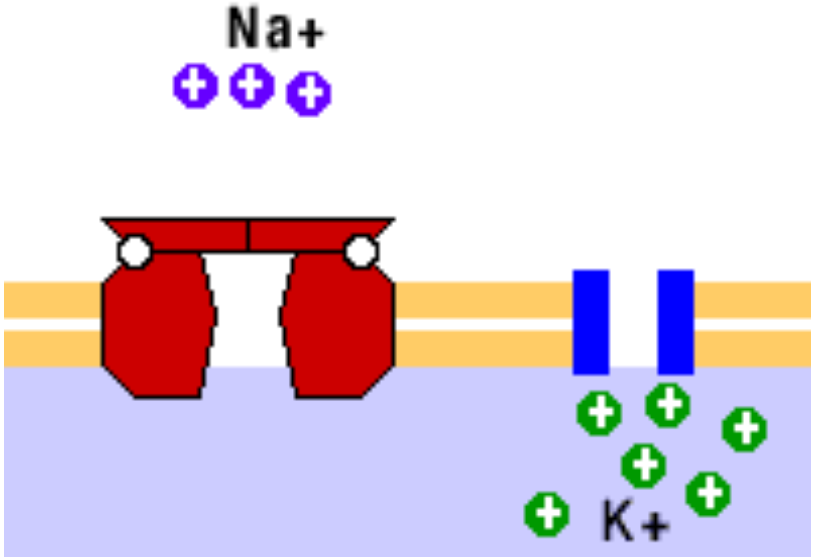
Membrane potential is mostly due to K^+

Membrane is almost impermeable to Na^+

When ion channels open:

Ions move in or out depending on electro-chemical gradient.

Resulting influx changes membrane potential.

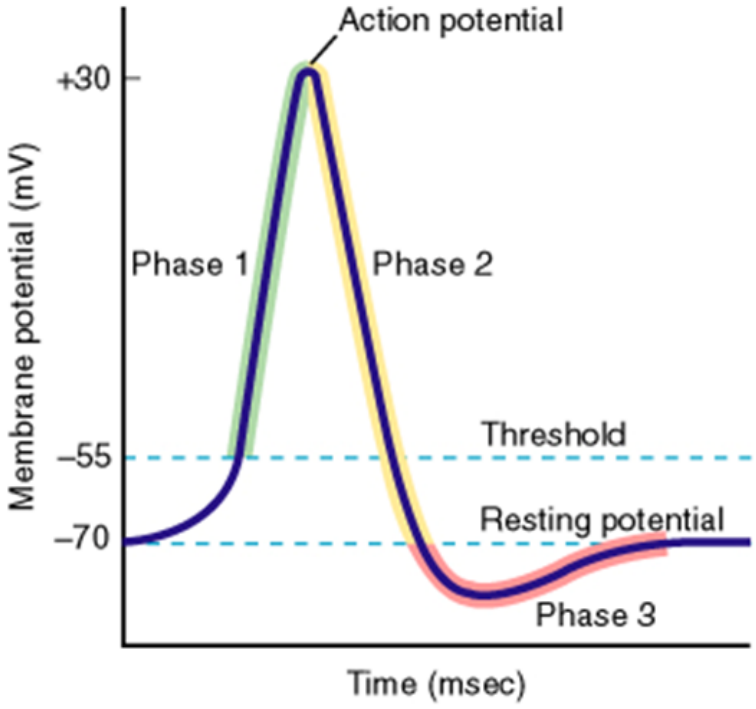


$$\Delta\Psi = \frac{RT}{F} \ln \frac{P_K[K^+_{out}] + P_{Na}[Na^+_{out}]}{P_K[K^+_{in}] + P_{Na}[Na^+_{in}]}$$

An action potential

a transient depolarization from the resting membrane potential.

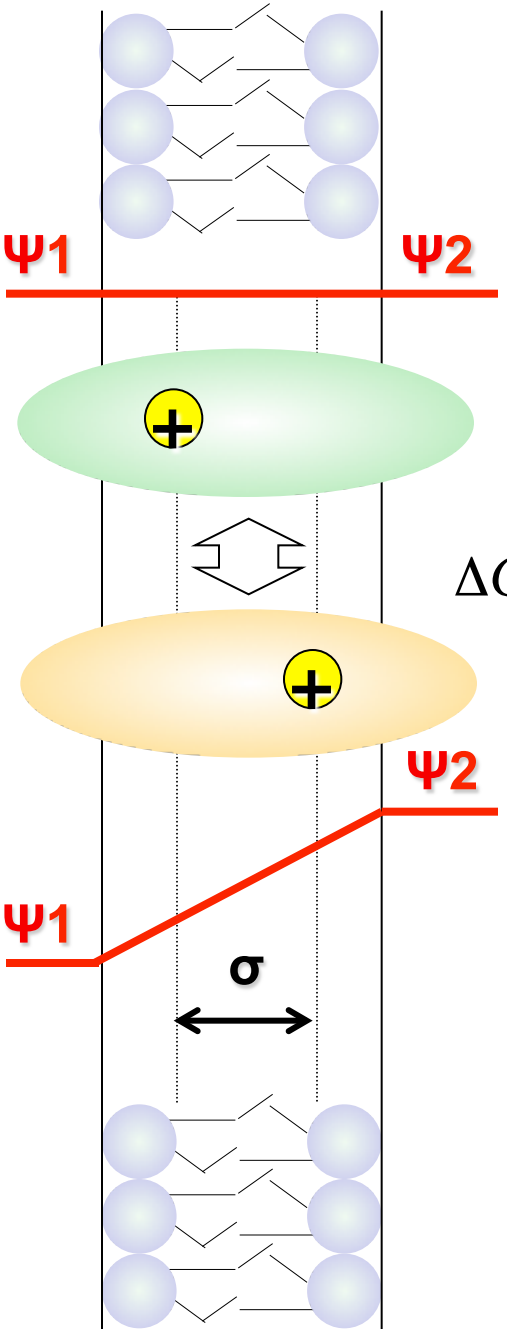
- ***All-or-none response***
- ***Refractory period***
- ***Moves at a constant speed***
- ***The peak potential is independent on distance***



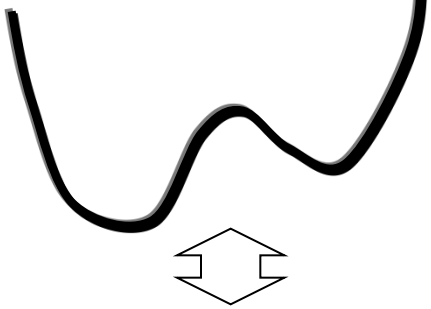
Pulses are quantized all the same

- pulse length 1 ms
- pulse strength $\Delta V = 100$ mV
- length and strength are determined by kinetics of ion channels

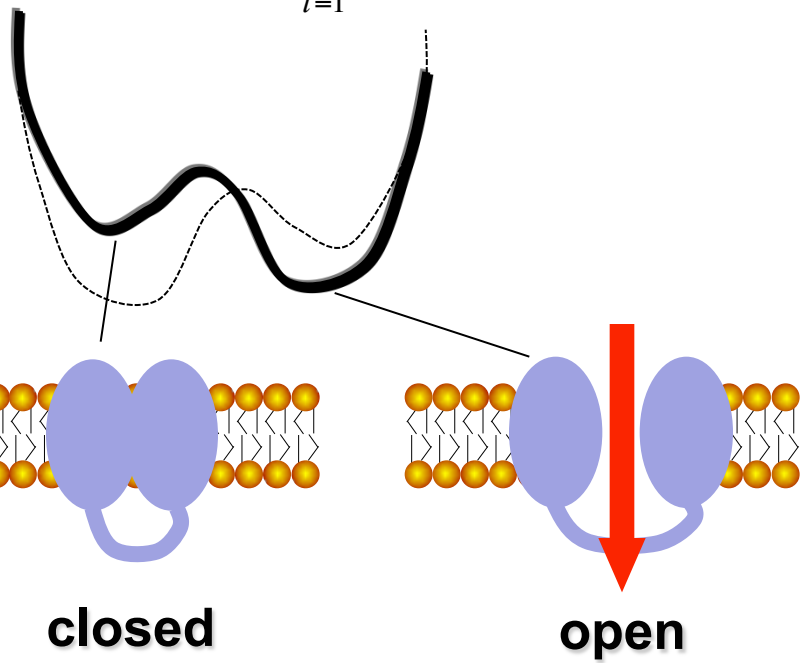
Global Transitions Induced by Voltage:



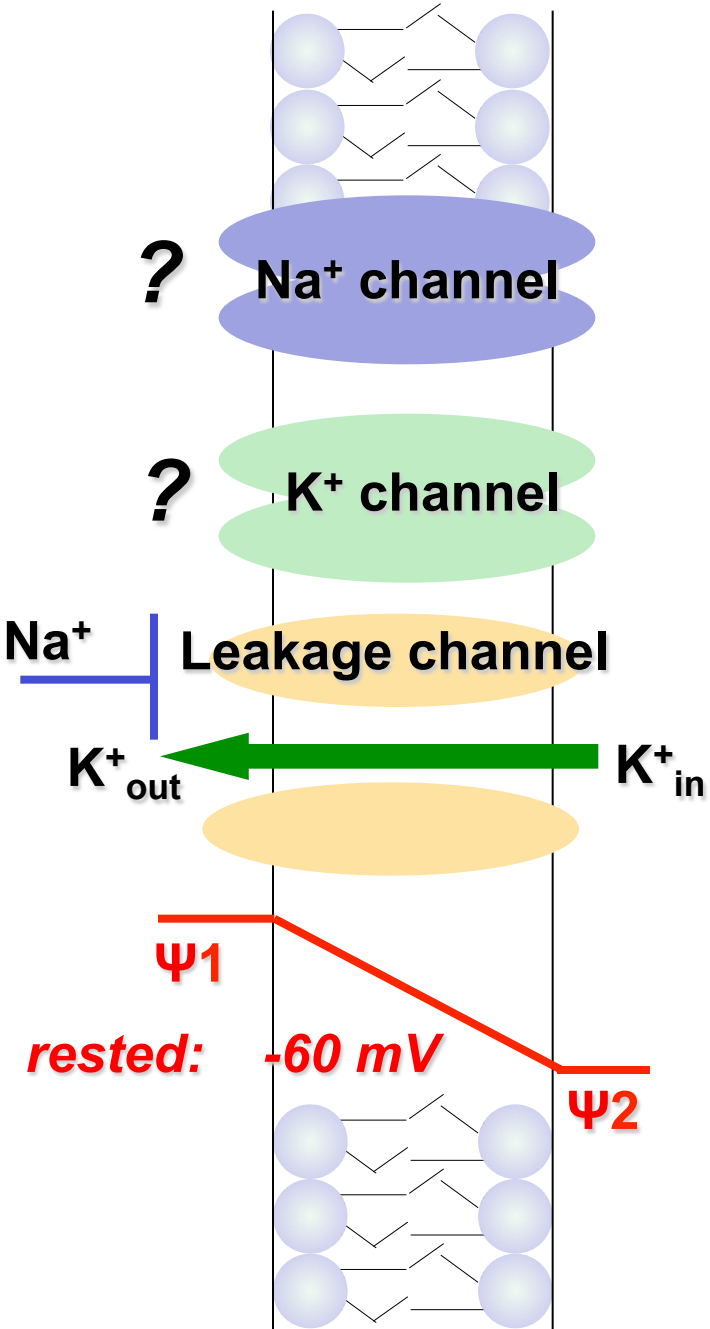
$$\Delta G = \Delta G_{\Psi independent}$$

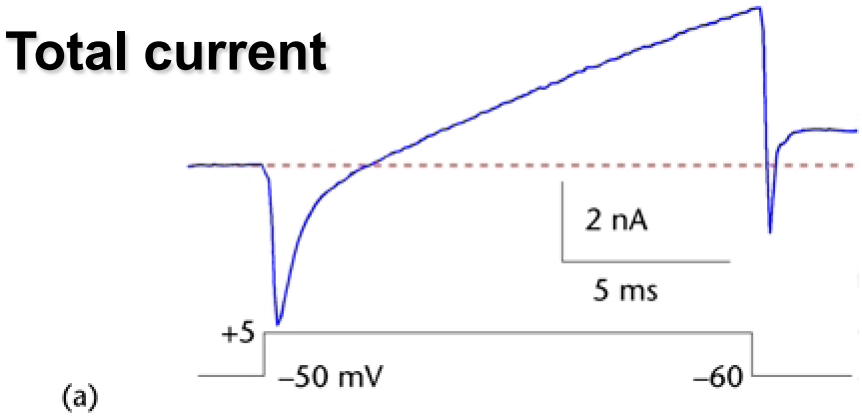


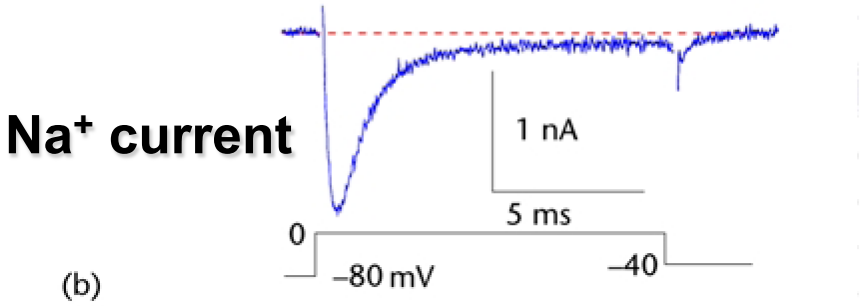
$$\Delta G = \Delta G_{\Psi independent} + \sum_{i=1}^{m} q_i \delta_i \Delta\Psi = \Delta G_{\Psi independent} + \alpha\Delta\Psi$$

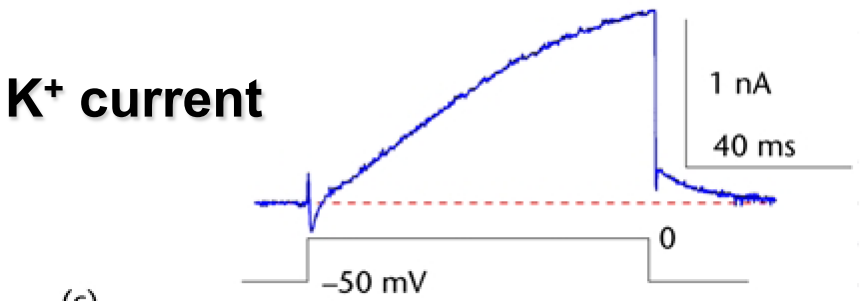


Action Potential – Na and K Currents:

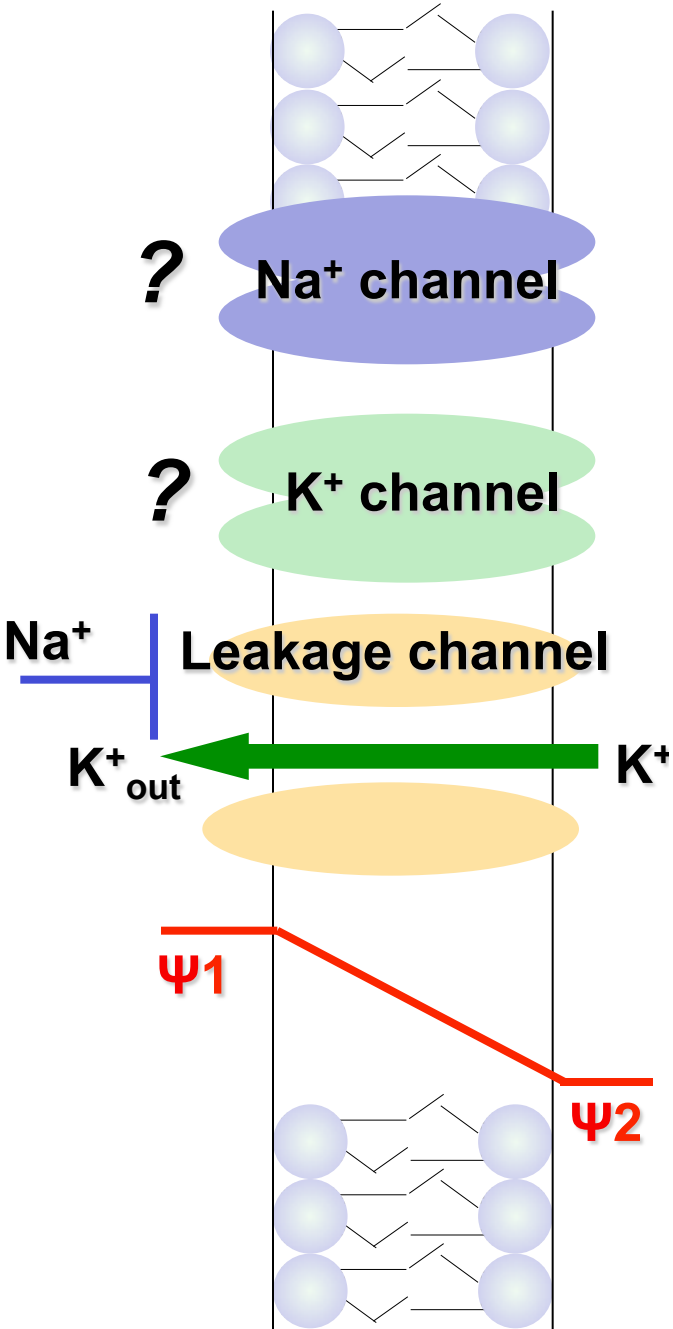


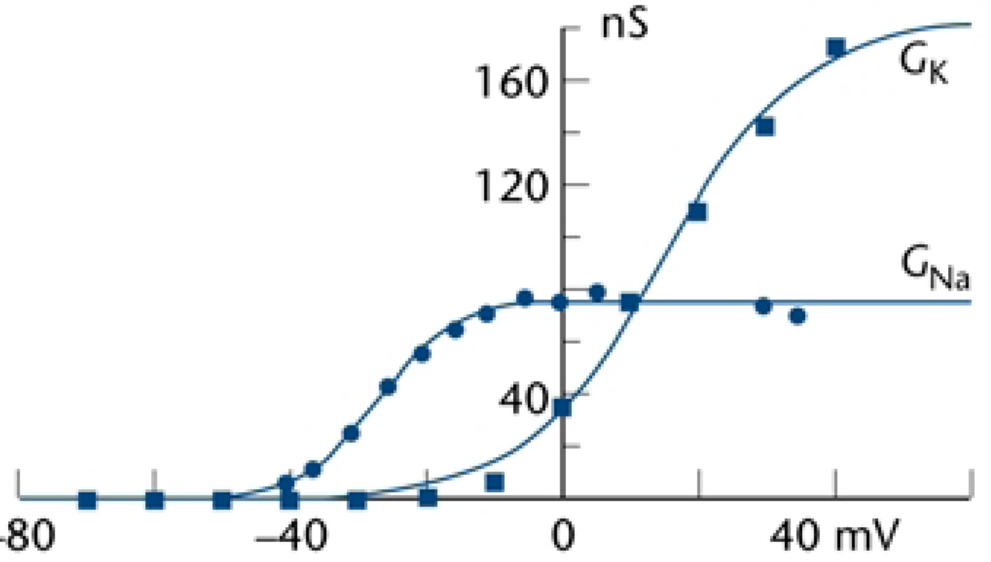




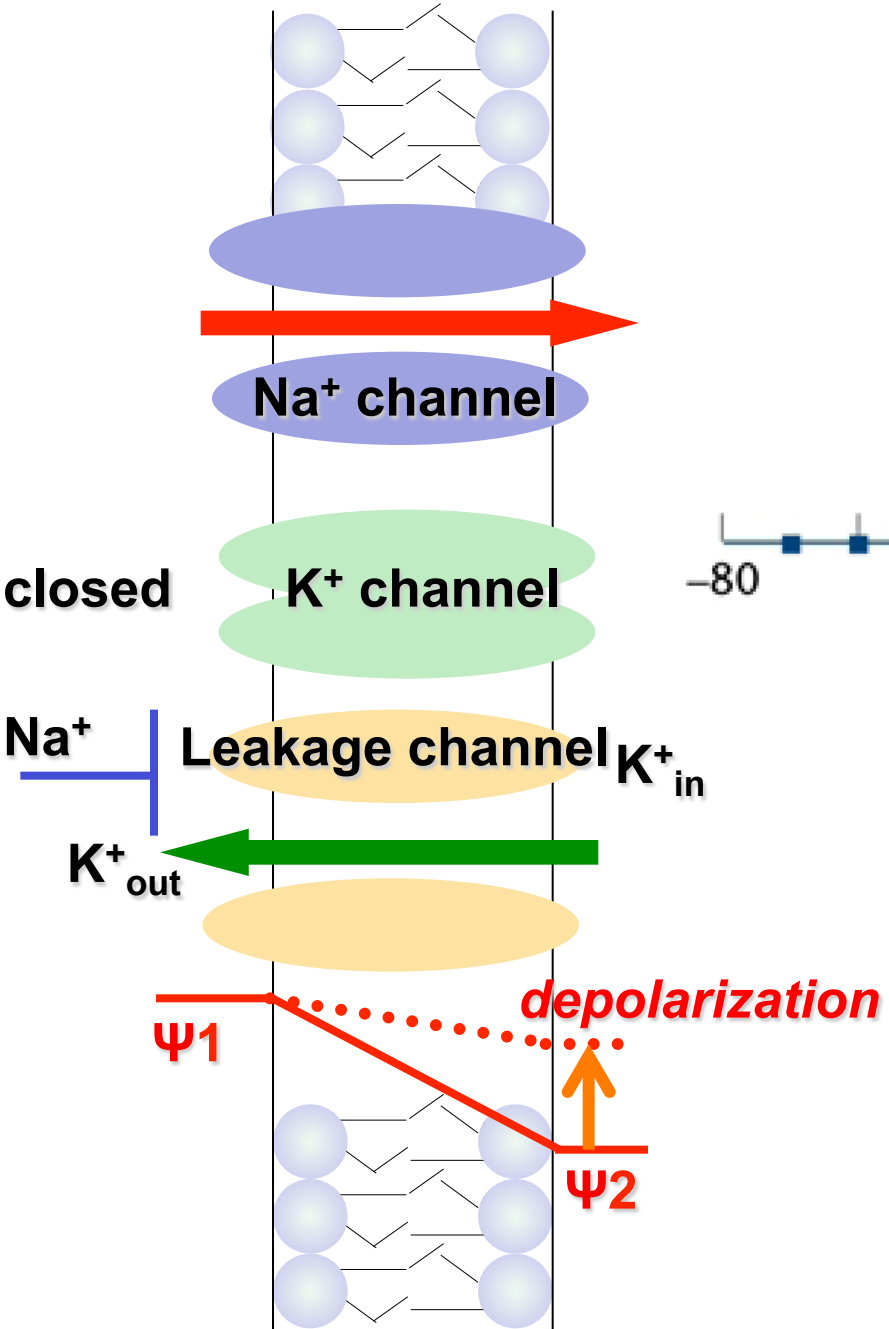


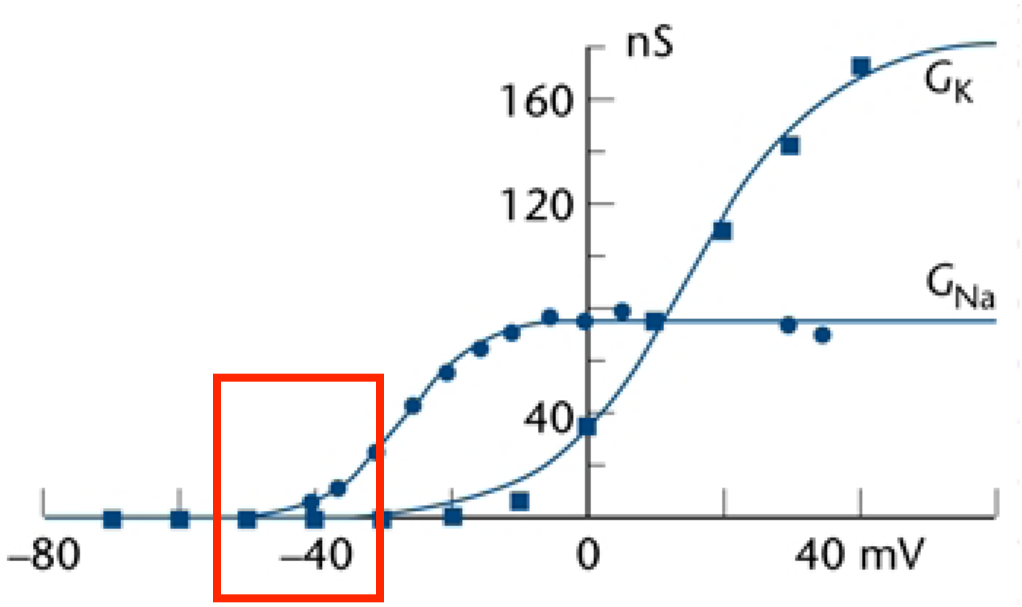
Action Potential – Channel Conductance:



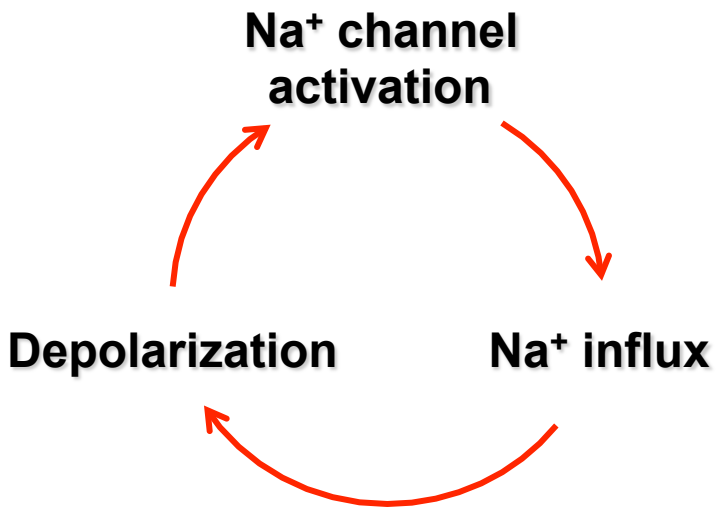


Action Potential – Channel Conductance:

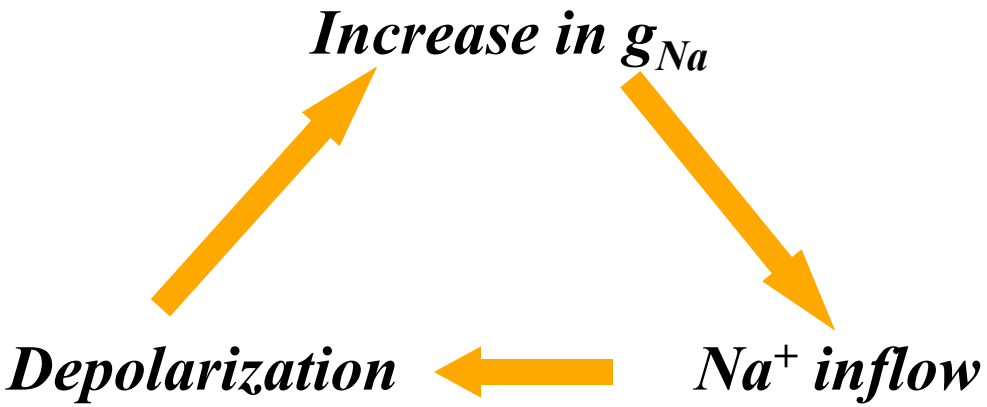




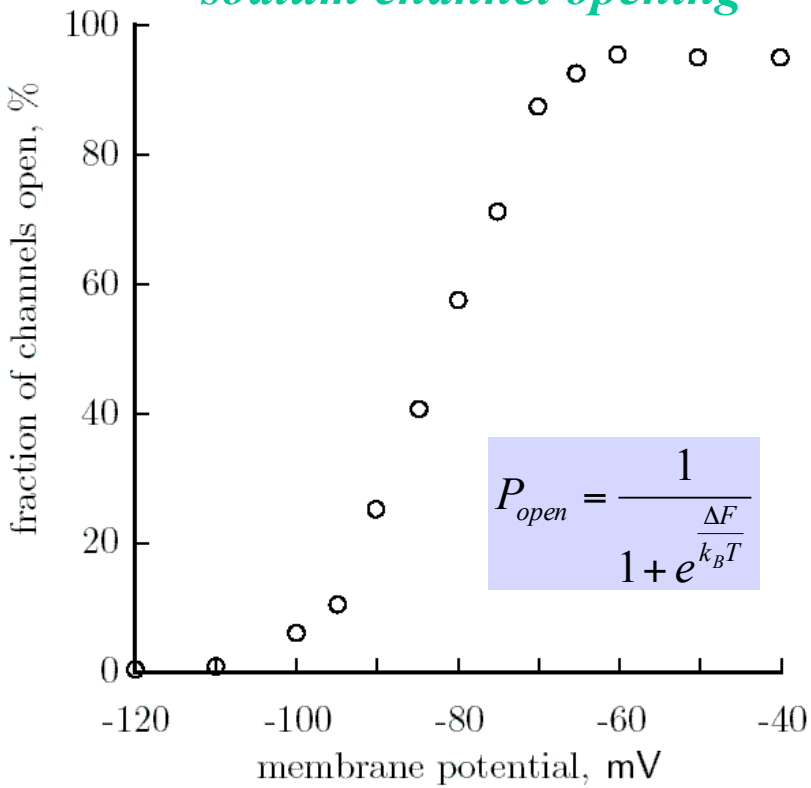
Positive feed-back loop



Voltage dependence of the g_{Na} leads to a positive feedback relationship between membrane potential and g_{Na}.

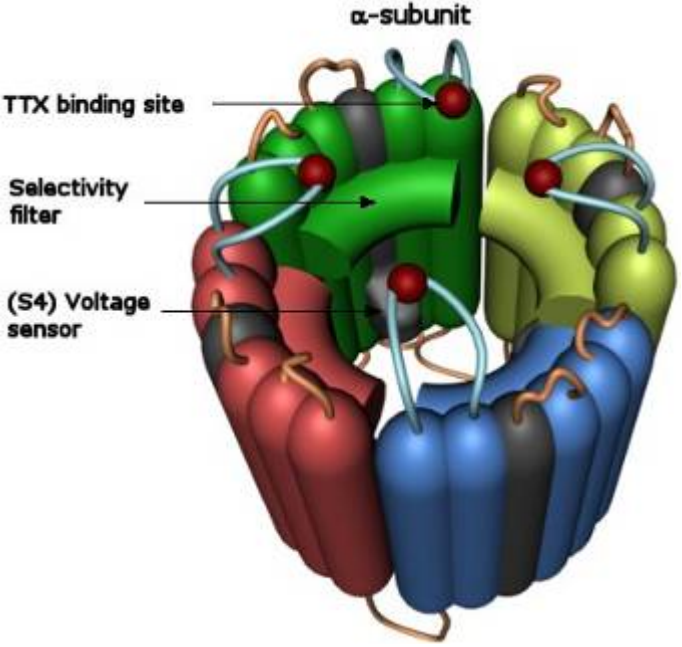


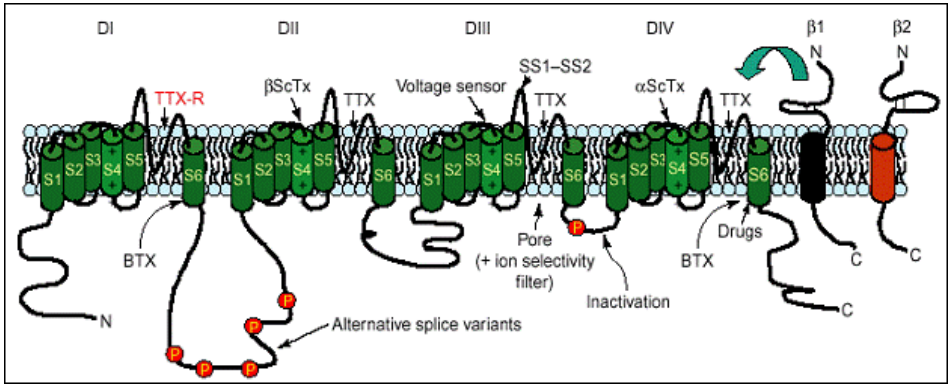
Voltage dependence of sodium channel opening

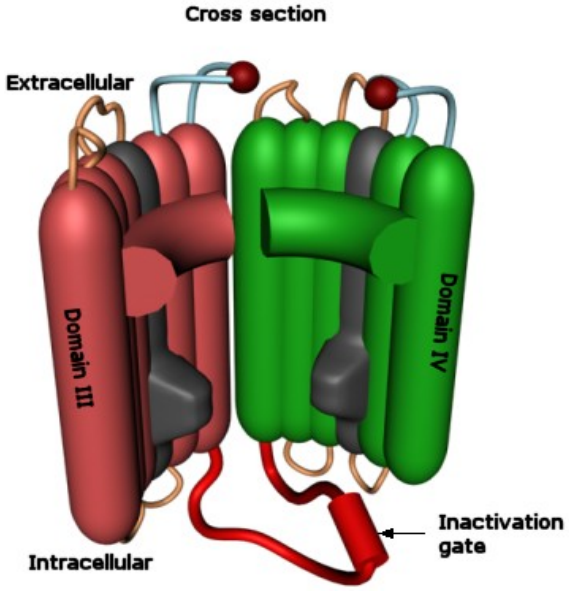


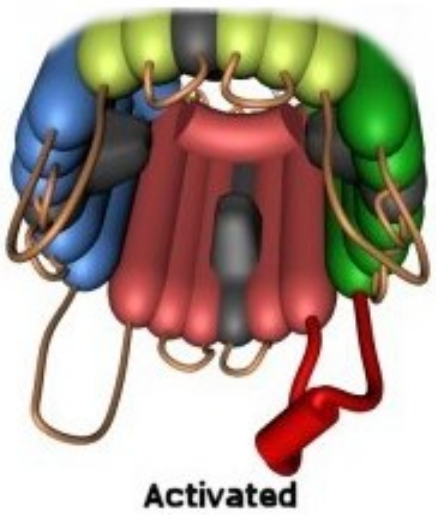
- *Very little Na^+ will cause a large depolarization.*
- *$[Na]_i$ and $[Na]_o$ don't change significantly.*
- *It responds to a small depolarization (from -70 to -50mV). This increases P_{Na} 500- 5000 fold*

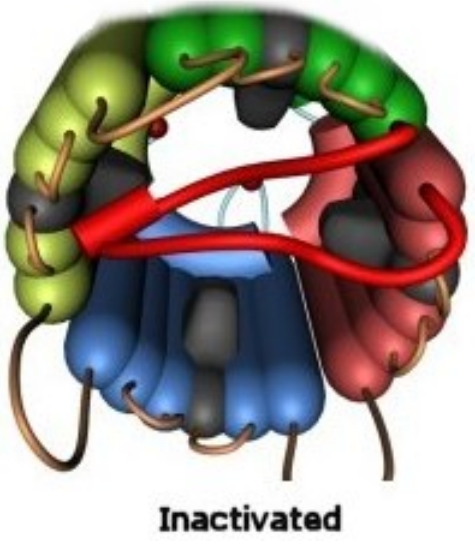
Sodium channels



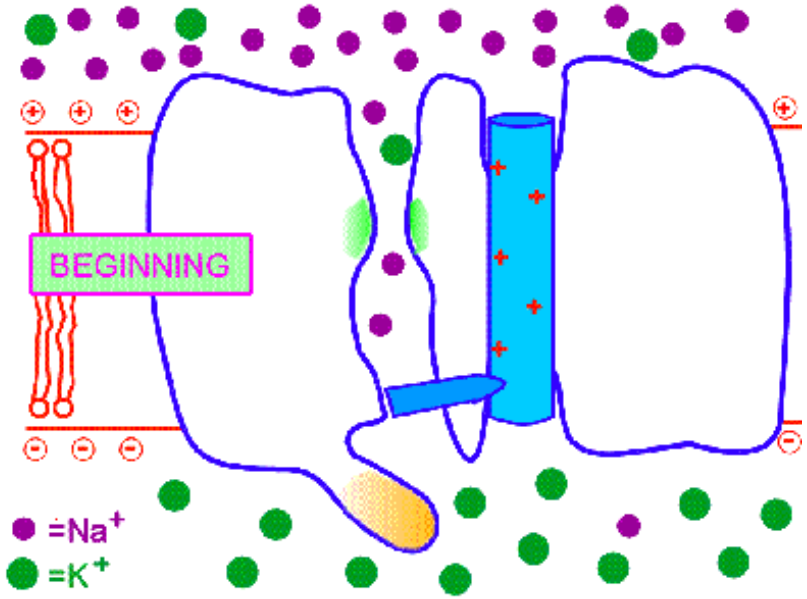




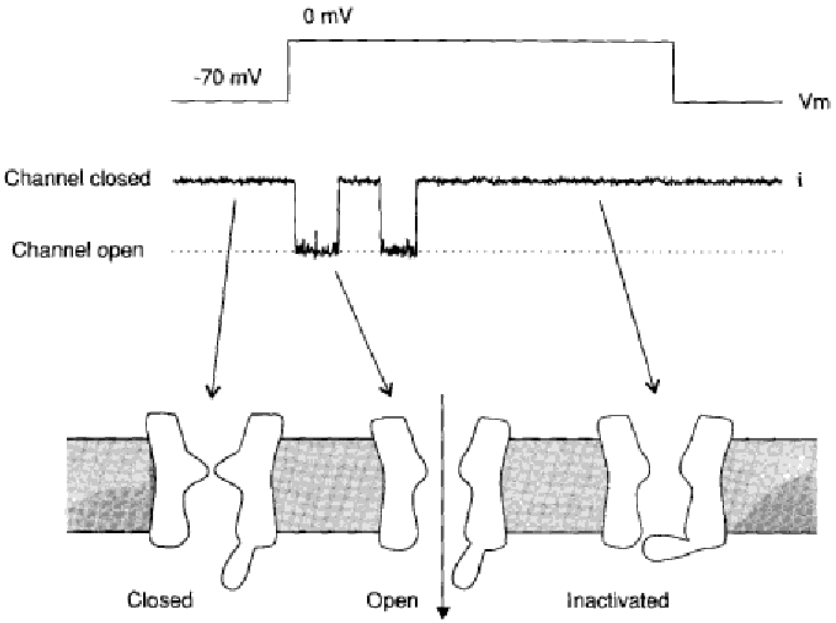




Voltage Gated Sodium Channel

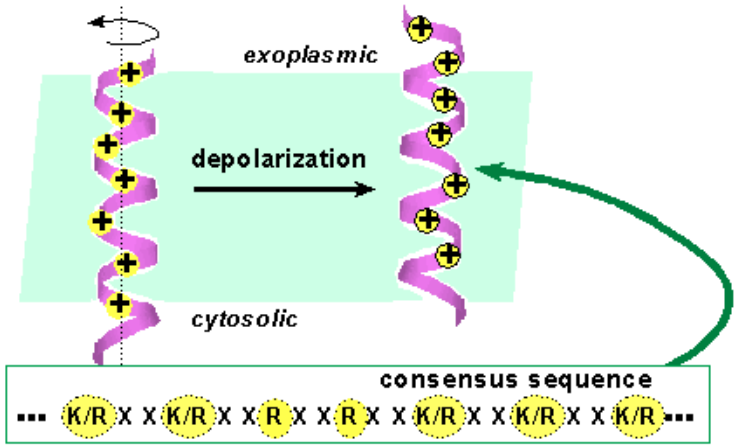


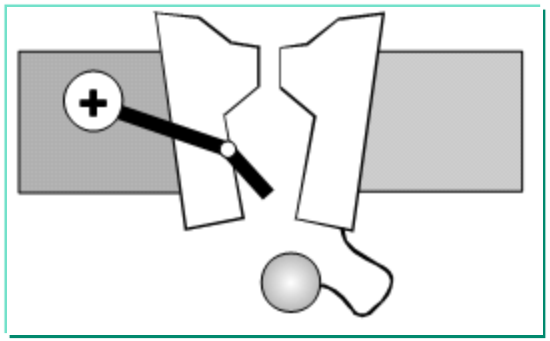
Voltage-dependent gating



Voltage-gated Ion Channels: Function

helix 4: voltage-sensitive, rotating, sliding

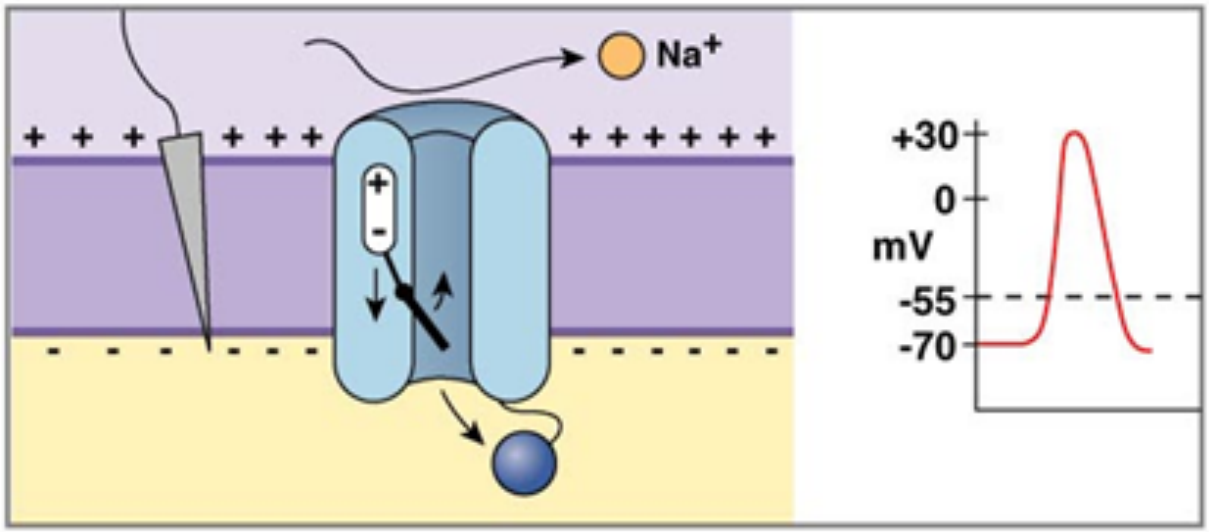




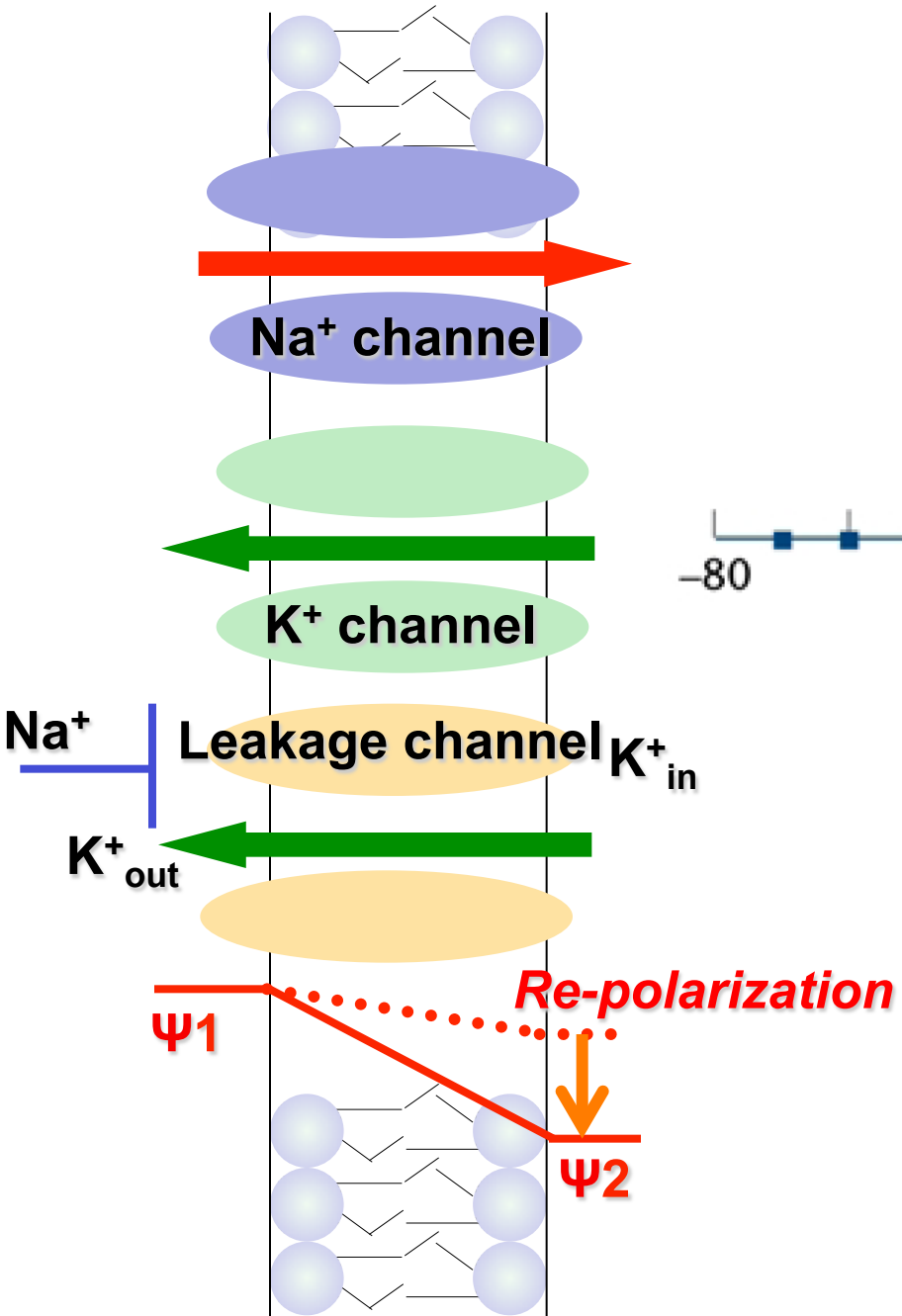
Voltage-gated Na^+ channels requires two gates

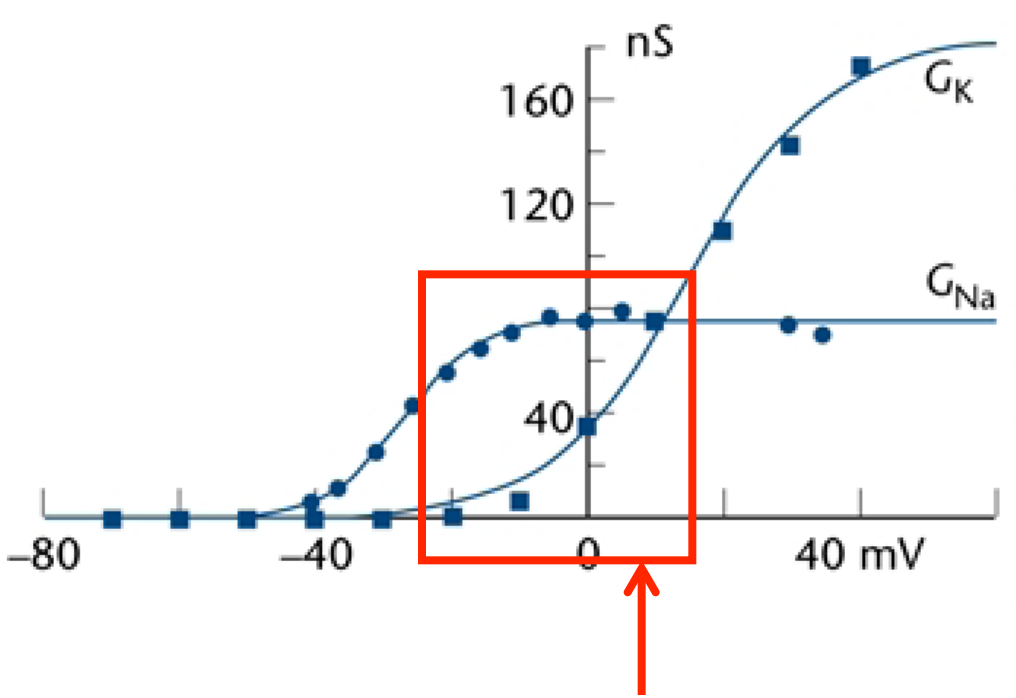
- Activation gate:
  - Closed at resting membrane potential
  - Opens when cell depolarizes, allowing Na^+ to enter
- Inactivation gate:
  - Open at resting membrane potential
  - Closes when cell depolarizes, but has 0.5 ms delay
- Both reset when cell repolarizes

During repolarization caused by K^+ leaving the cell, the two gates reset to their original positions.



Action Potential – Channel Conductance:

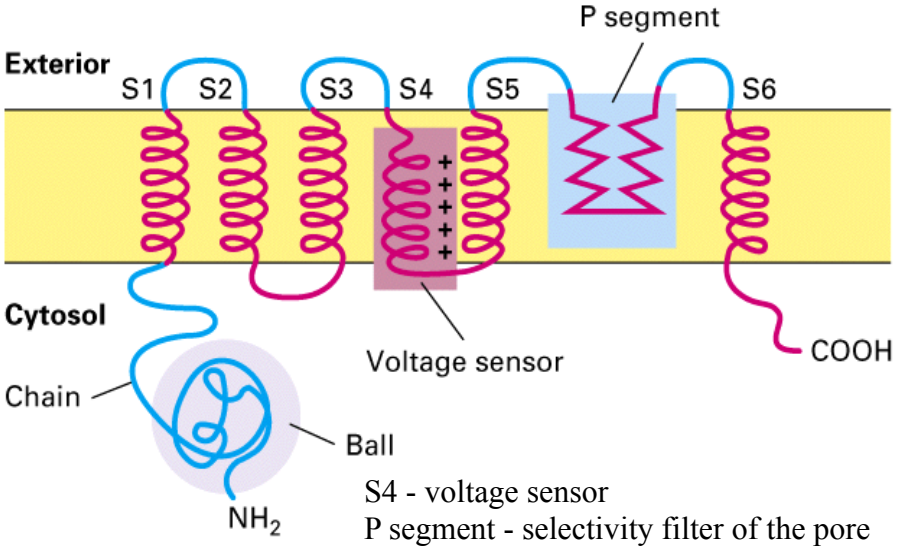




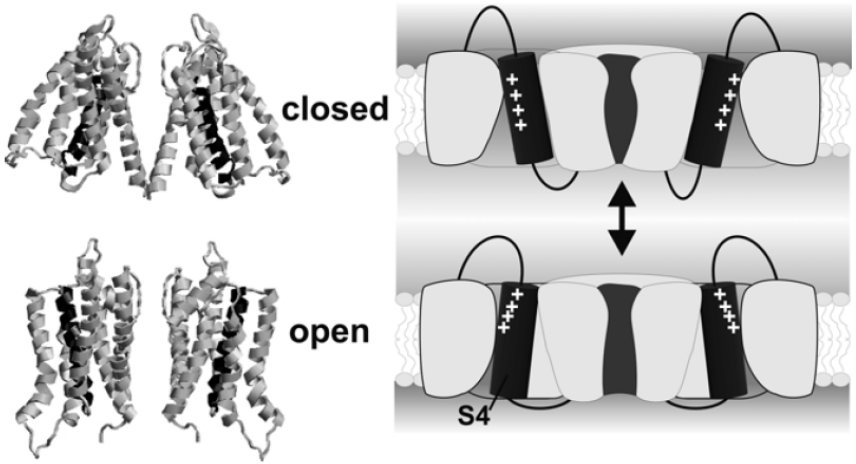
Activation of delayed rectifier

K^+ channel

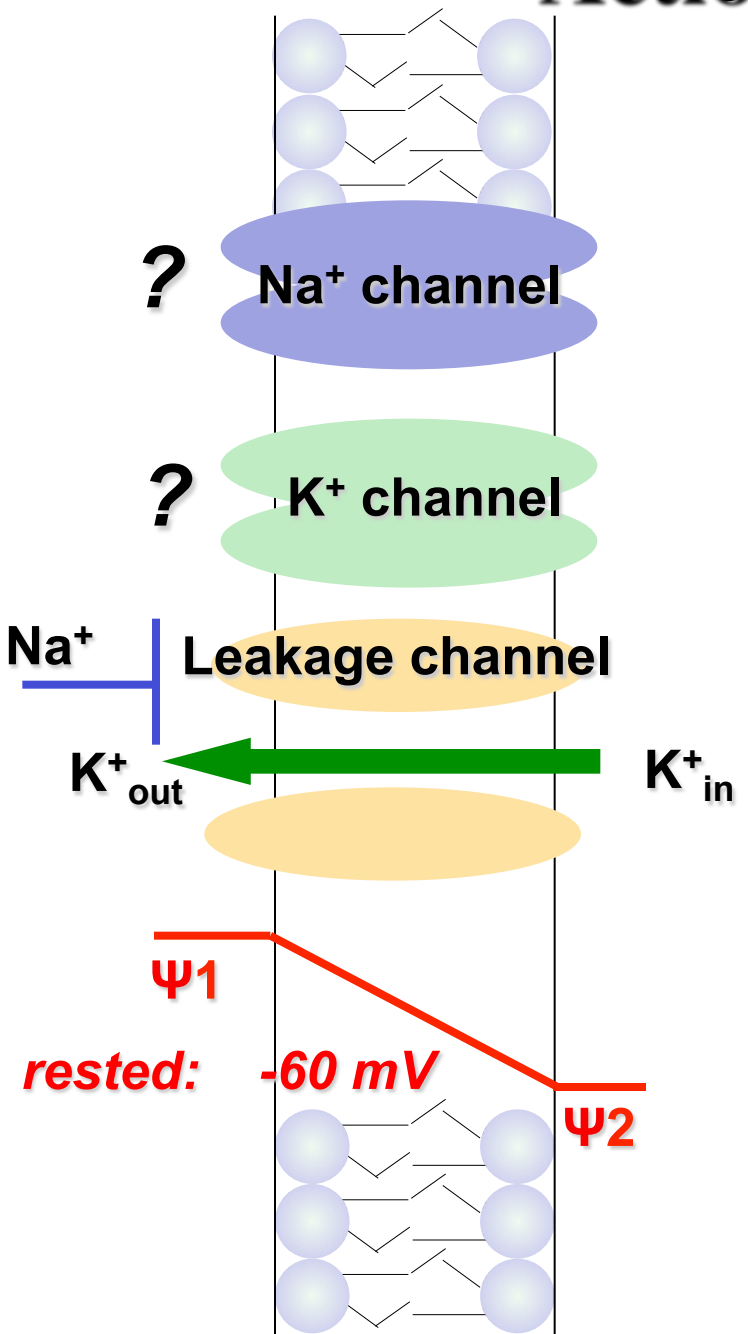
- *highly selective (permeability for K^+ is at least 10,000 times higher than for Na^+)*
- *opens slowly*
- *ion conductance is highly eff… limit, 10^8 ions/sec)*
- *has voltage-sensor*
- *inactivates rapidly*



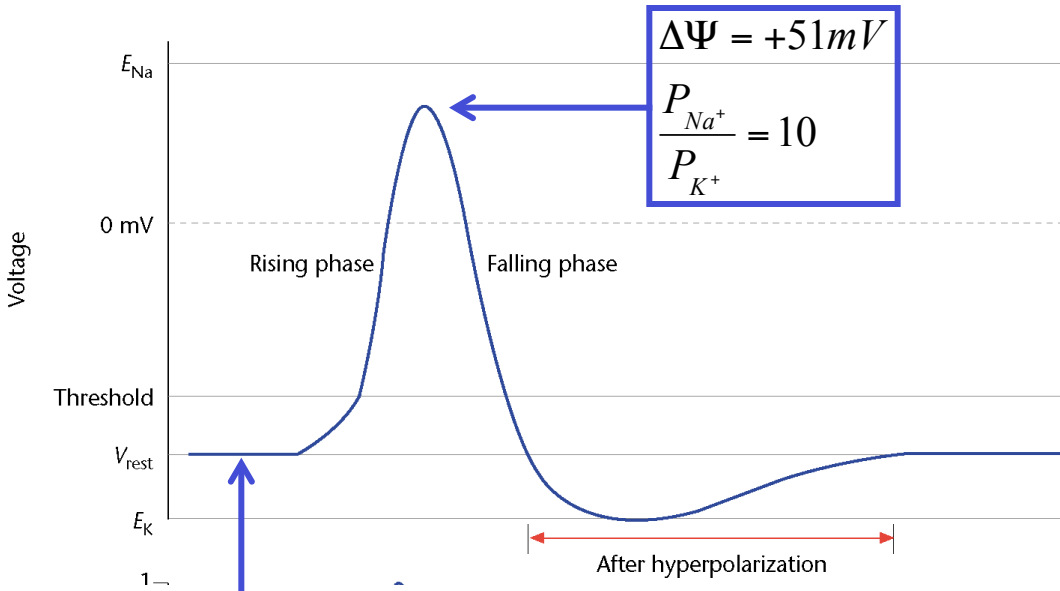
S4 - voltage sensor
P segment - selectivity filter of the pore



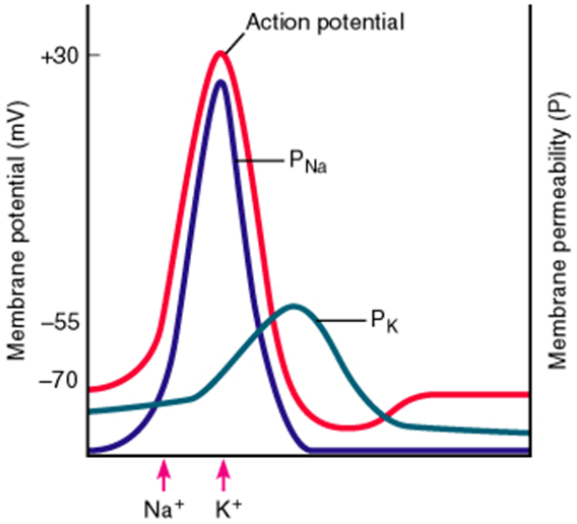
Action Potential

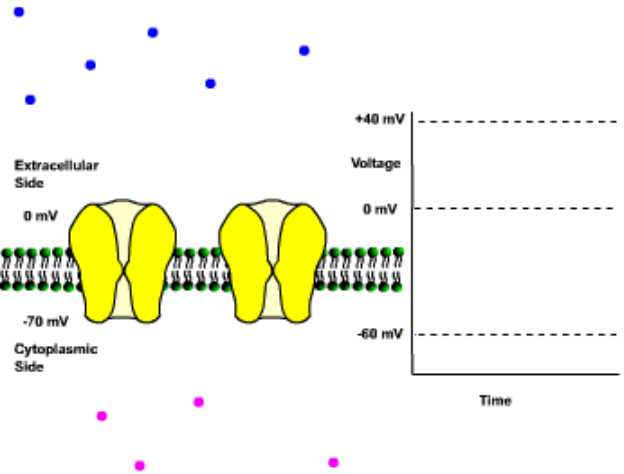


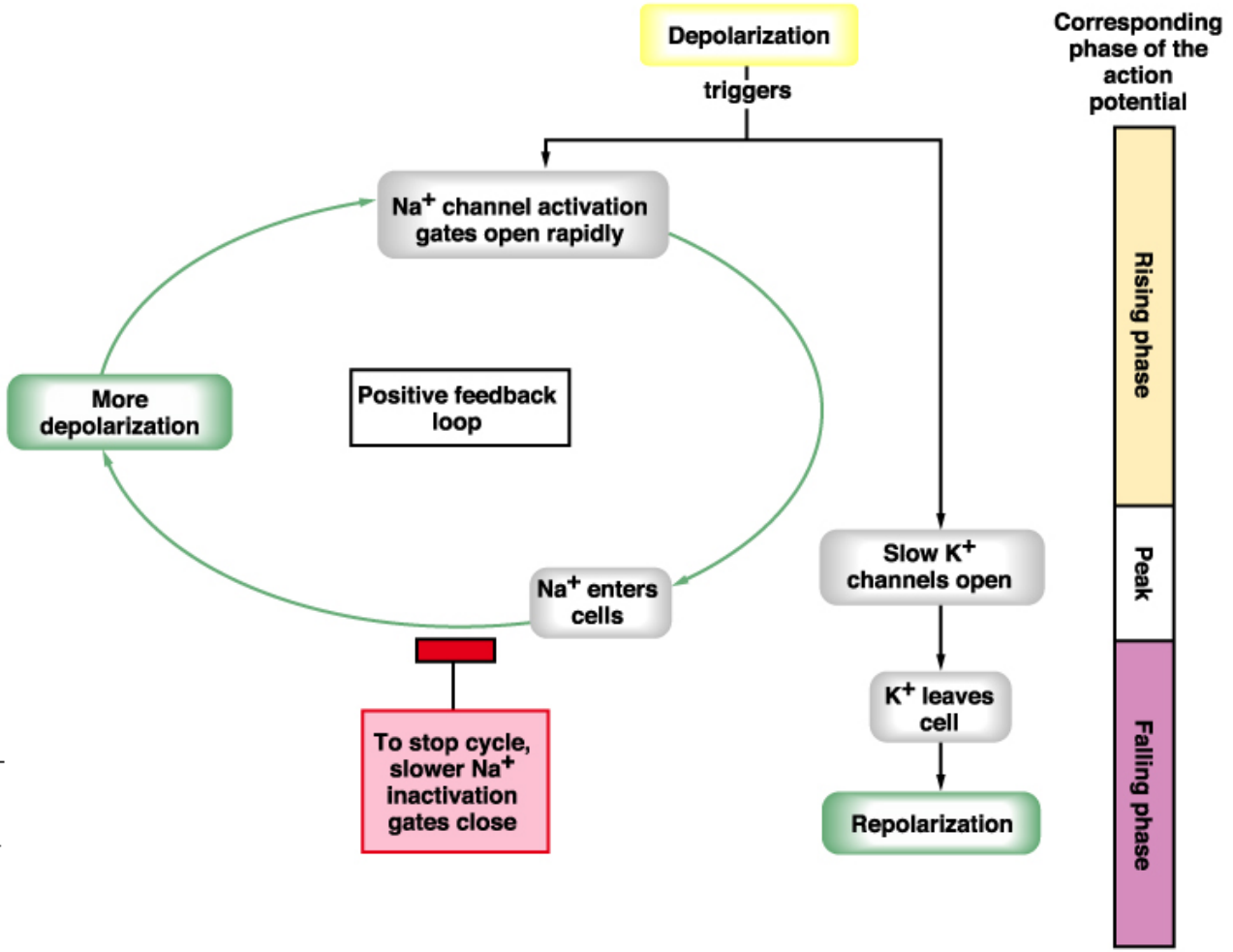
$$\Delta\Psi = \frac{RT}{F}\ln\frac{P_K[K^+_{out}] + P_{Na}[Na^+_{out}]}{P_K[K^+_{in}] + P_{Na}[Na^+_{in}]}$$



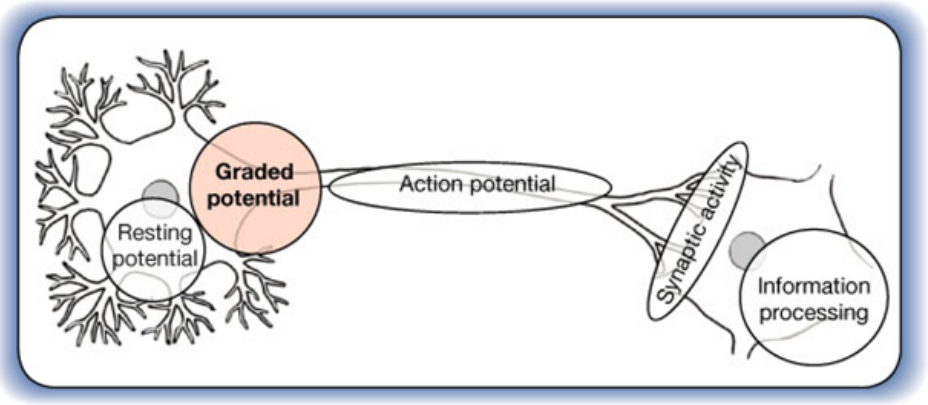
Ion movements during the action potential

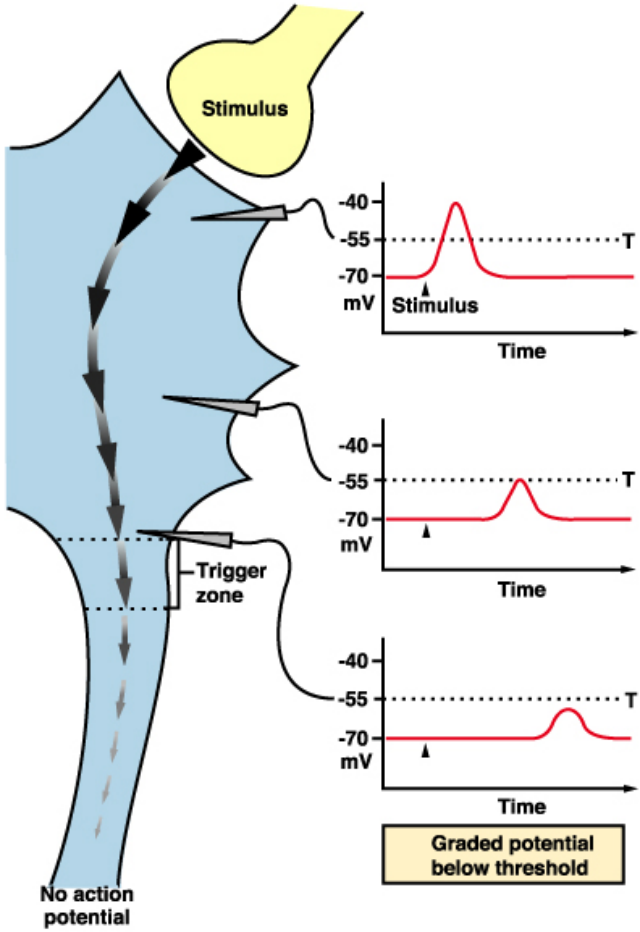






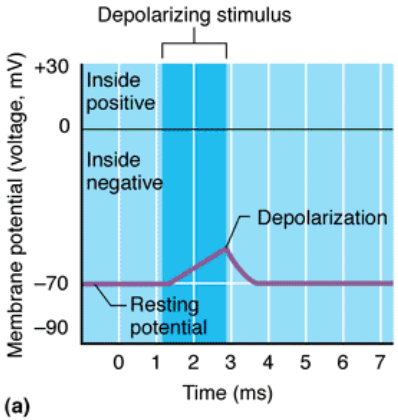
Graded Potentials

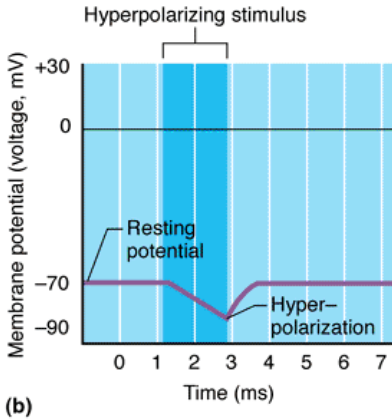




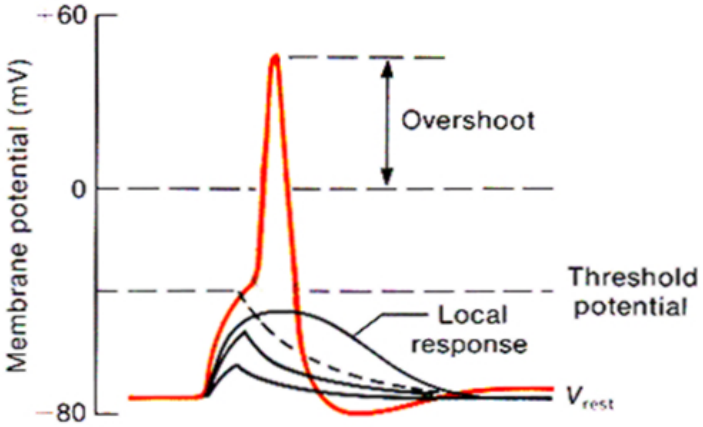
Graded potentials (depolarization or hyperpolarizations)

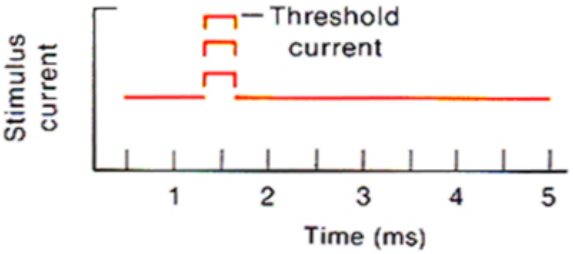
- Location any receptor on dendrites and cell body
- Begin at point where ions enter ECF (local current flow)
- Local current - net movement of positive charges
- Strength (= amplitude) ~ strength of triggering event
- Amplitude varies inversely with distance
- They travel until they reach the trigger zone
- They can be summed - to reach threshold

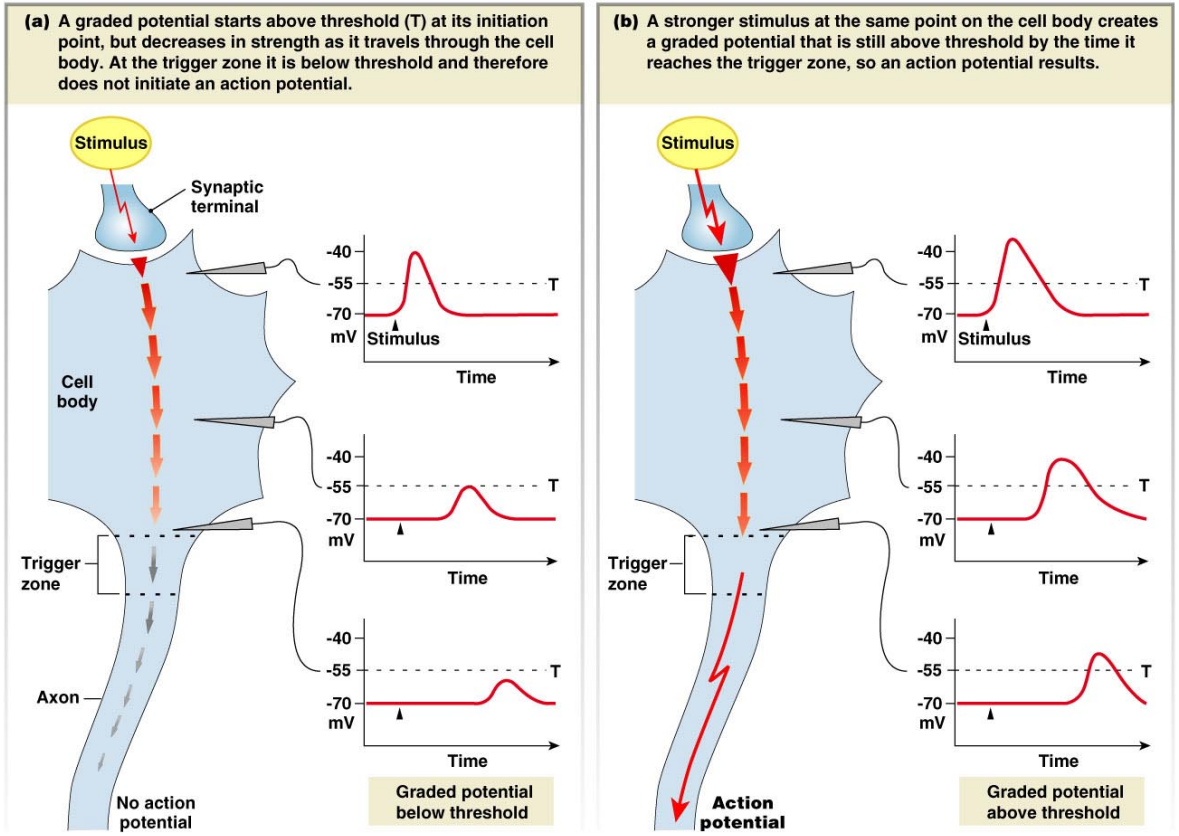




Stimuli stronger than the threshold result in an *action potential*.





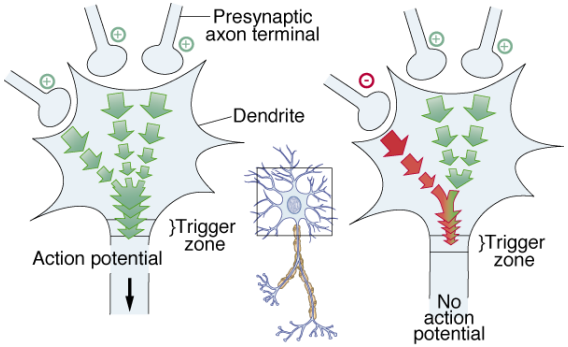


Subthreshold potential vs. suprathreshold potential

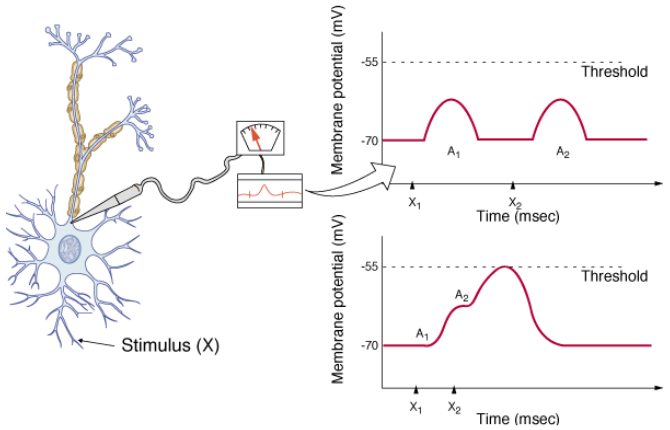
Integration of Neural Information Transfer

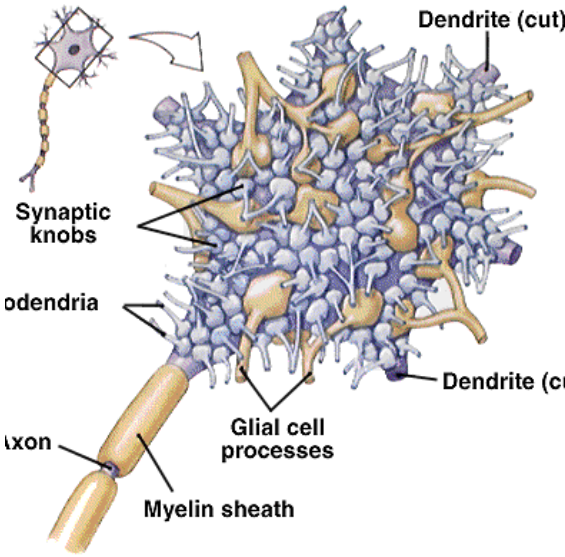
Multiple graded potentials are integrated at axon hillock to evaluate necessity of AP

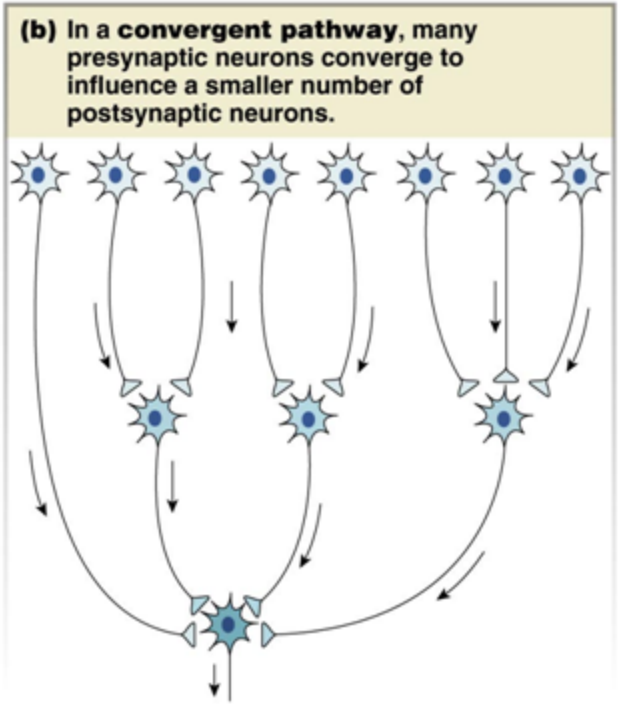
1. ***Spatial Summation:*** **stimuli from different locations are added up**



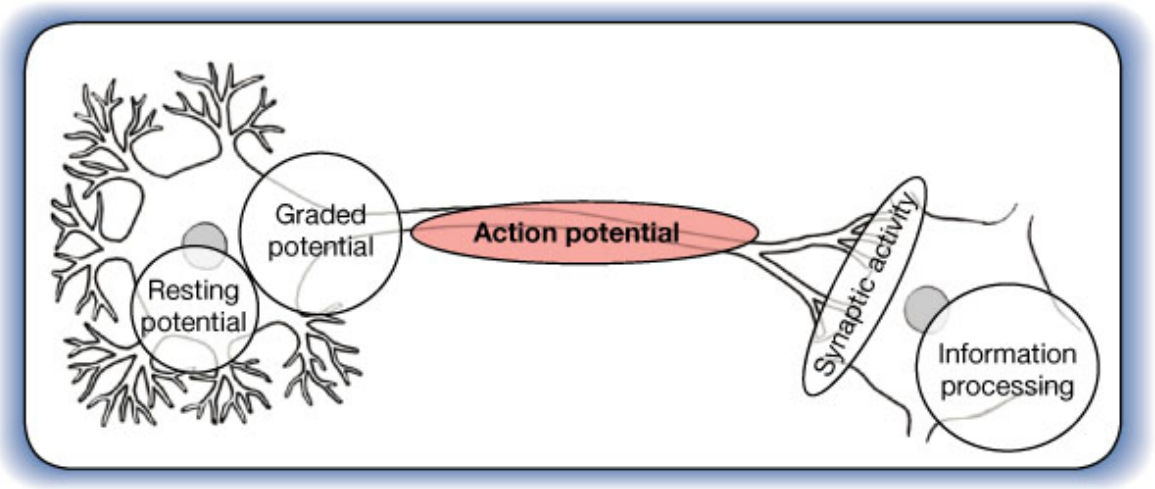
2. ***Temporal Summation:*** **sequential stimuli added up**

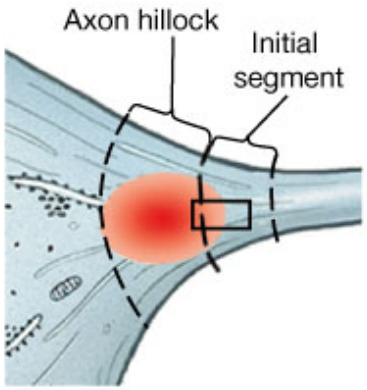






The Generation of an Action Potential



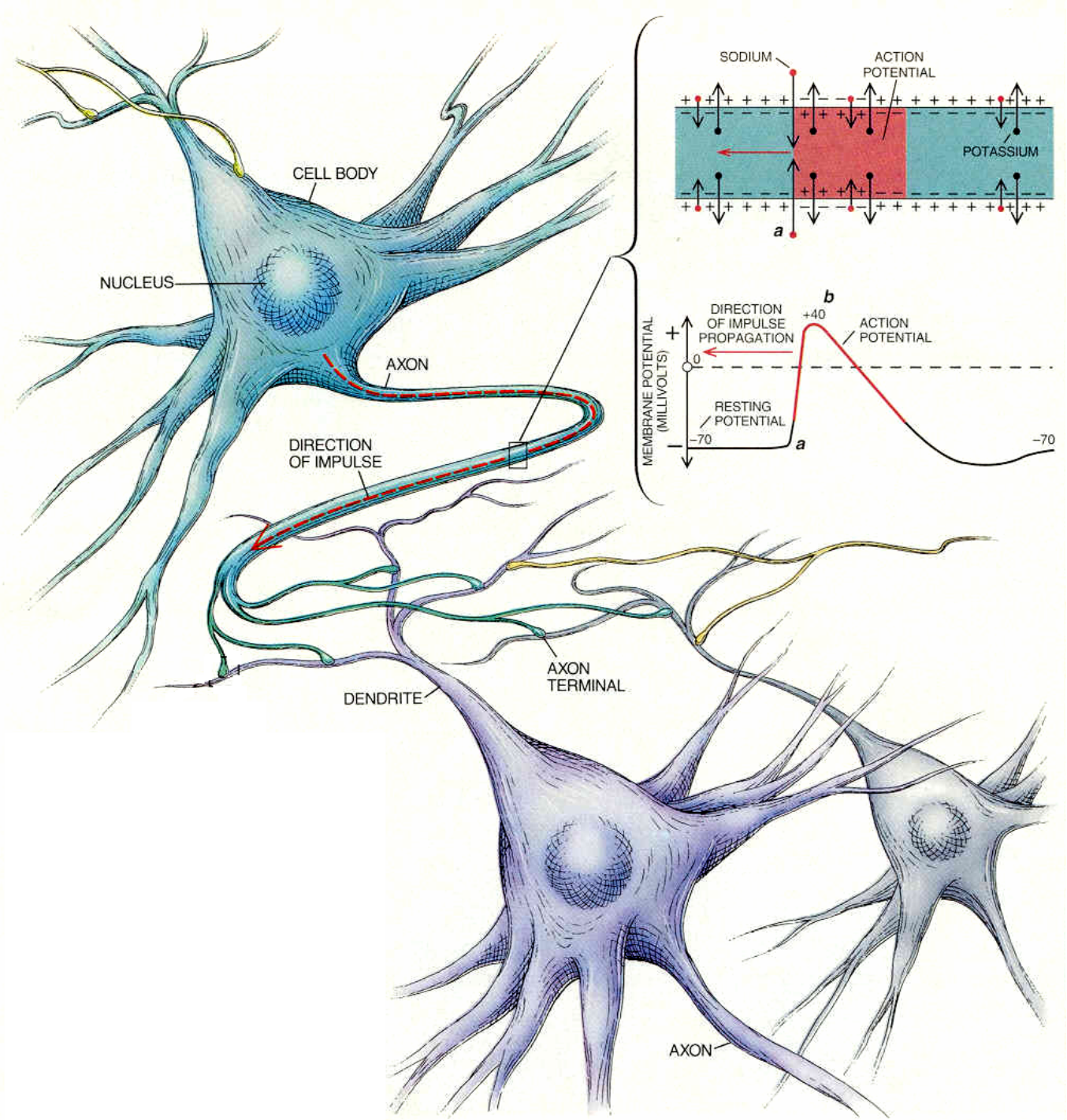


Trigger Zone

- Usually Axon Hillock
- and/or Initial segment of axon
- Many Na^+ Channels

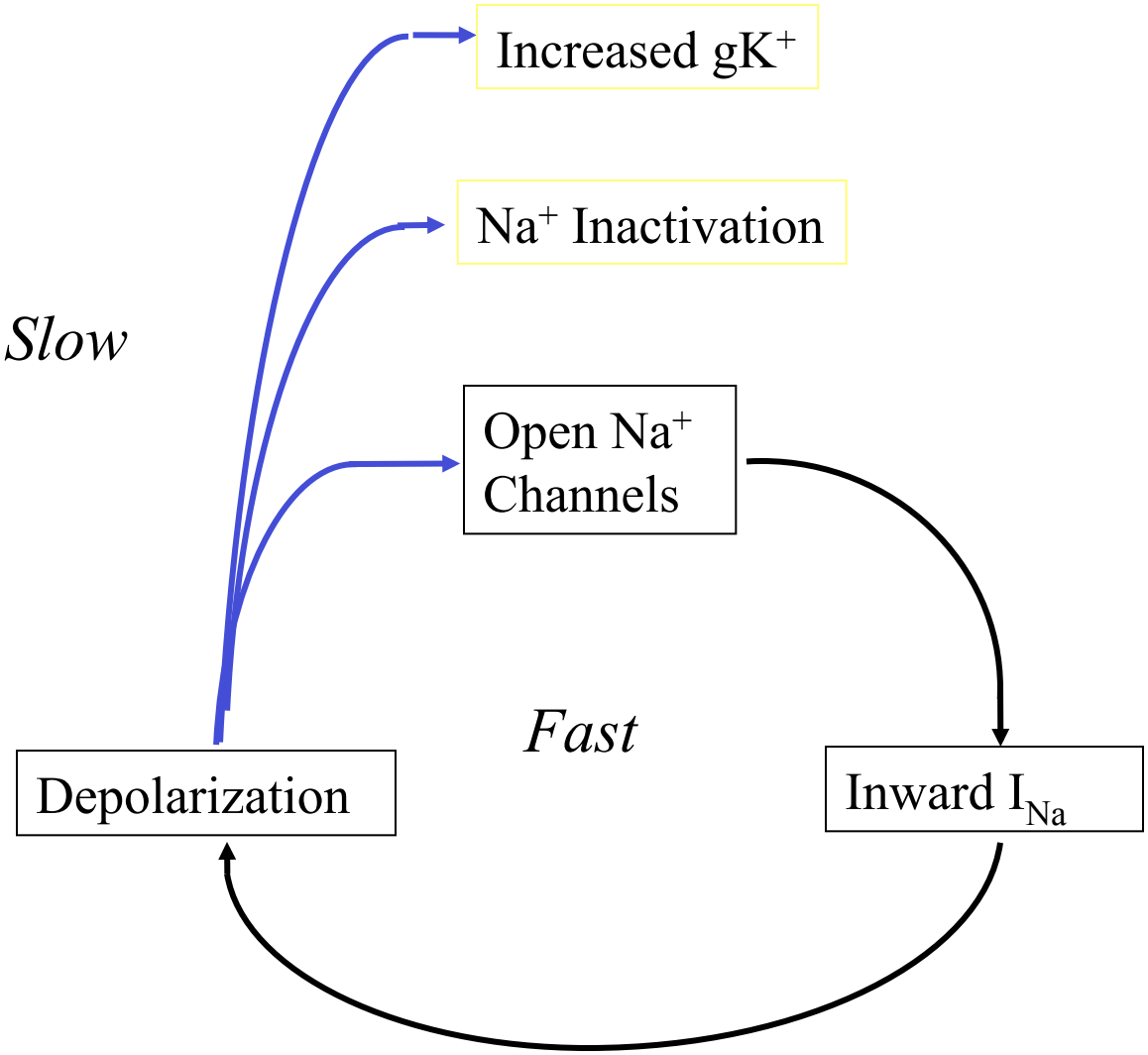
Some stimuli may be inhibitory

- Hyperpolarizing effect



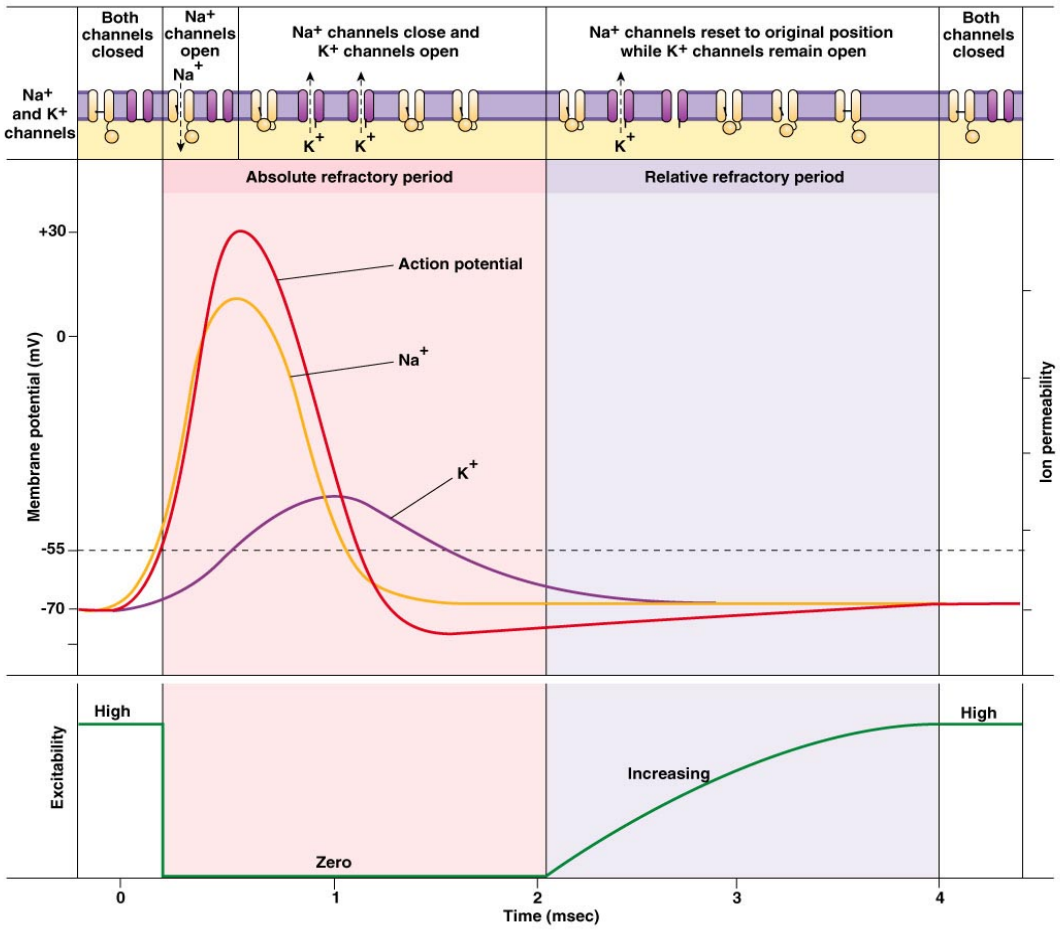
Signal transmition along the neuron.

Negative Feedback Cycle Underlies Falling Phase of the Action Potential



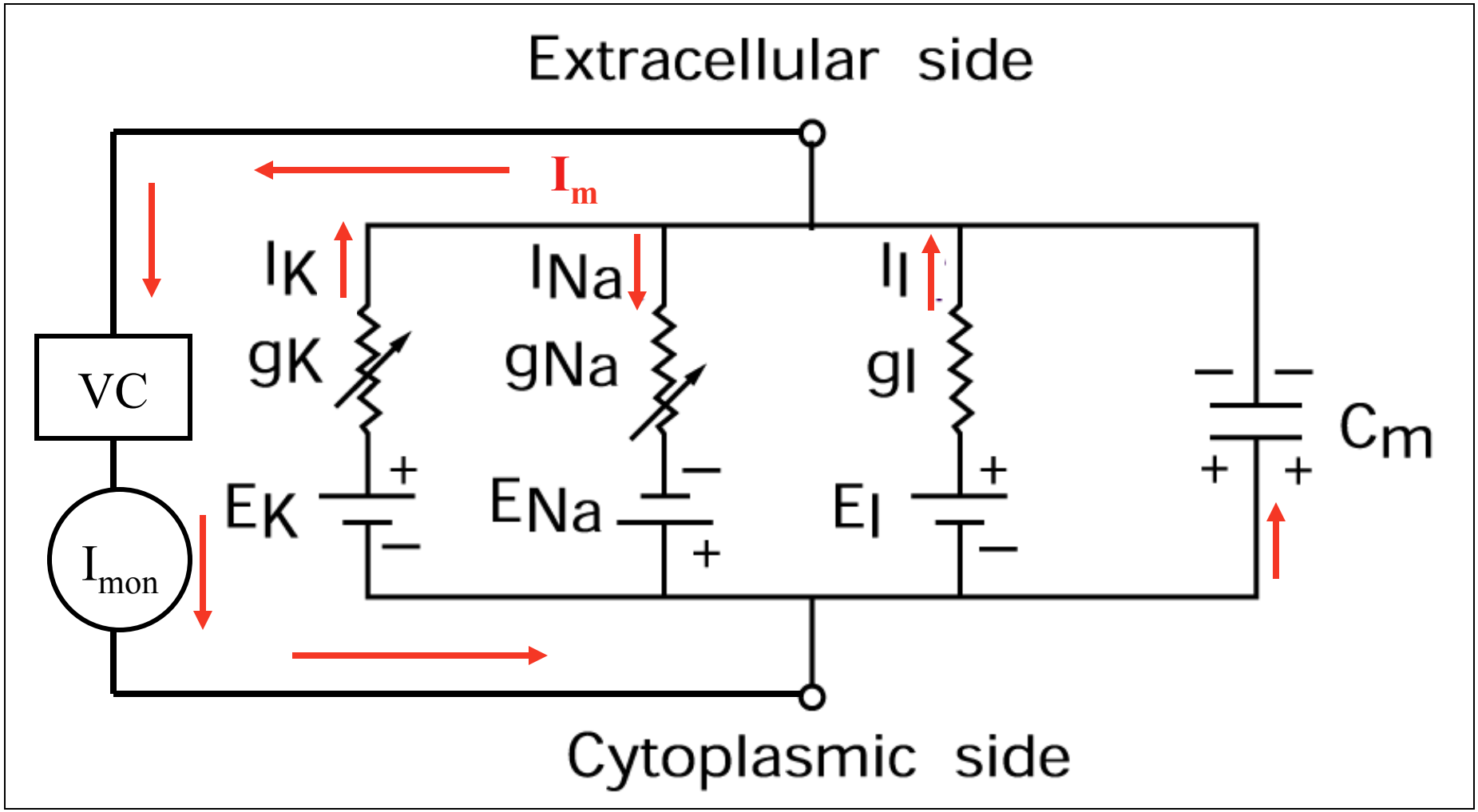
Absolute & Relative Refractory Periods

No movement of Na^+ possible

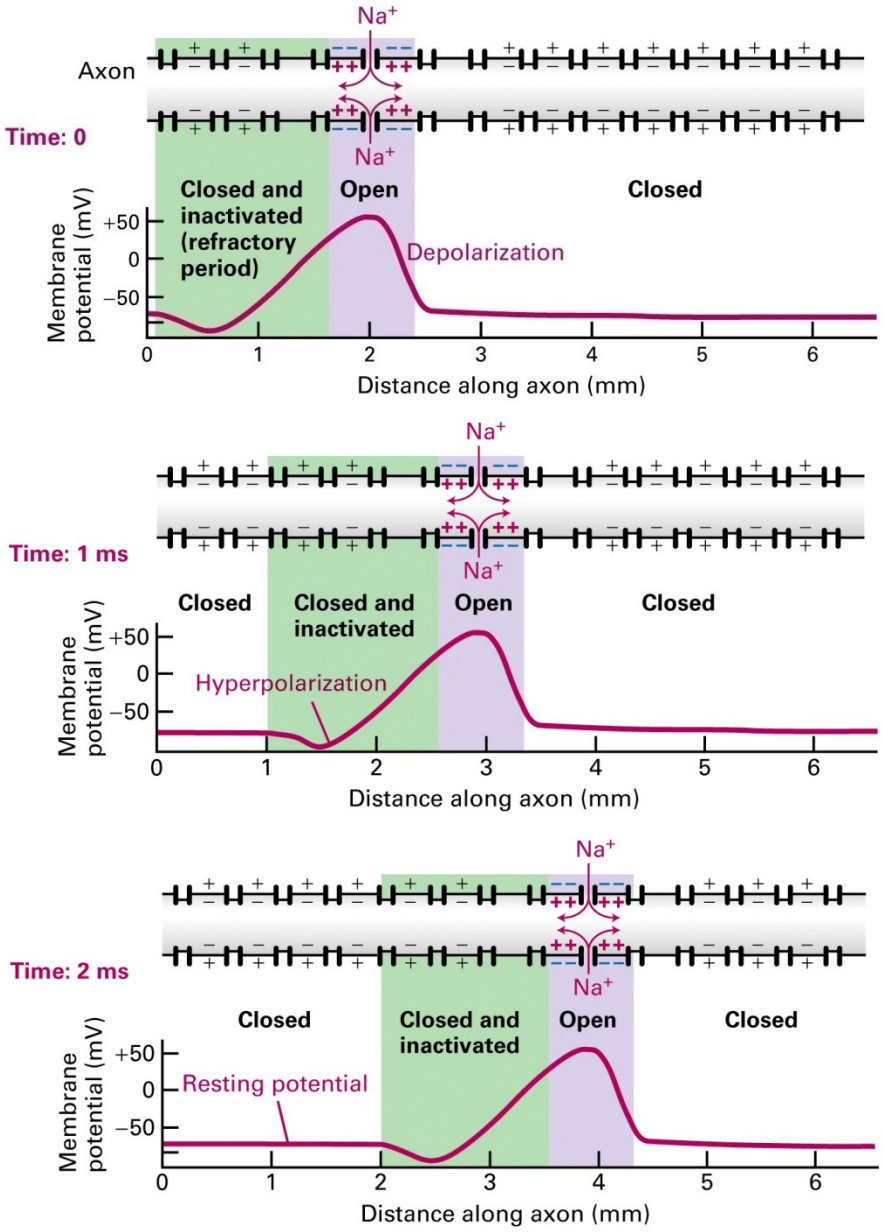


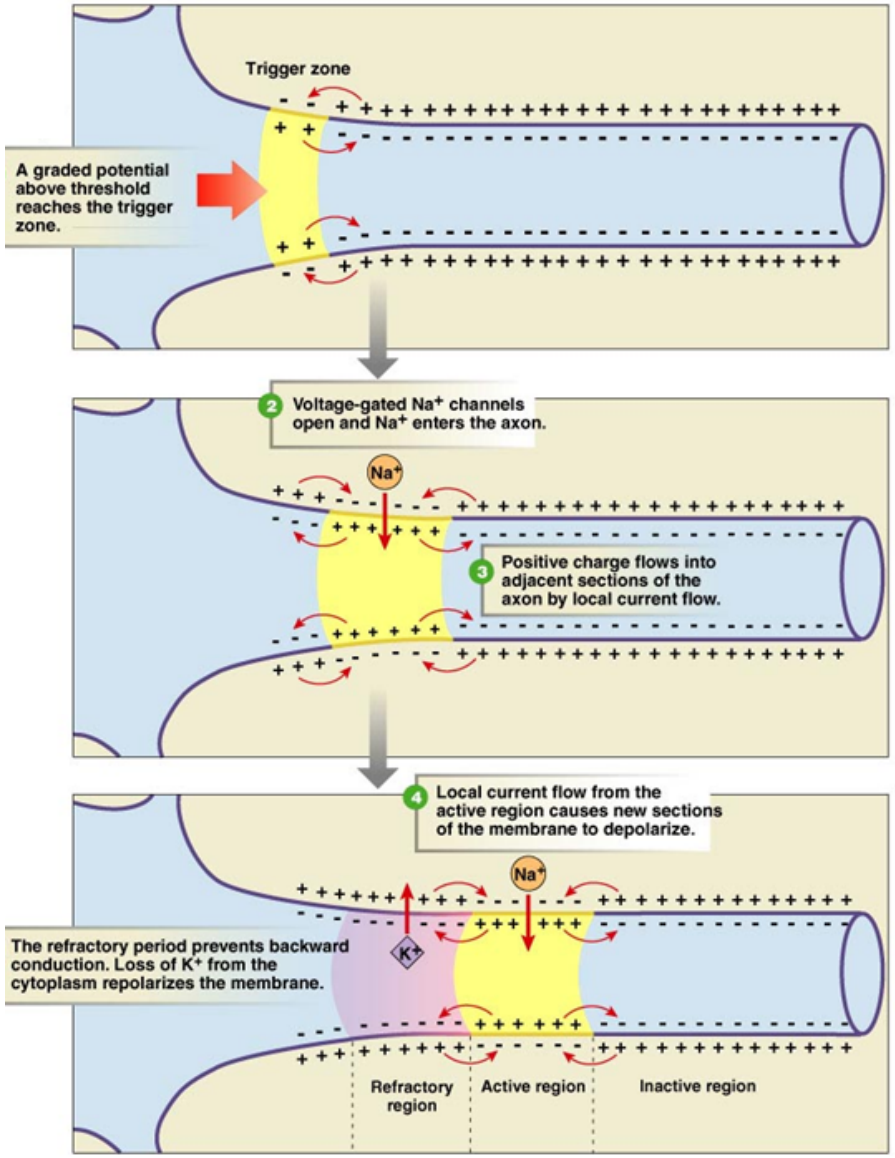
Na^+ channels reset to resting state, K^+ channels still open higher than normal stimulus necessary

Equivalent Circuit of the Membrane Connected to the Voltage Clamp



Propagation of action potentials in unmyelinated axons.

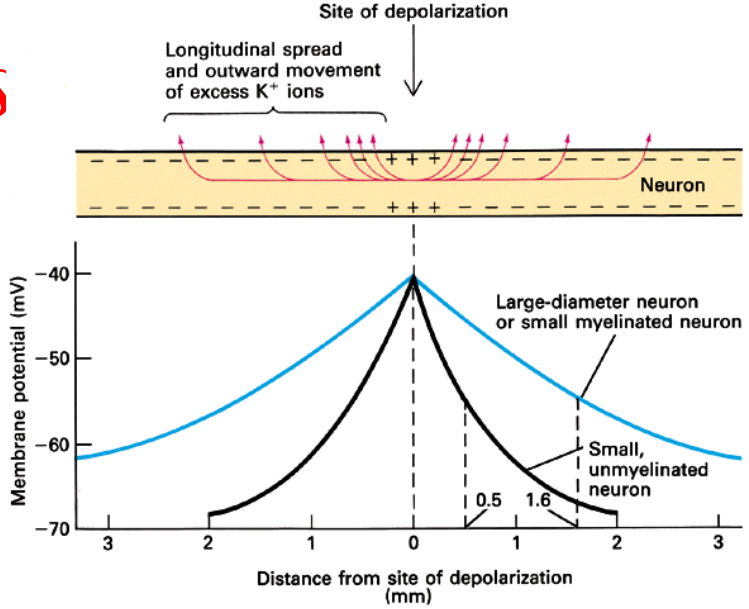




Conduction speed depends

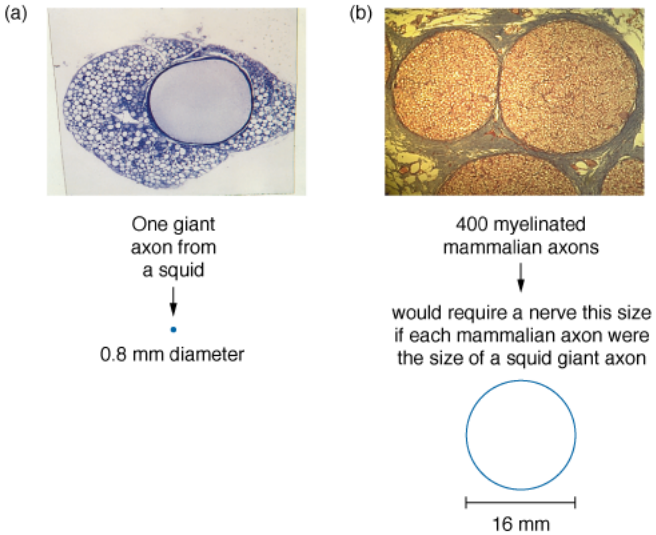
1. Axon diameter ***(the larger the faster)***

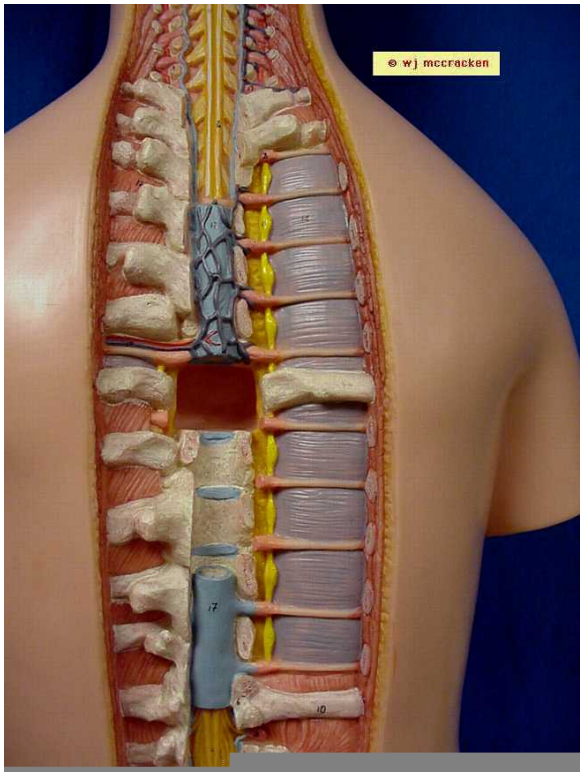
- Size constraints on axons become problem with increasing organismal complexity



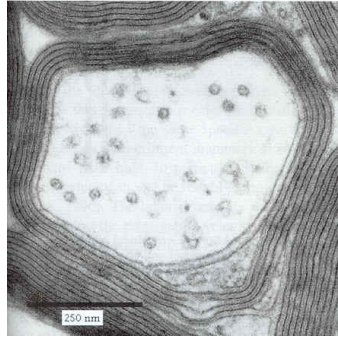
2. Membrane resistance

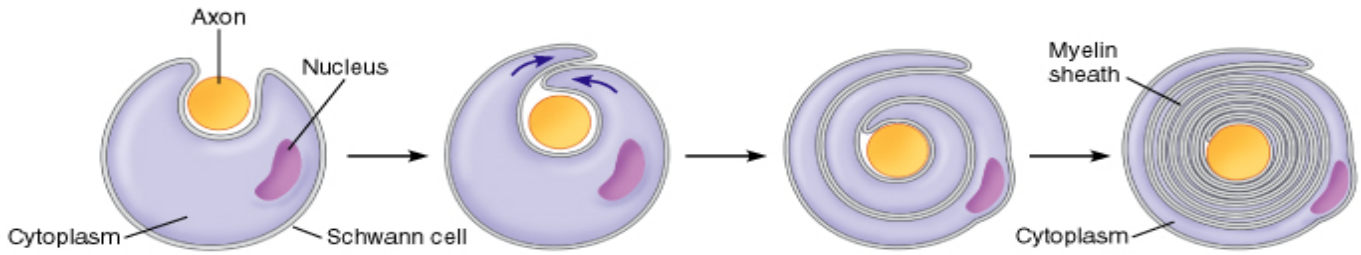
- High resistance of myelin sheath reduces leakage of current (ion) flow between axon and ECF
- Saltatory Conduction from node to node



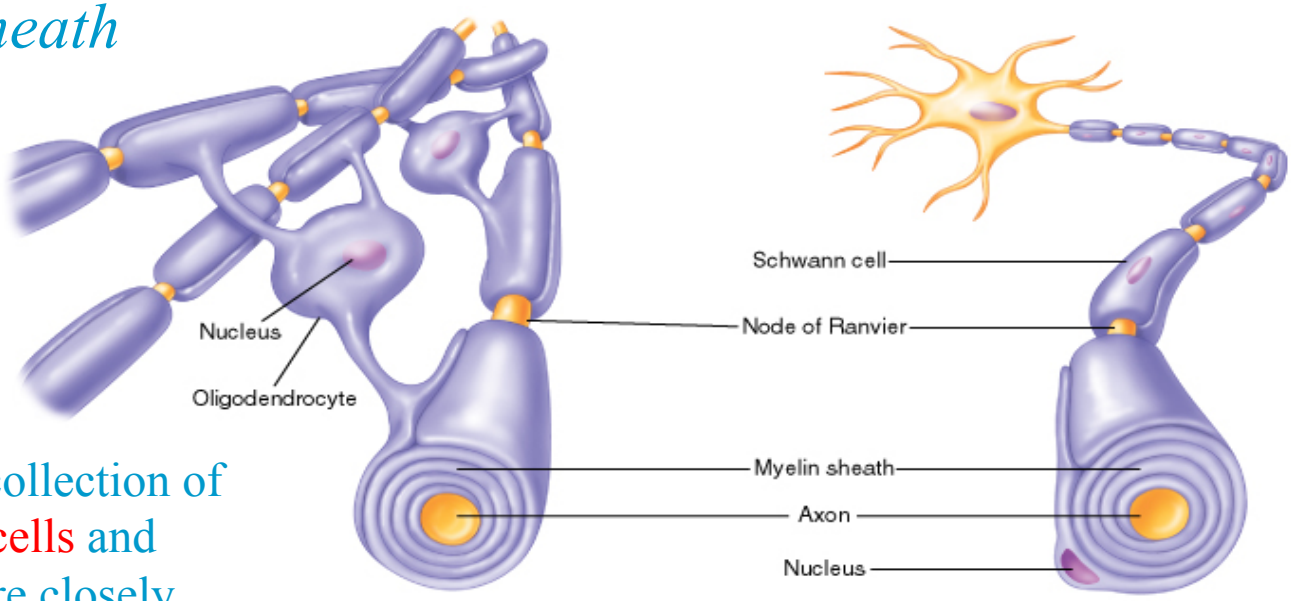


Among all types of neurons, myelinated neurons conduct action potentials most rapidly.





Formation of myelin sheath



The "myelin sheath" is a collection of cells called Schwann cells and oligodendrocytes that are closely associated with the neuron.

In nerve fibres with diameter ≥ 1 μm a myelin sheath are broken at intervals of ≈ ***1- 1.5*** *mm.*

Action potential propagation in myelinated axons

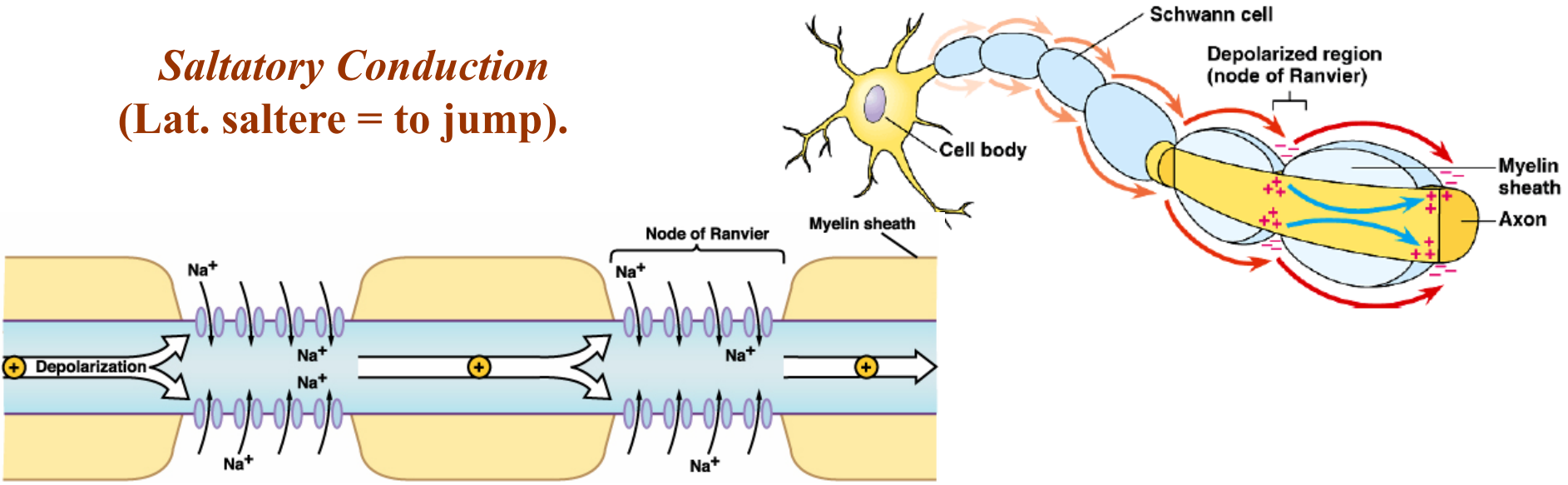
Nodes of Ranvier

Membrane resistance lowest at these points

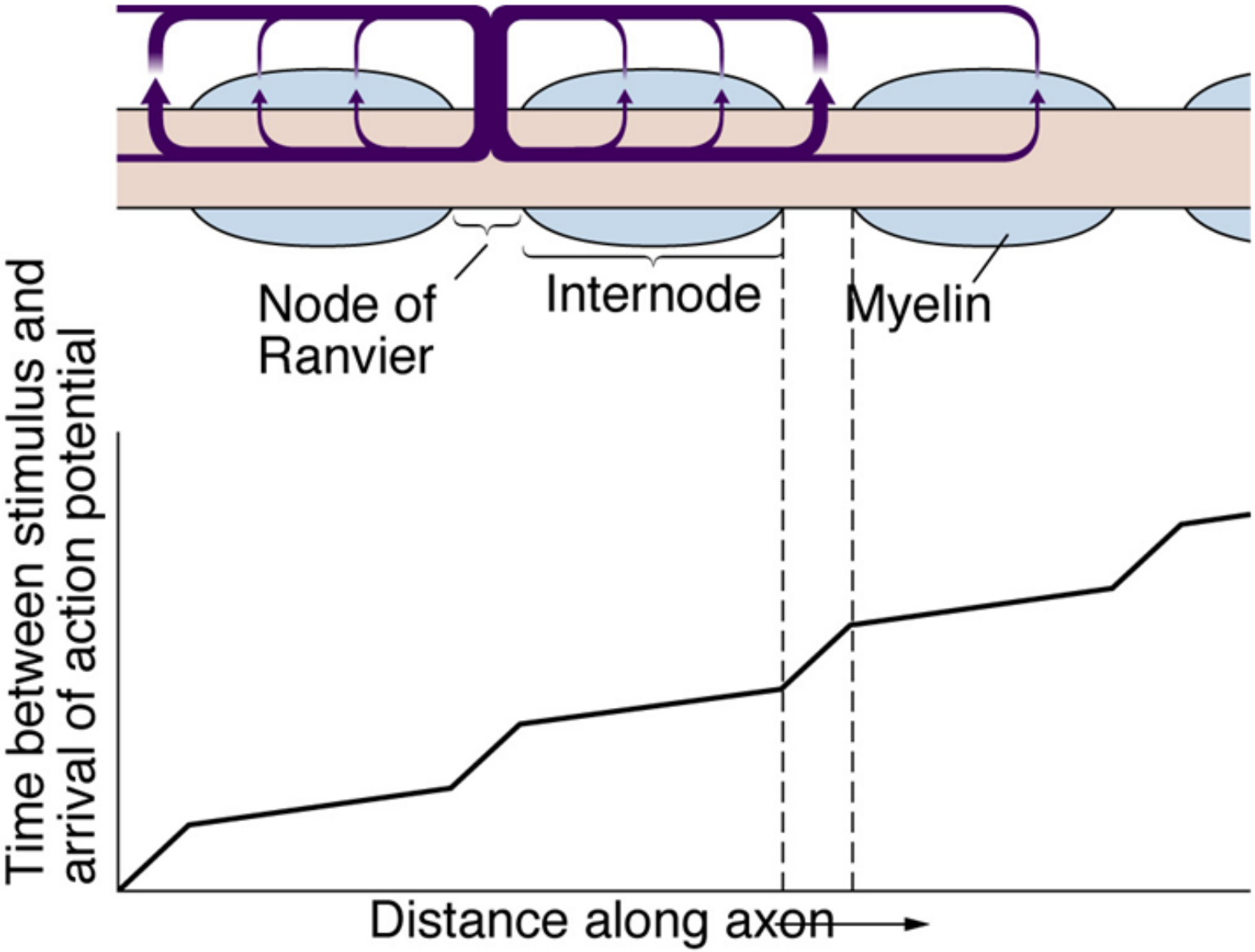
AP Propagation

- Starts at trigger zone
- AP flows to 1st Node of Ranvier
- Node has high density of voltage gated Na^+ channels
- Na^+ re-entry boosts strength of AP

Saltatory Conduction
(Lat. saltere = to jump).

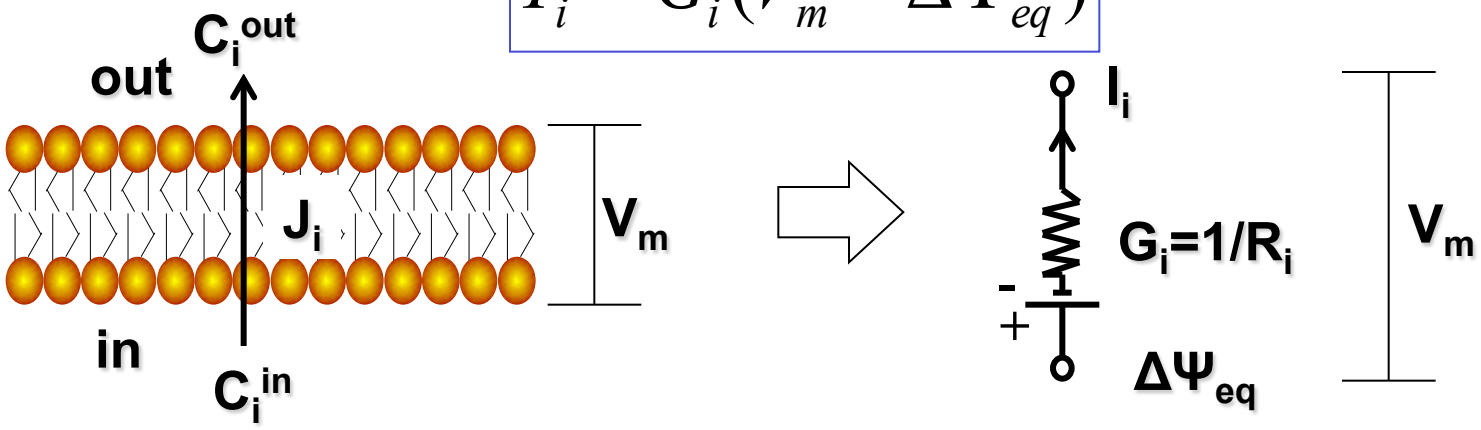


Myelin Speeds Up Action Potential Conduction

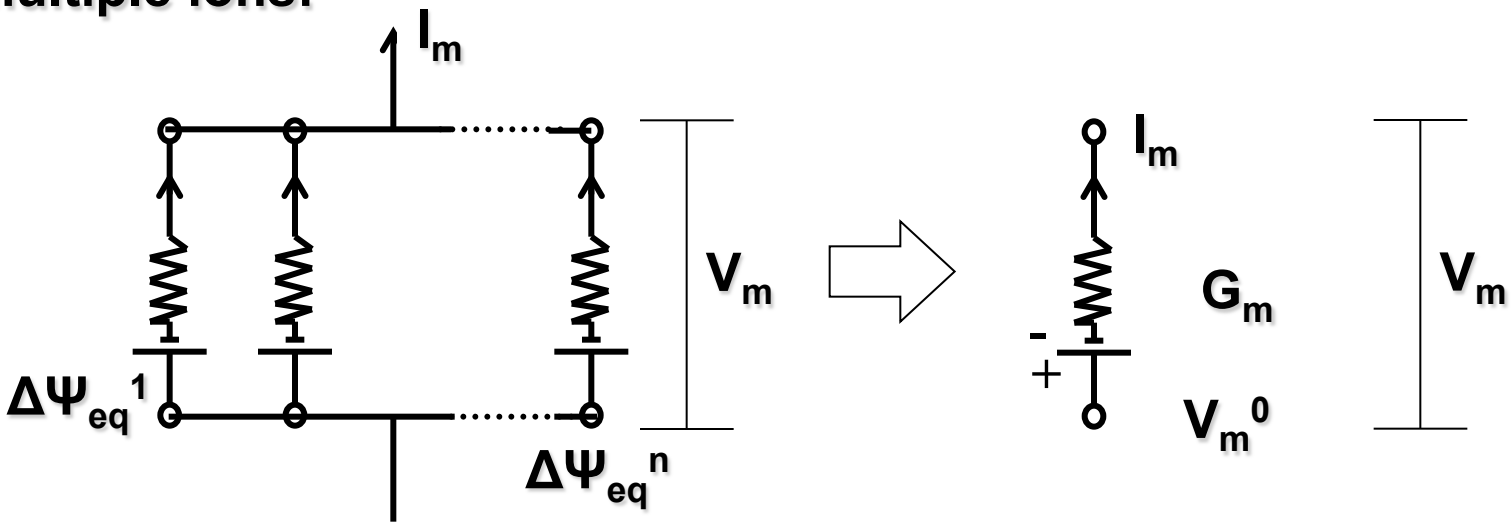


The Membrane Electrical Analog:

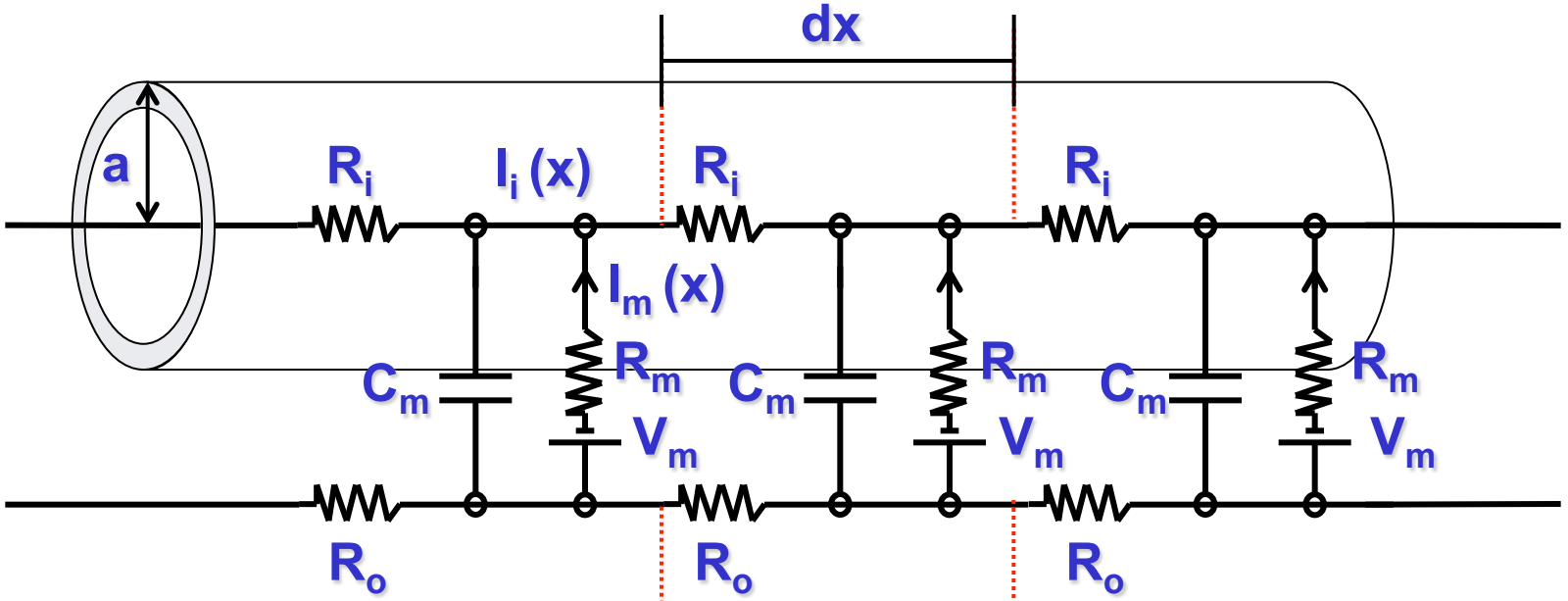
$$I_i = G_i(V_m - \Delta\Psi_{eq})$$



For multiple ions:



The Axon Electrical Analog:



I_i (x) – axial current

I_m (x) – ion current through membrane

R_i – axoplasm resistance

R_m – membrane resistance

C_m – membrane capacitance

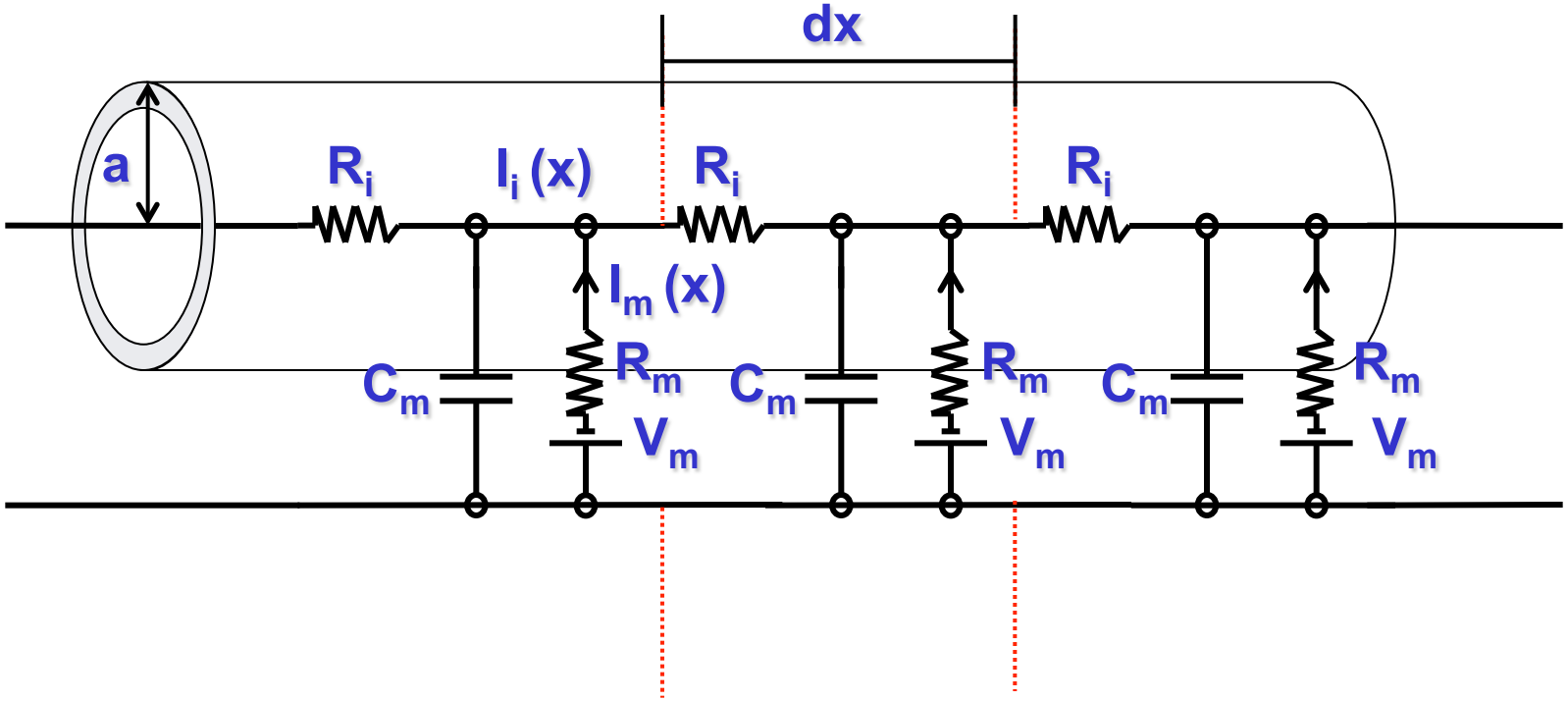
V_m – membrane potential

a – diameter of axon

dx – unit length

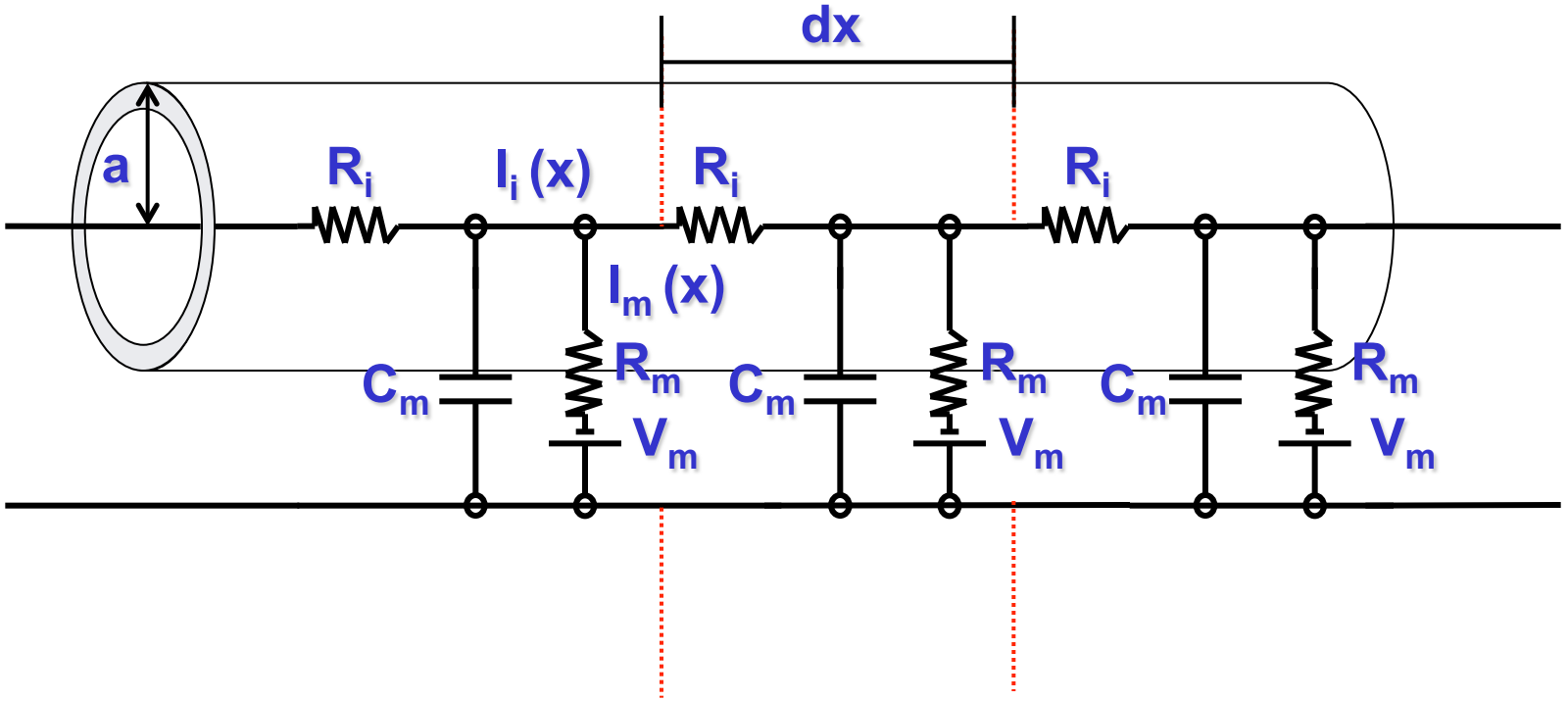
κ – electrical conductivity of axoplasm

The Axon Electrical Analog:



$R_o = 0$

The Axon Electrical Analog:

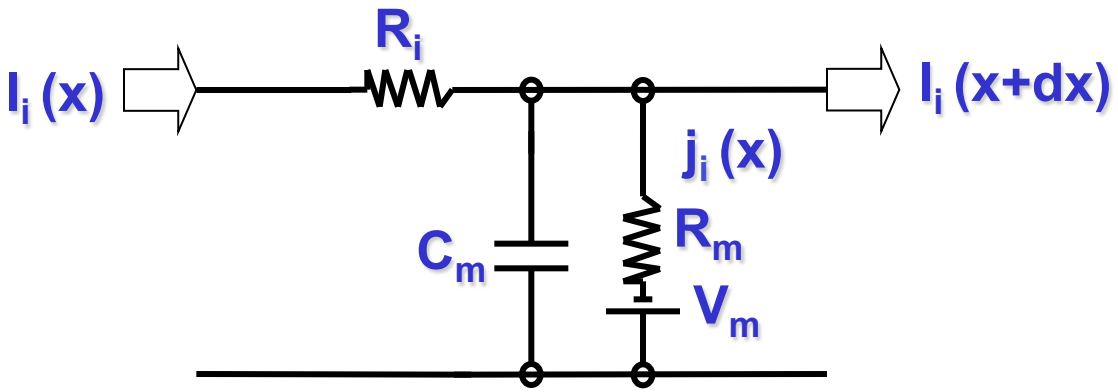


$$\frac{\partial V'_m(x,t)}{\partial t} = \frac{I_c}{C_m}$$

$$I_{total} = C_m \frac{\partial V'_m}{\partial t} + I_{ionic}$$

V'_m – difference in membrane potential from resting state

Passively Spreading Potential:



Change in the axial current must be balanced by the current through the membrane

$$I_x(x) - I_x(x+dx) = \frac{\partial I_x}{\partial x}dx = 2\pi a\left(j_{q,r}(x) + C\frac{\partial V_m}{\partial t} \right)dx$$

All ionic currents

Charge piling on the capacitor

Unknown functions:

$$V_m(x,t)$$
$$I_i(x,t)$$
$$j_{q,r}(x,t)$$

Linear Cable Equation:

Space constant:

$$\lambda_{axon} = \sqrt{\frac{a\kappa}{2G_{total}}}$$

Time constant:

$$\tau \cong \frac{C}{G_{total}}$$

Linear cable equation:

$$(\lambda_{axon})^2 \frac{\partial^2 V'_m}{\partial x^2} - \tau \frac{\partial V'_m}{\partial t} = V'_m$$

Solution:

$$V(x,t) = const \cdot \exp\left(\frac{-t}{\tau}\right) * t^{-1/2} \exp\left(\frac{-x^2}{4t(\lambda_{axon})^2 \tau}\right)$$

Characteristic parameters of nerve "cables" :

	Frog muscle neuron		*Squid gigantic axon*	
	a = 75 μm		a = 600 μm	
	External	Internal	External	Internal
Na^+	120 mM	9.2 mM	460 mM	50 mM
K^+	2.5 mM	140 mM	10 mM	400 mM
Cl^-	120 mM	3-4 mM	540 mM	40-100 mM
Resting potential:	-90 mV		-60 mV	
Space constant (λ_{axon})	**2 mm**		**5 mm**	
Time constant (τ)	24 ms		0.7 ms	
R_m	4000 Ohm/cm^2		700 Ohm/cm^2	
R_i	200 Ohm/cm		30 Ohm/cm	
C_m	6 μF/cm^2		6 μF/cm^2	

Non-Linear Cable Equation:

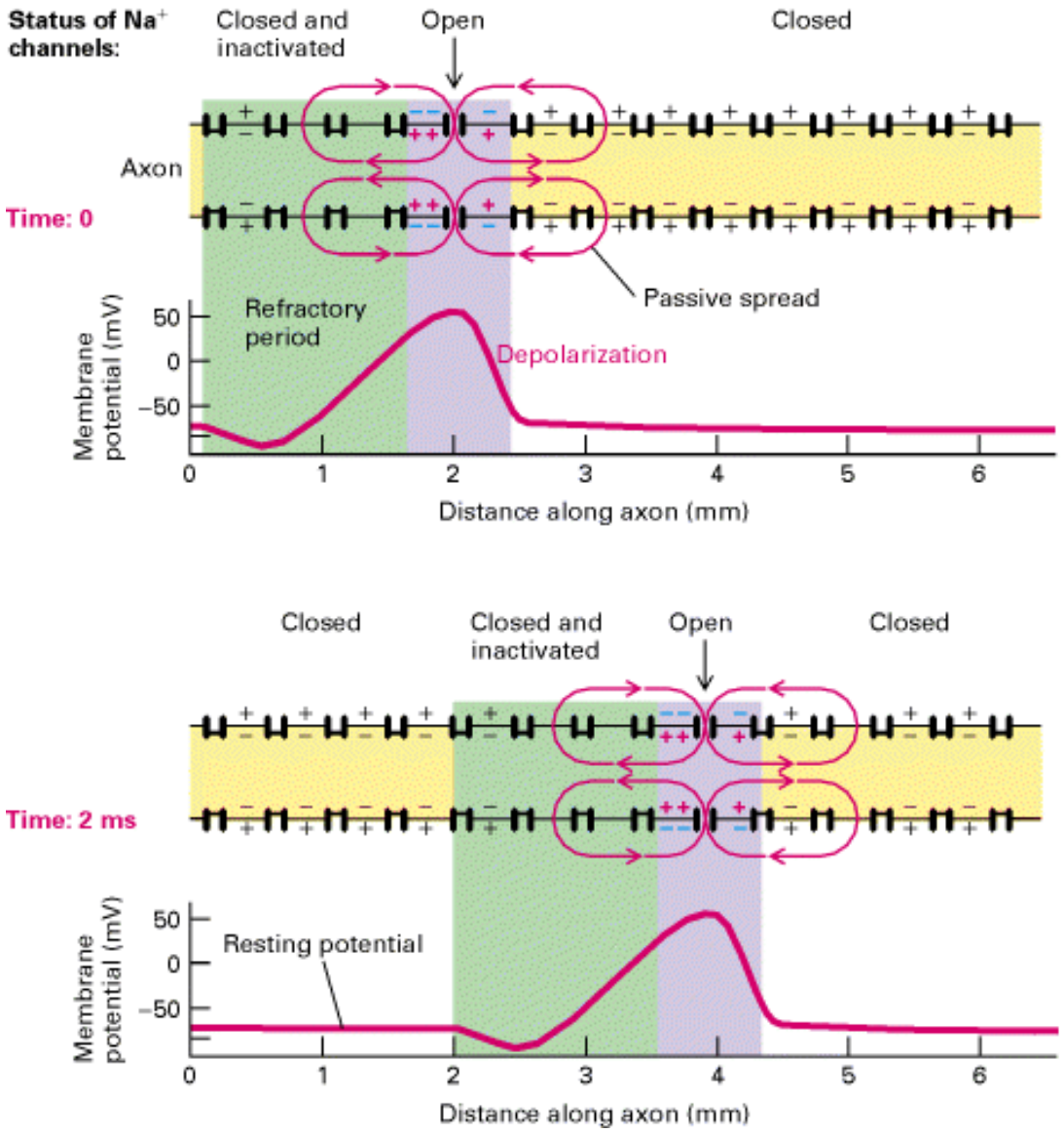
1. The wave propagation requires threshold stimulus

2. If the stimulus is too low or is of a wrong sign, it will result in decaying response (as described by the linear cable equation)

3. Above threshold stimulus creates a traveling wave of excitation, so that the response at a distance from the point of stimulation does not depend on the magnitude of the stimulus and has a predicted shape

4. The traveling wave moves at a constant speed along the axon.

Voltage-gating hypothesis:

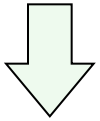


$$V(x,t) = V\left[0, \left(t - \frac{x}{\upsilon}\right)\right]$$

NON-Linear Cable Equation:

$$(\lambda_{axon})^2 \frac{\partial^2 V'_m}{\partial x^2} - \tau \frac{\partial V'_m}{\partial t} = V'_m$$

Linear cable equation:



$$(\lambda_{axon})^2 \frac{\partial^2 V'_m}{\partial x^2} - \tau \frac{\partial V'_m}{\partial t} = V'_m \frac{(V'_m - V_1)(V'_m - V_2)}{V_1 V_2}$$

NON-Linear cable equation:

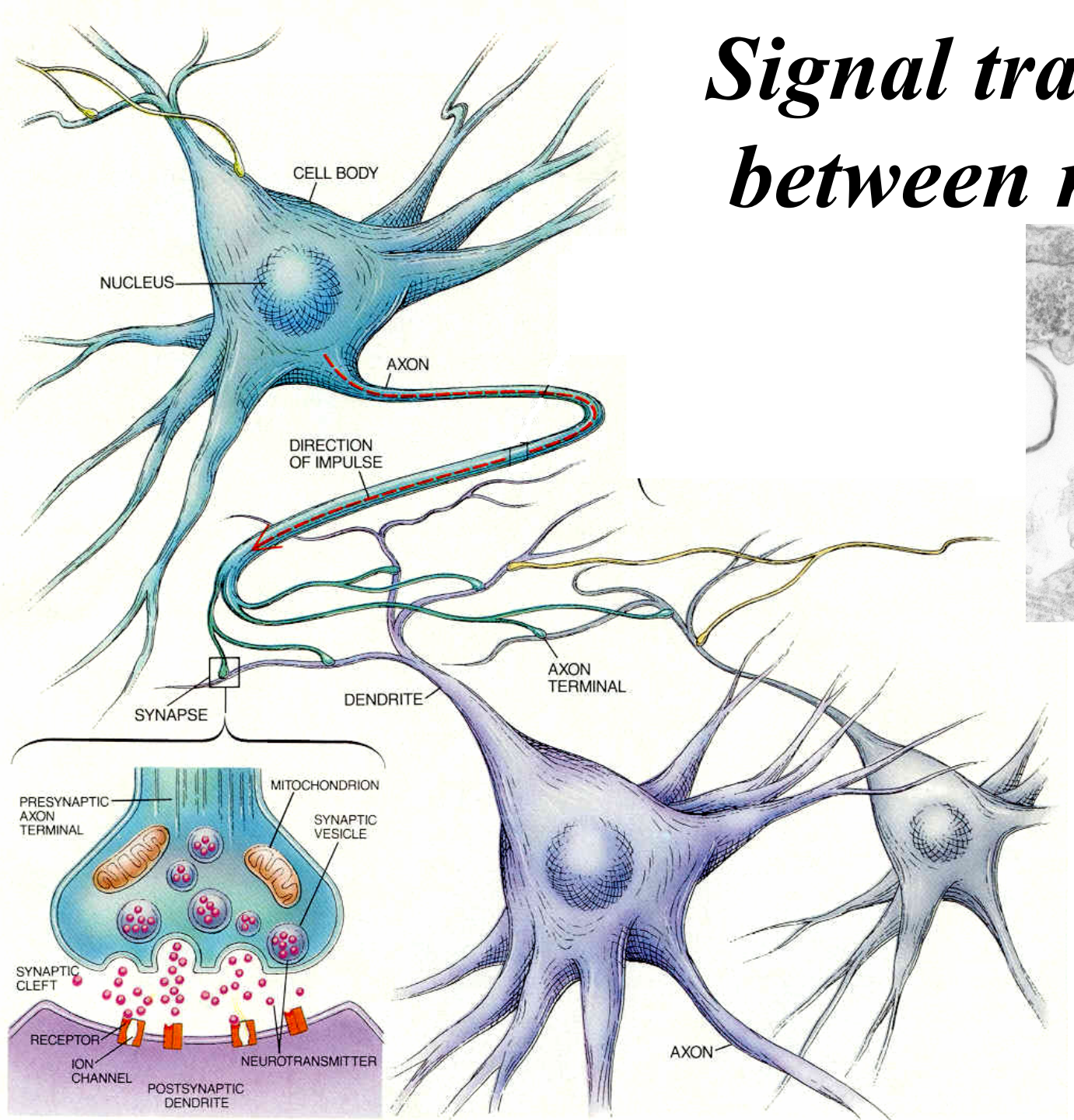
$$\left(\frac{\lambda_{axon}}{\upsilon}\right)^2 \frac{d^2 V'_m}{dt^2} - \tau \frac{\partial V'_m}{\partial t} = V'_m \frac{(V'_m - V_1)(V'_m - V_2)}{V_1 V_2}$$

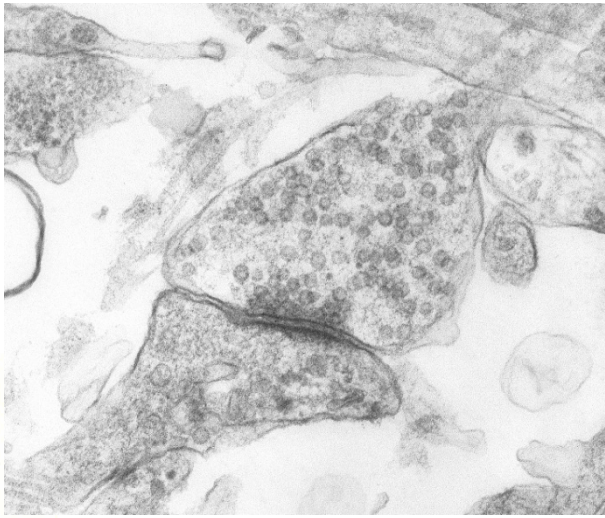
$$\upsilon = \pm \frac{\lambda_{axon}}{\tau} \sqrt{\frac{2}{s}} \left(\frac{s}{2} - 1\right)$$

$$s = \frac{V_1}{V_2}$$

Traveling-wave solution

Signal transmition between neurons.





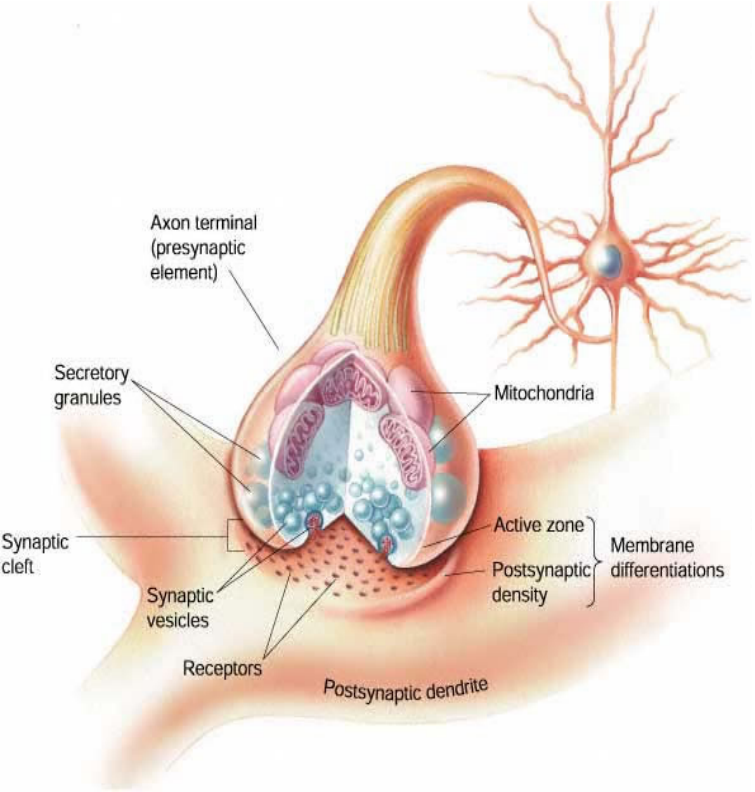
Synaptic transmission

There are:

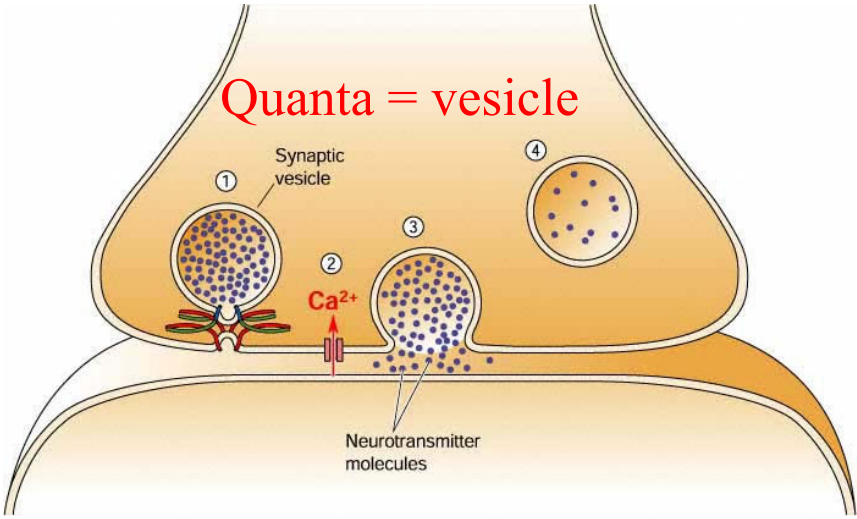
***electric synapses* (excitatory only)**

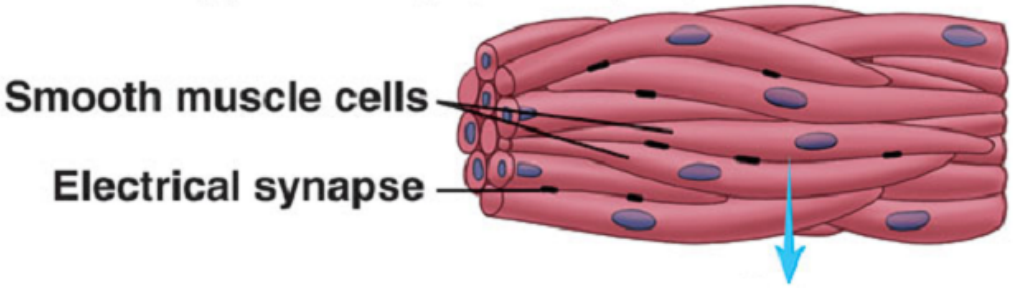
***chemical synapses* (excitatory, inhibitory or facilitating)**

Synaptic cleft – the space separating membranes of the two cells making the connection (26 – 40 nm).

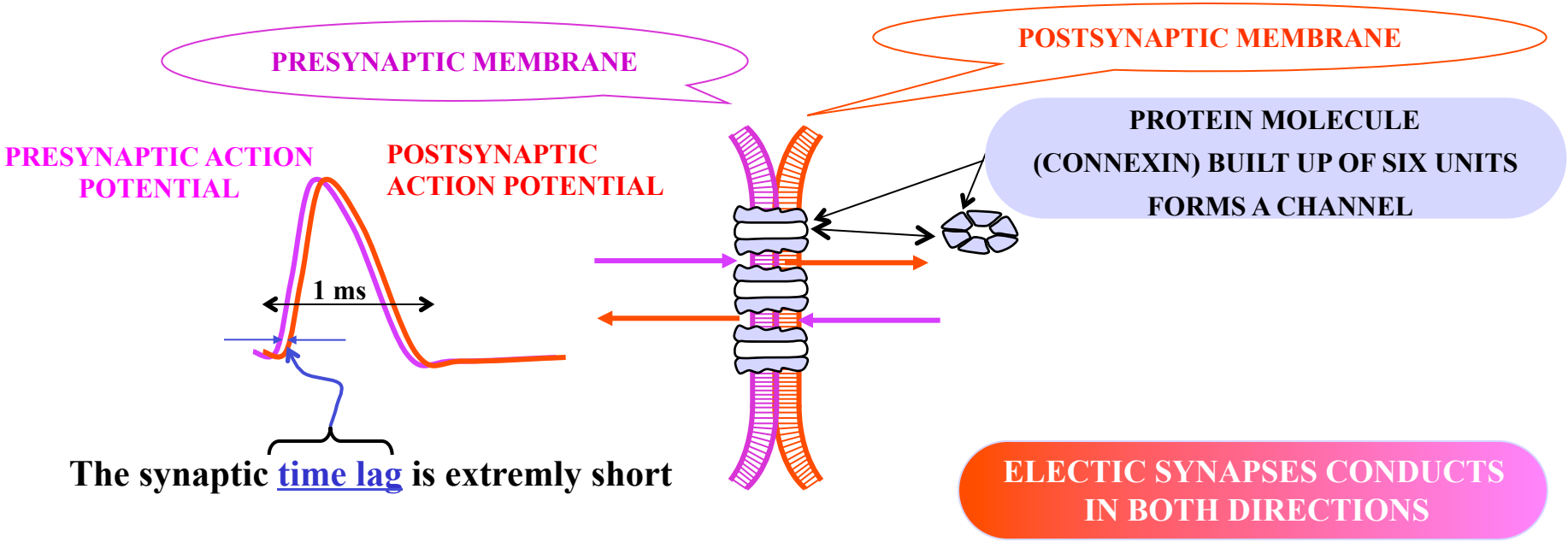


There are about 10^{15} synapses in a human brain.



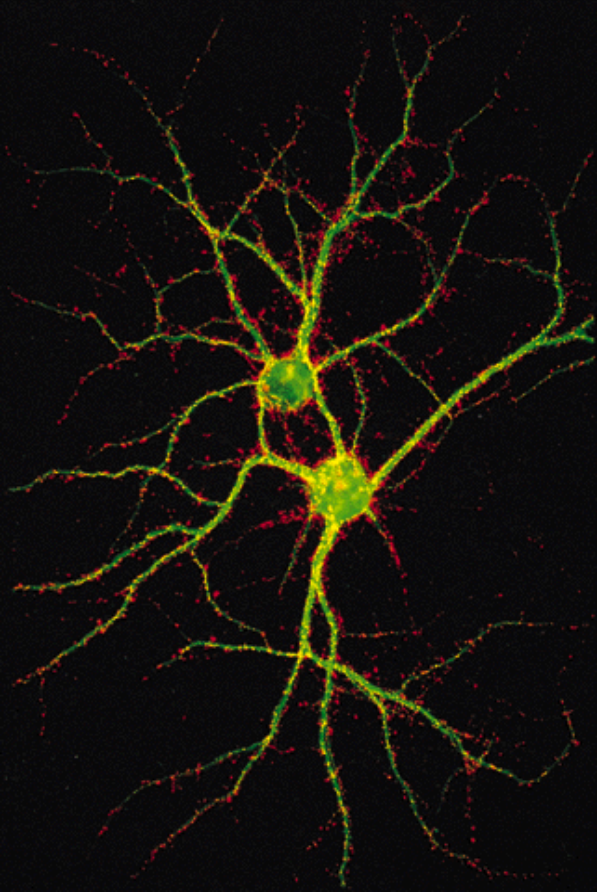


Fast communication betwen cells the electric synapse.

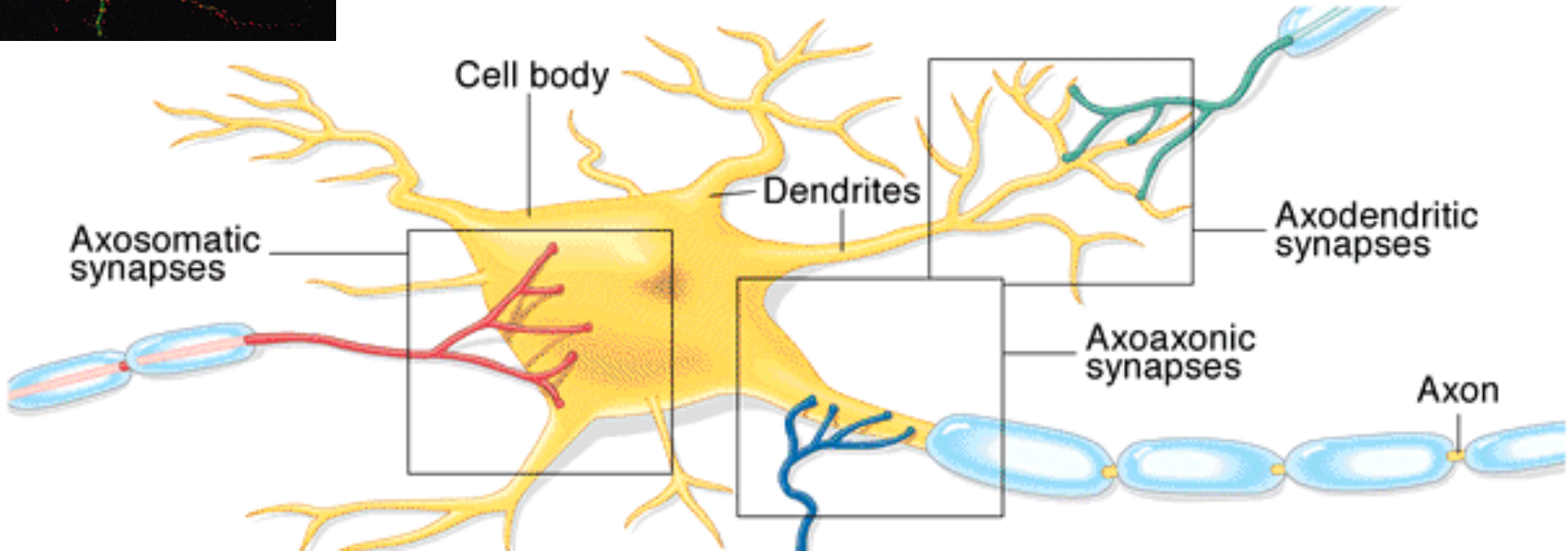


The Ca-concentration and the pH level controls the function of an electric synapse

A fish has many electric synapses, these fast working units make possible the lightning – fast whisk of their tail. A good lot of electric synapses may be found in some parts of the human brain, too, (hippocampus, hypothalamus, spinal marrow, etc.), as well as in the retina.



Types of Chemical Synapses

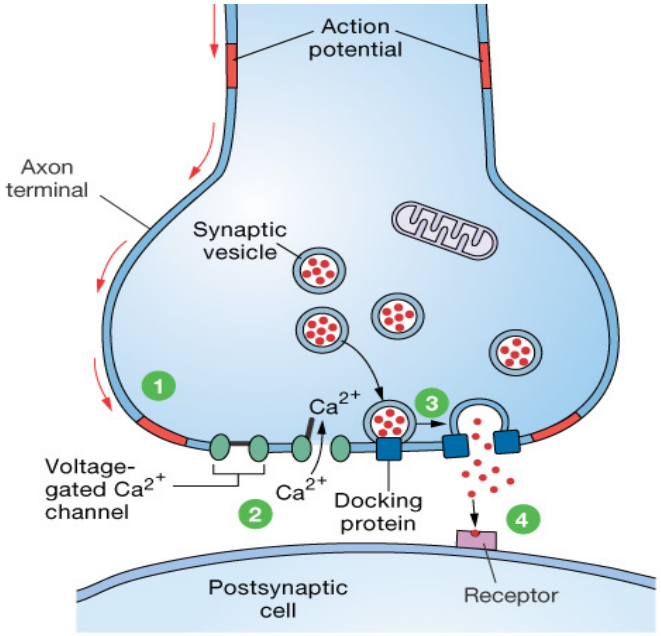


Synapse: most vulnerable step in signal propagation

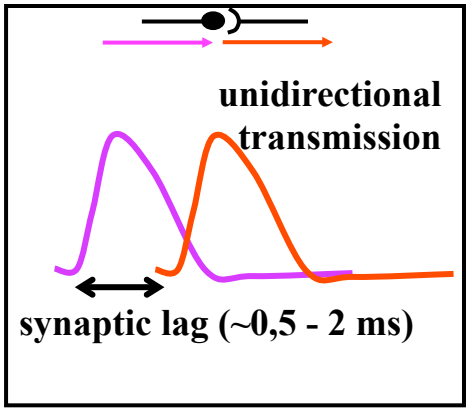
Many disorders of synaptic transmission, *e.g.*:

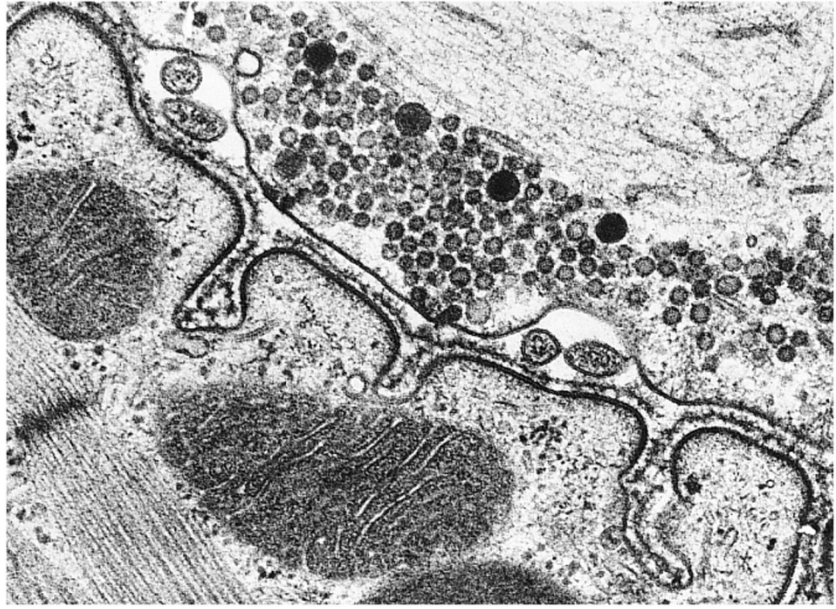
- ***Myasthenia gravis*** (PNS)
- ***Parkinson's*** (CNS)
- ***Schizophrenia*** (CNS)
- ***Depression*** (CNS)
- ***Many toxins***

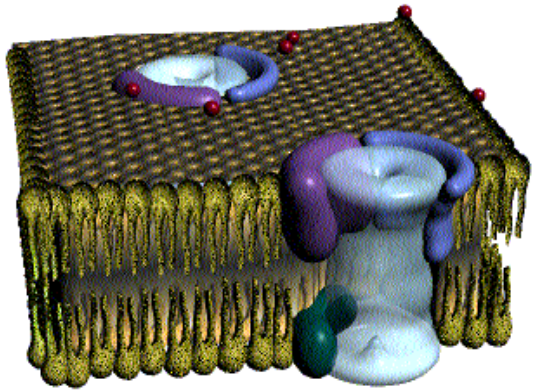
Axon terminals have mitochondria & synaptic vesicles containing neurotransmitter

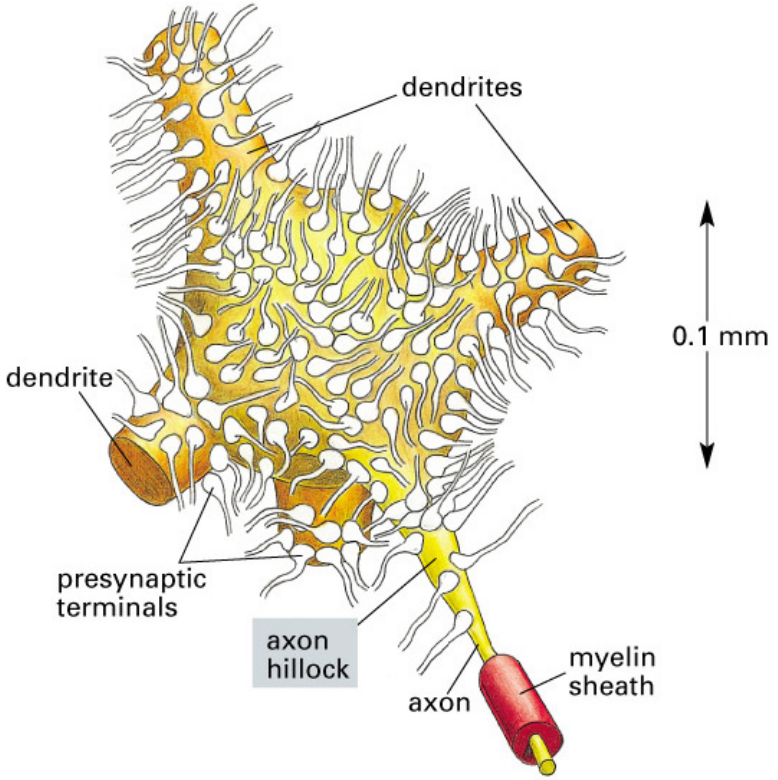


The signal transmission through a chemical synapse.









Neurons receive as many as 200,000 terminals

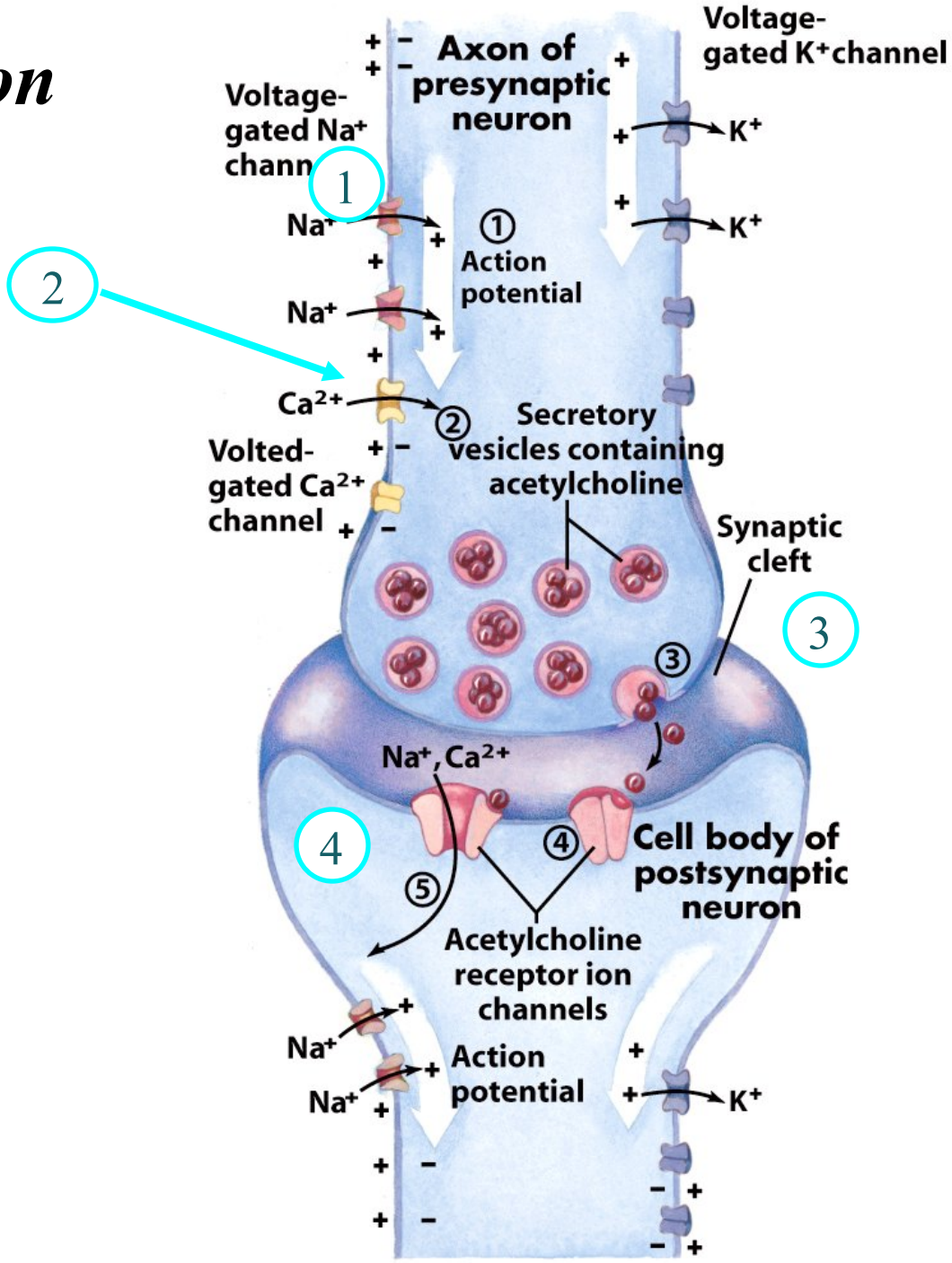
Synaptic transmission

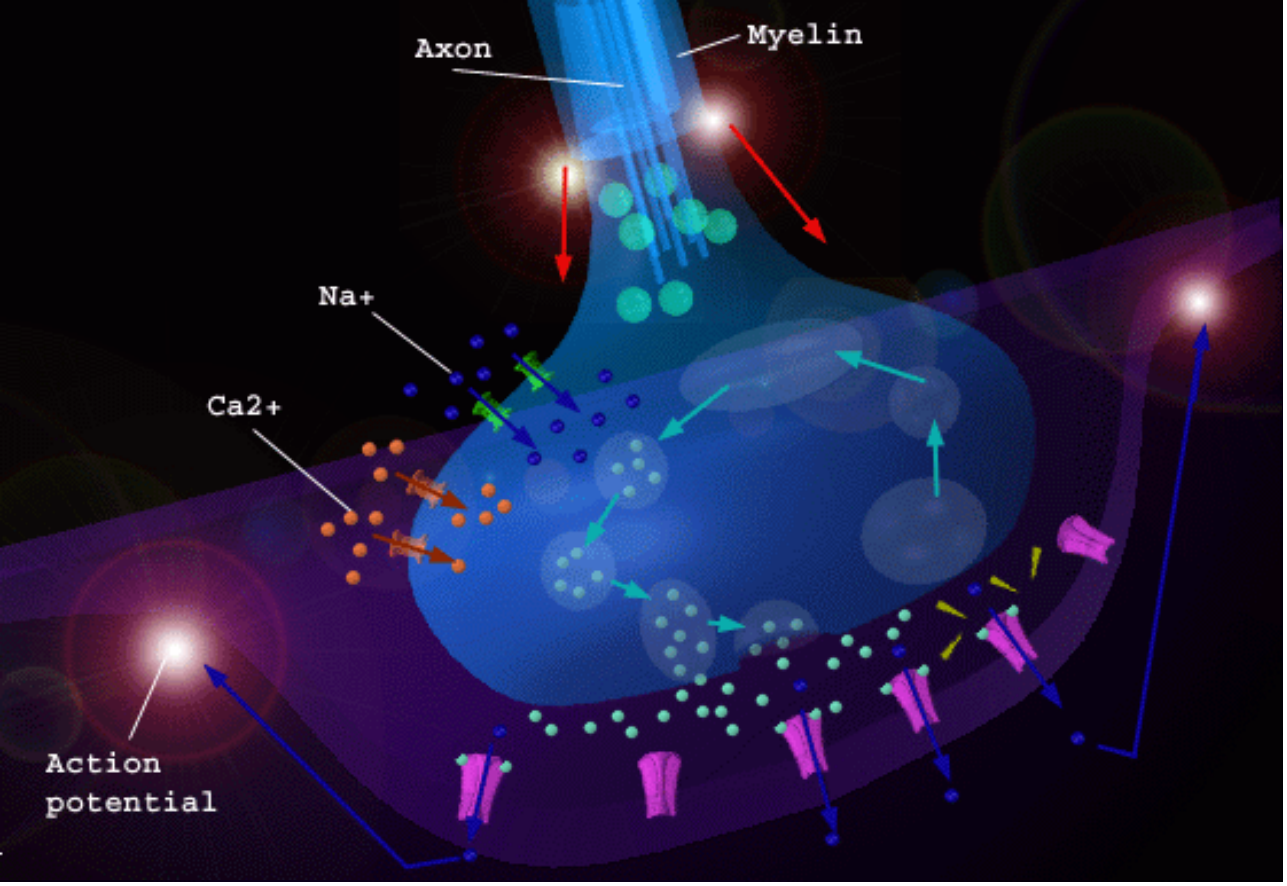
1. *Action potential, moving along axon's voltage-gated Na $^{+}$ and K $^{+}$ channels, arrives at terminal.*

2. *Action potential opens voltage-gated Ca^{++} channels.*

3. *Ca^{++} influx triggers neurotransmitter release into the synaptic cleft.*

4. *The binding of neurotransmitters to receptor proteins in the postsynaptic membrane is linked to an alteration in its ion permeability.*

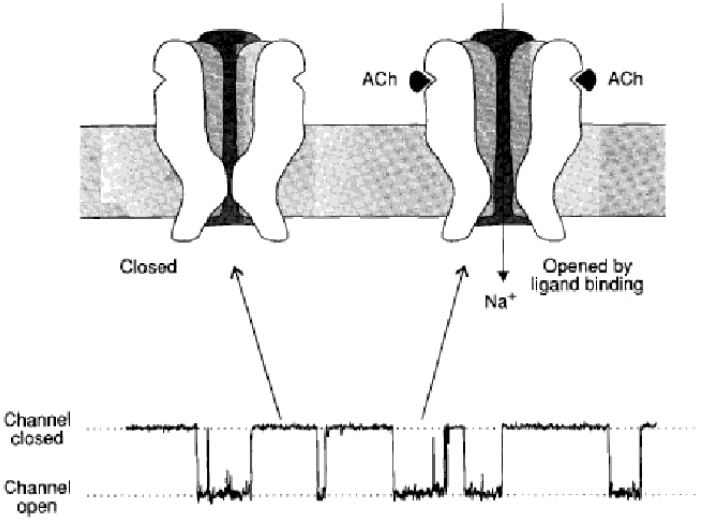


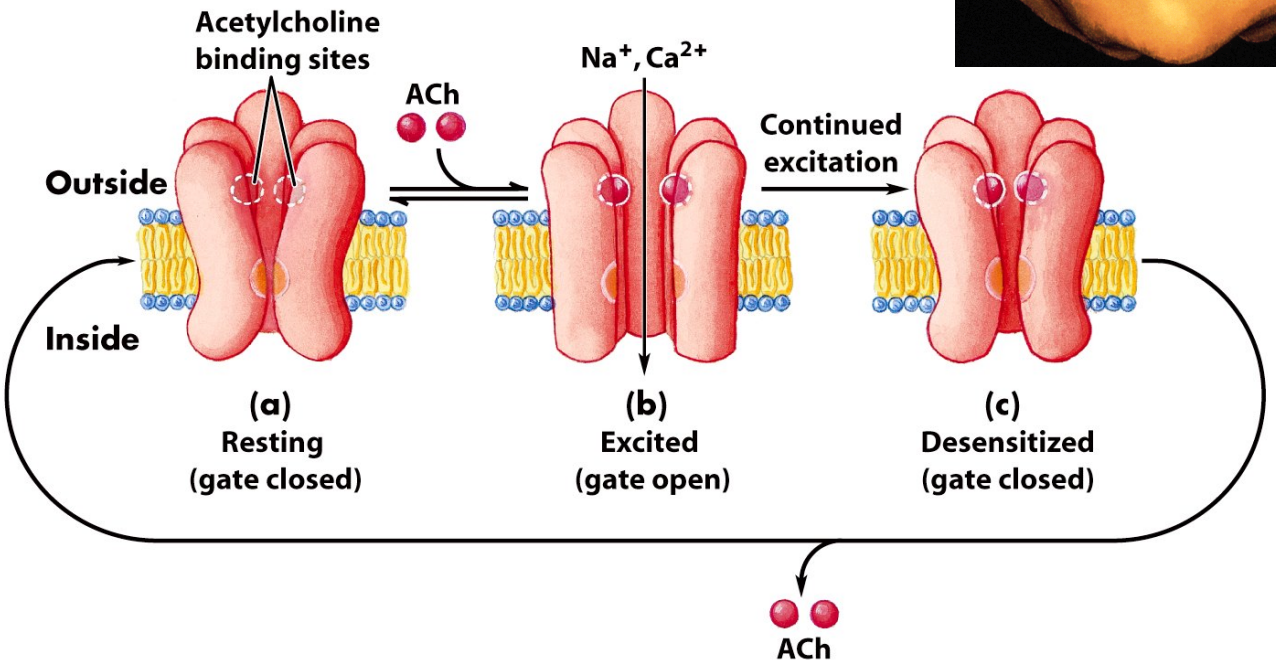


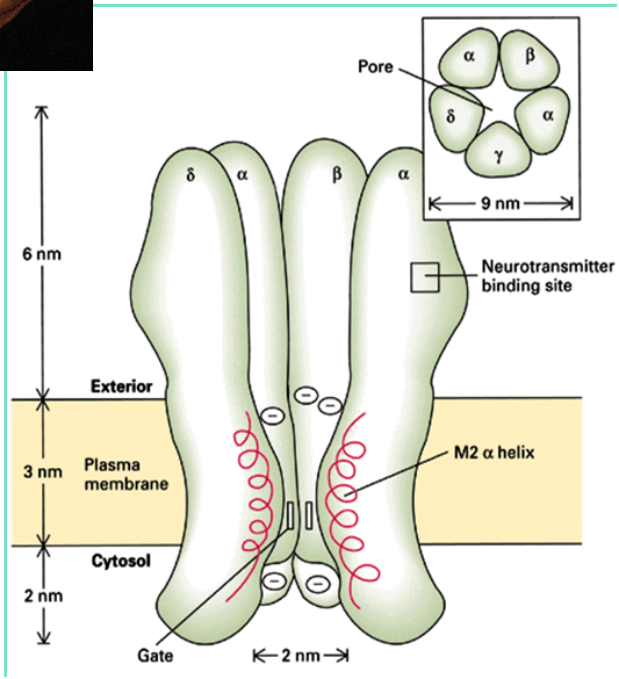
Trasmission of the nervous impulse

The transmitter release of about 10 vesicles is required to generate a postynaptic potential that is big enough to result in an action potential.

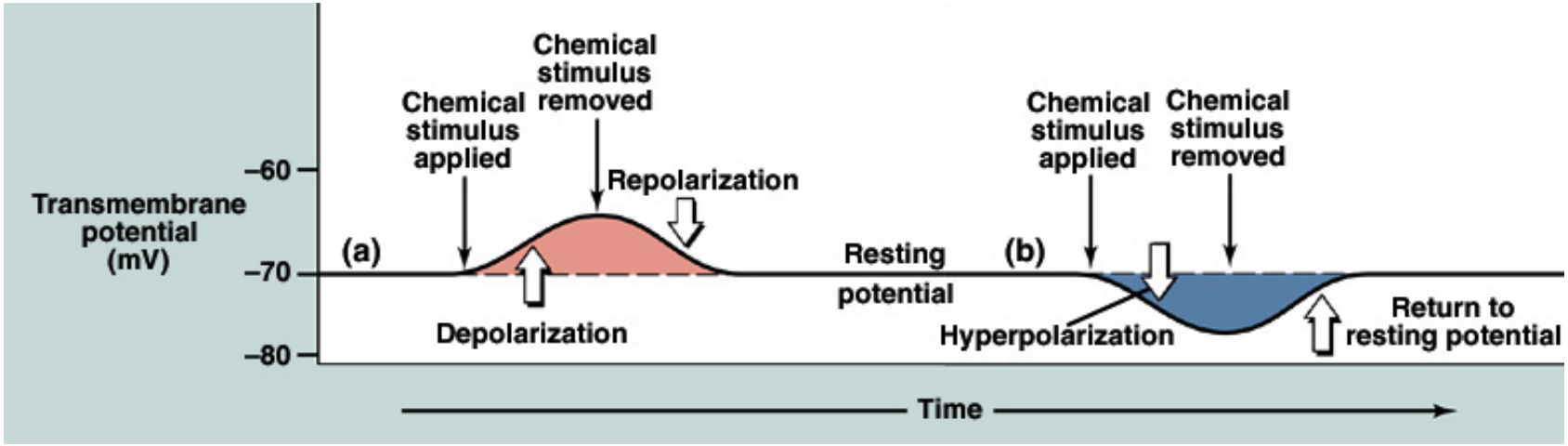
Ligand-gated channel – acetyl choline gated channel







Transmitter effects on E_m



- Most chemical stimuli result in an influx of cations
  - This causes a depolarization of the membrane potential
- At least one transmitter opens an anion influx
  - This results in a hyperpolarization.

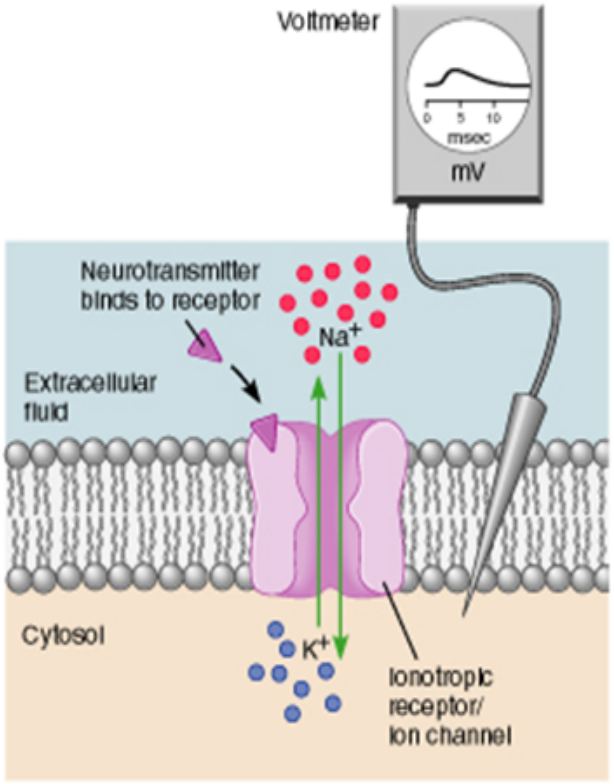
Cation-conducting channels *- acetylcholine-, serotonin- and glutamate receptors*

Anion-conducting channels *- glycine and g-aminobutiric (GABA) acid -gated receptors*

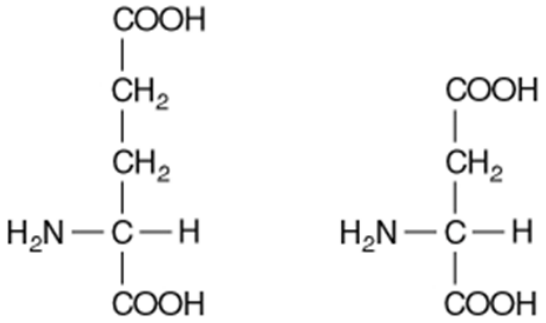
EPSPs and IPSPs

- If the transmitter opens a cation influx, the resulting depolarization is called an *Excitatory Post Synaptic Potential* (EPSP).
- These individual potentials are sub-threshold.
- If the transmitter opens an anion influx, the resulting hyperpolarization is called an *Inhibitory Post Synaptic Potential* (IPSP)
- All these potentials are additive.

Excitatory synapses



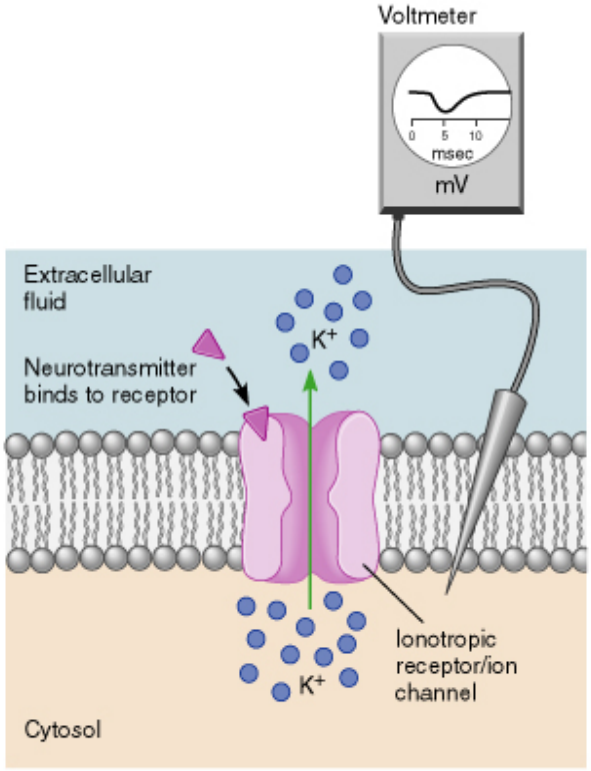
Fast response



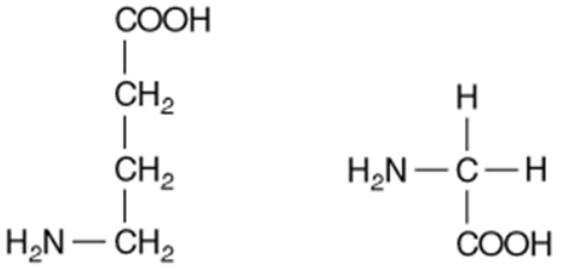
Glutamate **Aspartate**

Excitatory amino acid neurotransmitters

Inhibitory synapse



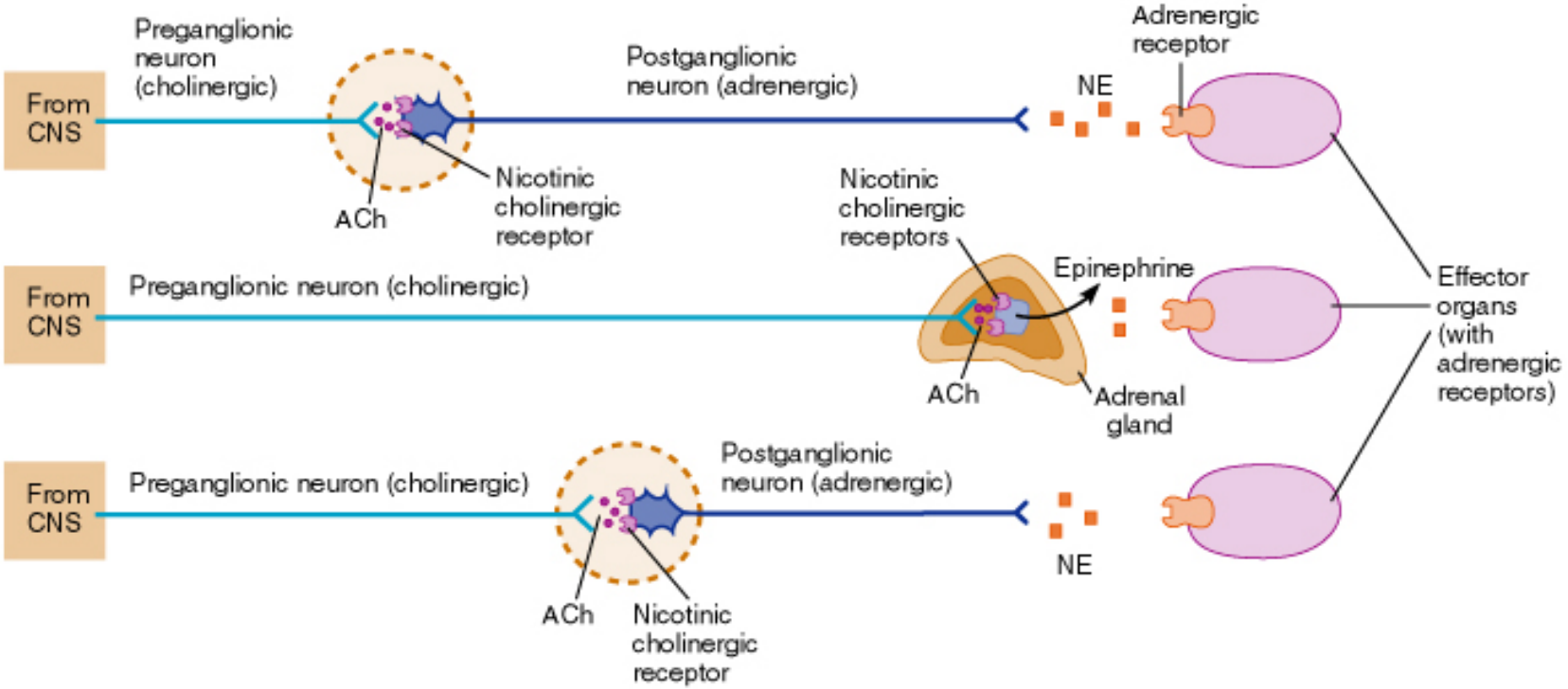
Fast response



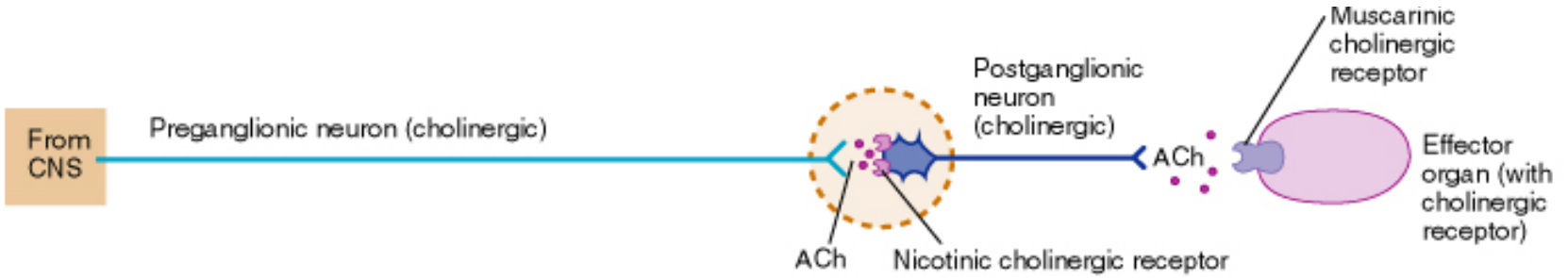
Gamma-amino butyric acid (GABA) **Glycine**

Inhibitory amino acid neurotransmitters

Neurotransmitters and receptors in the autonomic nervous system



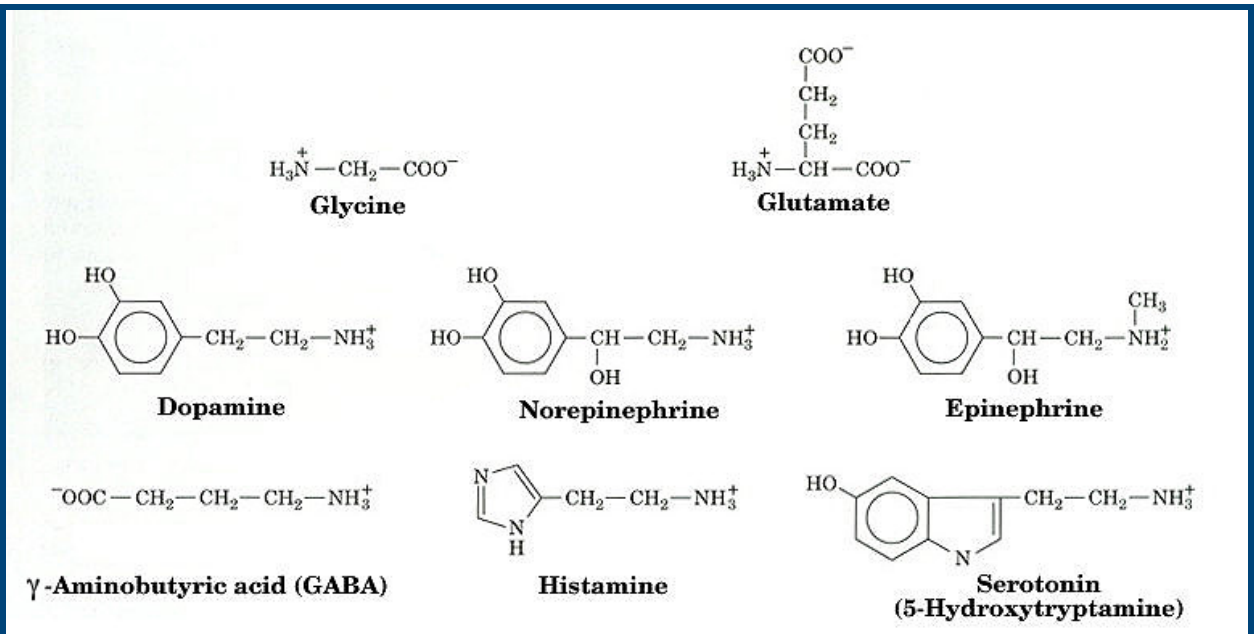
Sympathetic nervous system



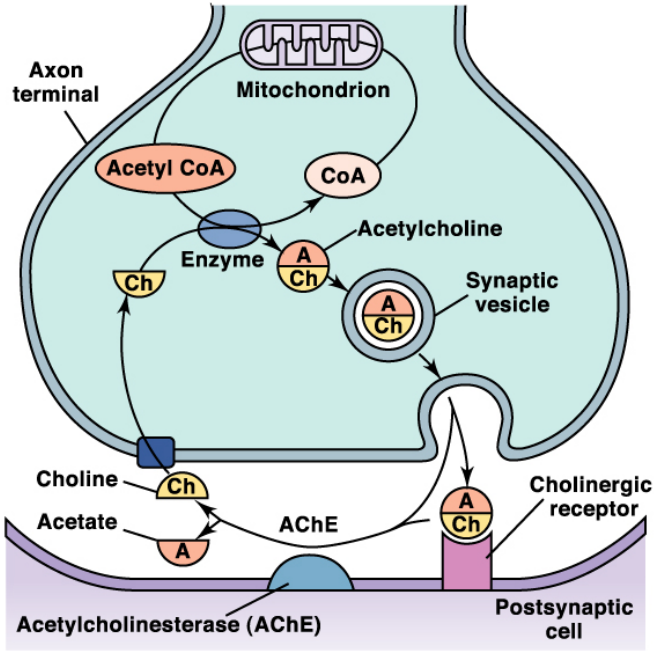
Parasympathetic nervous system

Neurotransmitters:

- Acetylcholine; a class by itself
- Amino acids; Glycine, Glutamate, Gamma-aminobutyric acid (GABA), Aspartate
- Amino acid-derived amines; Catecholamines (Dopamine, Norepinephrine, Epinephrine), Serotonin (5-HT), Histamine
- Purines; Adenosine, ATP
- Polypeptides; Enkaphalins, Endorphins, Dynorphins, Substance P, Somatostatin, Bradykinin, Neuropeptide Y



Synthesis and recycling of acetylcholine at the synapse



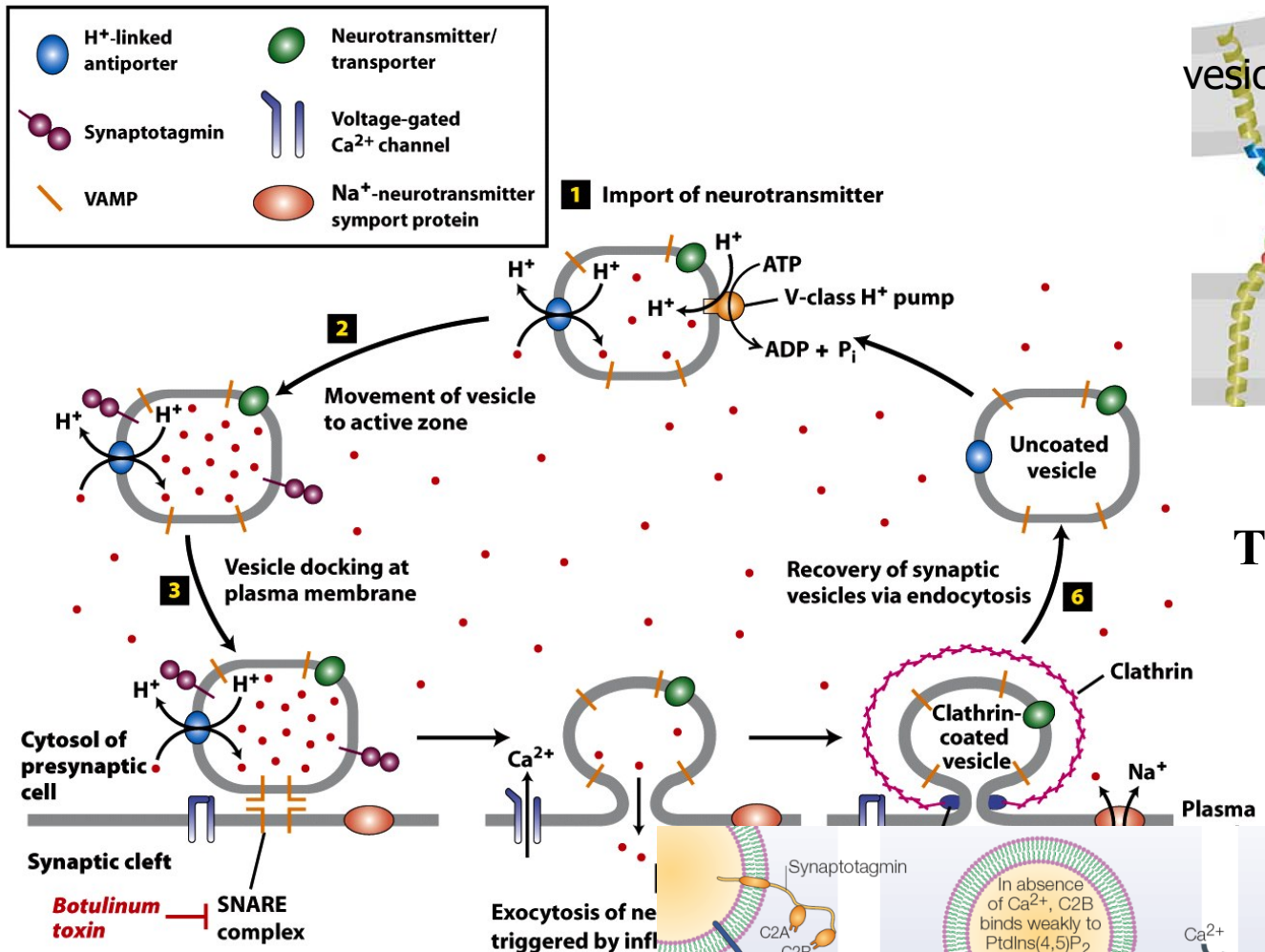
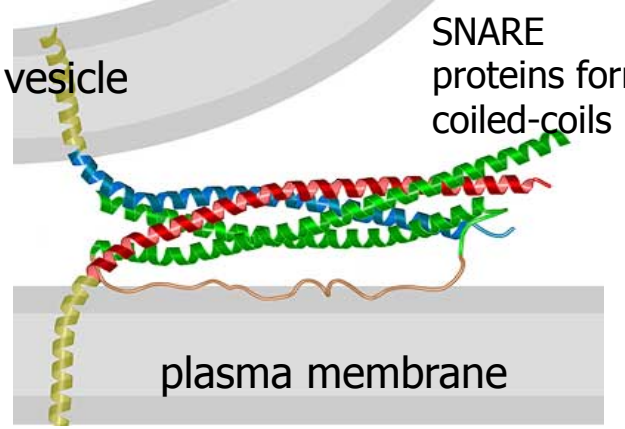
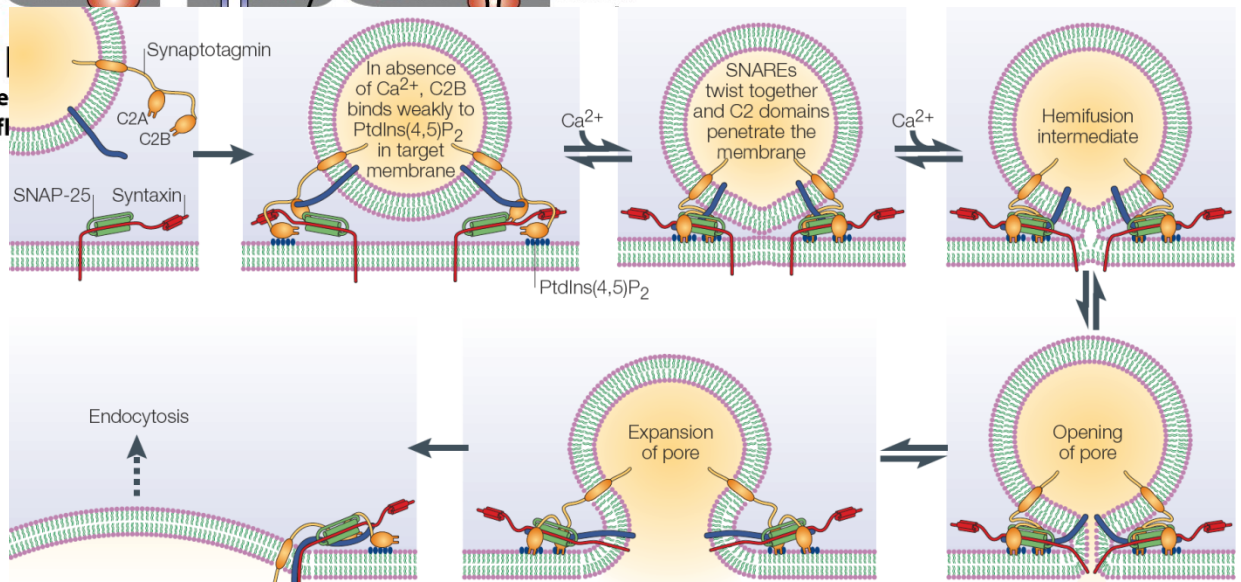


Figure 23-20
Molecular Cell Biology, Sixth Edition

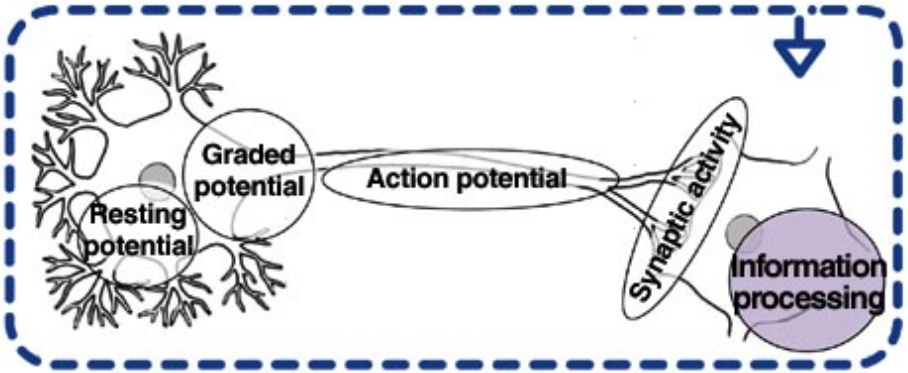


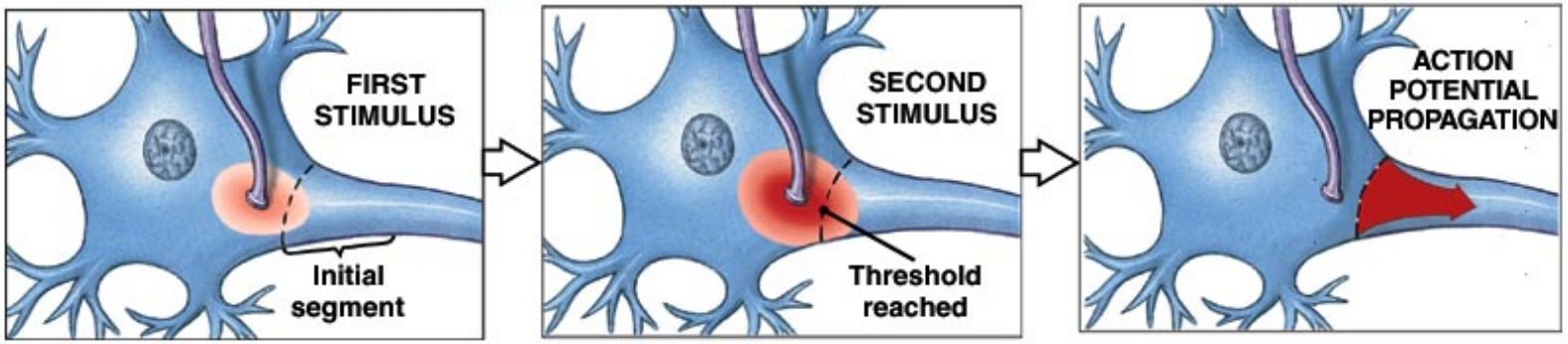
The Docking Complex



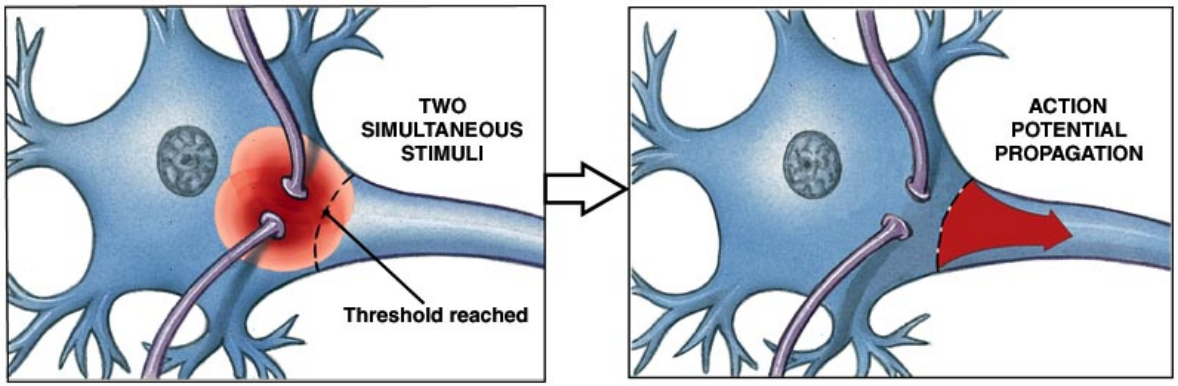
Chapman ER. Synaptotagmin: a Ca(2+) sensor that triggers exocytosis?
Nat Rev Mol Cell Biol. 2002 Jul; 3(7):498-508.

Signal integration





(a) Temporal summation

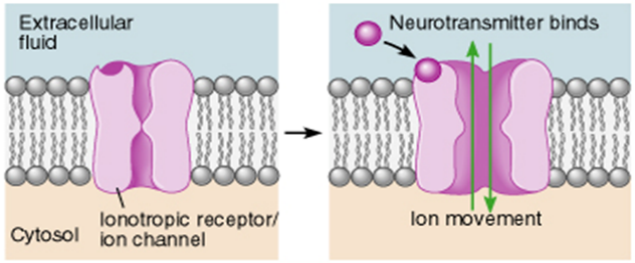


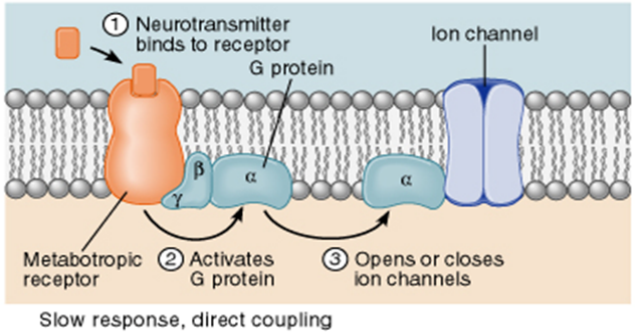
(b) Spatial summation

Postsynaptic Responses

Can lead to either EPSP or IPSP

Any one synapse can only be either excitatory or inhibitory



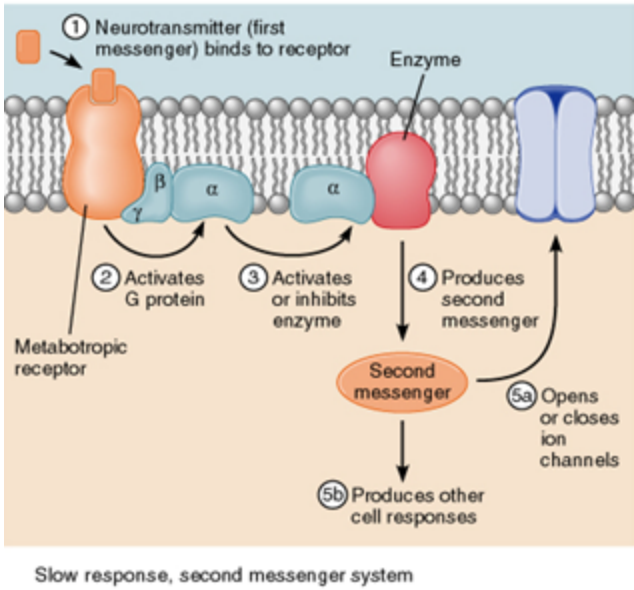


Fast synaptic potentials

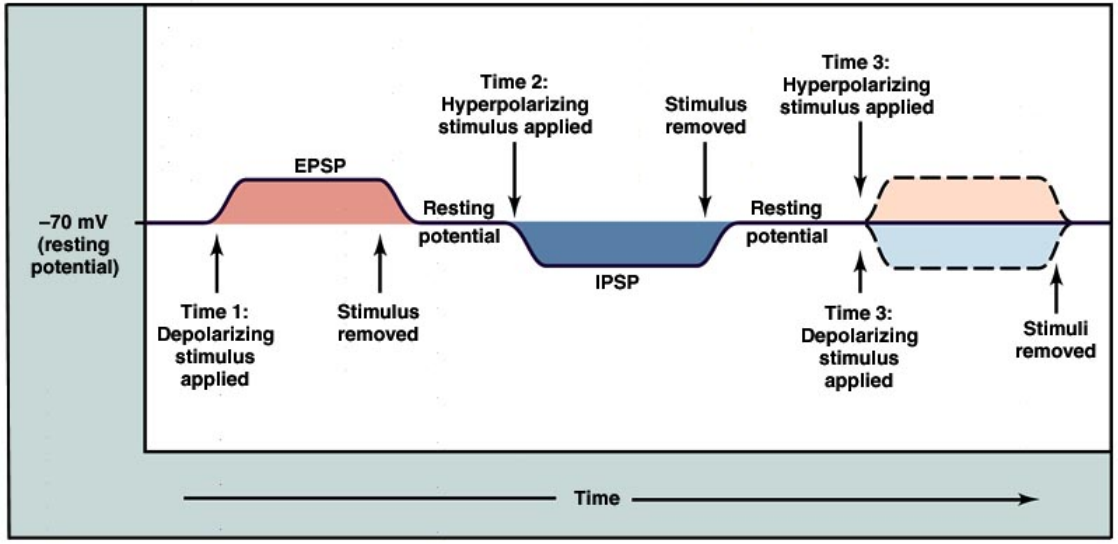
Opening of chemically gated ion channel
Rapid & of short duration

Slow synaptic potentials

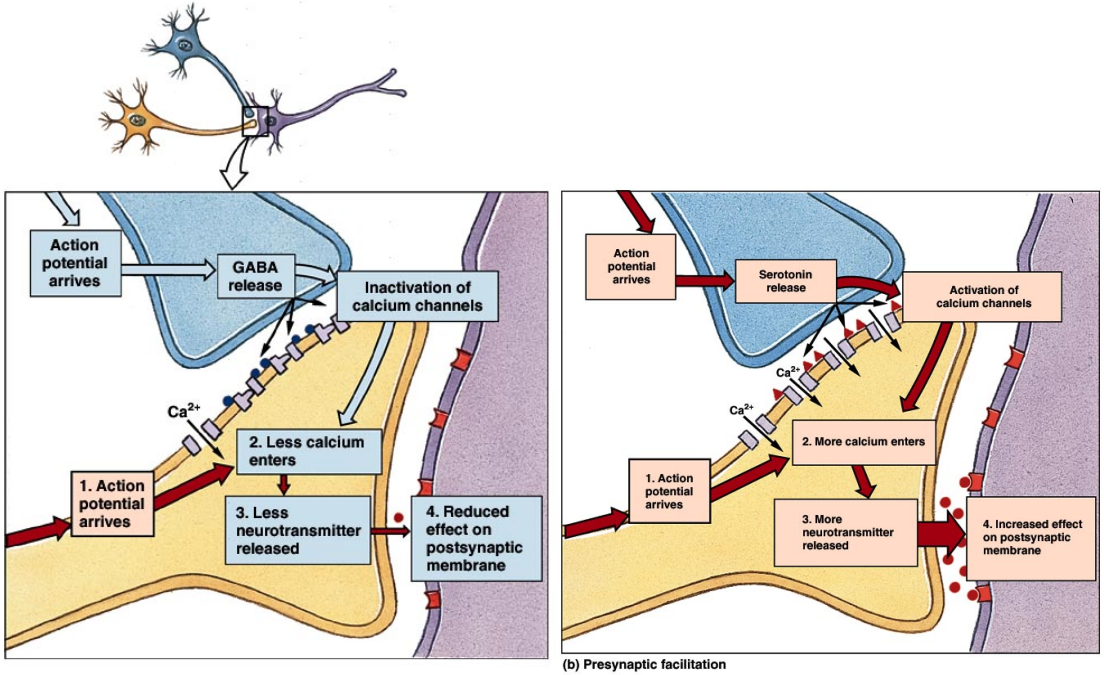
Involve G-proteins and 2nd messengers
Can open or close channels or change protein composition of neuron



Post-synaptic integration



Presynaptic facillitation and inhibition



Factors Influencing Transmitter Release

- **Amplitude** of arriving Action Potential
- Nerve terminal's ability to synthetize, package, store, mobilize, and release neurotransmitter
- Prior activity of presynaptic ending
- Concentration of Ca^{++} in ECF

Factors that limit the maximum response of a receptor cell to strong stimuli

- A finite number of channels
- Receptor potential cannot exceed the reversal potential of the receptor current
- Impulse frequencies are limited by the refractoriness

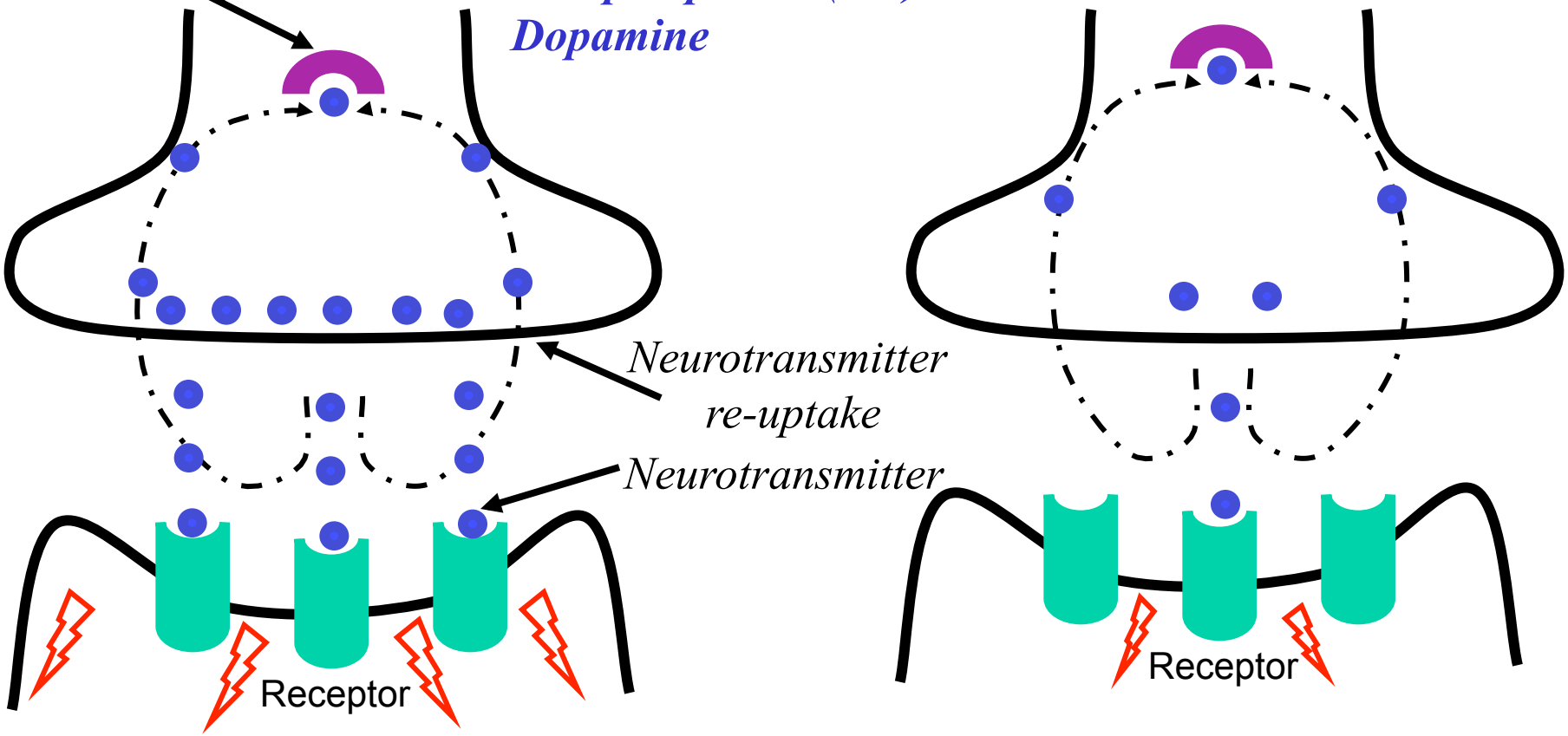
Depression

*In **normal brain activity**, neurotransmitters are constantly being released, re-absorbed, and then broken down.*

*In **depression**, fewer neurotransmitters are being released which leads to a reduction in stimulation of target brain cells.*

Neurotransmitter breakdown occurs here via an enzyme

Neurotransmitters:
5-hydroxytryptamine (5-HT) (Serotonin)
Norepinephrine (NE)
Dopamine



Antidepressants

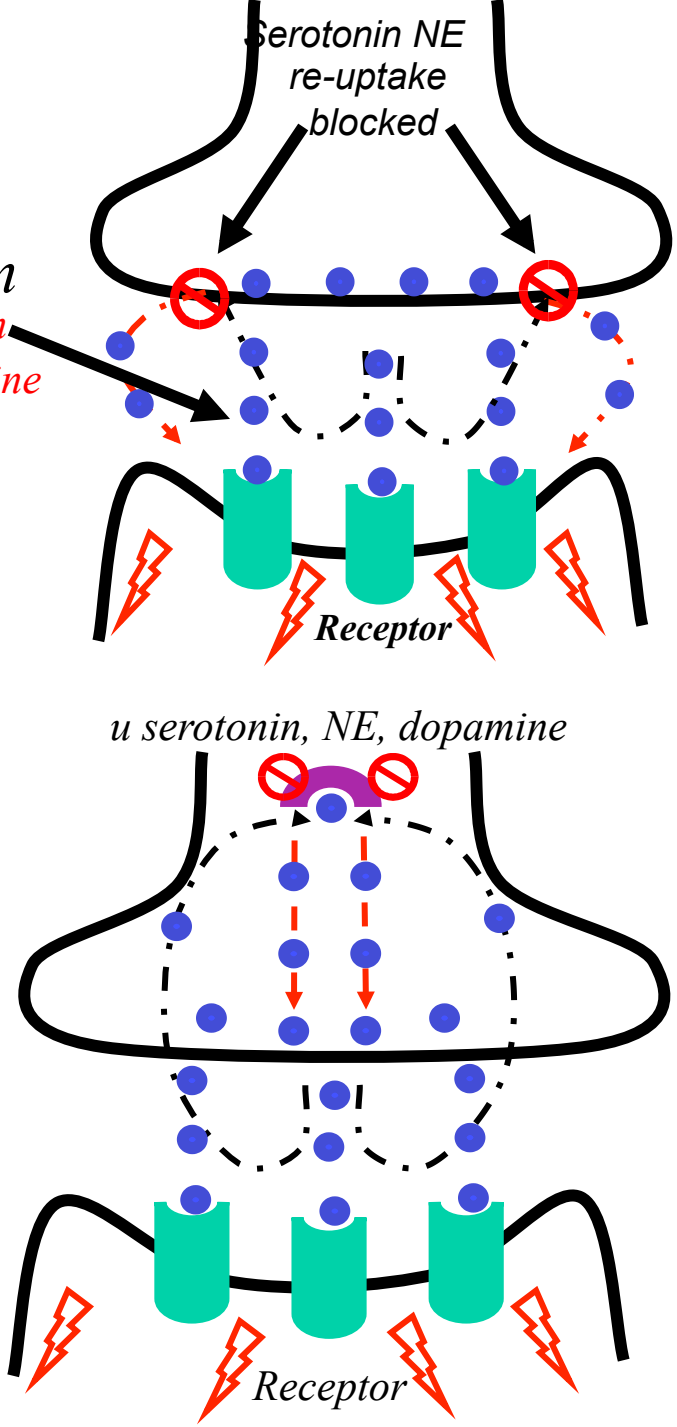
Tricyclic Agents: **(ELAVIL; TOFRANIL; PAMELOR)** – *block the re-uptake of serotonin and NE*

Heterocyclic Agents: (DESYREL; WELLBUTRIN; ZYBAN) – *block different neurotransmitter to variable degrees*

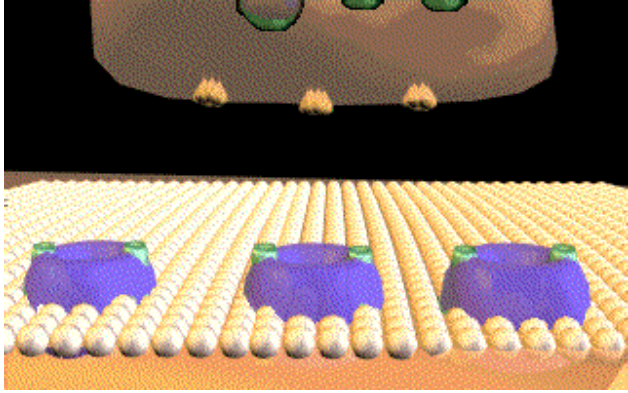
Selective Serotonin Reuptake Inhibitors (SSRI's): **(PROZAC; ZOLOFT; PAXIL; CELEXA)**

Serotonin - NE Re-uptake Inhibitors (SNRI's) **(EFFEXOR)**

Monoamine Oxidase Inhibitors (MAOI's): **(NARDIL PARNATE)**



GABA



- *GABA binds to GABA receptor (coupled to a chloride channel – chloride enter the cell).*

- *The cells fire less – a greater inflow of chloride – more negative interior – promoting neuronal hyperpolarization.*

Alcohol acts on channels

(I) *Ethanol binds to the GABA receptor inhibiting it – relaxation and sedation.*

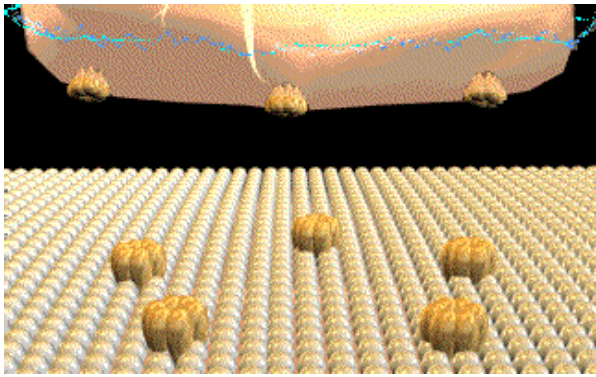
(II) *Alcohol opens a specific type of ionic channel (GIRK).*

- *This channel allows that brain cells eliminate potassium, thus reducing their activity.*

- *The result is a slow-down in brain function, perceived as a relaxing sensation by the drinker.*

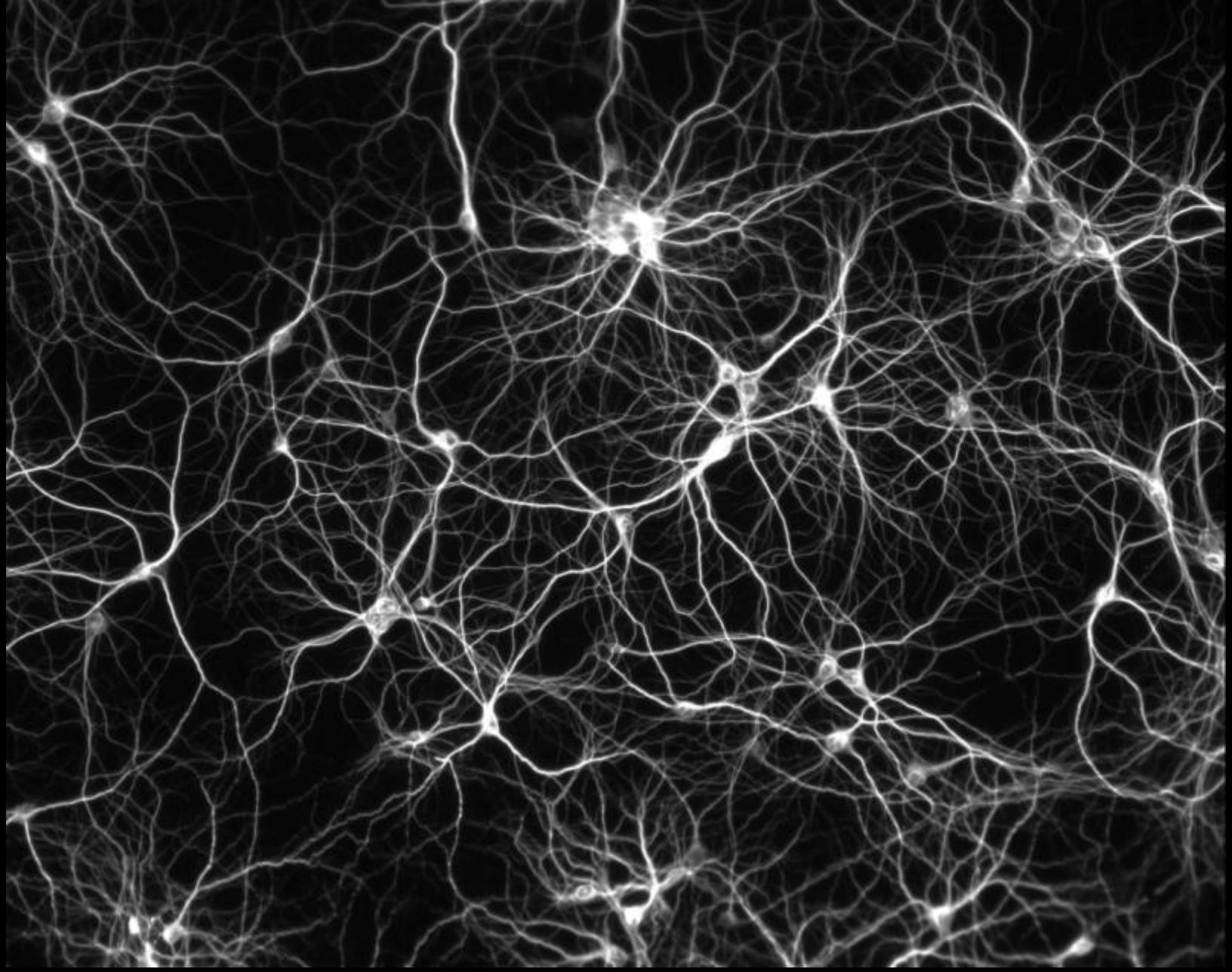
The Dopamine Function in the Brain

- *A neurotransmitter responsible for motivation and pleasure.*
- *The dopamine molecules attach themselves to dopaminergic receptors in the membrane of the post-synaptic neuron.*



Cocaine

- *It blocks the reuptake of dopamine in dopaminergic synapeses at the brain reword system.*
- *Dopamine remains in the synaptic gap. The effect remains until cocaine is removed. „The pleasure effect”*
- *The prolonged use of cocaine makes the brain to adapt to it – the synthesis of dopamine decreases.*
- *When without cocaine the drug user experiences the opposite of pleasure (due to the low levels of dopamine) - fatigue, depression and altered moods.*



Total power used by the brain ~ 20 watt