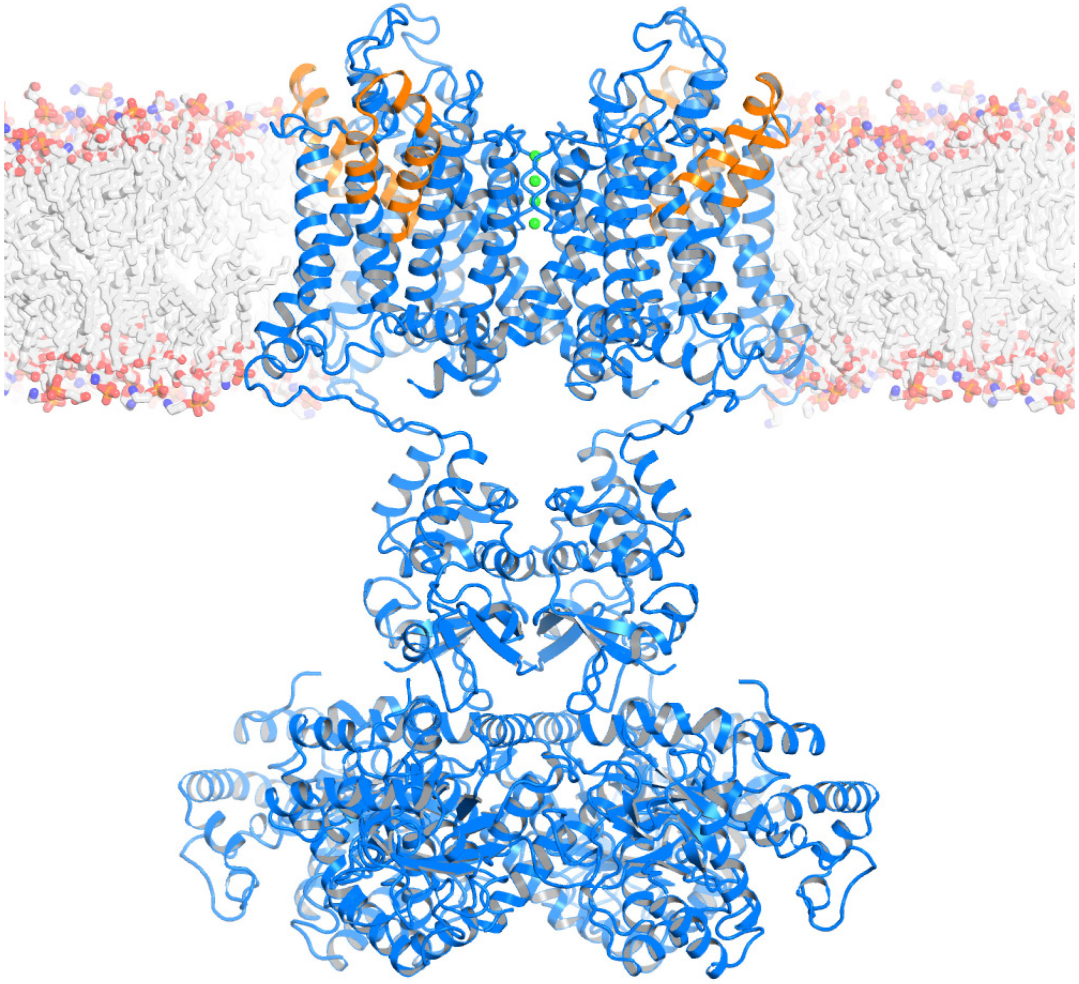
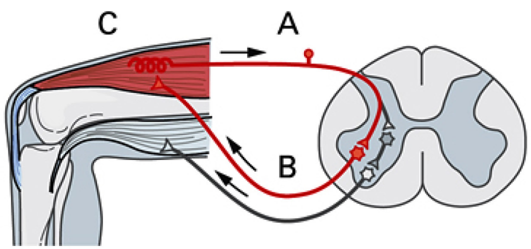
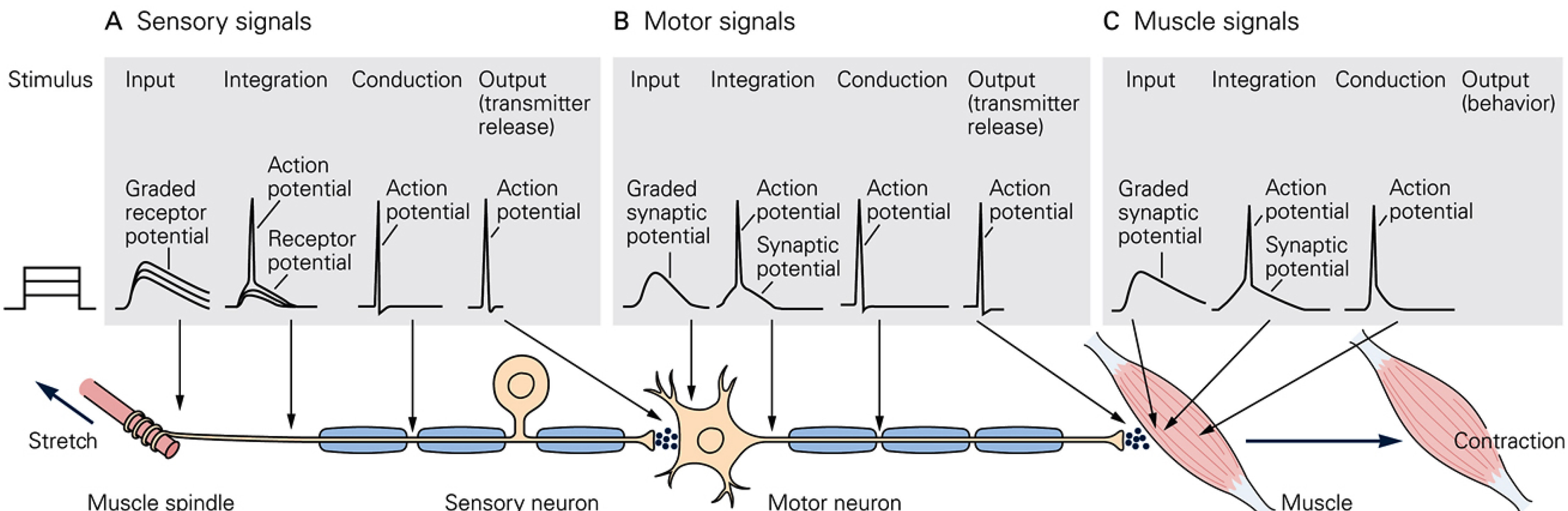
Chapter 8:
Ion Channels



Ion Channels and Electrochemical Signaling





Properties of Ion Channels

HIGH PERMEABILITY – Conduct ions quickly

- *Tens of millions of ions pass through pore per second*
- *Ions move down their electrochemical gradient*
- *Cause changes in membrane potential*

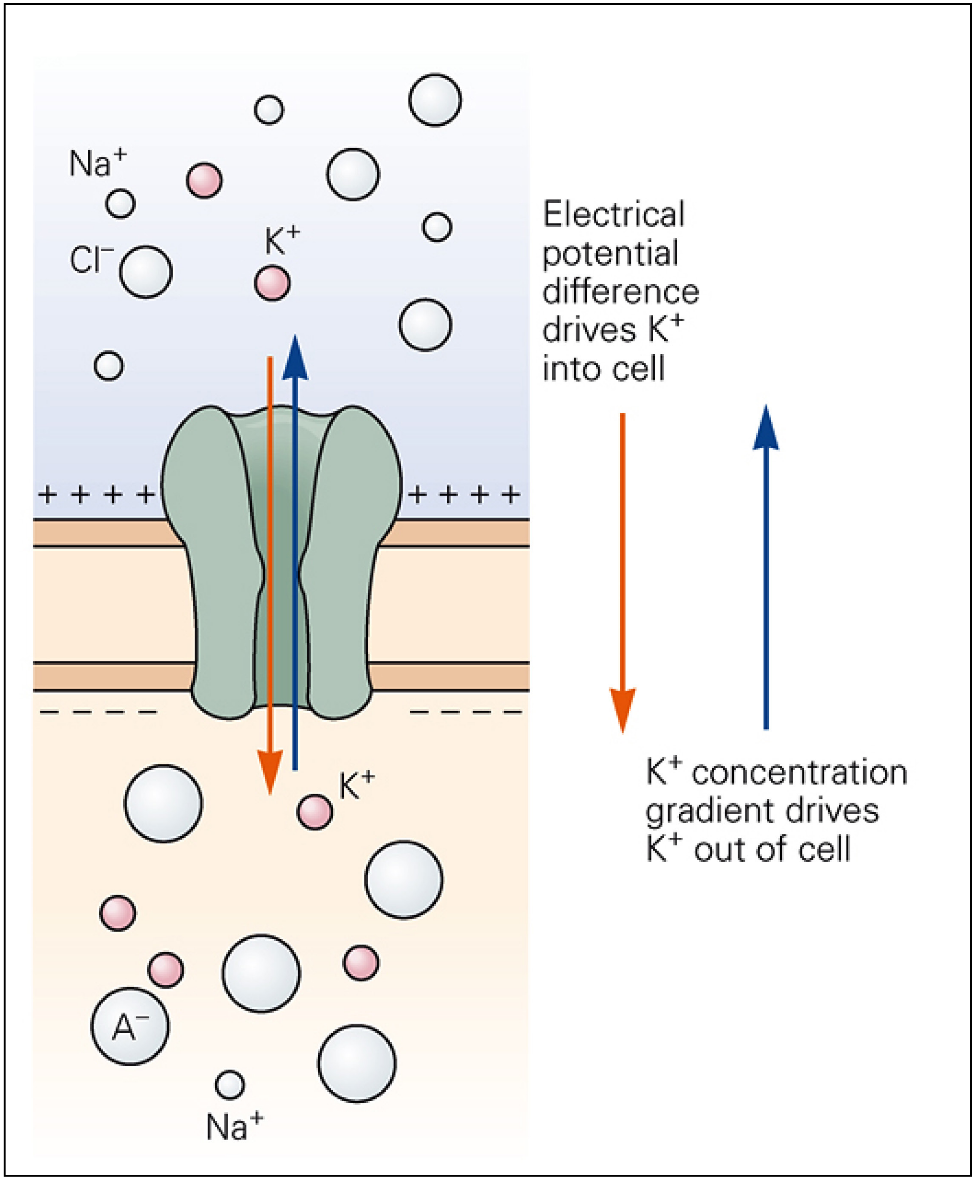
SPECIFICITY – Recognize and select specific ions

- *Na^+ channels*
- *K^+ channels*
- *Ca^{2+} channels*
- *Cl^- channels*
- *Channels permeable to both Na^+ and K^+ (and sometimes Ca^{2+})*

GATING – Open and close in response to specific signals

- *Ligand-gated channels*
- *Voltage-gated channels*
- *Mechanically-gated channels*
- *Some channels are not gated, but are always open (called resting or leak channels).*

Forces Acting on Ions



Electrochemical driving force =
chemical driving force +
electrical driving force

Important terms

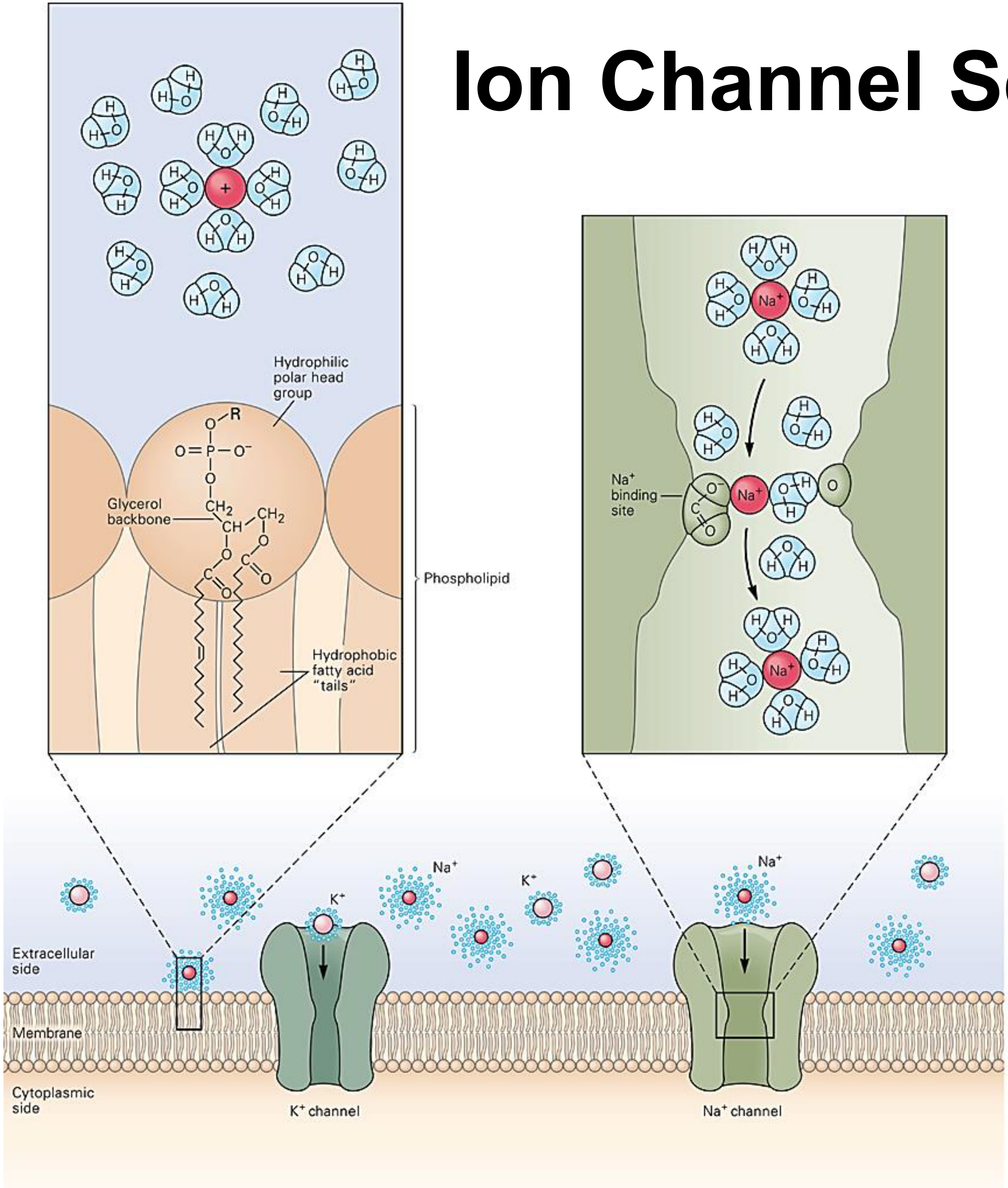
- Voltage (V) is the electrical potential difference across the membrane
- Current (I) is the net flow of ions through the channel

Ions flow across open channels according to Ohm's Law

$$V=IR$$

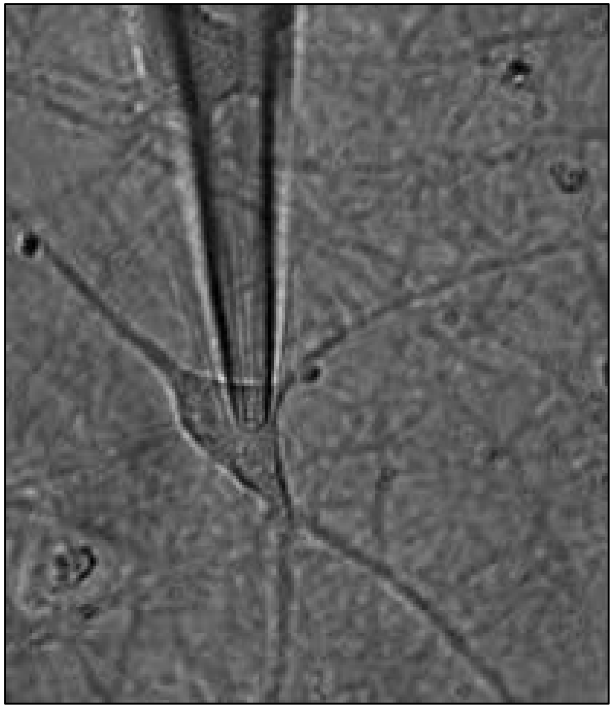
$$I=V/R$$

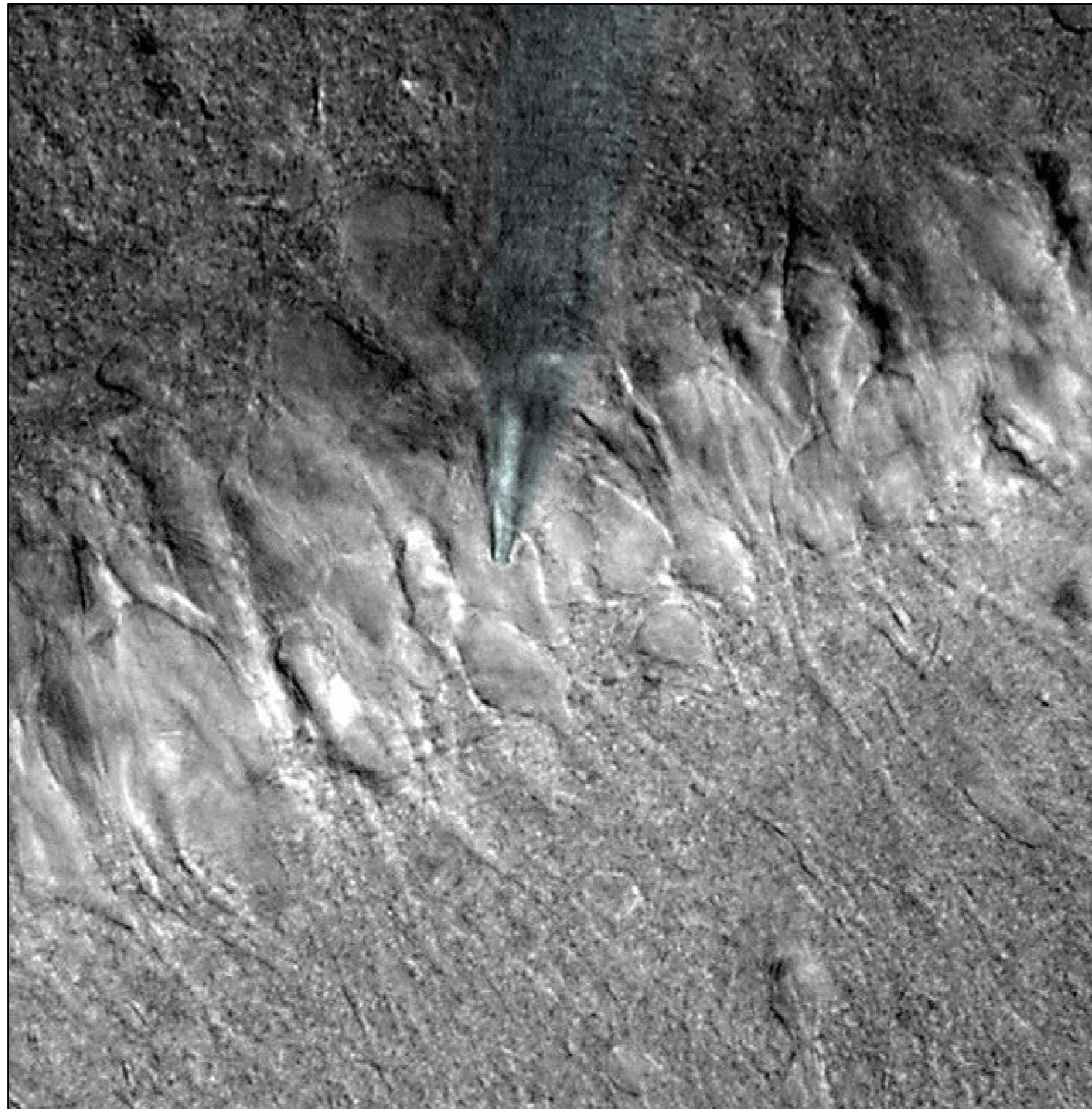
Ion Channel Selectivity Filter



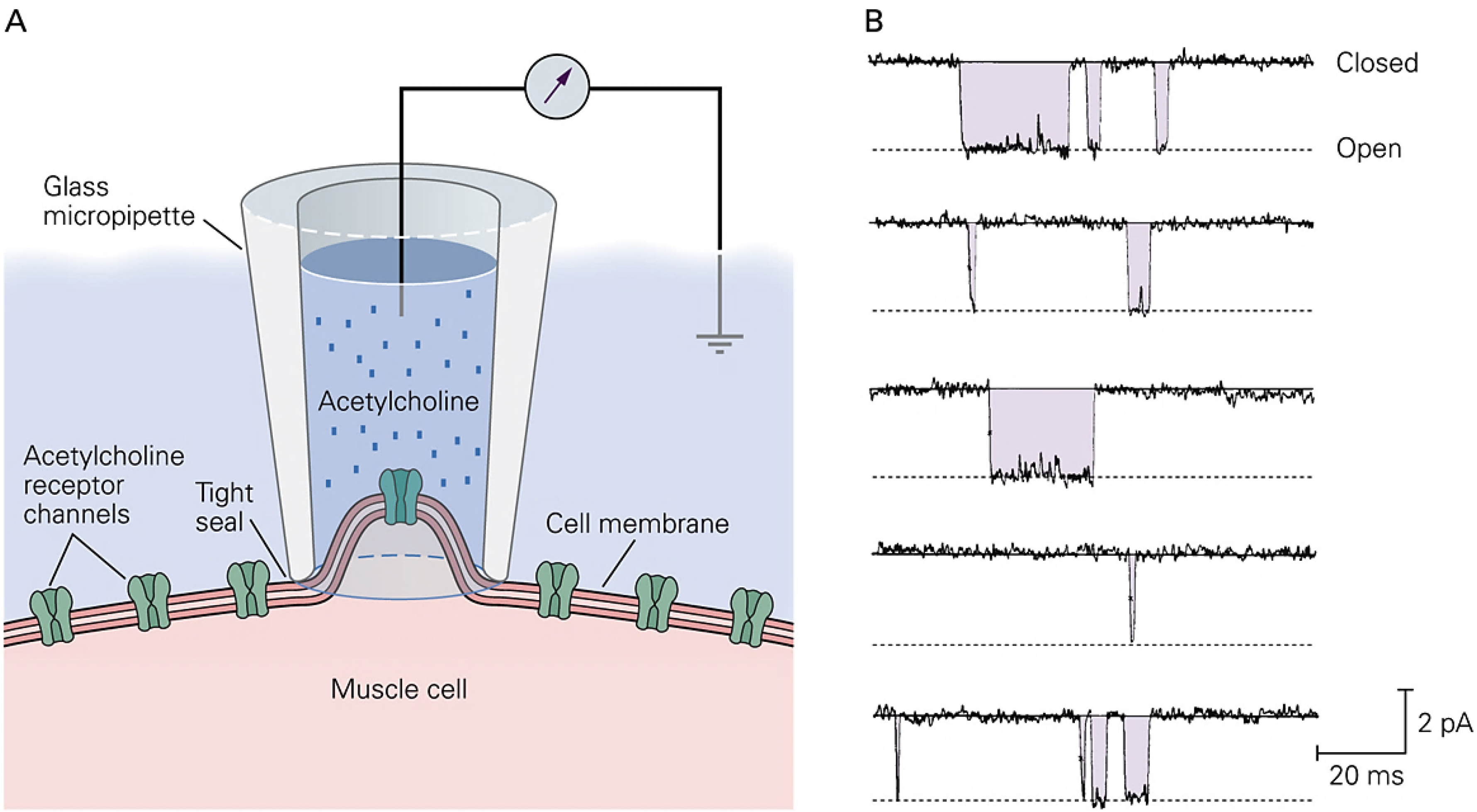
- The selectivity filter is the narrowest part of an open channel's pore.
- The channel's specificity is determined by its selectivity filter's diameter and chemical interactions with ions.

Studying Channels using Patch Clamp

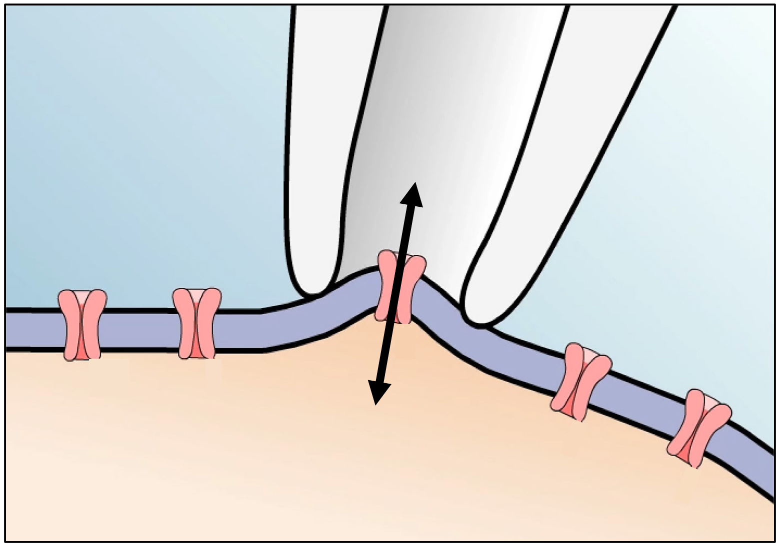


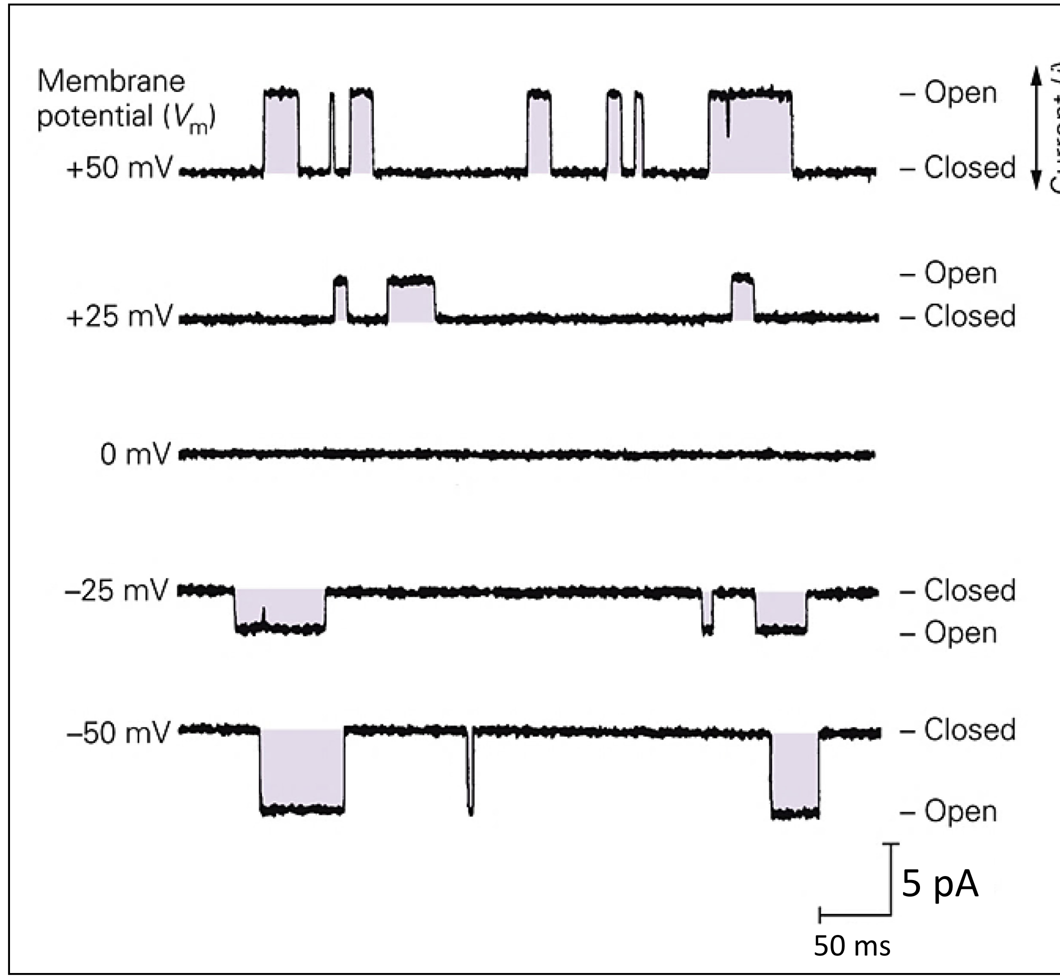


Studying Channels using Patch Clamp

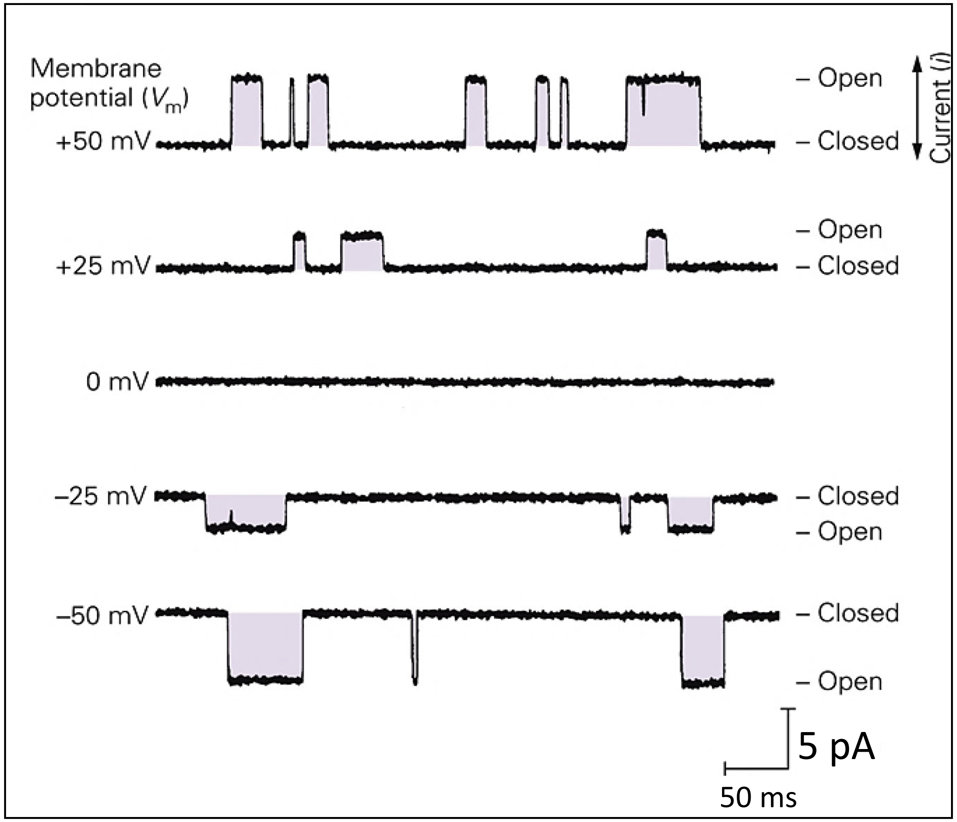


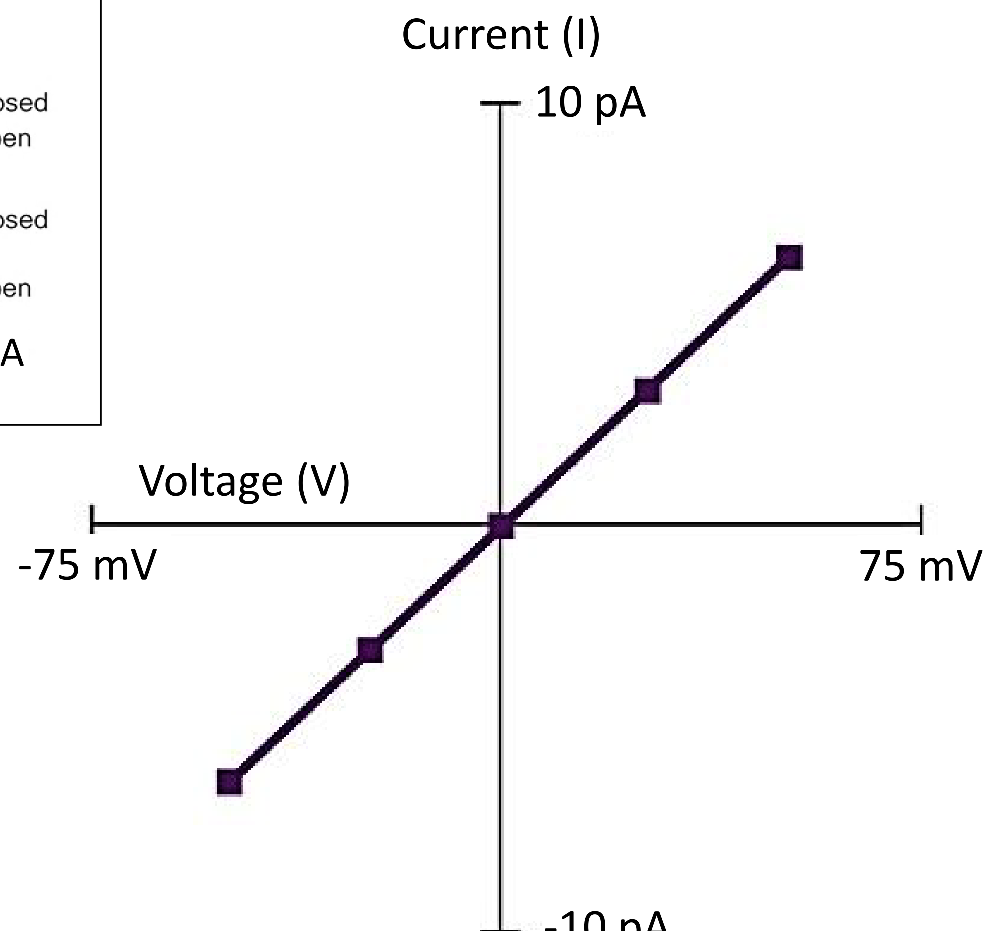
Single-Channel Patch Clamp Data



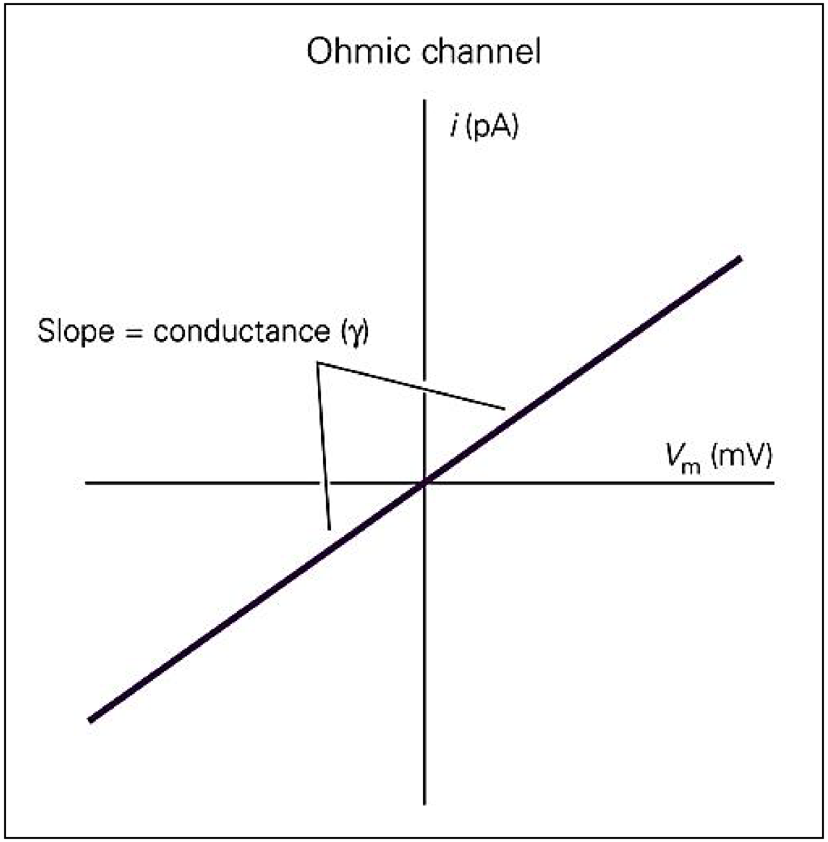


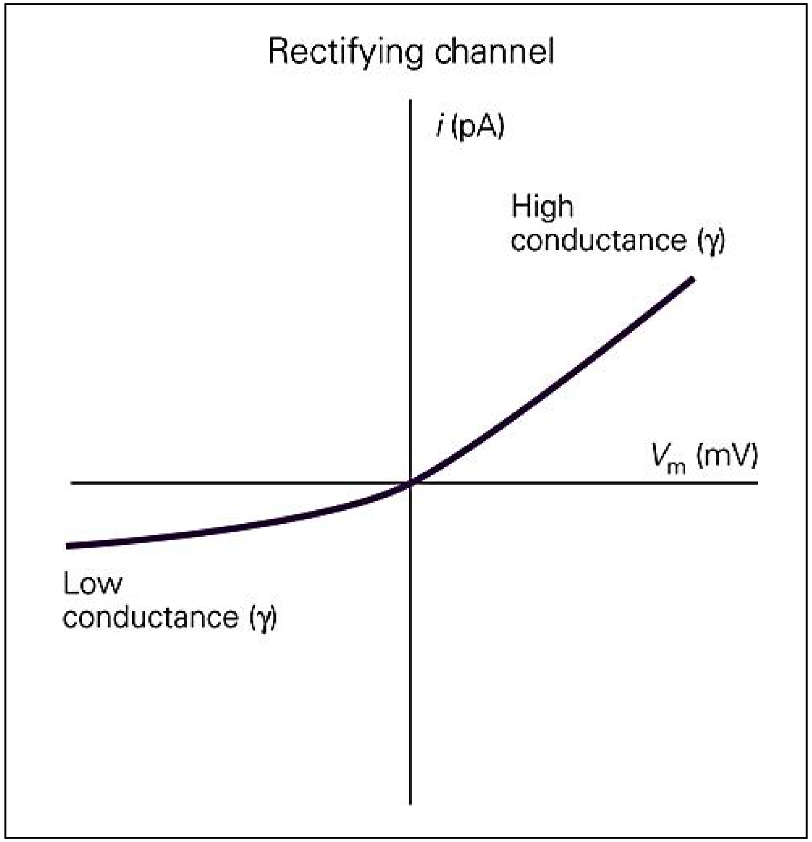
Making an IV Plot with single-channel data





Interpreting IV Plots





Ohm's Law

V=IR

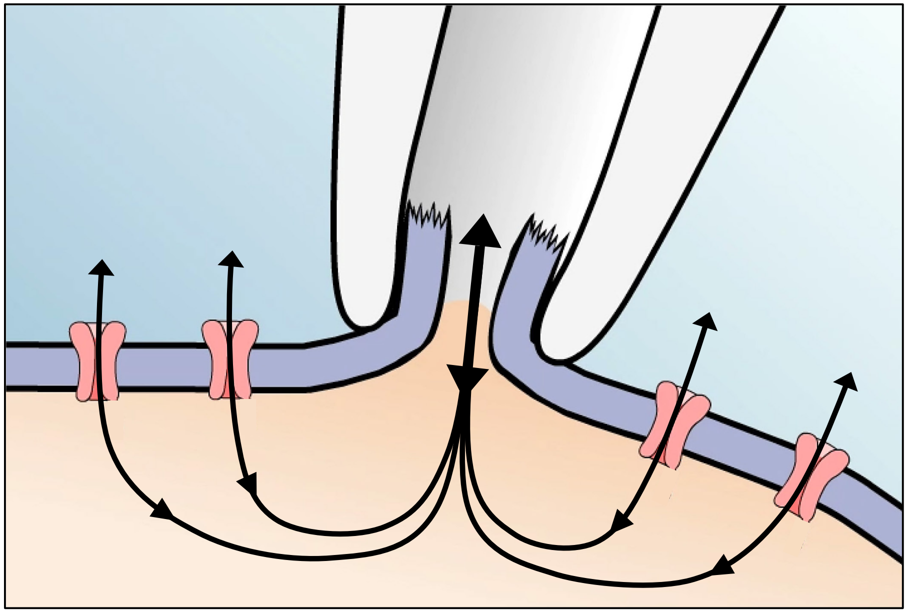
I=V/R

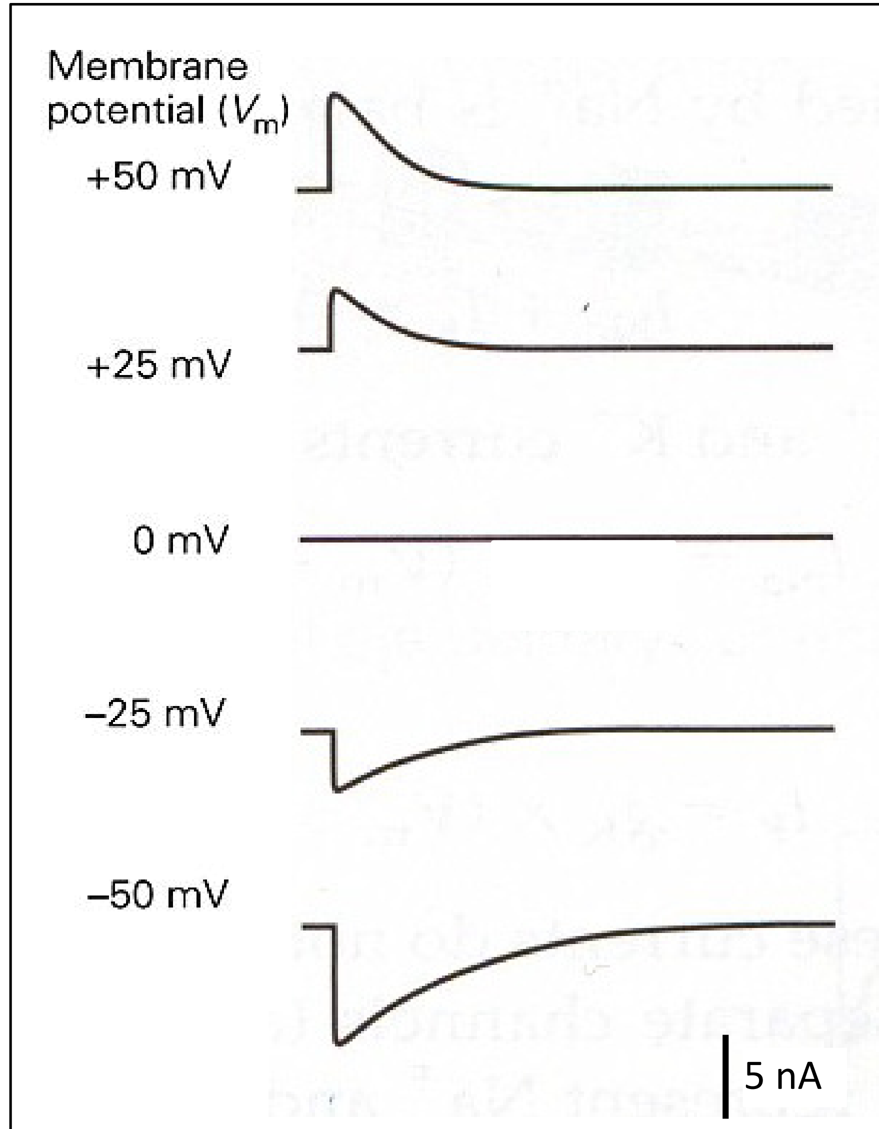
γ or g = 1/R
(conductance)

I=gV

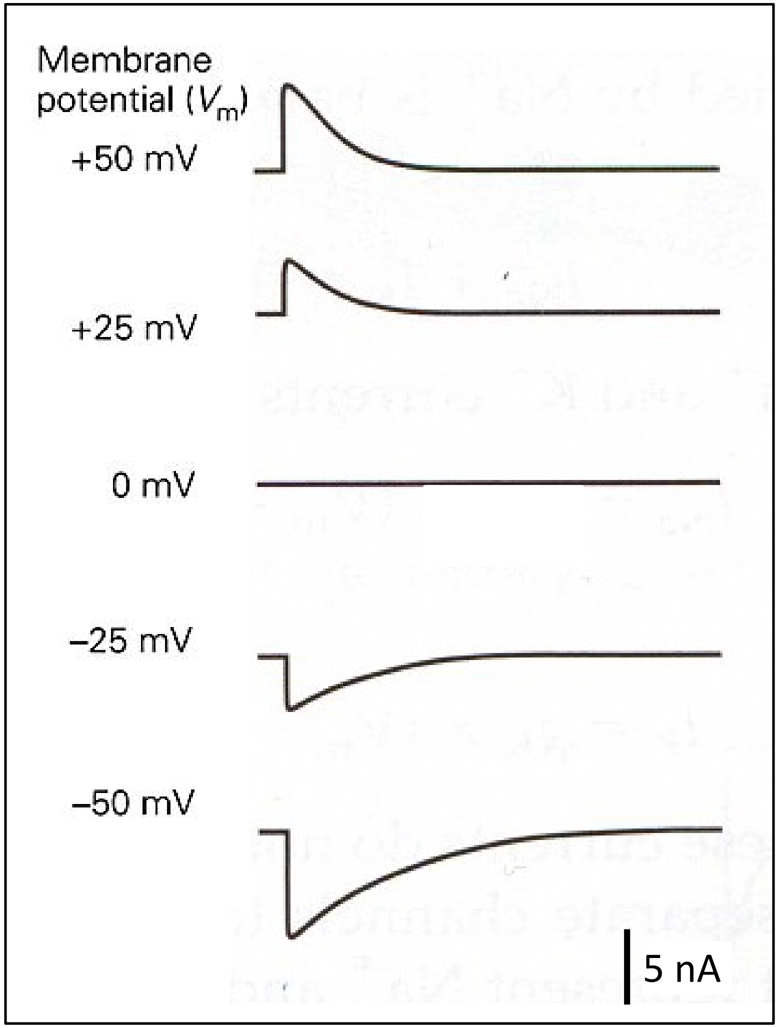
(y=mx)

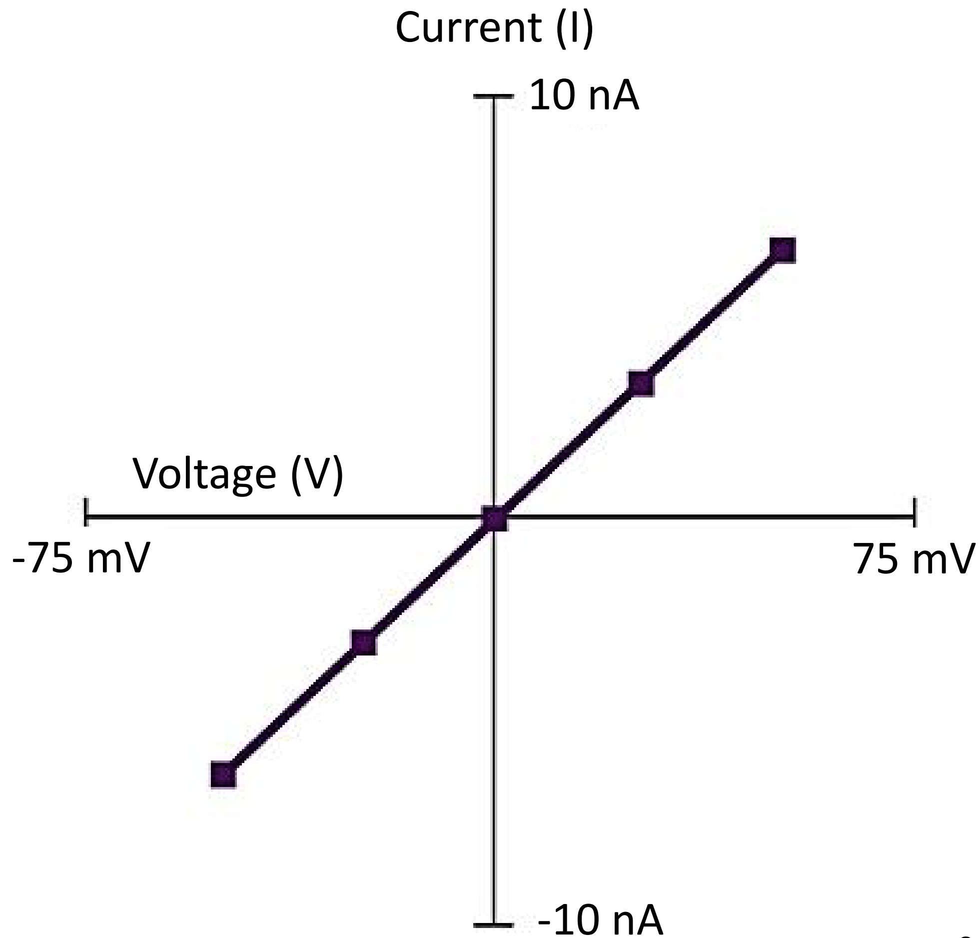
Whole-Cell Patch Clamp Data



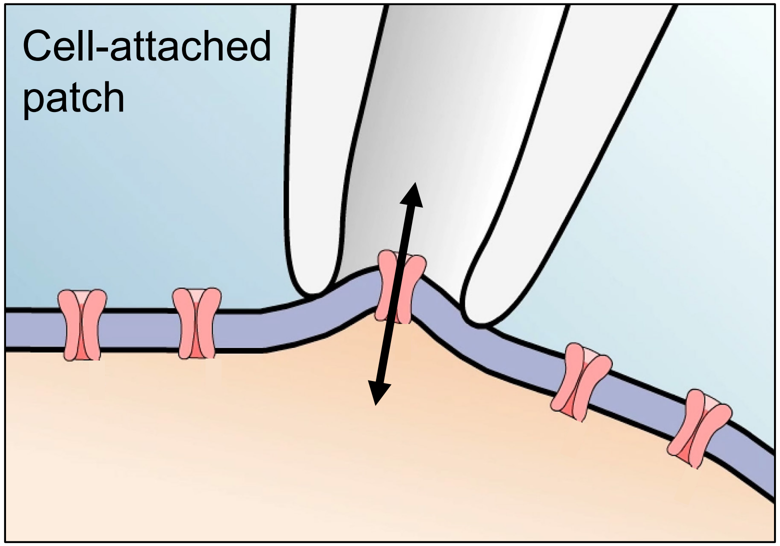


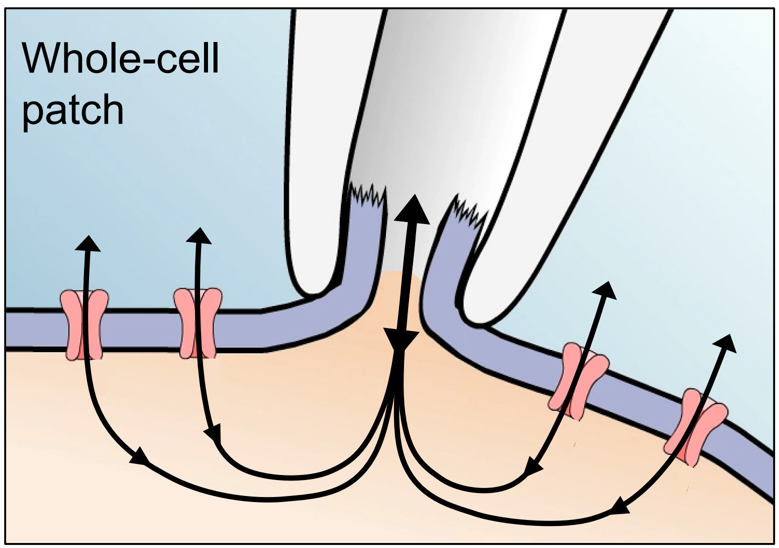
Making an IV Plot with whole-cell data





Currents produced by ACh receptor channels





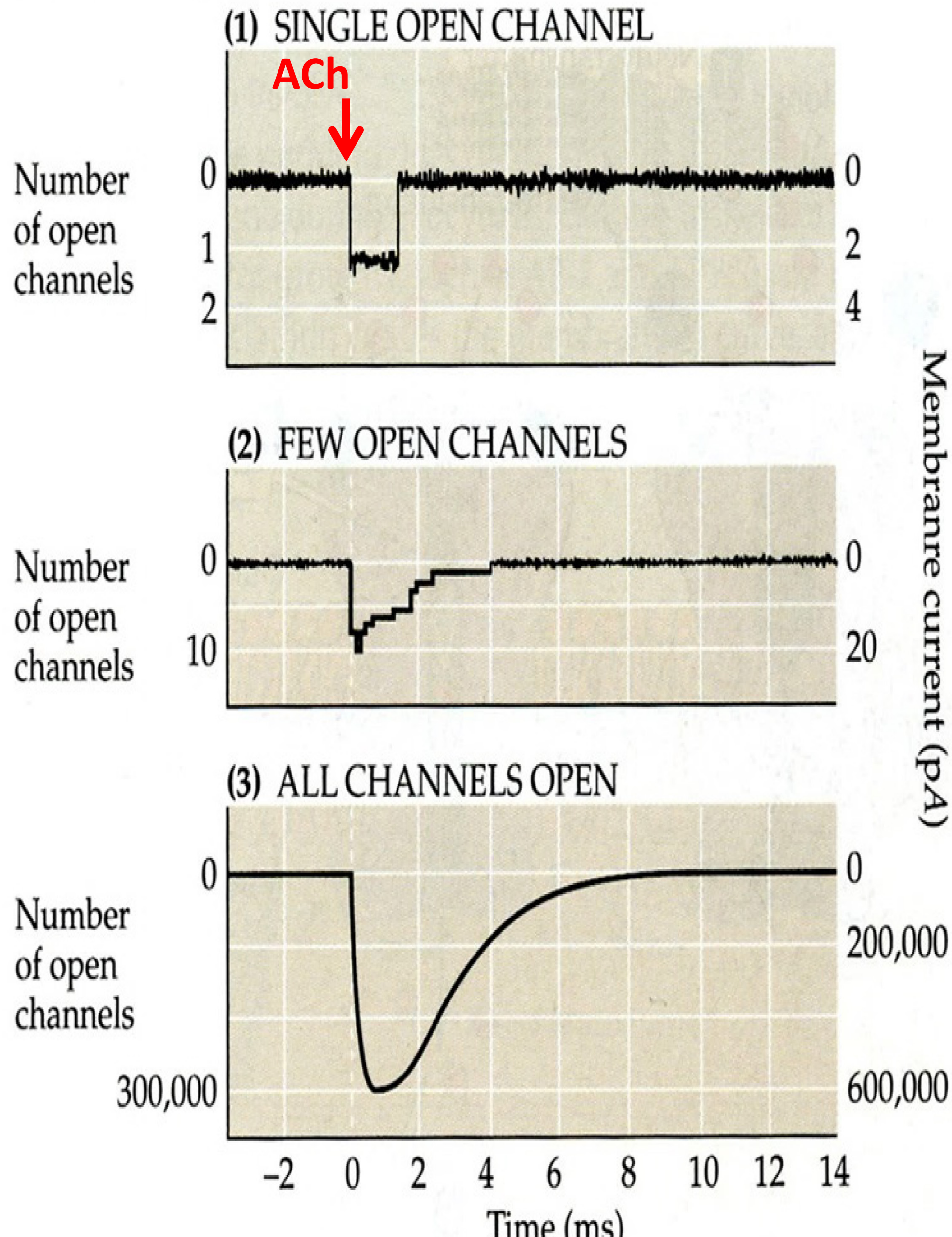


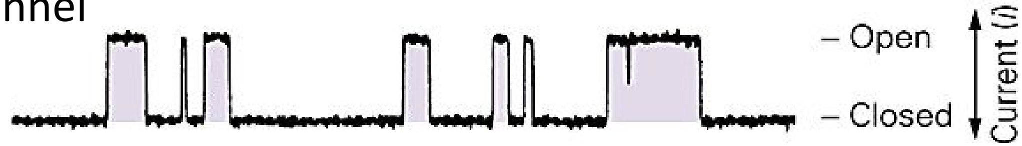
Fig 5-17b, Purves

Interpreting Current Tracings

For each current tracing, state the following…

- Single-channel or whole-cell tracing?
- Inward or outward current?
- What direction is the ion flowing across the membrane?

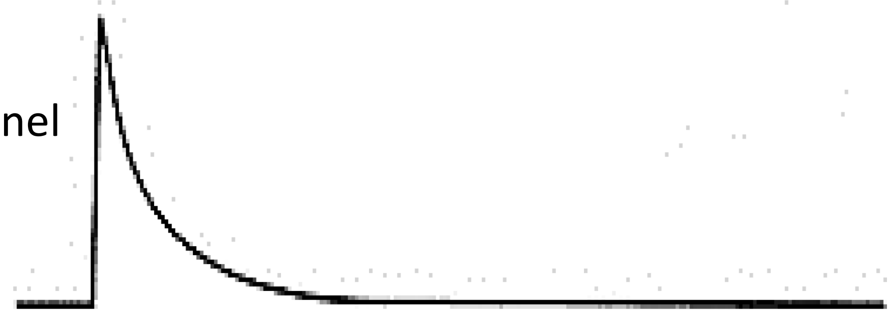
Na^+ channel



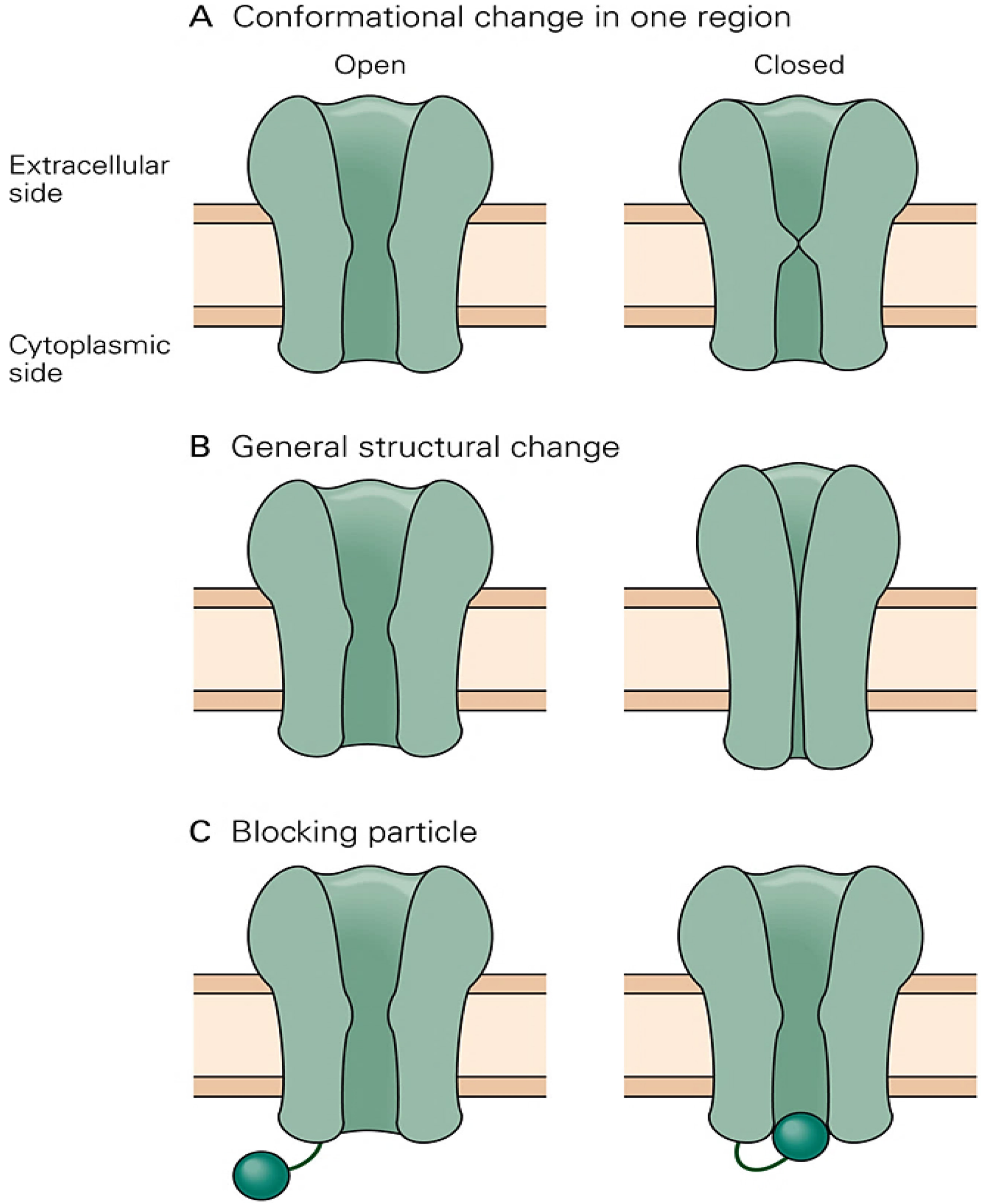
Ca^{+2} channel

Cl^- channel

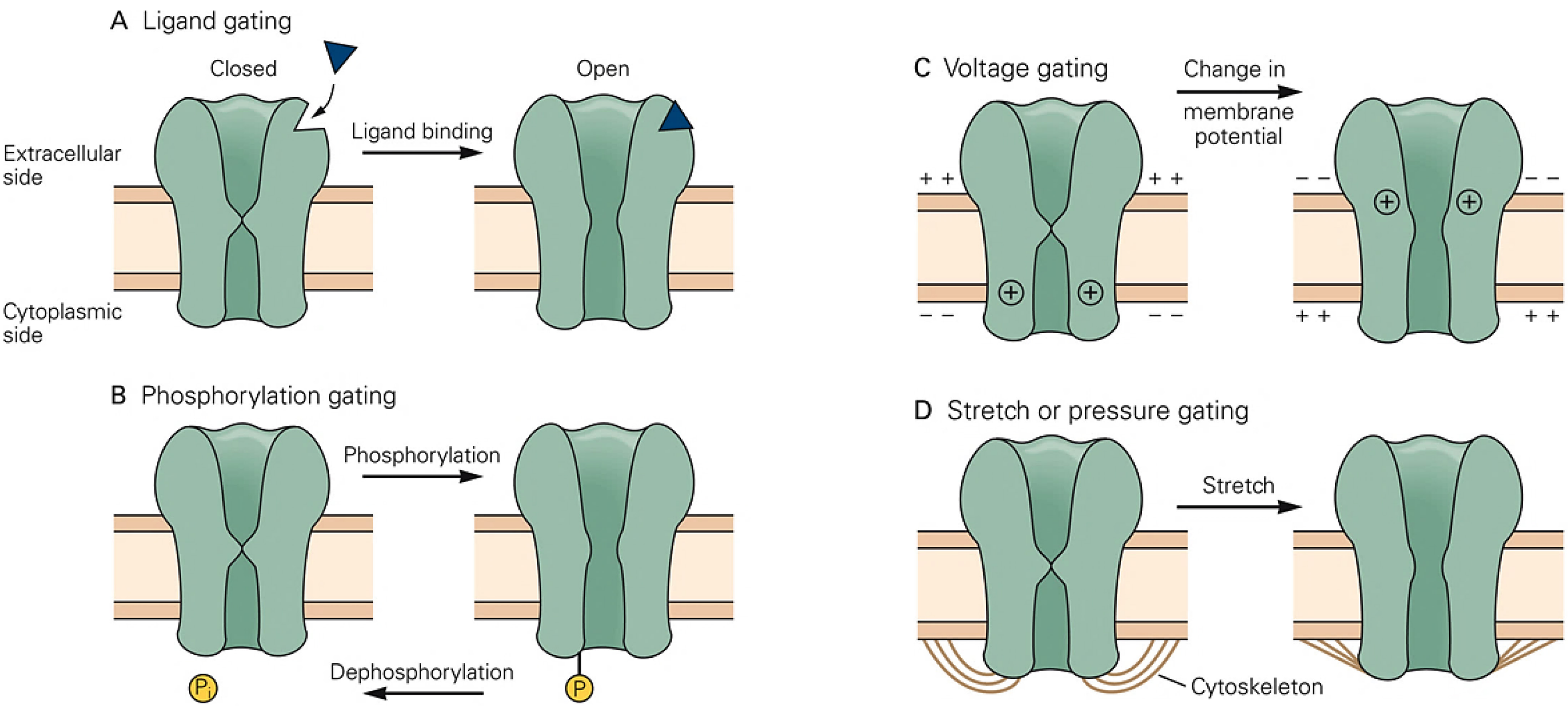
K^+ channel



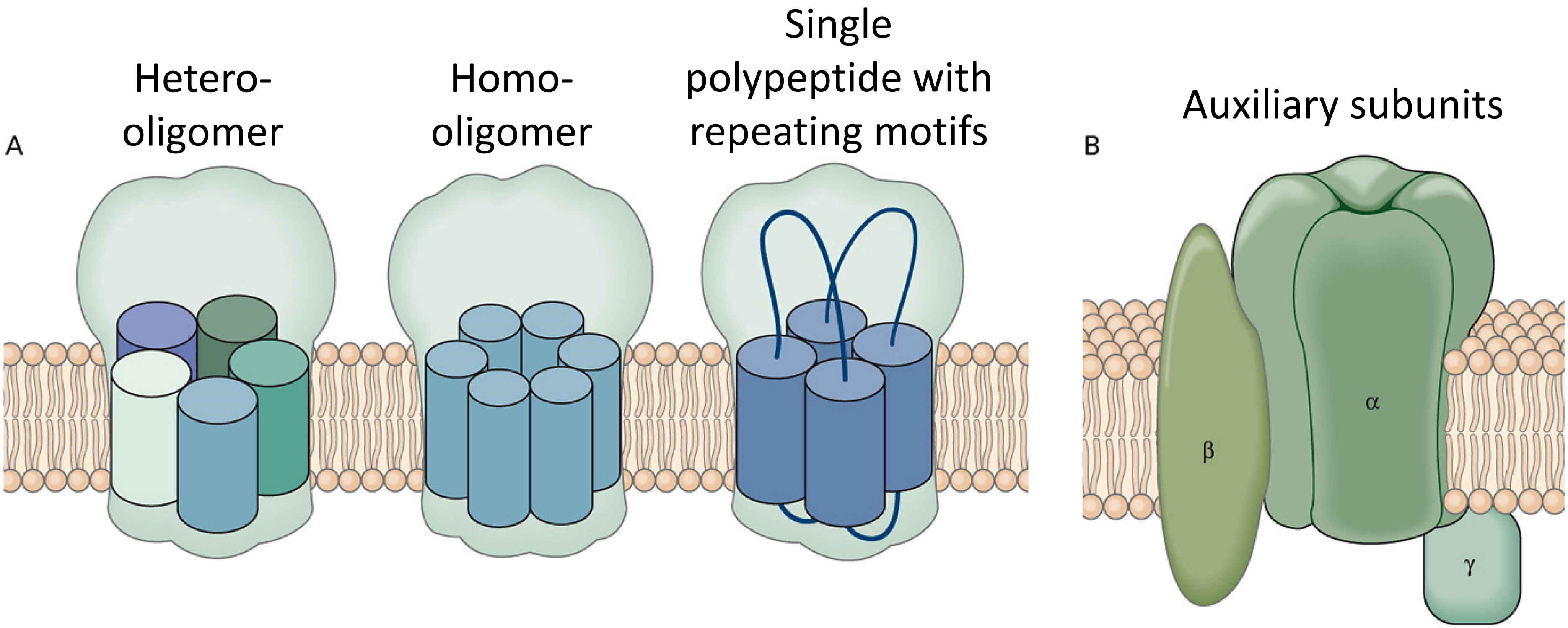
Models of Ion Channel Gating



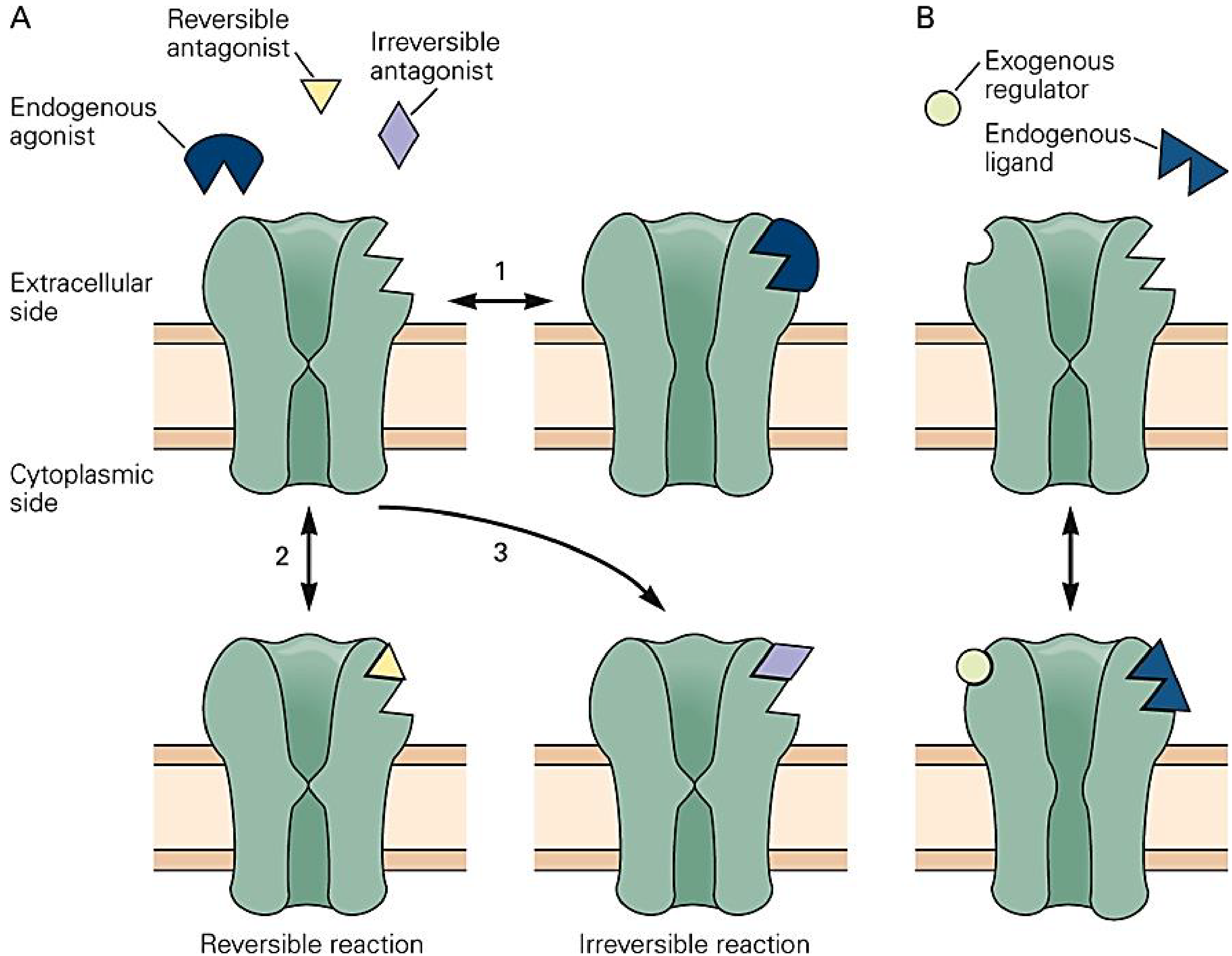
Stimuli that Cause Gating



Channel Composition

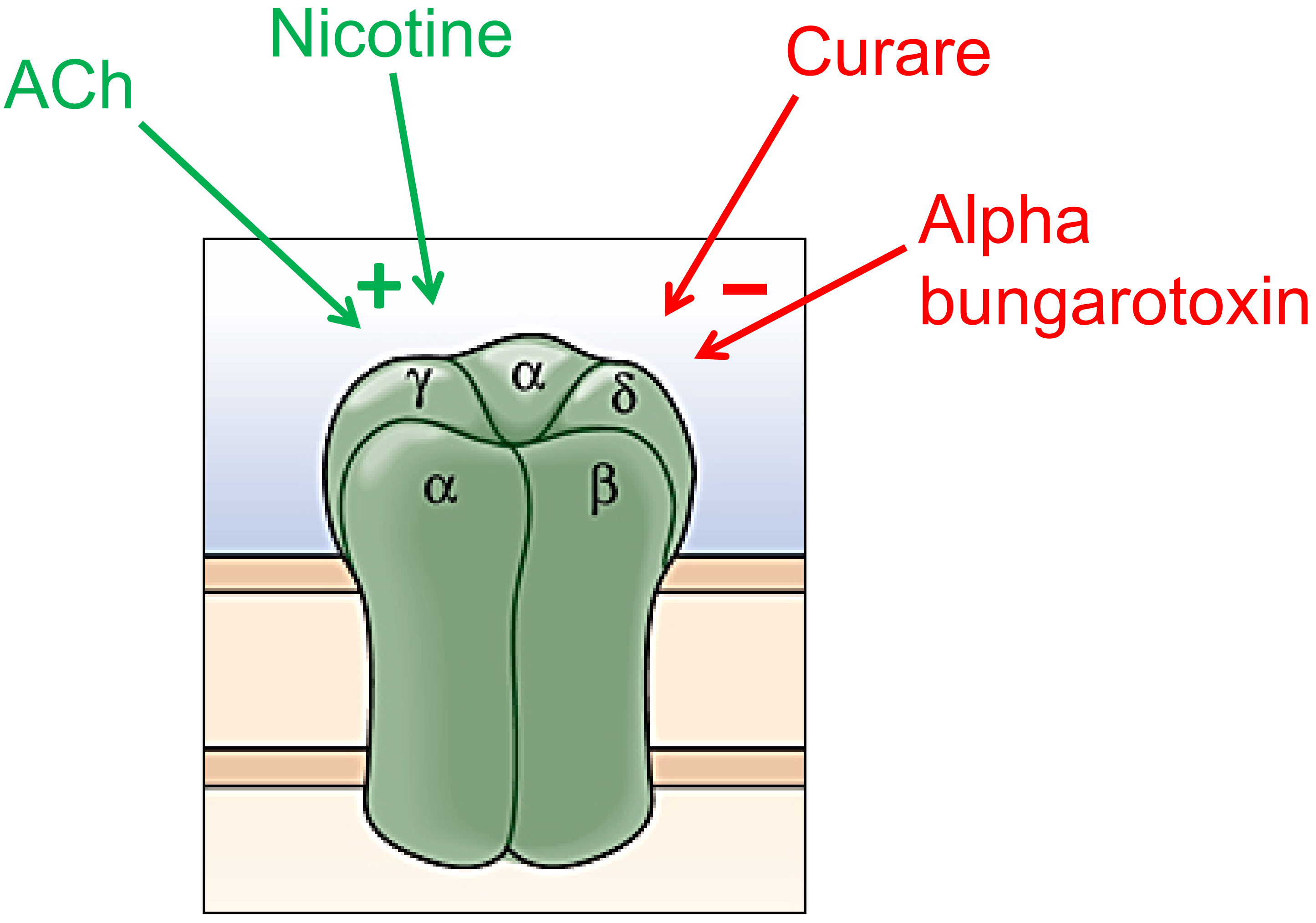


Ligand-Gated Channels



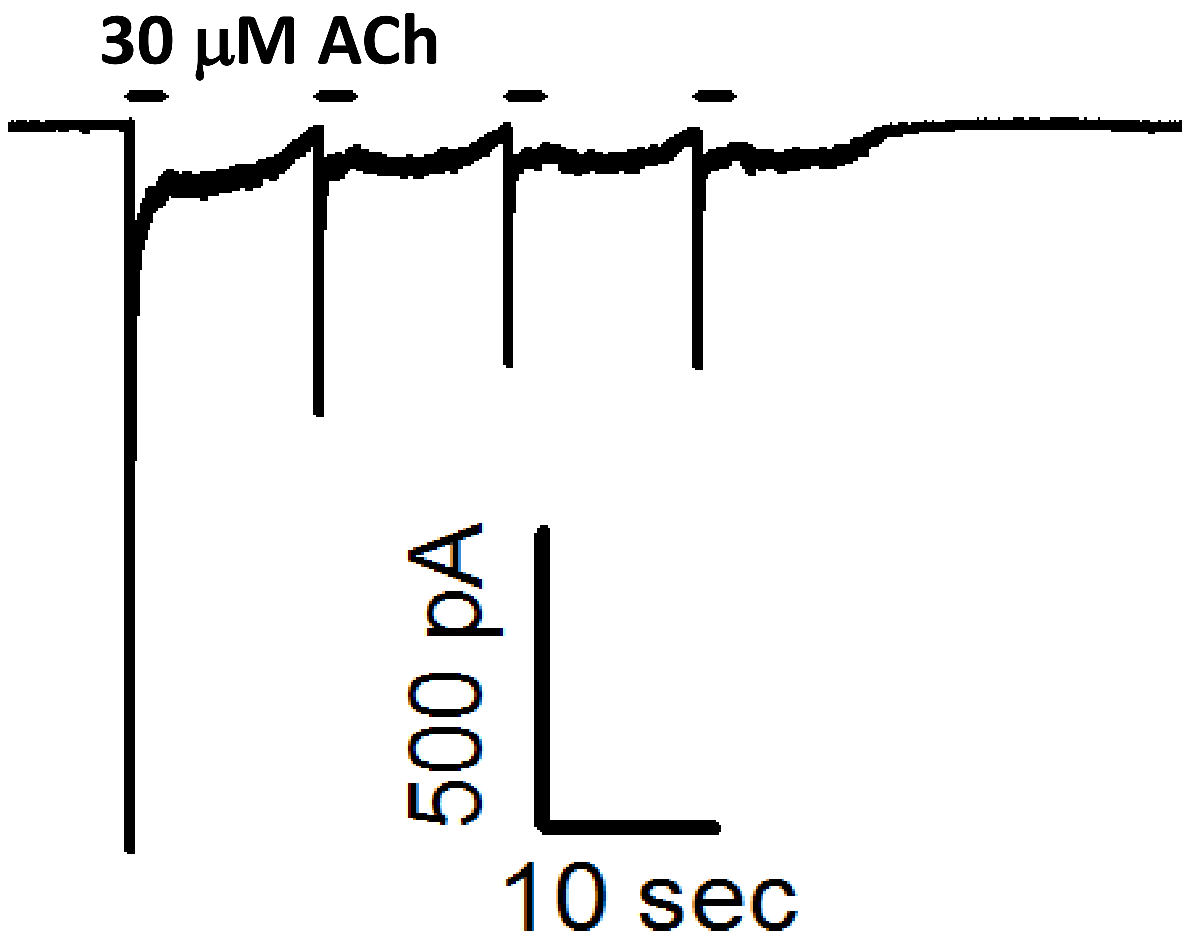
- Agonists vs. Antagonists
- Endogenous vs. Exogenous

An example of a ligand-gated channel: The Nicotinic Acetylcholine Receptor (nAChR)

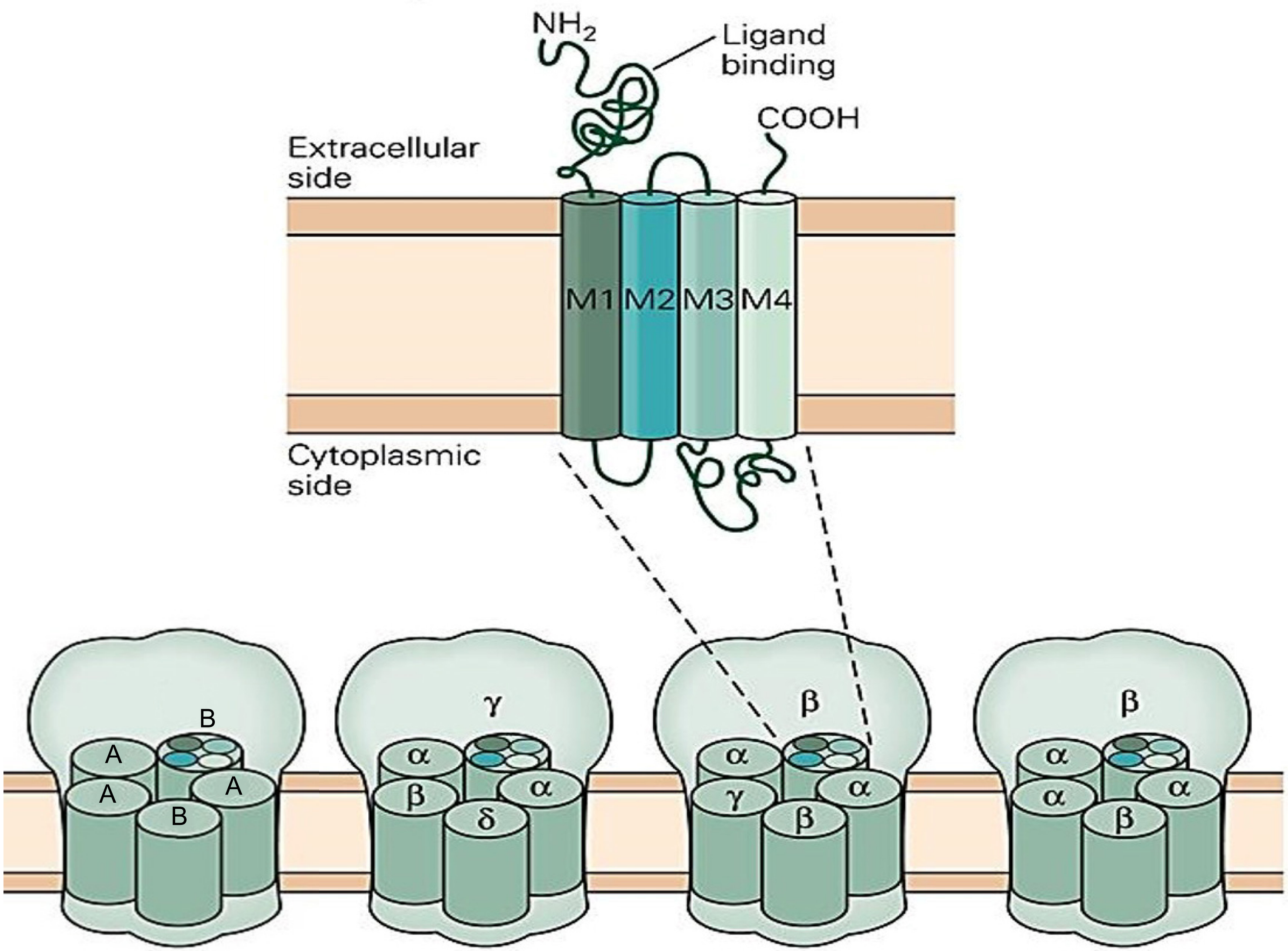


Desensitization of Ligand-Gated Channels

Repeated or prolonged ACh application leads to decreased responsiveness



Pentameric Ligand-Gated Channels



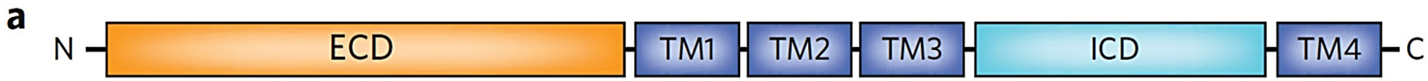
5-HT3 *(Na+ and K+)*

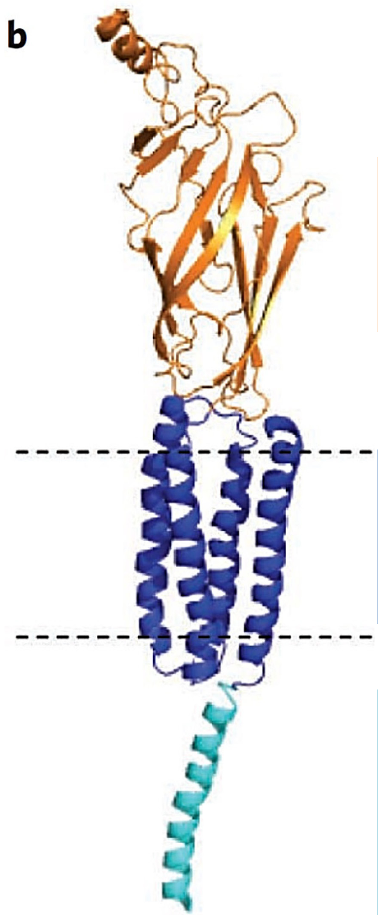
nACh *(Na+ and K+)*

GABAA *(Cl-)*

Glycine *(Cl-)*

Pentameric Ligand-Gated Channels



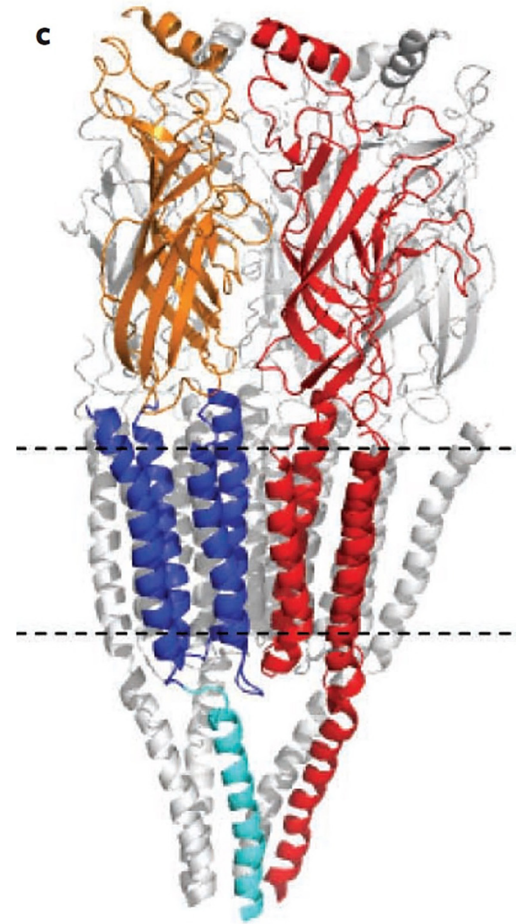


A single subunit

The N-terminal extra-cellular domain is ligand-binding site

Transmembrane regions M1-M4 make up the channel pore

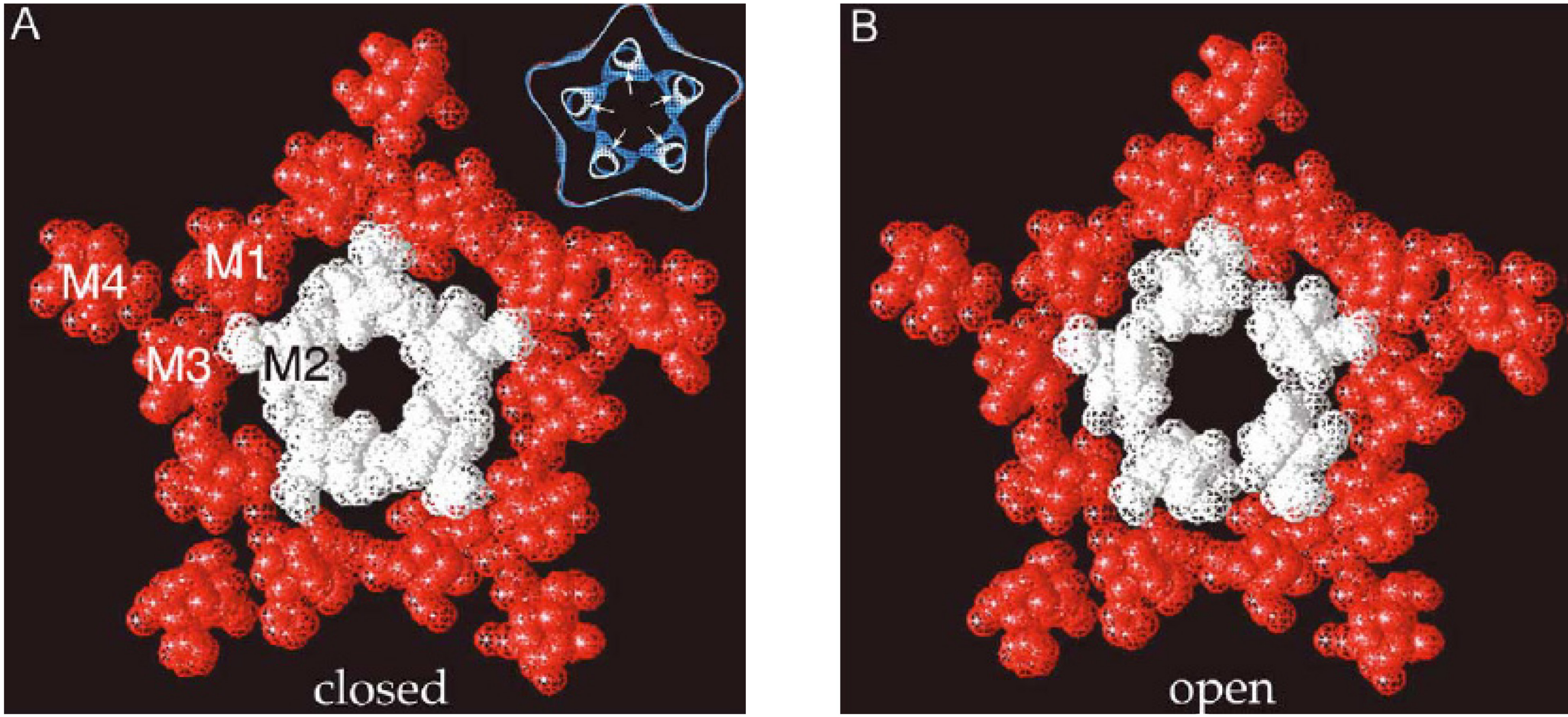
The intracellular domain between M3-M4 allows for receptor localization and regulation



5 subunits together make the functional channel

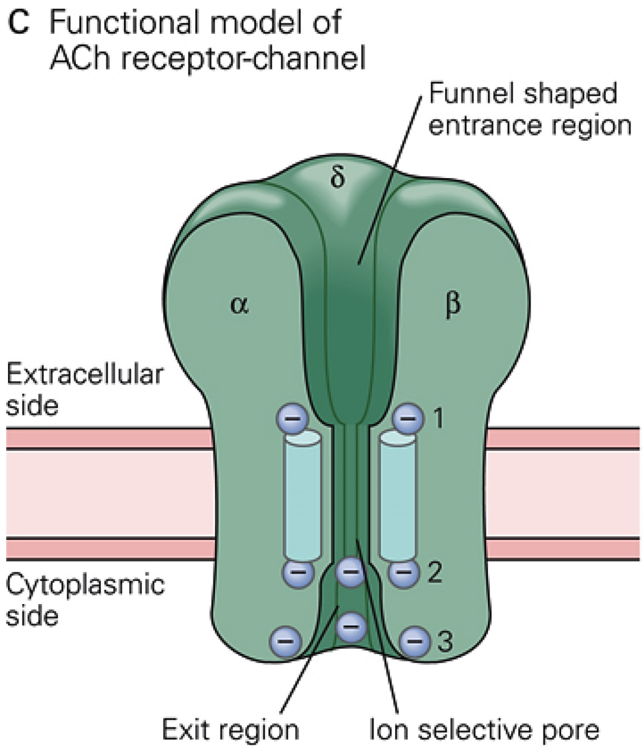
Nature Chemical Biology 7:759–760

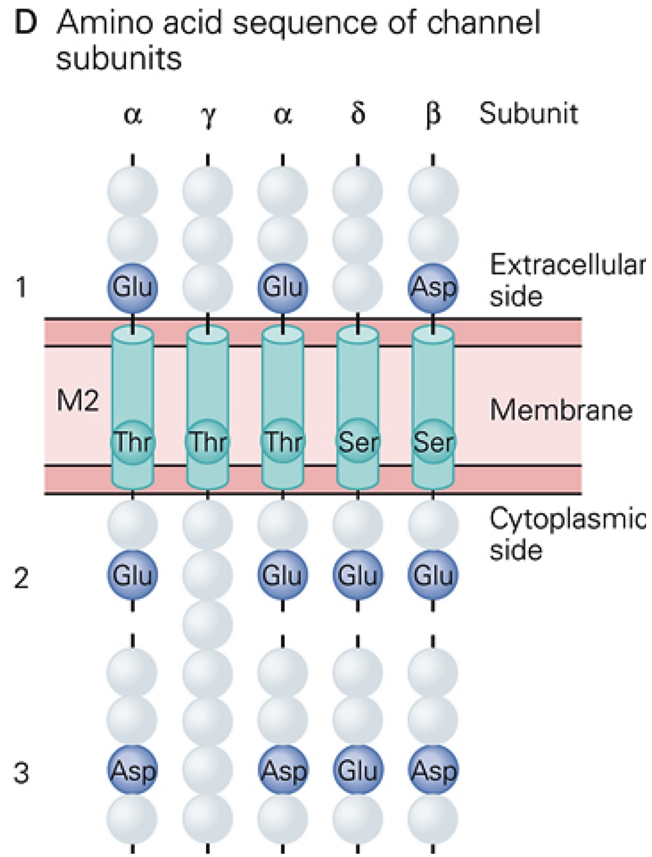
Pentameric Ligand-Gated Channels



The M2 region from each of the 5 subunits acts as the selectivity filter and determines ion selectivity of the channel

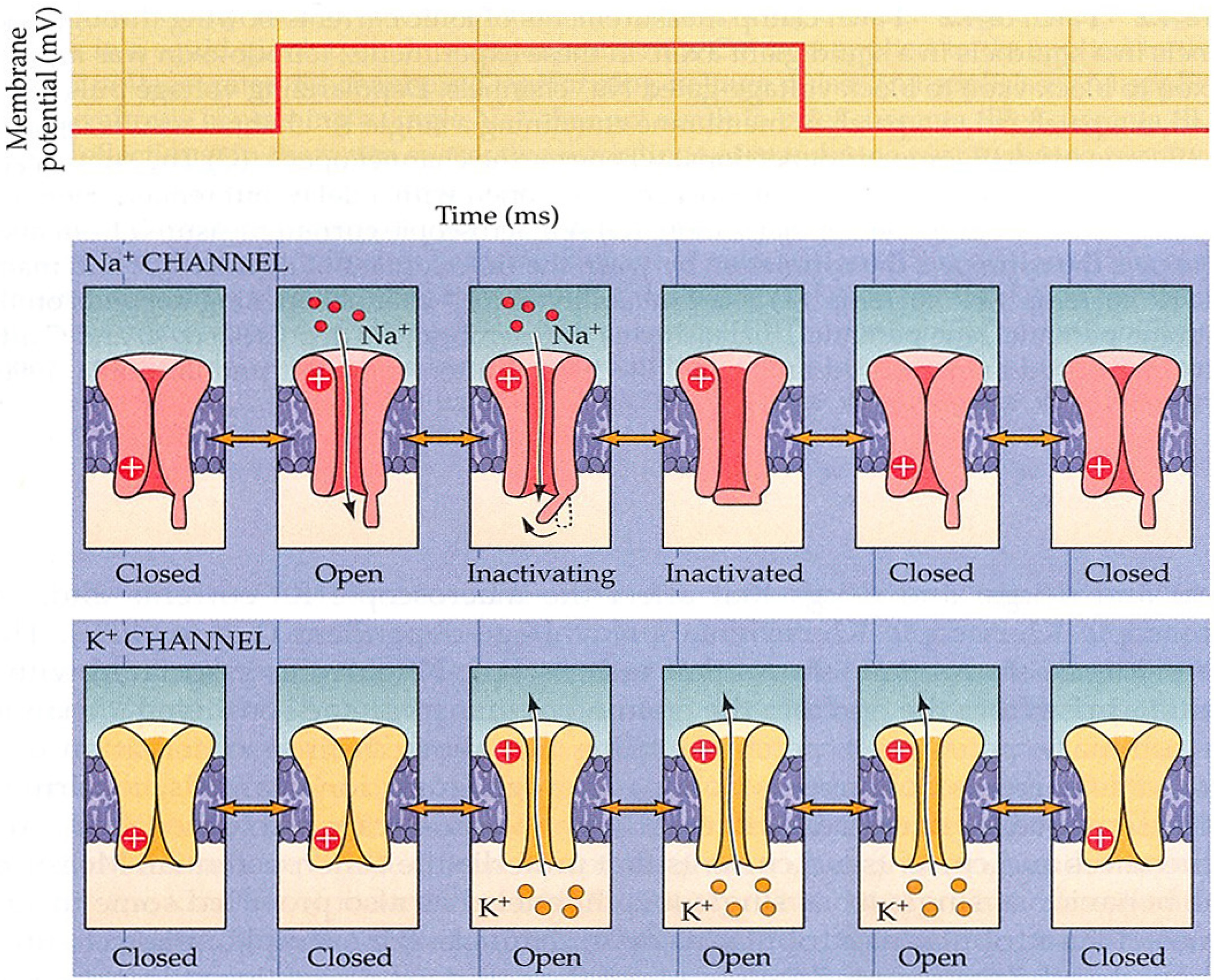
The Nicotinic AChR Selectivity Filter





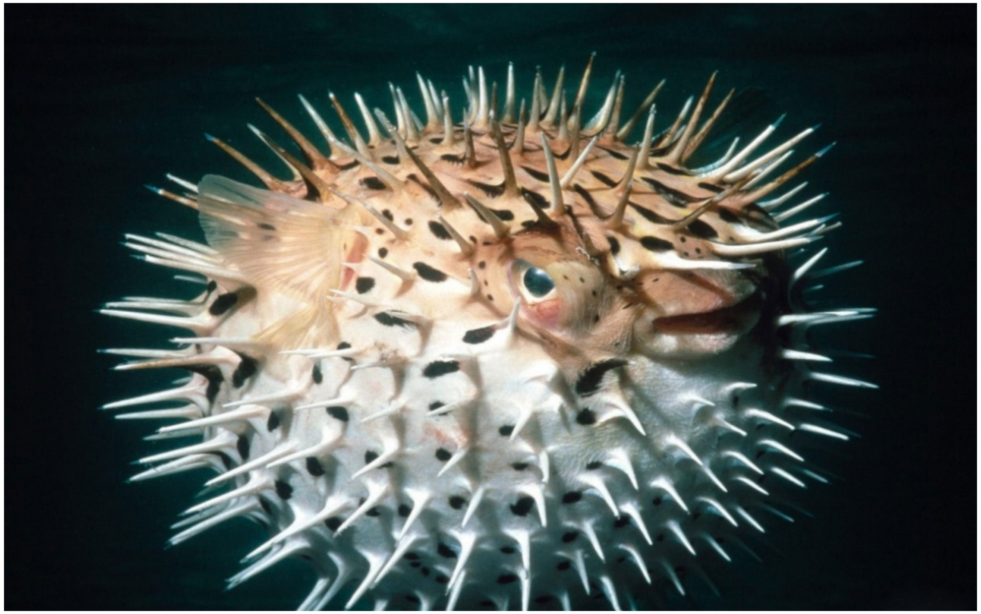
How would the M2 regions of nACh receptors and GABA$_A$ receptors differ?

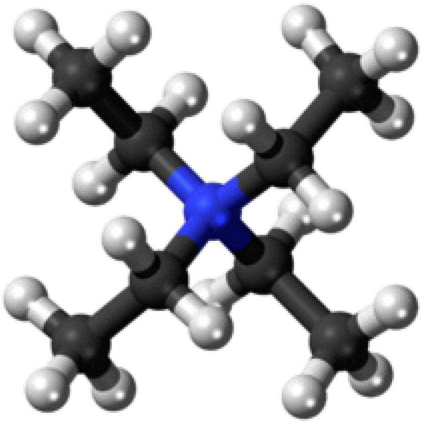
Voltage-Gated Channels



Pharmacology of Voltage-Gated Channels

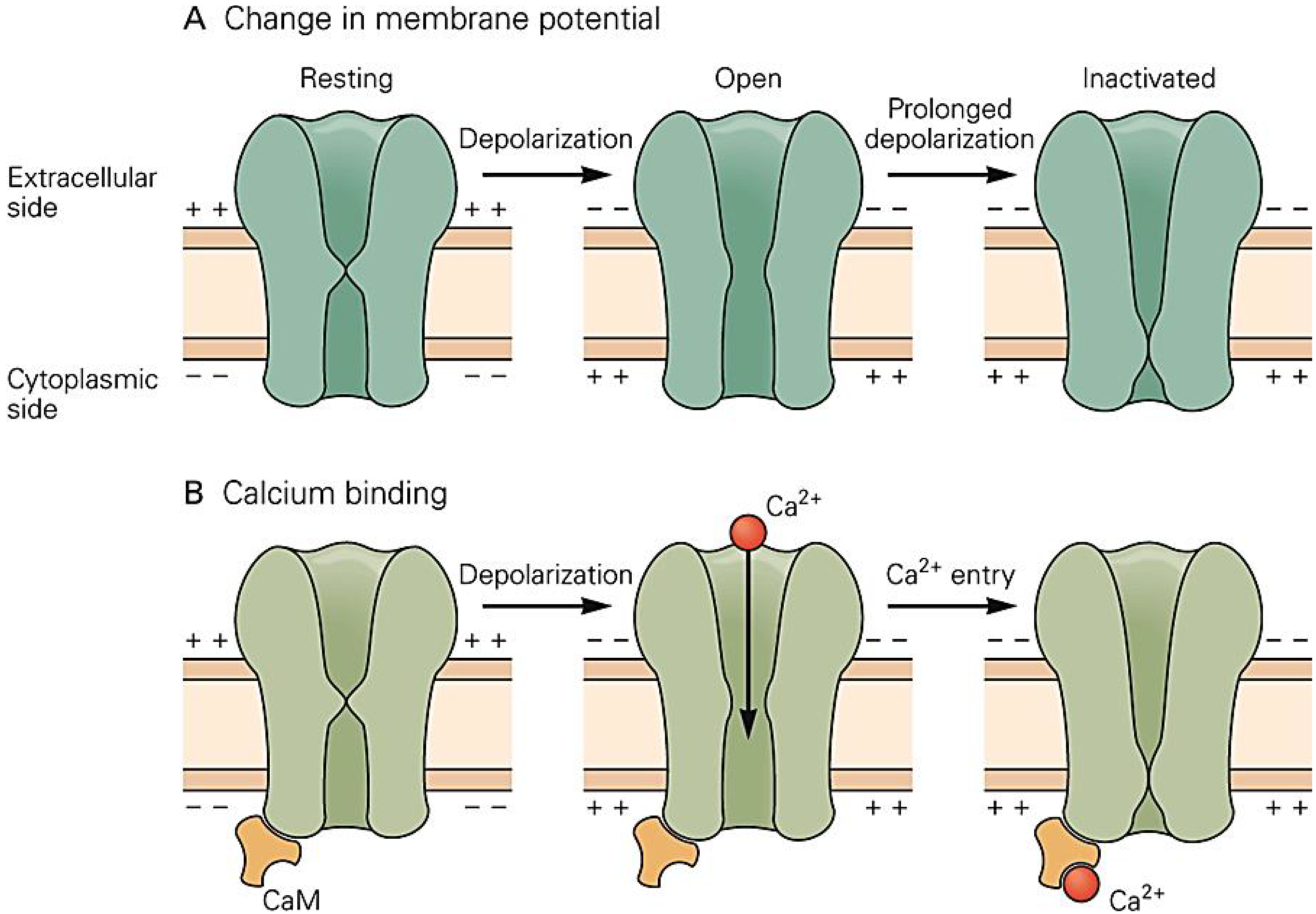
TTX (tetrodotoxin) blocks some types of voltage-gated sodium channels





TEA (tetraethylammonium) blocks some types of voltage-gated potassium channels

Voltage-Gated Channels

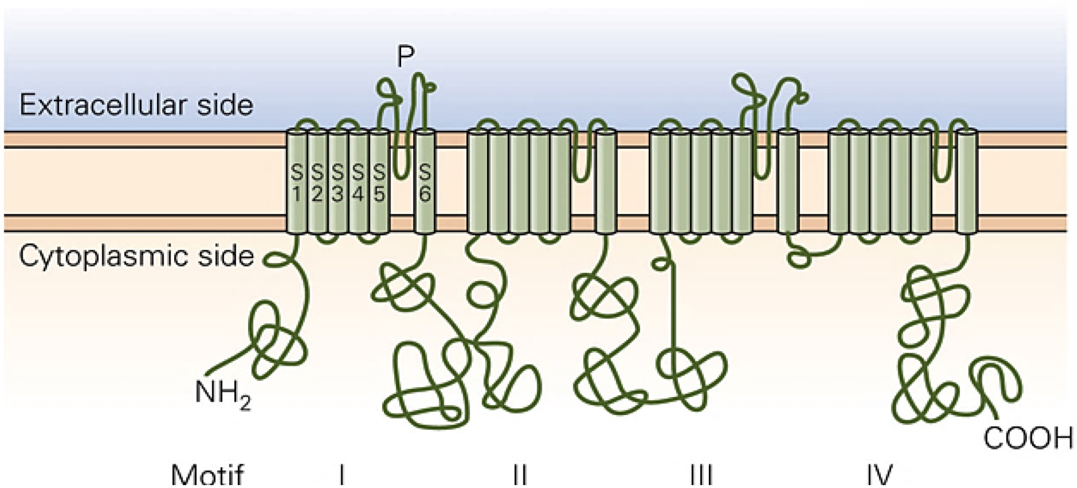


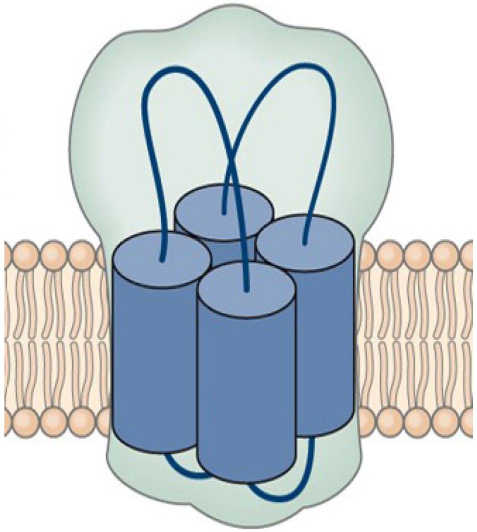
Voltage-gated channels have three different states:

- Closed (resting)
- Open
- Inactivated

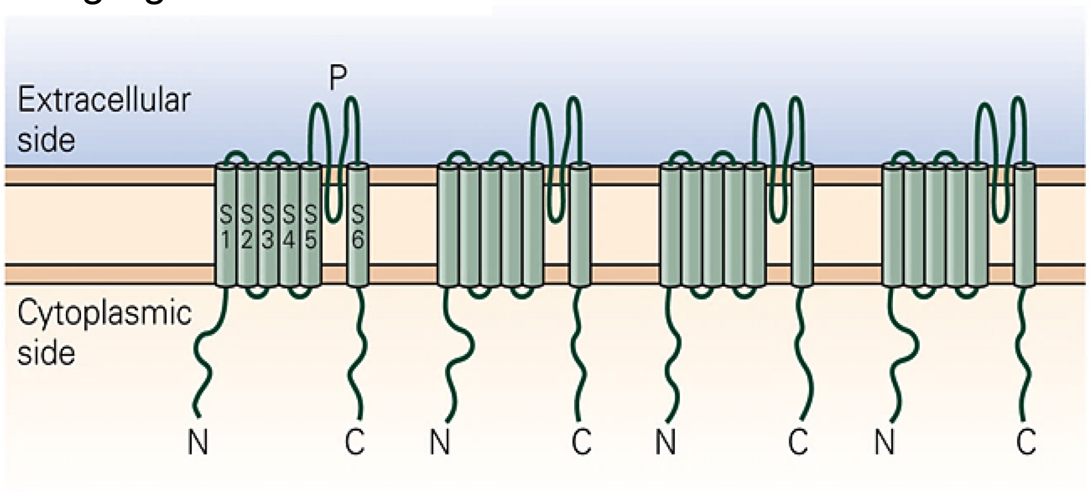
Structure of Voltage-Gated Channels

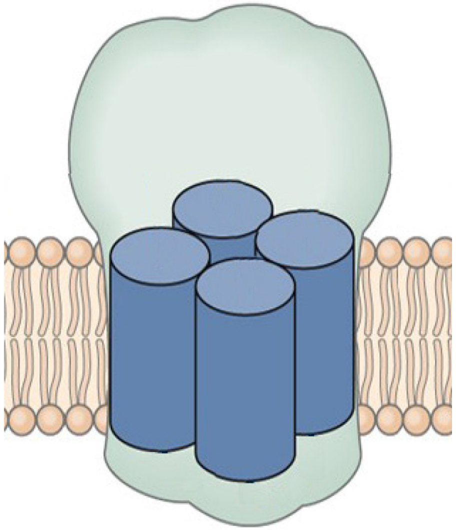
Voltage-gated Na^+ channel and Ca^{2+} channel





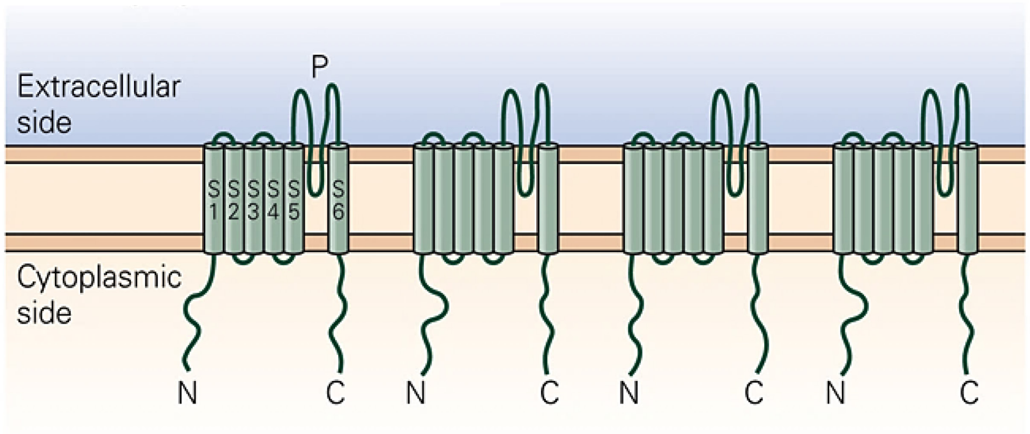
Voltage-gated K^+ channel

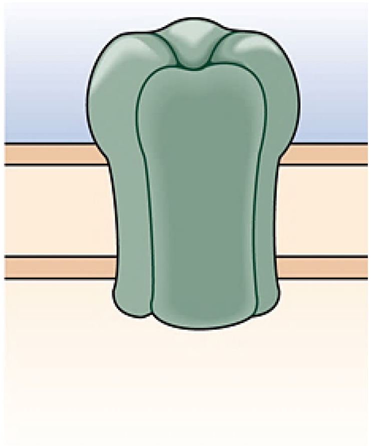




Looking Closely at K^+ Channels

Voltage-gated K^+ channel

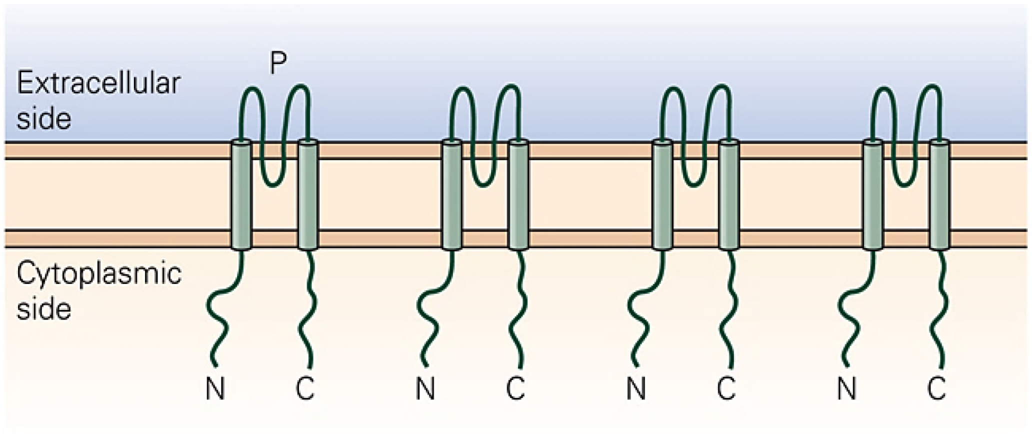


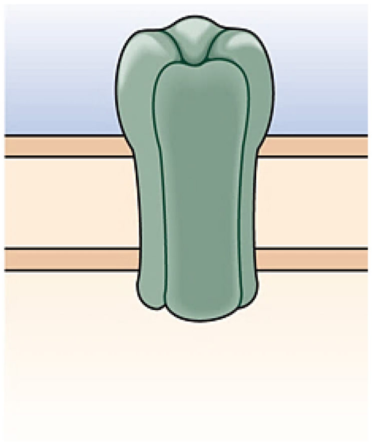


Found in mammals

Central pore that is voltage-gated

Simpler K^+ channel



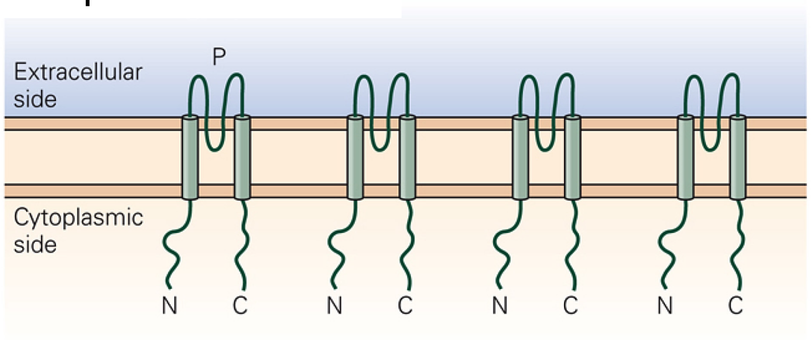


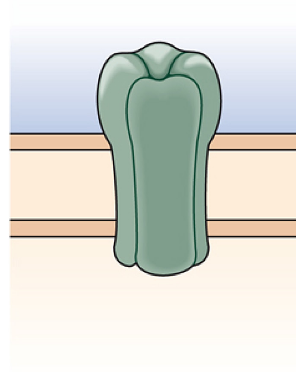
Found in all forms of animal life, including mammals and bacteria

Central pore only, Not voltage-gated

Structure of the K$^+$ Channel Pore

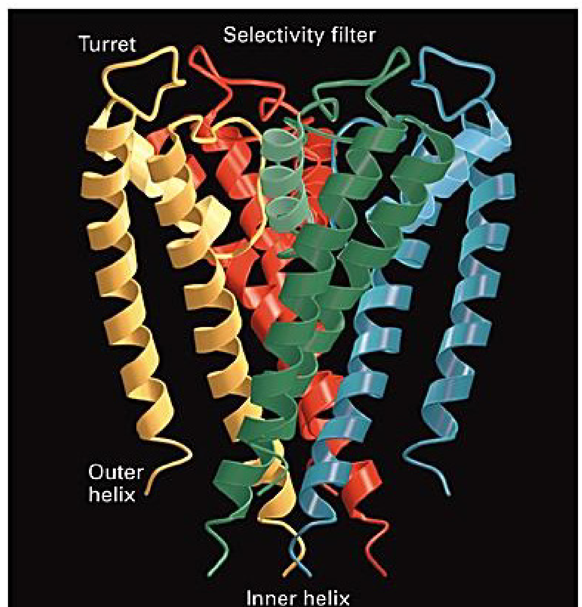
Simple K$^+$ channel



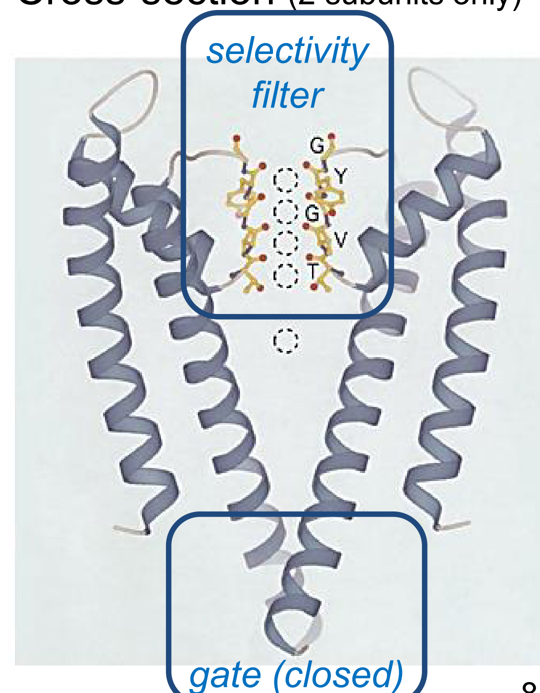


Looking down the channel

Cross-section



Cross-section (2 subunits only)



Structure of the K^+ Channel Pore

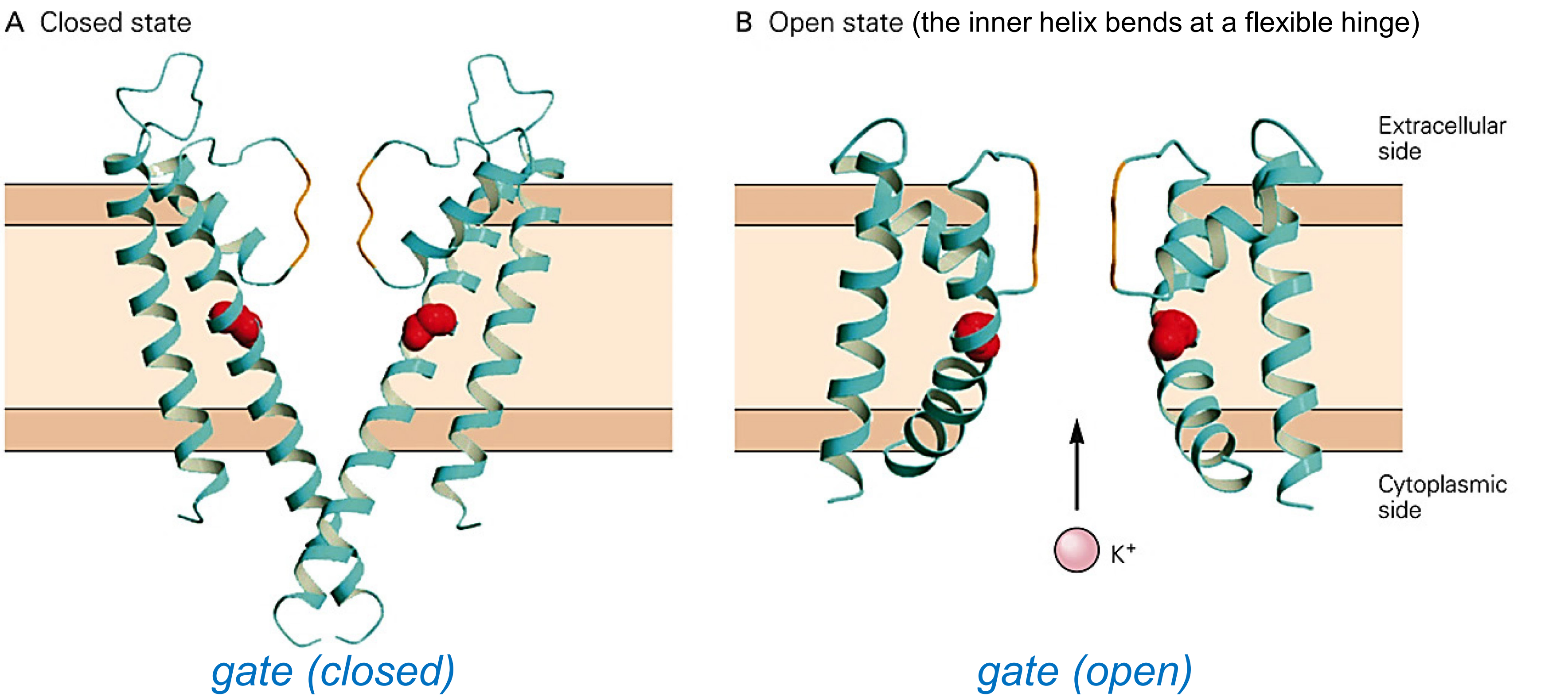
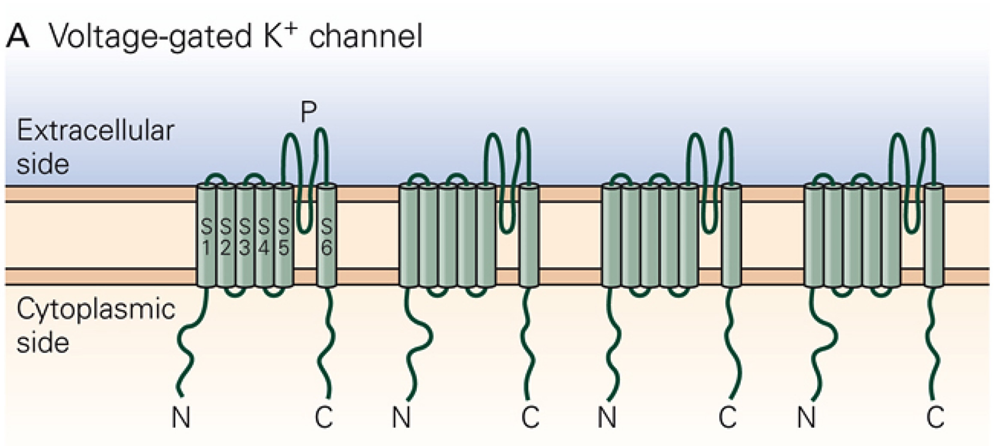


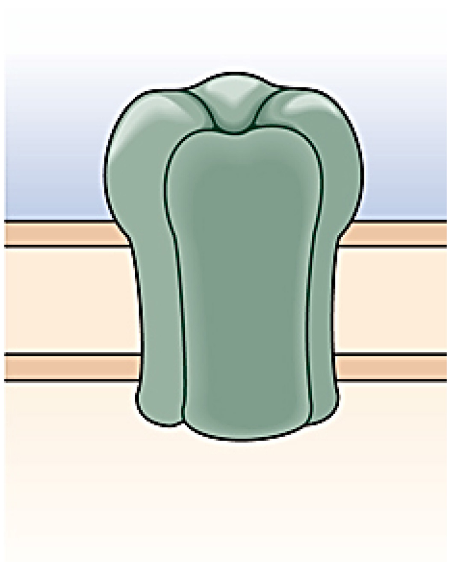
Figure 5–16 Gating of bacterial potassium channels. Only two of four subunits are shown.

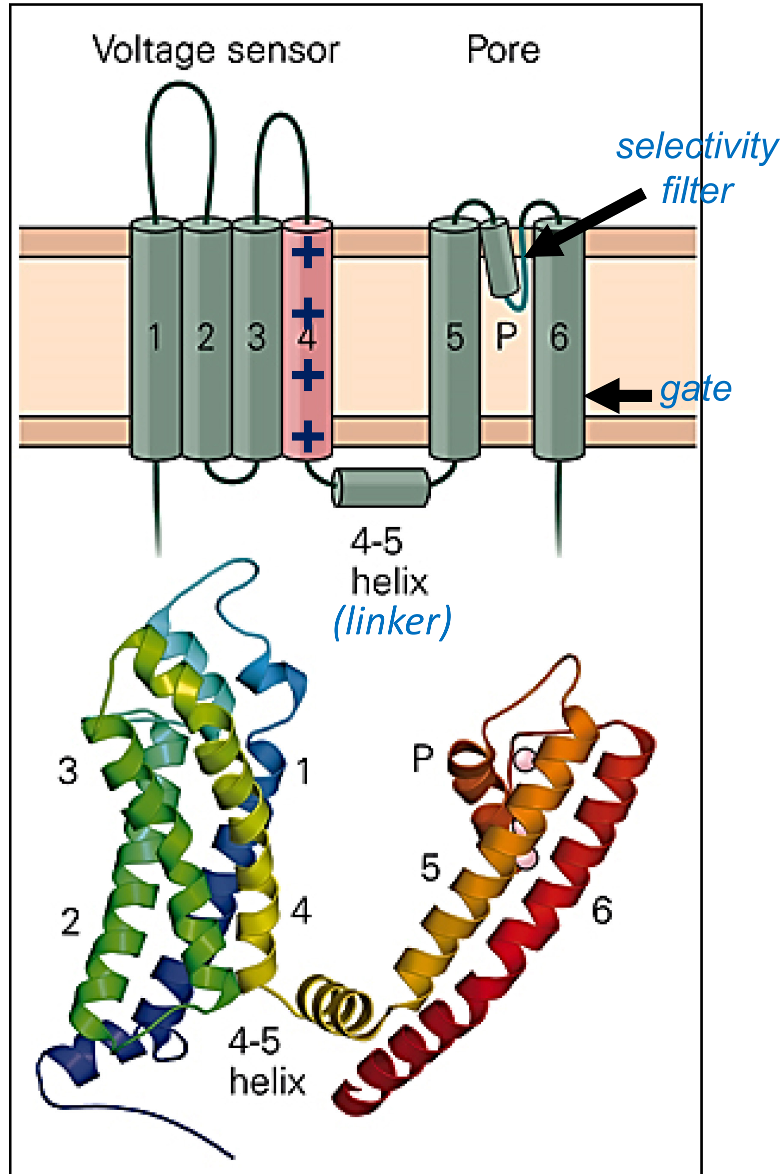
A. In the closed state the internal mouth of the pore formed by the inner helixes is too narrow to allow K^+ to pass (based on the X-ray crystal structure of the KcsA channel).

B. In the open state the inner helixes are bent at a conserved glycine residue (**red**), widening the internal mouth of the pore (based on the X-ray crystal structure of the MthK channel). (Reproduced, with permission, from Yu et al. 2005; after Jiang et al. 2002.)

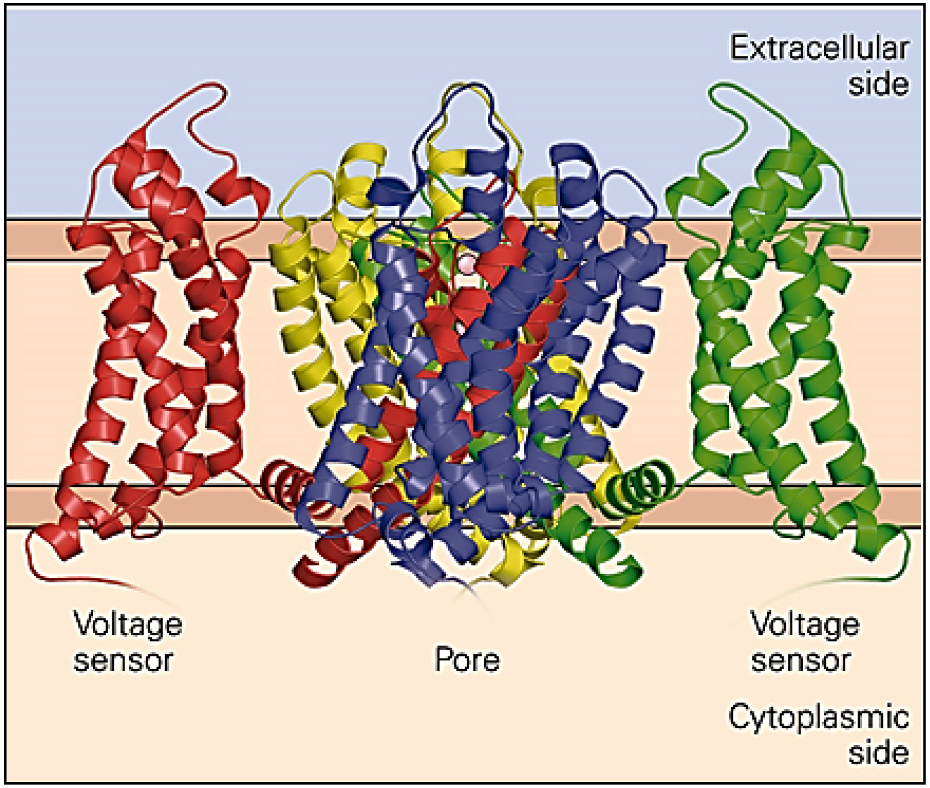
Structure of the Voltage-Gated K+ Channel

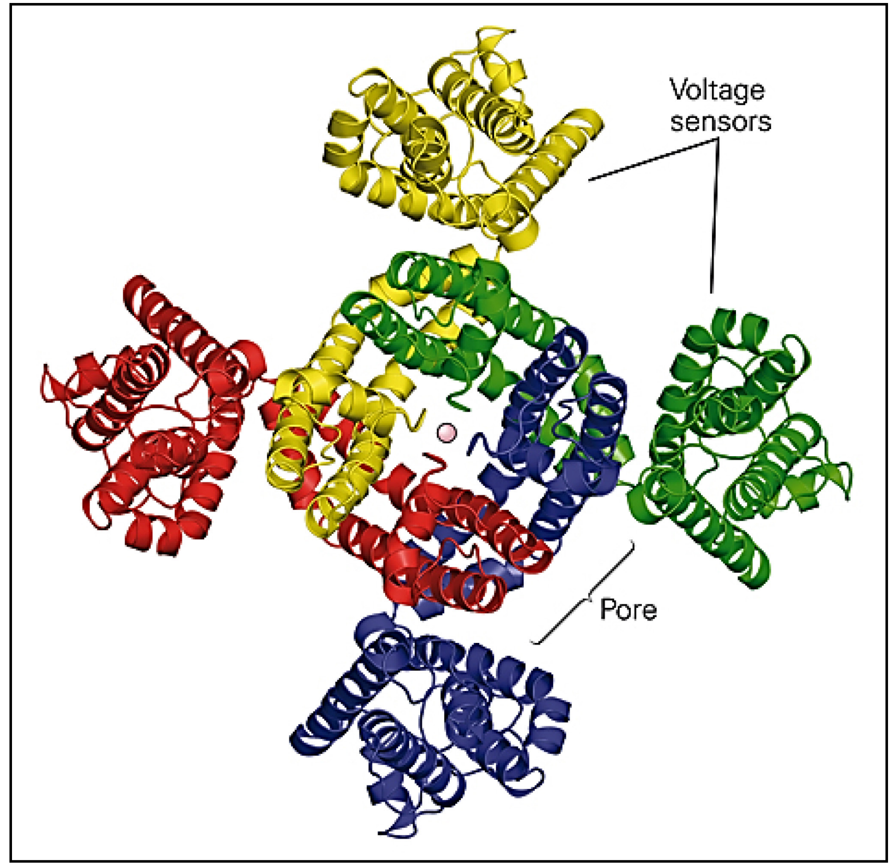






Structure of the Voltage-Gated K^+ Channel

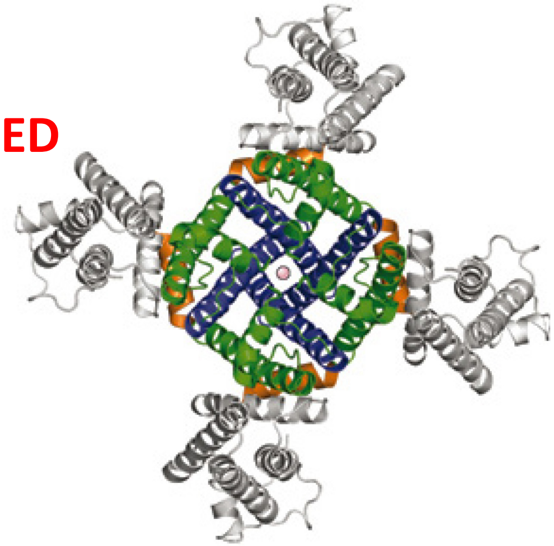


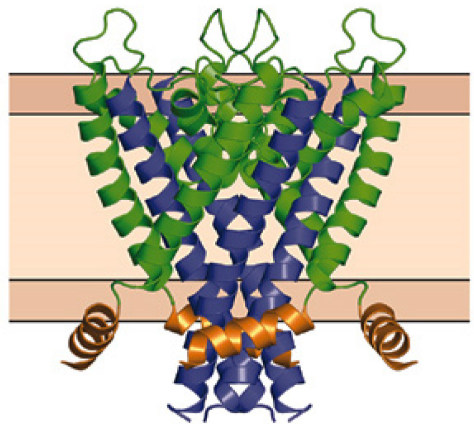


Gating of the Voltage-Gated K^+ Channel

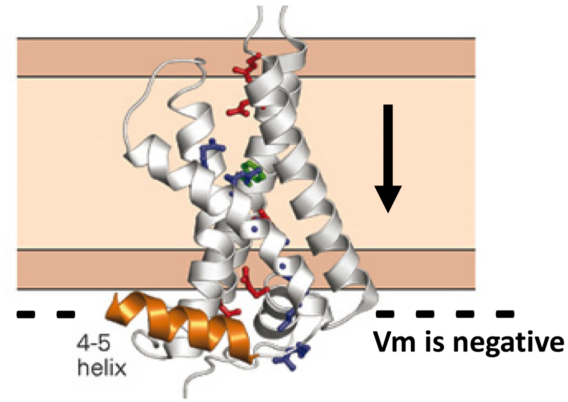
Entire channel | Pore and gate position | Voltage sensor position

CLOSED

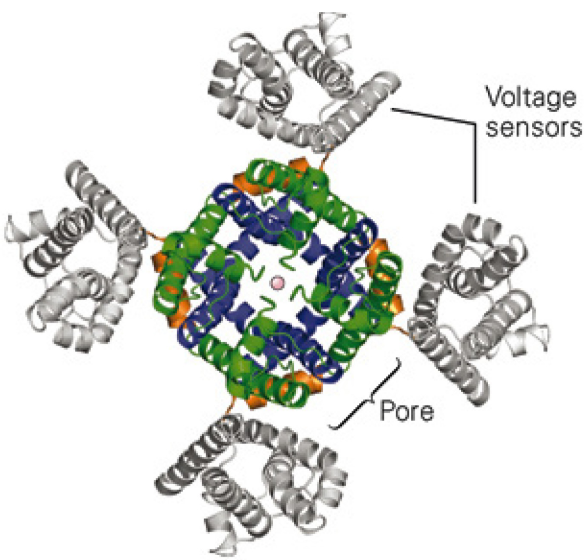


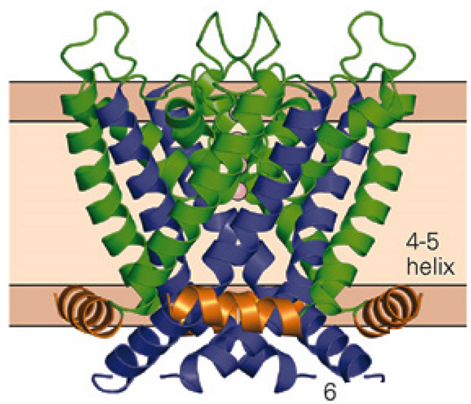


Positive charges of S4 are pulled downward by negative Vm, pushing pore gate closed

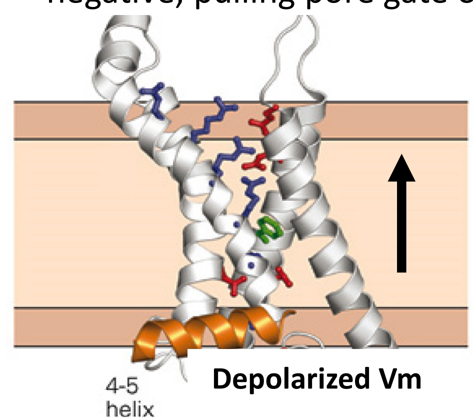


OPEN

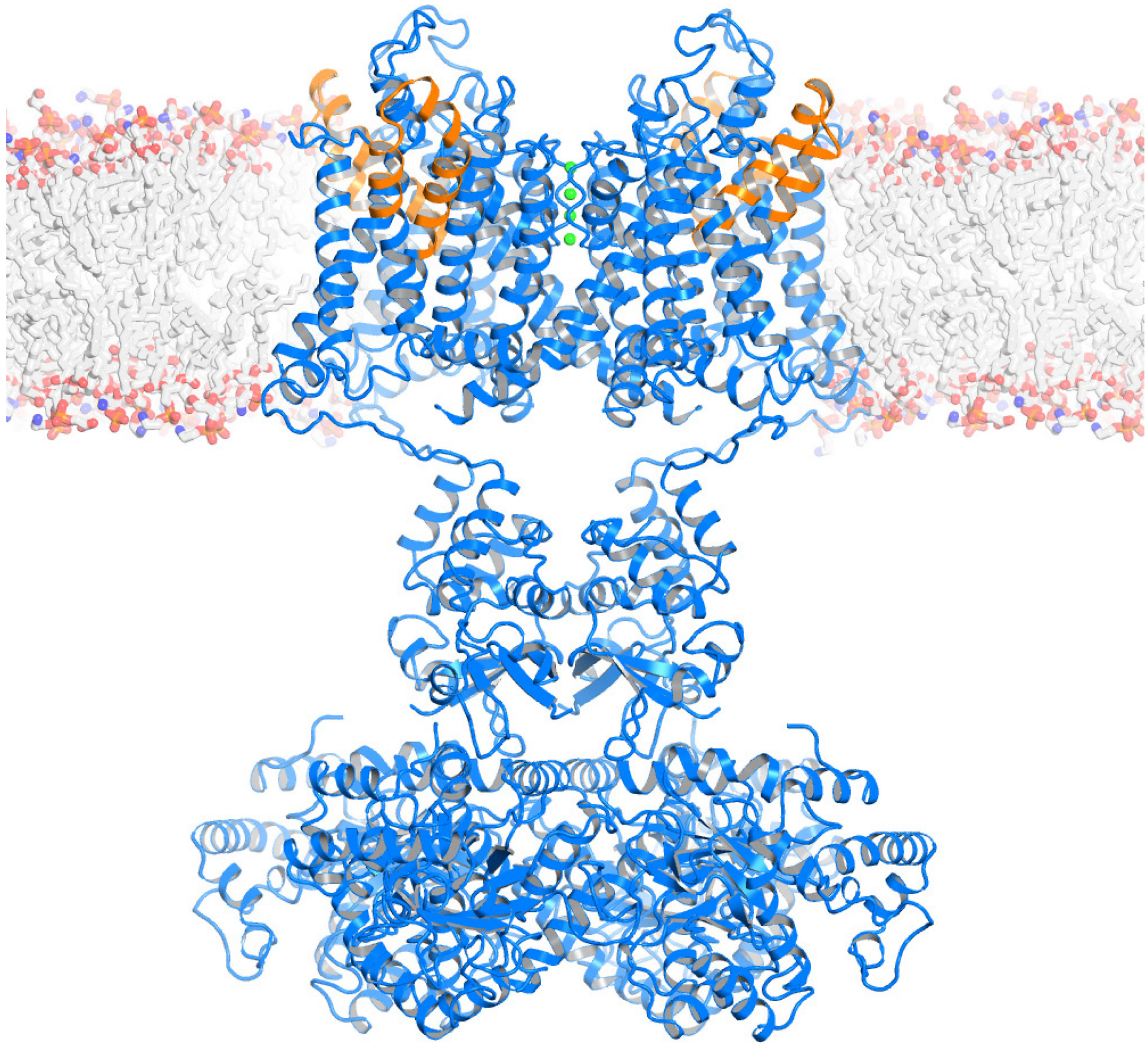




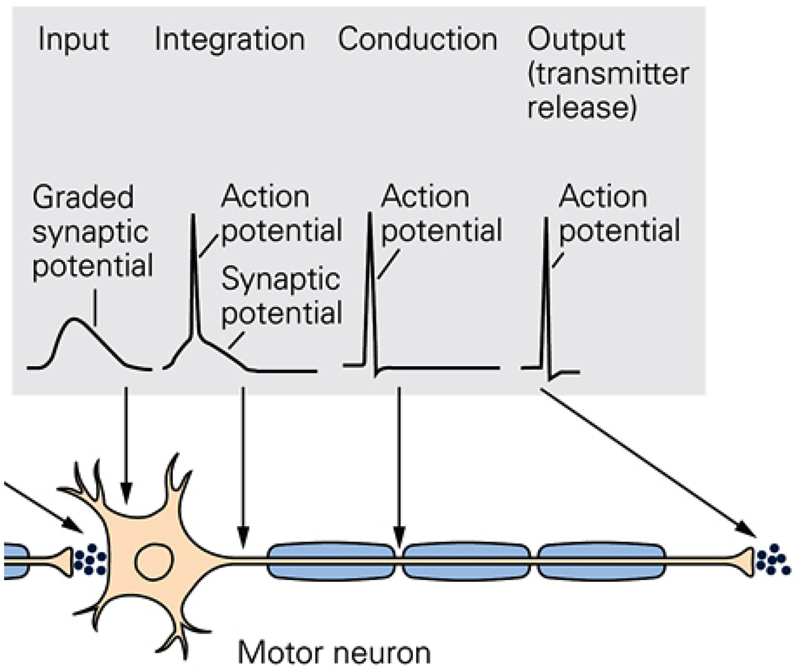
Positive charges of S4 swing upward when membrane is less negative, pulling pore gate open



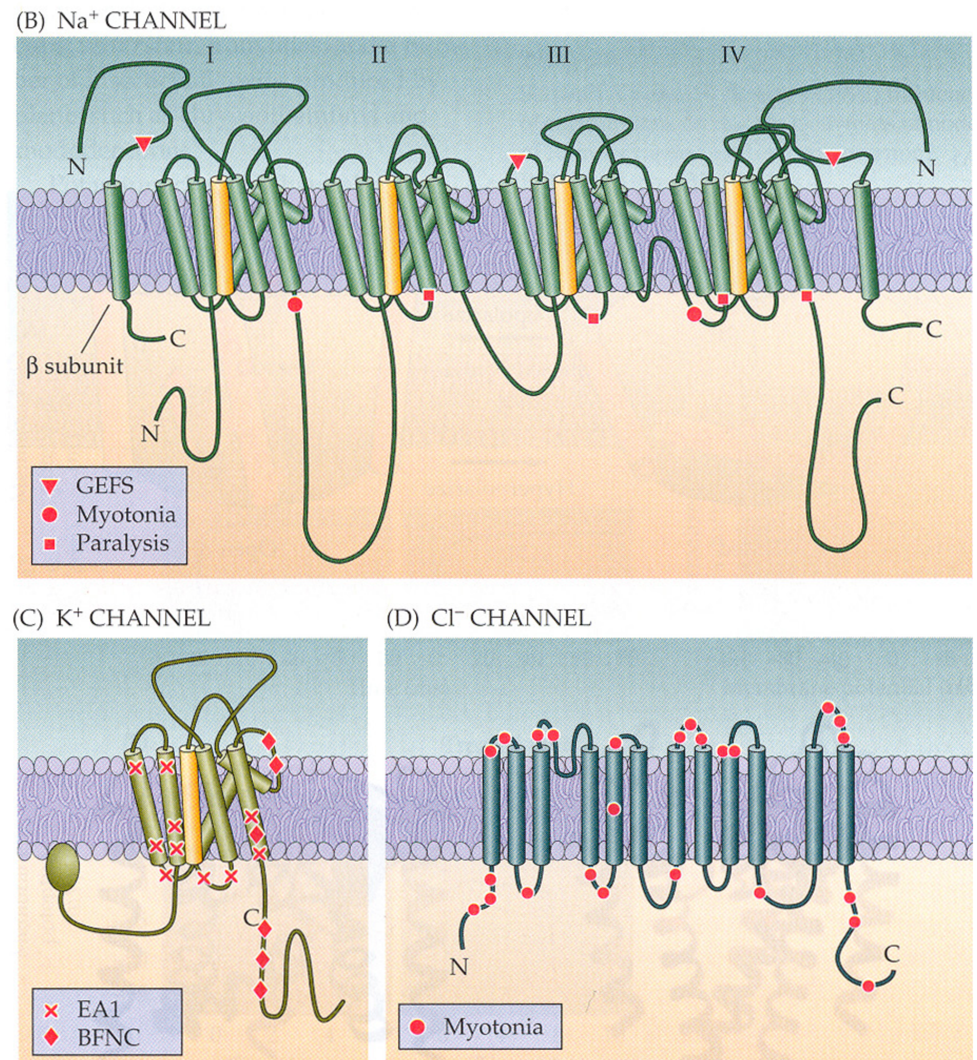
Structure of the Voltage-Gated K^+ Channel



Proper ion channel structure and function is critical for signaling



Channelopathies are diseases caused by altered ion channels



Purves et al., Neuroscience 4th edition, pp 76-77