# UNIT2
# Membrane Physiology, Nerve, and Muscle

4. Transport of Substances Through the Cell Membrane
5. Membrane Potentials and Action Potentials
6. Contraction of Skeletal Muscle
7. Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling
8. Contraction and Excitation of Smooth Muscle

## ➢ Transport of Substances Through the Cell Membrane

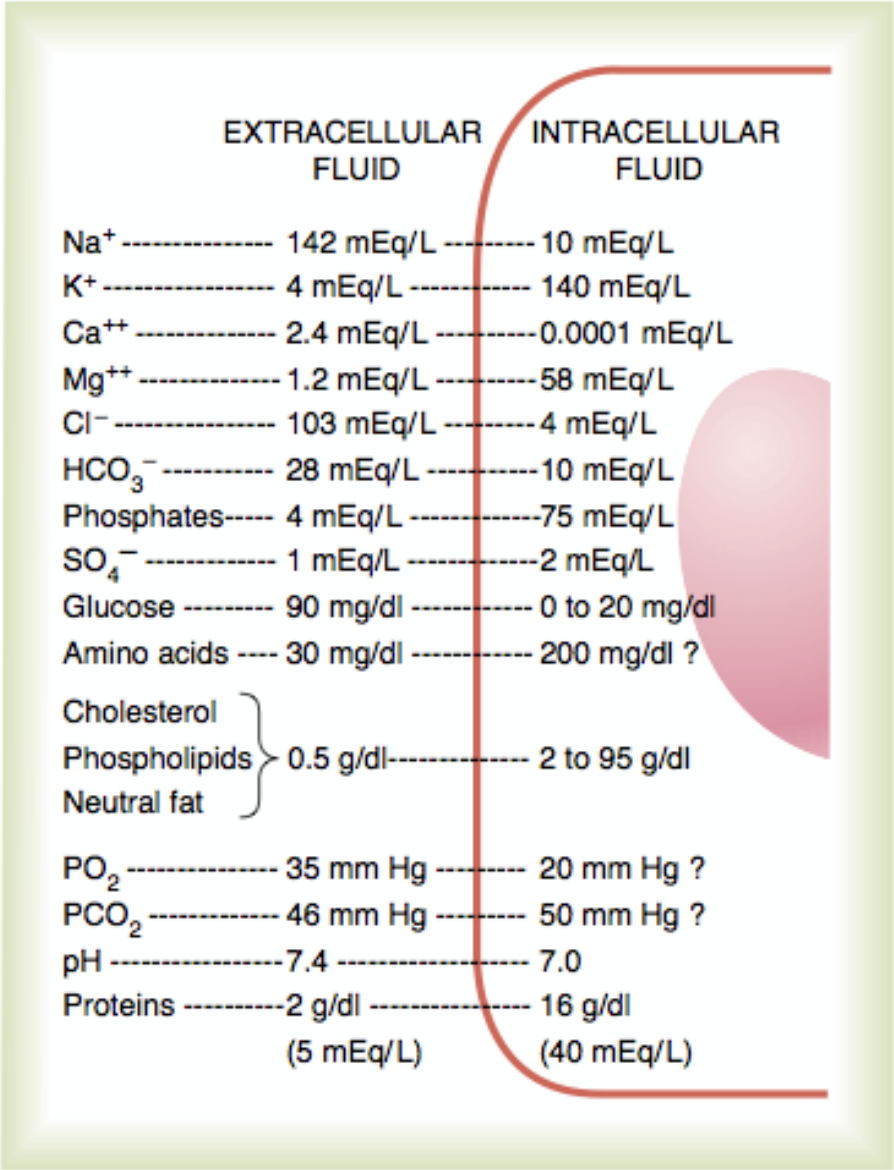


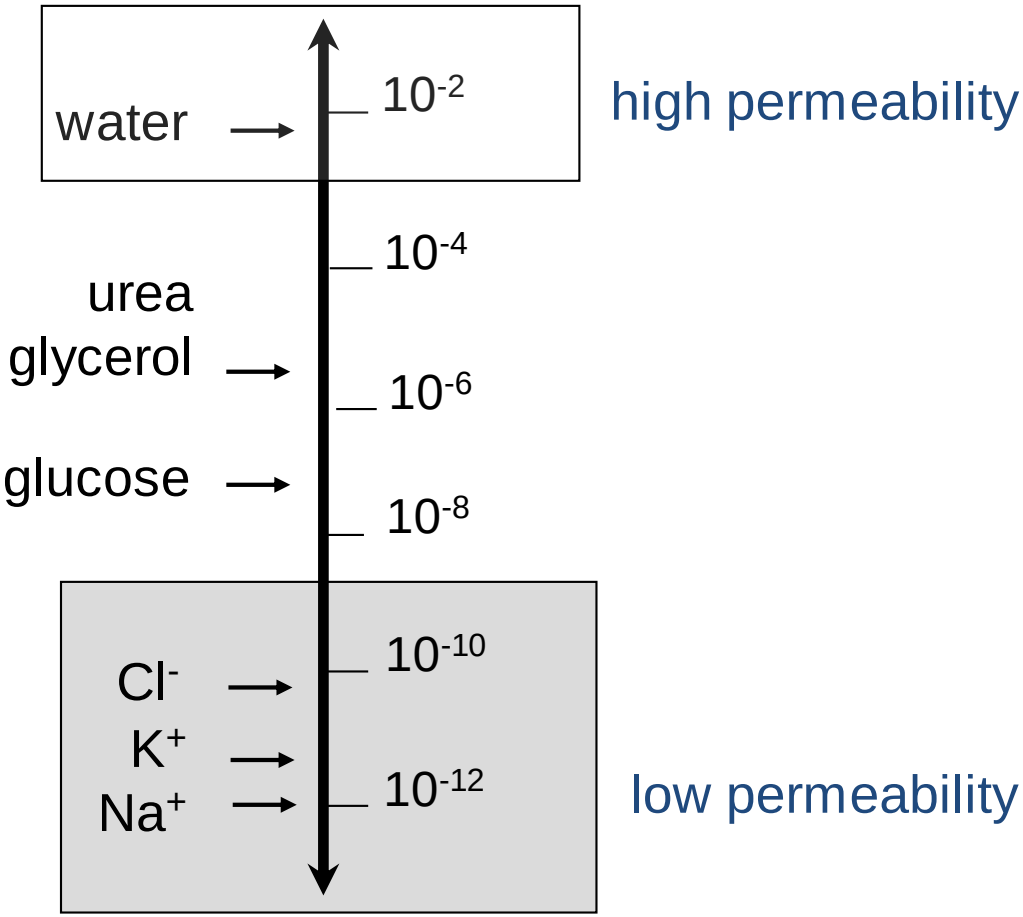

**Figure 4–1**

Chemical compositions of extracellular and intracellular fluids.

- the extracellular fluid contains a large amount of sodium but only a small amount of potassium.
- Exactly the opposite is true of the intracellular fluid.

# Permeability coefficients (cm/sec)

*(** across an artificial lipid bilayer)*



# The Lipid Barrier of the Cell Membrane, and Cell Membrane Transport Proteins

➢ *lipid bilayer barrier to water and water-soluble substances*

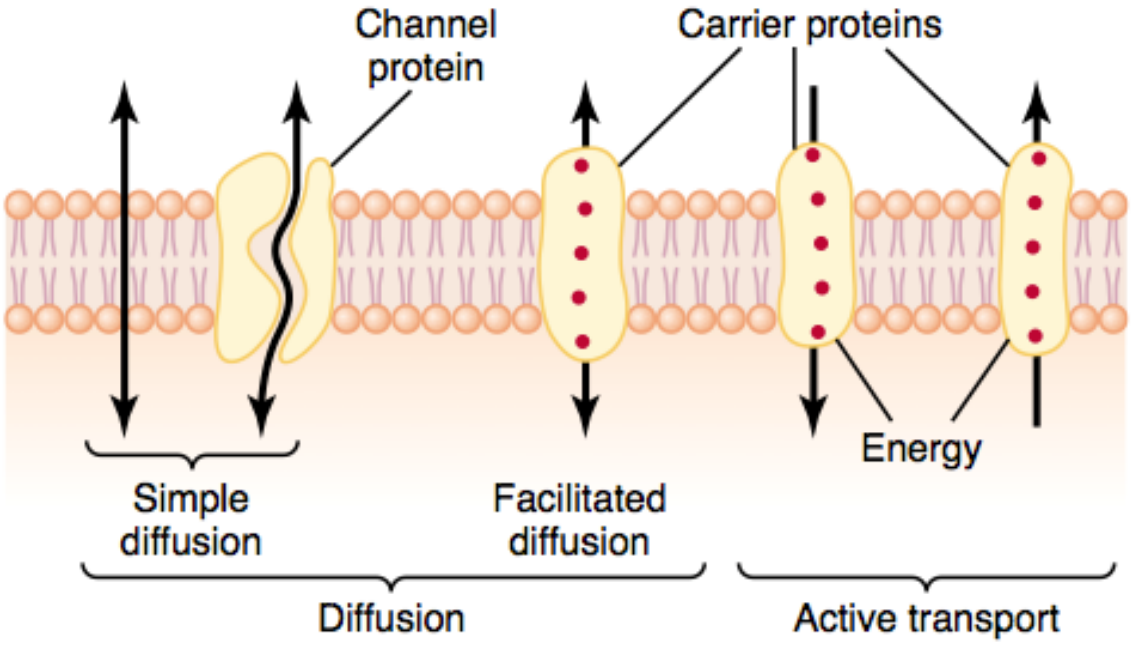



**Figure 4–2**

Transport pathways through the cell membrane, and the basic mechanisms of transport.

- *channel proteins* have watery spaces all the way through the molecule and allow free movement of water as well as selected ions or molecules
- *carrier proteins* bind with molecules or ions that are to be transported; conformational changes in the protein molecules then move the substances through the interstices of the protein to the other side of the membrane.

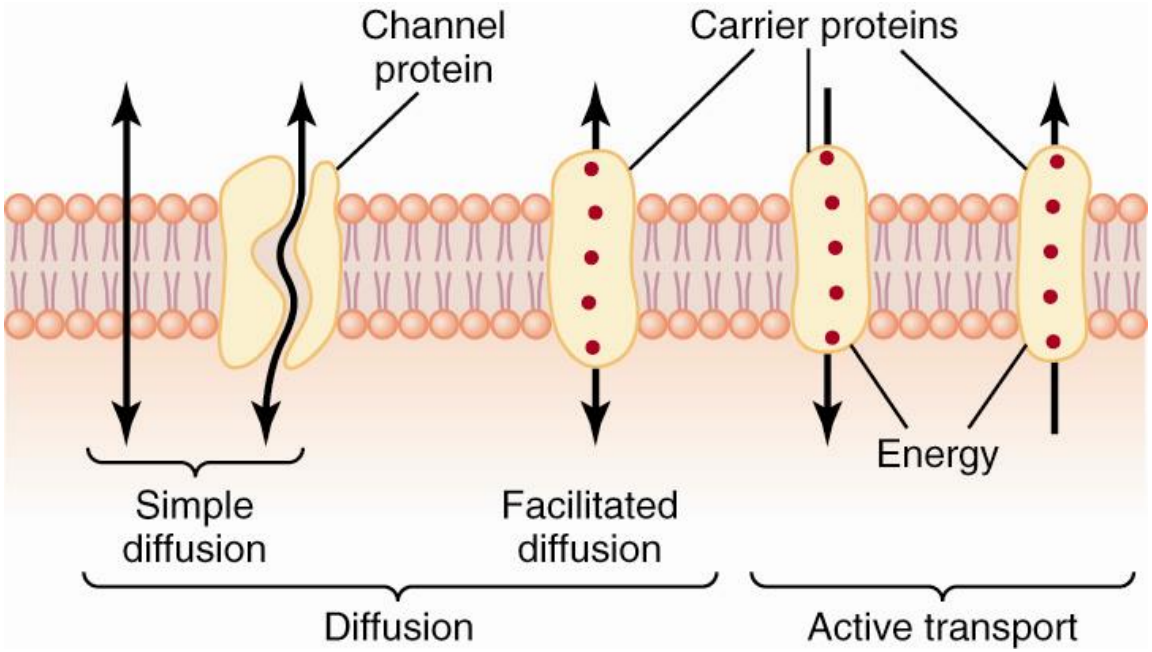
# DIFFUSION

## Diffusion

- occurs down a concn. gradient
- no mediator or involves a "channel" or "carrier"
- no additional energy

## Active Transport

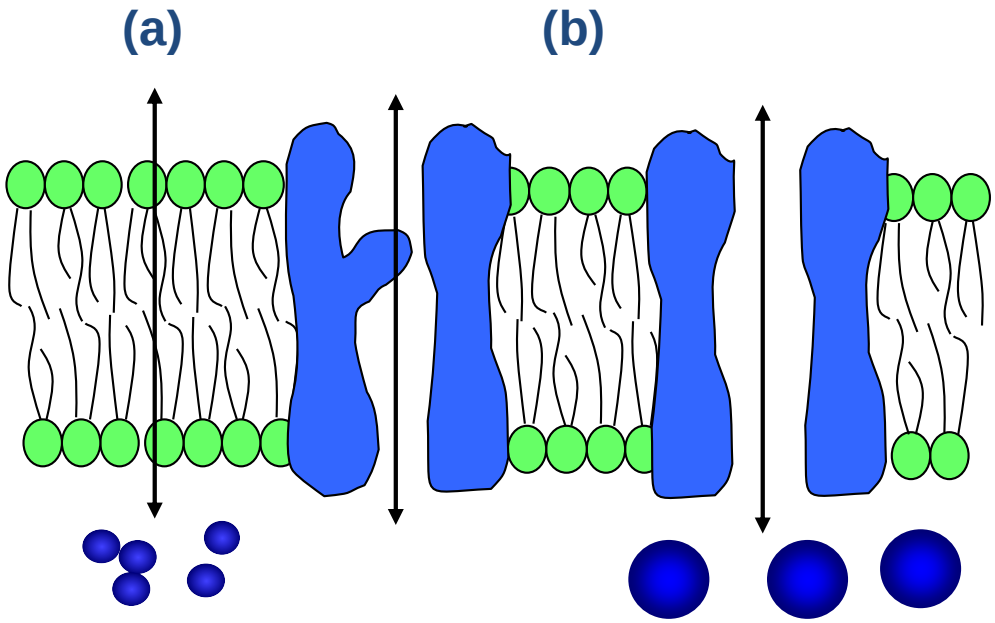
- occurs against a concn. gradient
- involves a "carrier"
- requires **ENERGY**



# Simple Diffusion

**(a)** lipid-soluble molecules move readily across the membrane (rate depends on **lipid solubility**)

**(b)** water-soluble molecules cross via channels or pores



## Diffusion Through Protein Channels, and "Gating" of These Channels

- The protein channels are distinguished by two important characteristics: (1) they are often selectively permeable to certain substances, and (2) many of the channels can be opened or closed by gates.

### Ion Channels

#### Characteristics:

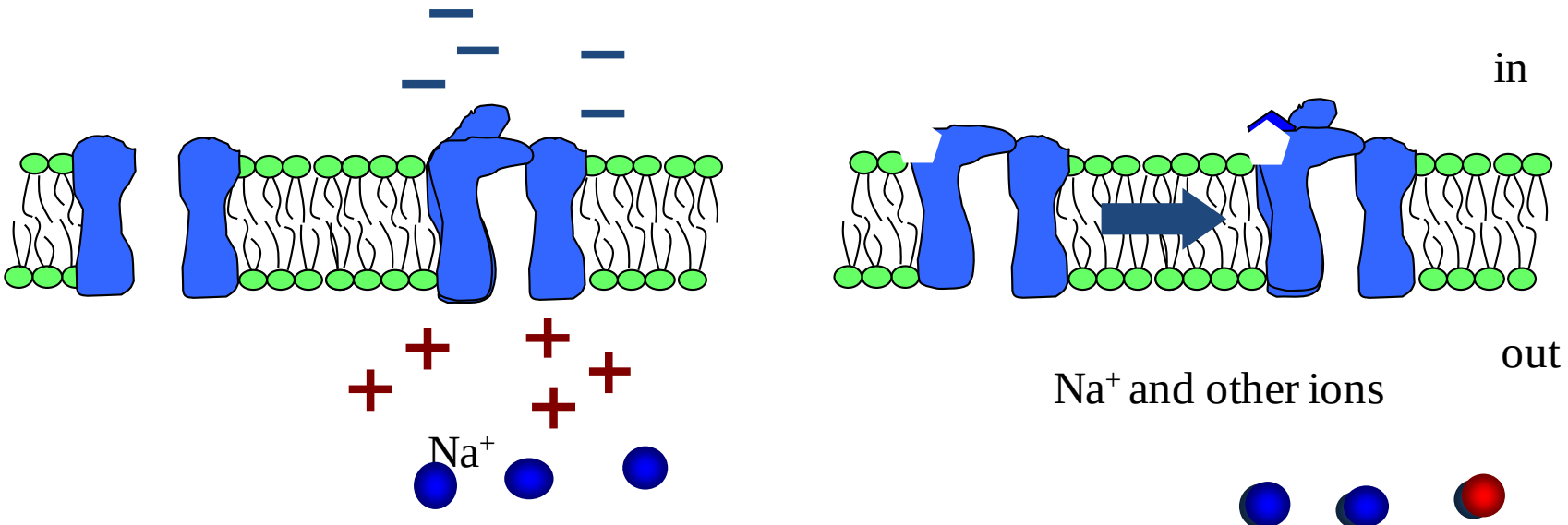
**ungated**

- determined by size, shape, distribution of charge, etc.

**Gated**

The opening and closing of gates are controlled in two principal ways:

- voltage (e.g. voltage-dependent $Na^+$ channels)
- chemically (e.g. nicotinic ACh receptor channels)



- **Open-State Versus Closed-State of Gated Channels.**

- “ *Patch Clamp:* method for recording current flow through a single protein channel. ”
- Nobel Prize in Physiology & Medicine -1991

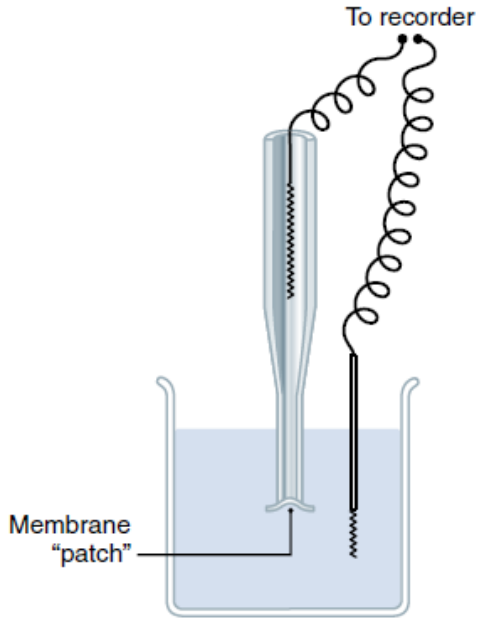
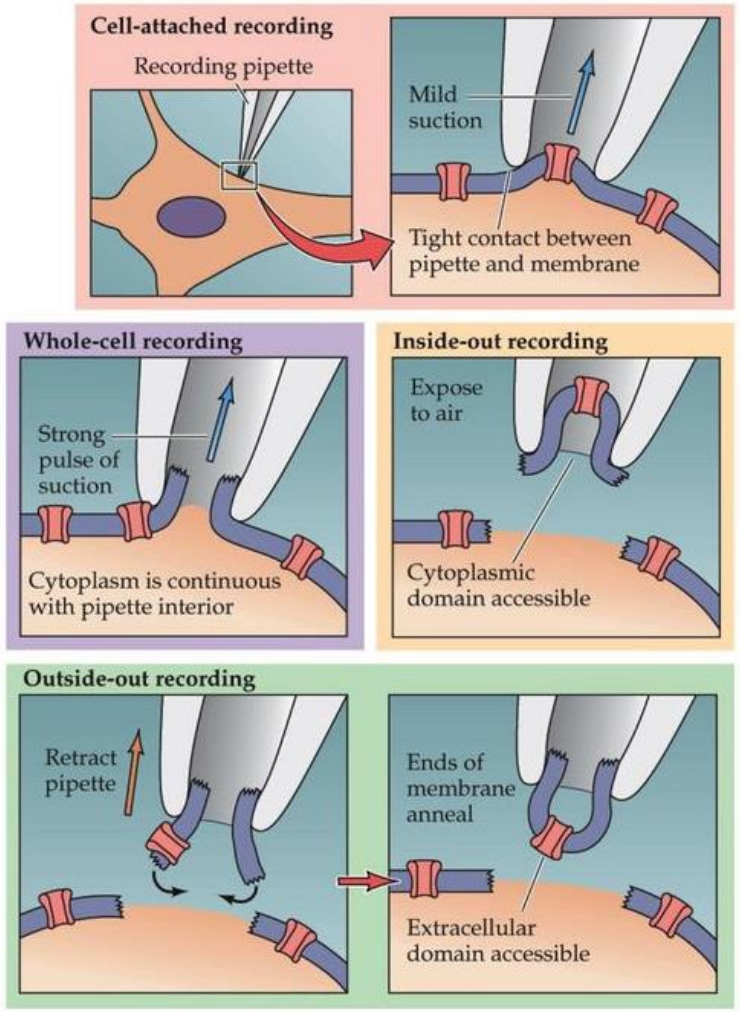
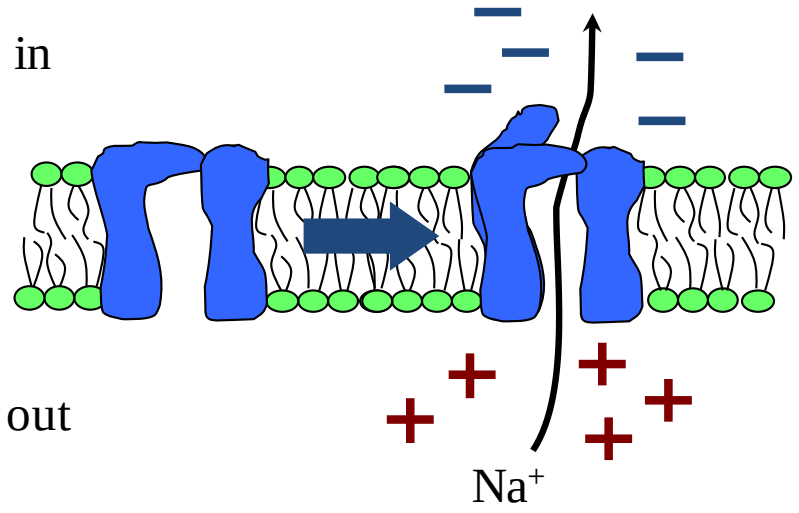
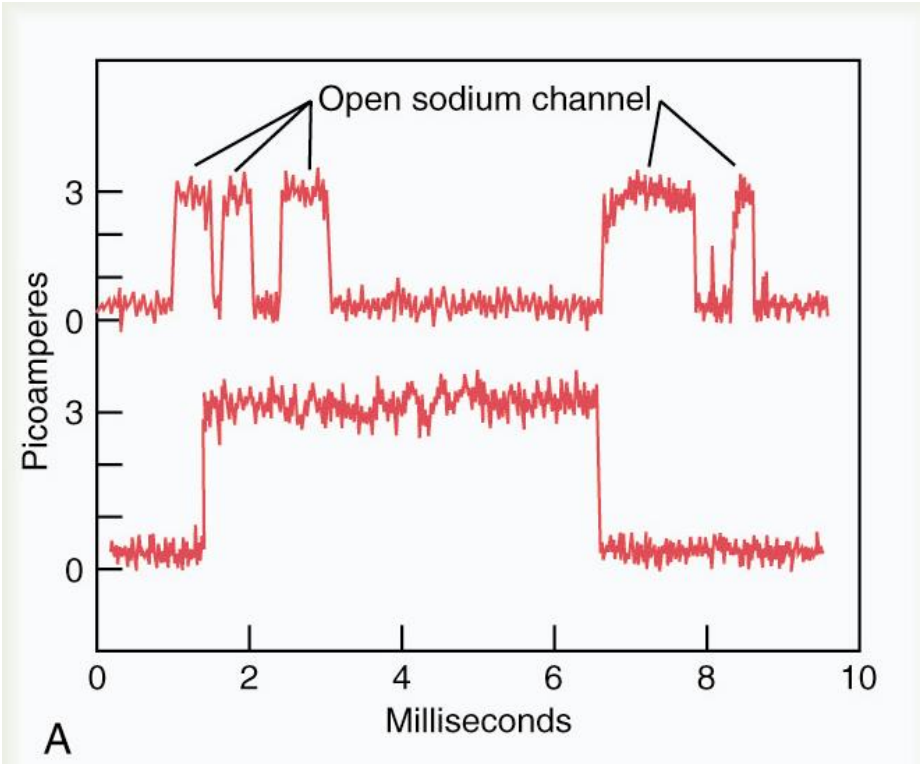



**Figure 4-6** *A*, Record of current flow through a single voltage-gated sodium channel, demonstrating the “all or none” principle for opening and closing of the channel. *B*, The “patch-clamp” method for recording current flow through a single protein channel. To the left, recording is performed from a “patch” of a living cell membrane. To the right, recording is from a membrane patch that has been torn away from the cell.



## Ion Channels



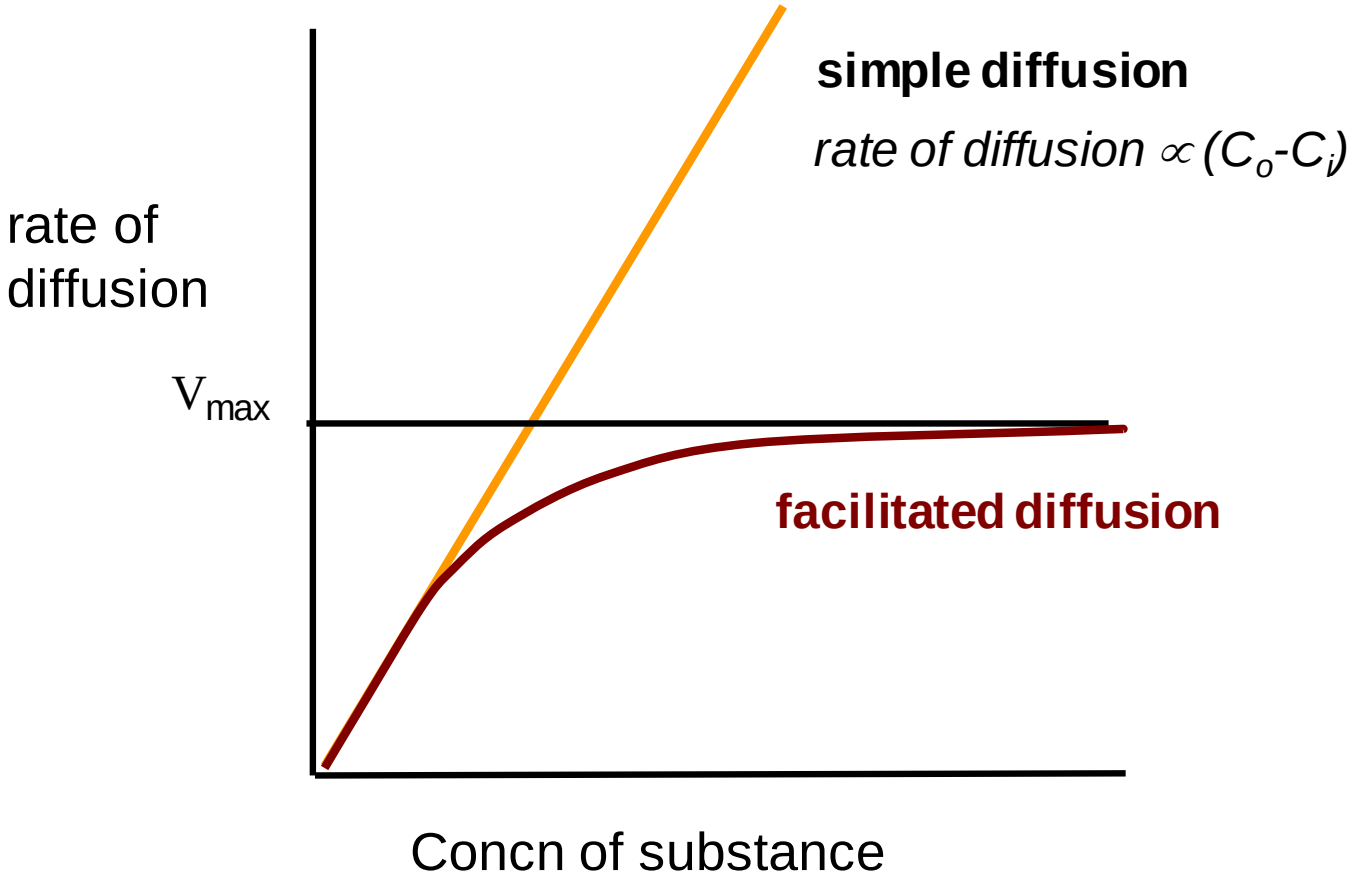




- This figure shows two recordings of electrical current flowing through a single sodium channel when there was an approximate 25-millivolt potential gradient across the membrane. Note that the channel conducts current either “all or none.”

# Facilitated Diffusion

- Facilitated diffusion is also called carrier-mediated diffusion because a substance transported in this manner diffuses through the membrane using a specific carrier protein to help. That is, the carrier facilitates diffusion of the substance to the other side.

## Simple vs. Facilitated




***What limits maximum rate of facilitated diffusion?***

**Rate of diffusion is limited by**

- $V_{max}$ of the carrier protein
- the density of carrier proteins in the membrane (i.e., number per unit area)

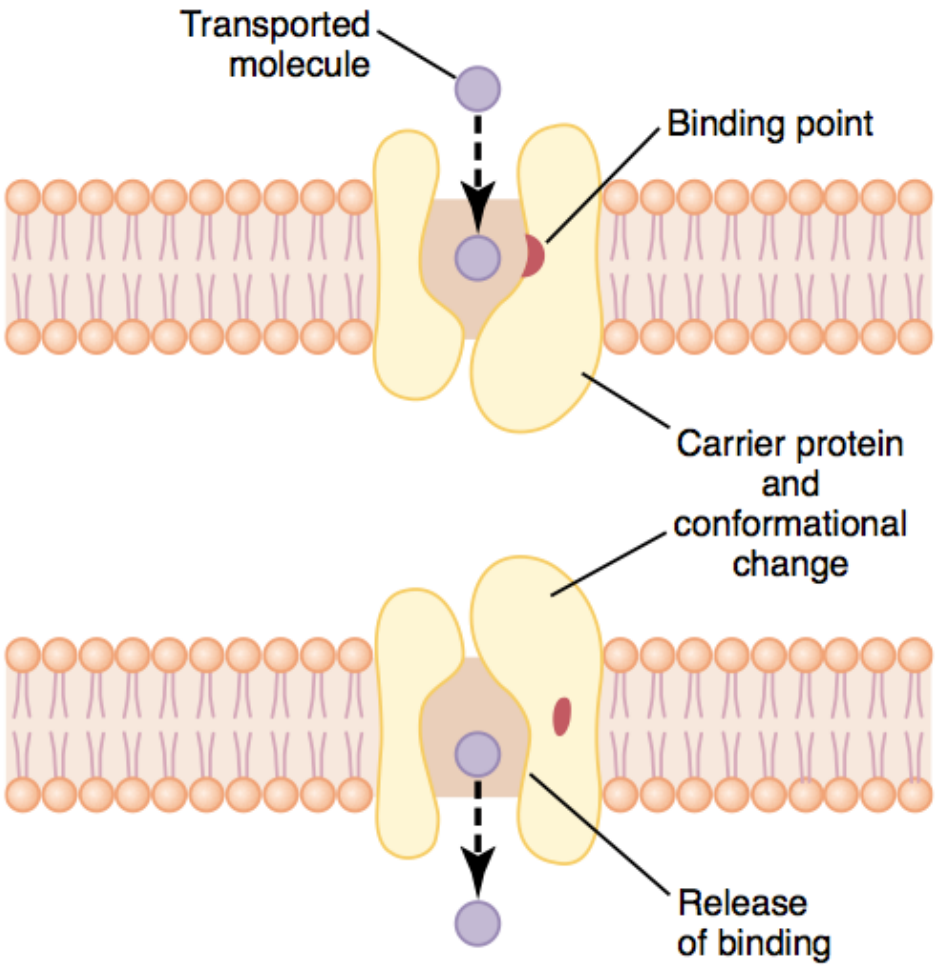



**Figure 4–7**

Postulated mechanism for facilitated diffusion.

# Factors That Affect Net Rate of Diffusion

## 1. Concentration difference ($C_o$-$C_i$)

net diffusion $\propto$ D ($C_o$-$C_i$)

## 2. Electrical potential (EMF)

The **Nernst potential** (*equilibrium potential*) is the theoretical intracellular electrical potential that would be equal in magnitude but opposite in direction to the concentration force.

*EMF (mV) = ±61 log ($C_o$ / $C_i$)*

## 3. Pressure difference

Higher pressure results in increased energy available to cause net movement from high to low pressure.

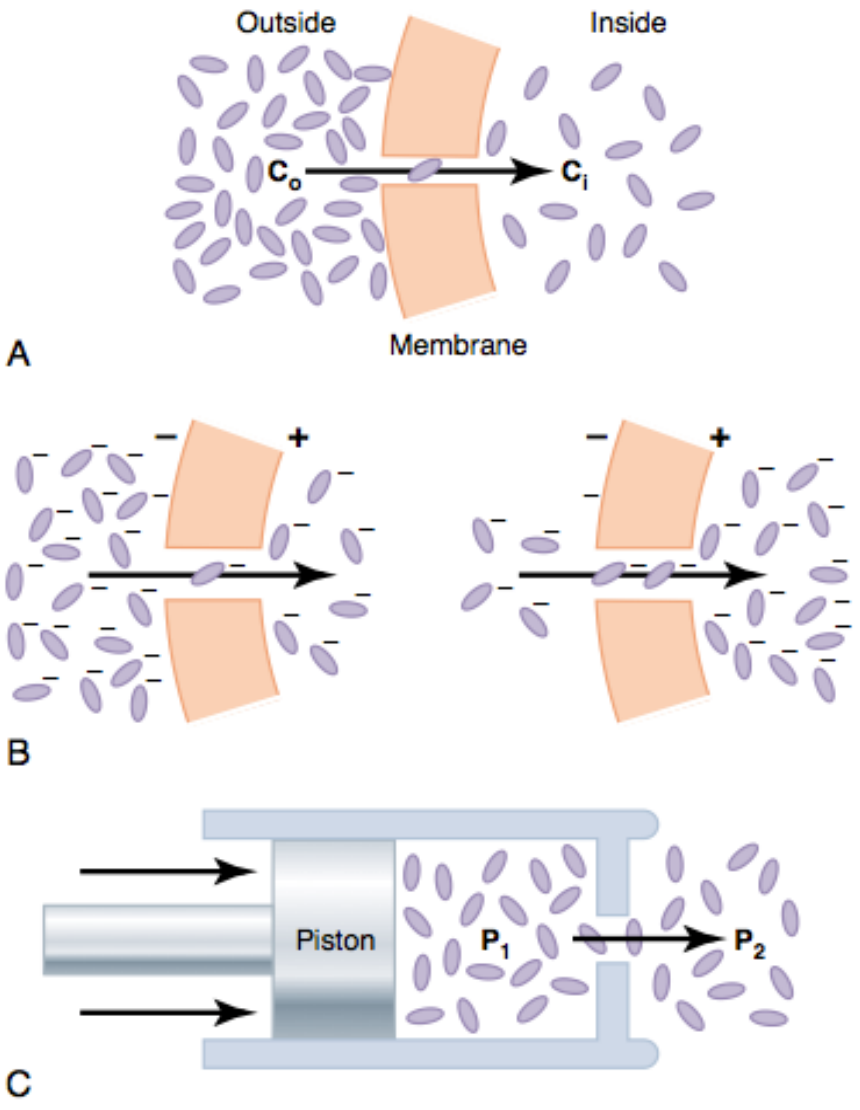



**Figure 4–8**

Effect of concentration difference *(A)*, electrical potential difference affecting negative ions *(B)*, and pressure difference *(C)* to cause diffusion of molecules and ions through a cell membrane.

## OSMOSIS ACROSS SELECTIVELY PERMEABLE MEMBRANES— "NET DIFFUSION" OF WATER

- **Osmosis** occurs from pure water toward a water/salt solution. Water moves down its concn gradient.

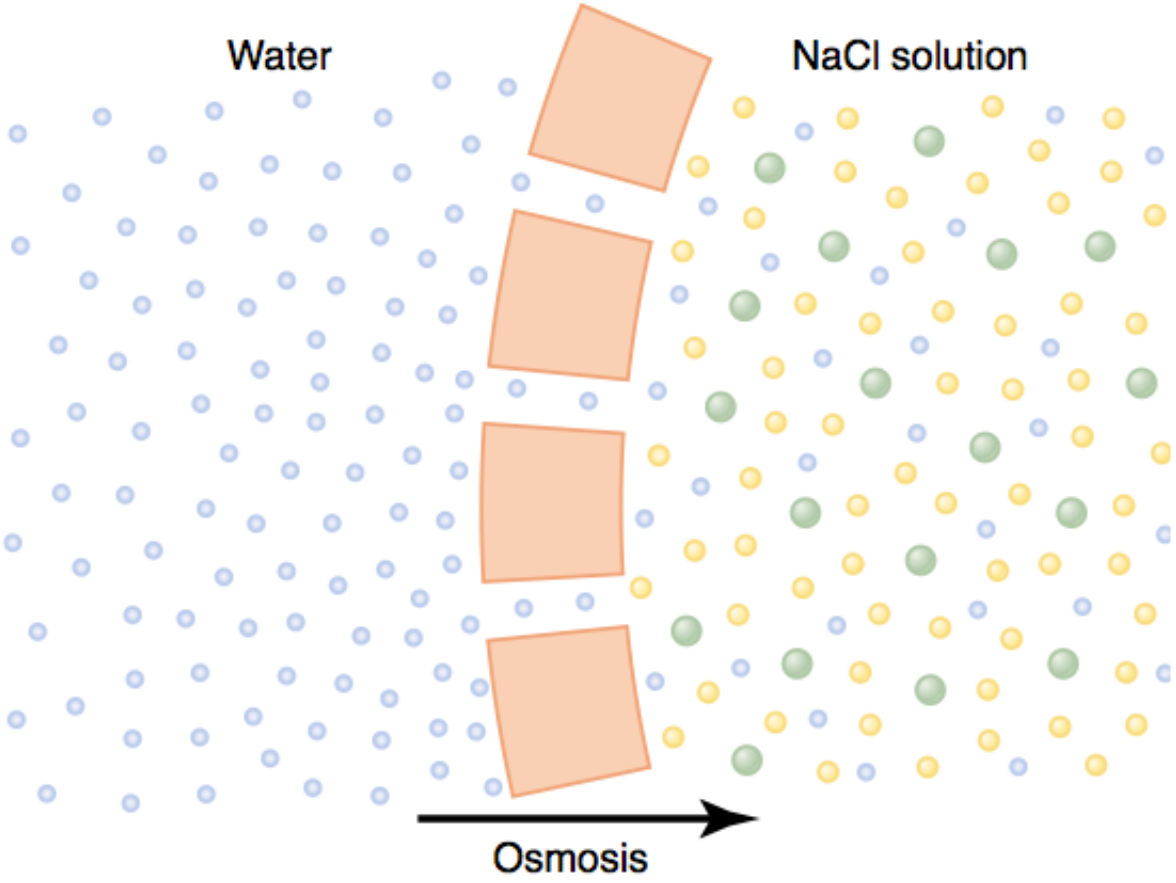



**Figure 4–9**

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.

## ➢ Osmotic Pressure

- The exact amount of pressure required to stop osmosis is called the osmotic pressure of the sodium chloride solution.

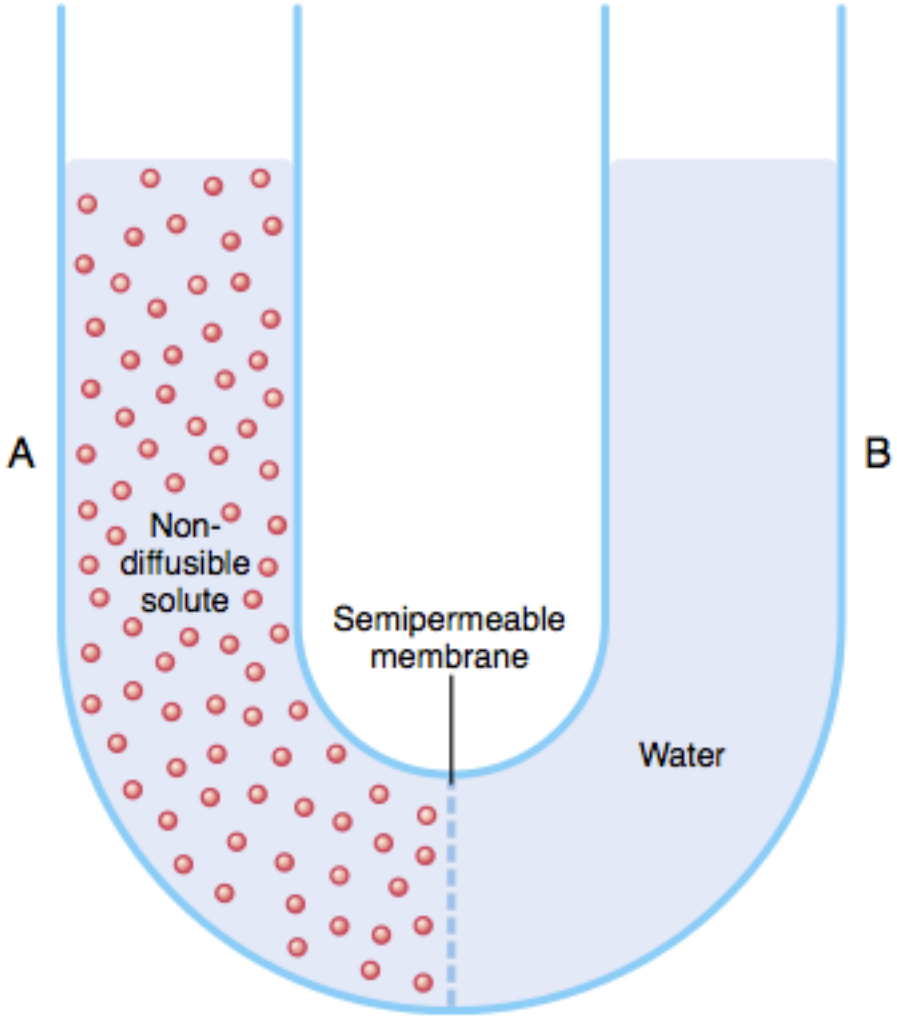



**Figure 4–10**

Demonstration of osmotic pressure caused by osmosis at a semi-permeable membrane.

# Relation between osmolarity and molarity

mOsm (milliosmolar) = index of the concn
or mOsm/L of particles per liter soln

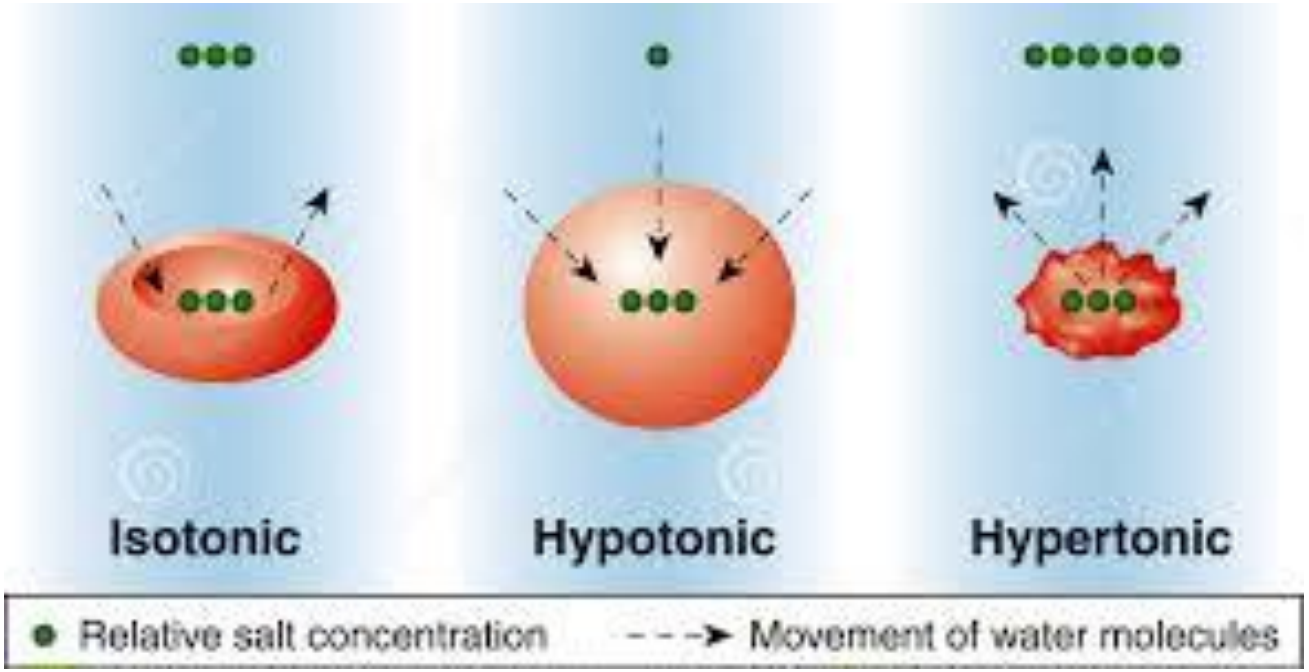
mM (millimolar) = index of concn of
or mM/L molecules per liter soln

150 mM NaCl = 300 mOsm

300 mM glucose = 300 mOsm

# Isotonic, Hypotonic and Hypertonic

- The terms isotonic, hypotonic, and hypertonic refer to whether solutions will cause a change in cell volume.
- Solutions with an osmolarity the same as the cell are called isosmotic, regard- less of whether the solute can penetrate the cell membrane.




Watch video #1

# Clinical Abnormalities of Fluid Volume Regulation

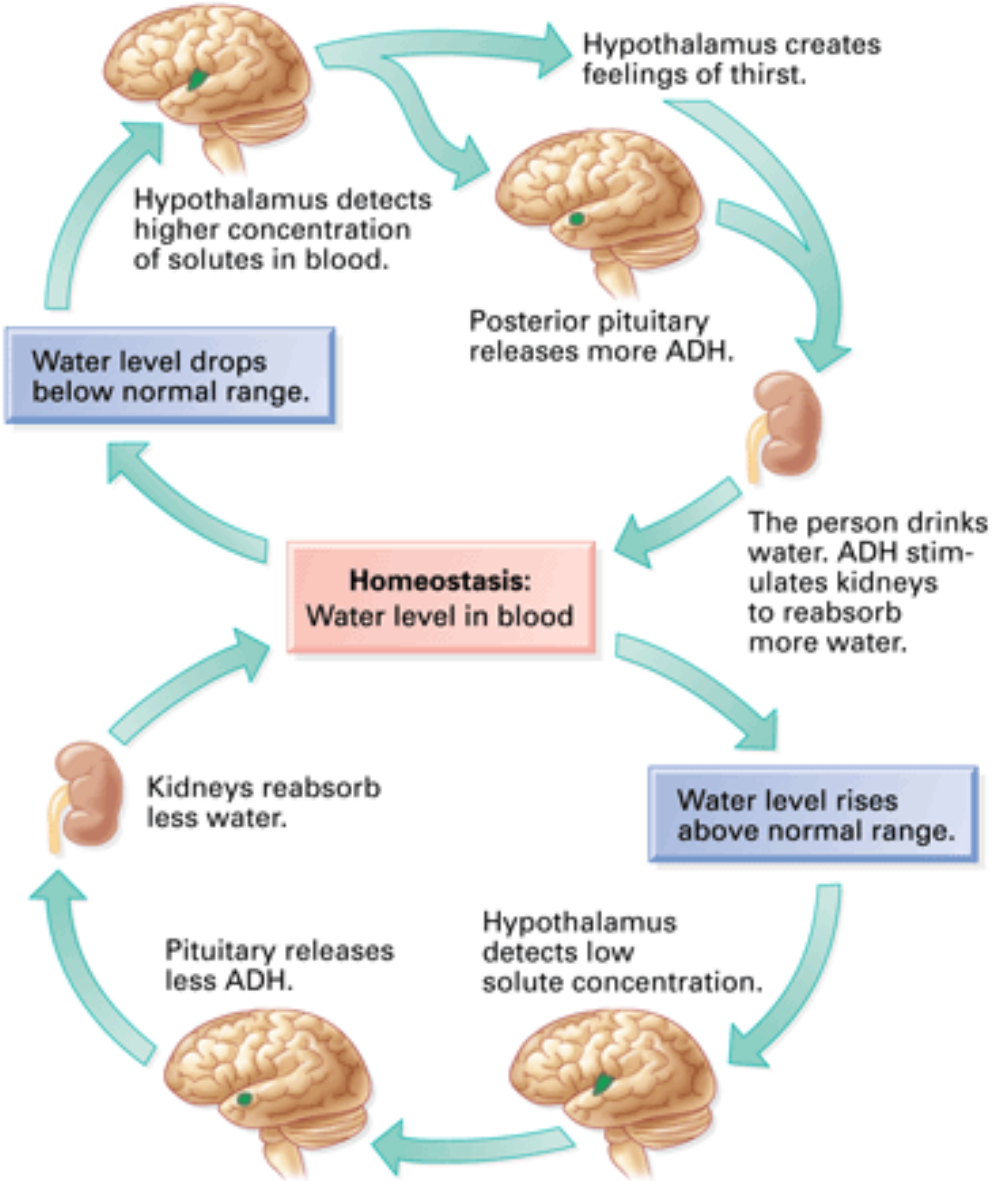
**Hypernatremia** (increased plasma Na):

- increased water loss
- excessive sweat loss

**decreased ADH secretion or responsiveness to ADH (Antidiuretic Hormone (ADH)

**Hyponatremia** (decreased plasma Na):

- large water ingestion
- **Syndrome of Inappropriate ADH Secretion** (SIADH) **too much ADH leads to water retention, hyponatremia, and excretion of concentrated urine.


Hypothalamus creates feelings of thirst.
Hypothalamus detects higher concentration of solutes in blood.
Posterior pituitary releases more ADH.
Water level drops below normal range.
The person drinks water. ADH stimulates kidneys to reabsorb more water.
Homeostasis: Water level in blood
Kidneys reabsorb less water.
Water level rises above normal range.
Pituitary releases less ADH.
Hypothalamus detects low solute concentration.

# “Active Transport” of Substances Through Membranes

## **Primary** Active Transport

- molecules are “pumped” against a concentration gradient at the expense of energy (ATP)
  – *direct use of energy*

## **Secondary** Active Transport

- transport is driven by the energy stored in the concentration gradient of another molecule ($Na^+$)
  – *indirect use of energy*

- **Primary Active Transport**

## 1. $Na^+/K^+$ ATPase

- **carrier protein** located on the plasma membrane of all cells

- plays an important role in regulating osmotic balance by maintaining $Na^+$ and $K^+$ balance
- requires one to two thirds of cells **energy**!

**α subunit**

- 100,000 MW
- binds ATP, 3 $Na^+$, and 2 $K^+$

**β subunit**

- 55,000 MW
- function ???

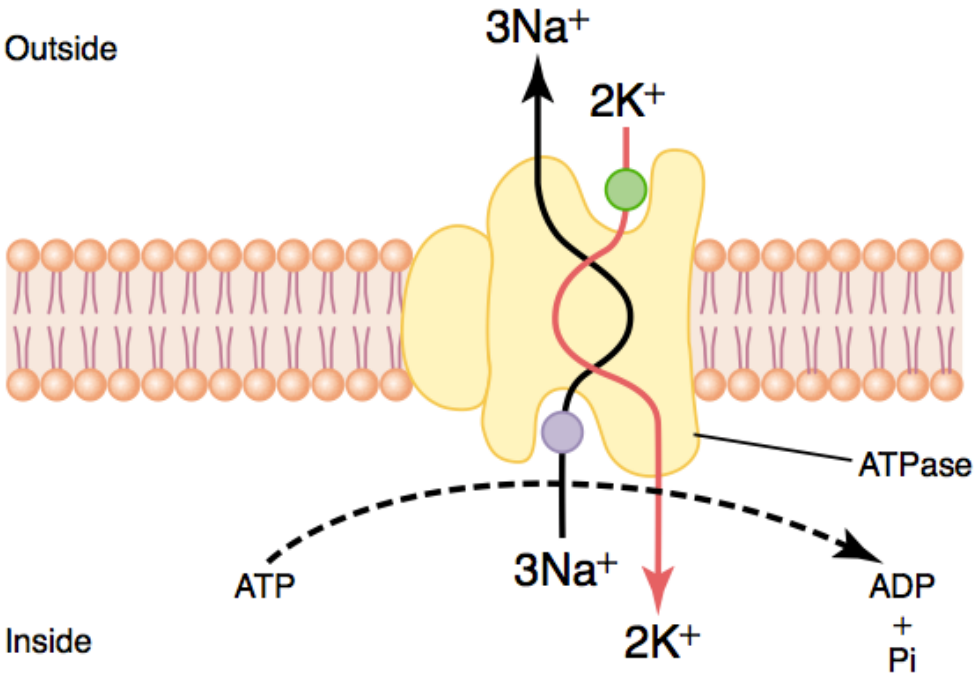



**Figure 4–11**

Postulated mechanism of the sodium-potassium pump. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, phosphate ion.

## 2. $Ca^{2+}$ ATPase

- present on the cell membrane and the sarcoplasmic reticulum
- maintains a low cytosolic $Ca^{2+}$ concentration

## 3. $H^{+}$ ATPase

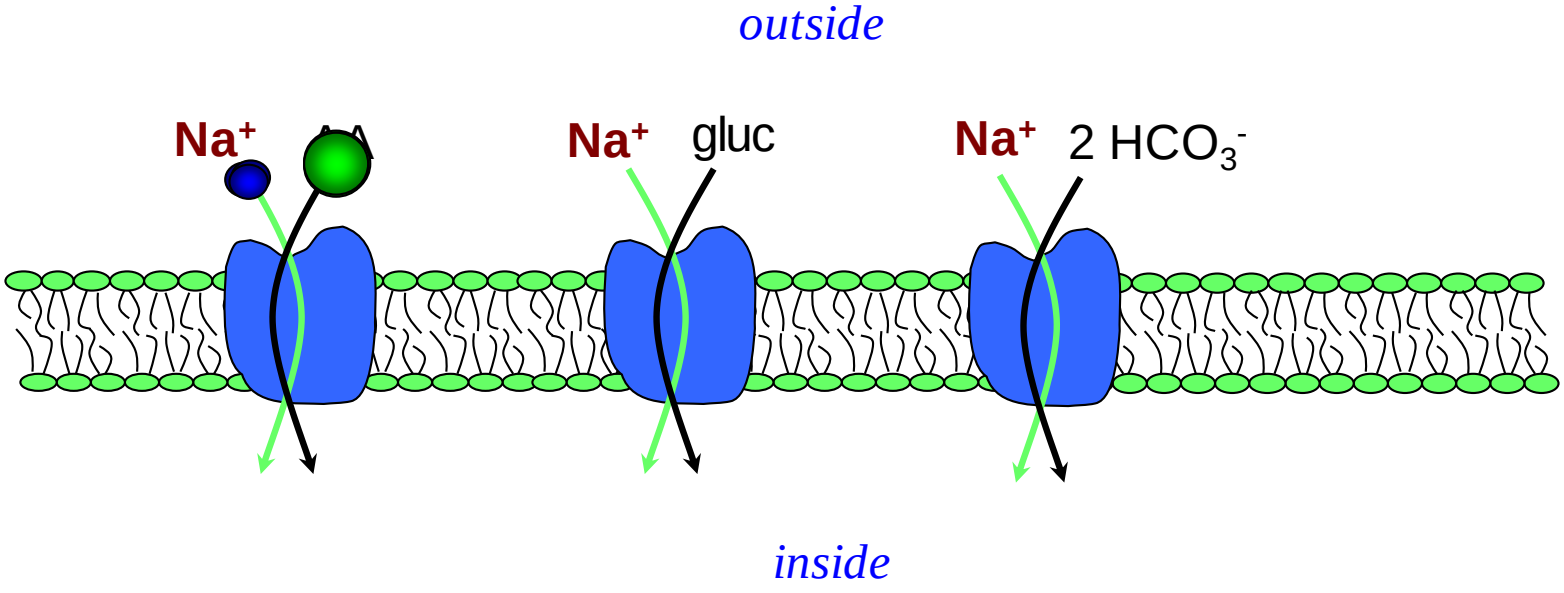
- found in parietal cells of gastric glands (HCl secretion) and intercalated cells of renal tubules (controls blood pH)
- concentrates $H^{+}$ ions up to 1 million-fold

- **Secondary Active Transport**

*- co-transport and counter-transport -*

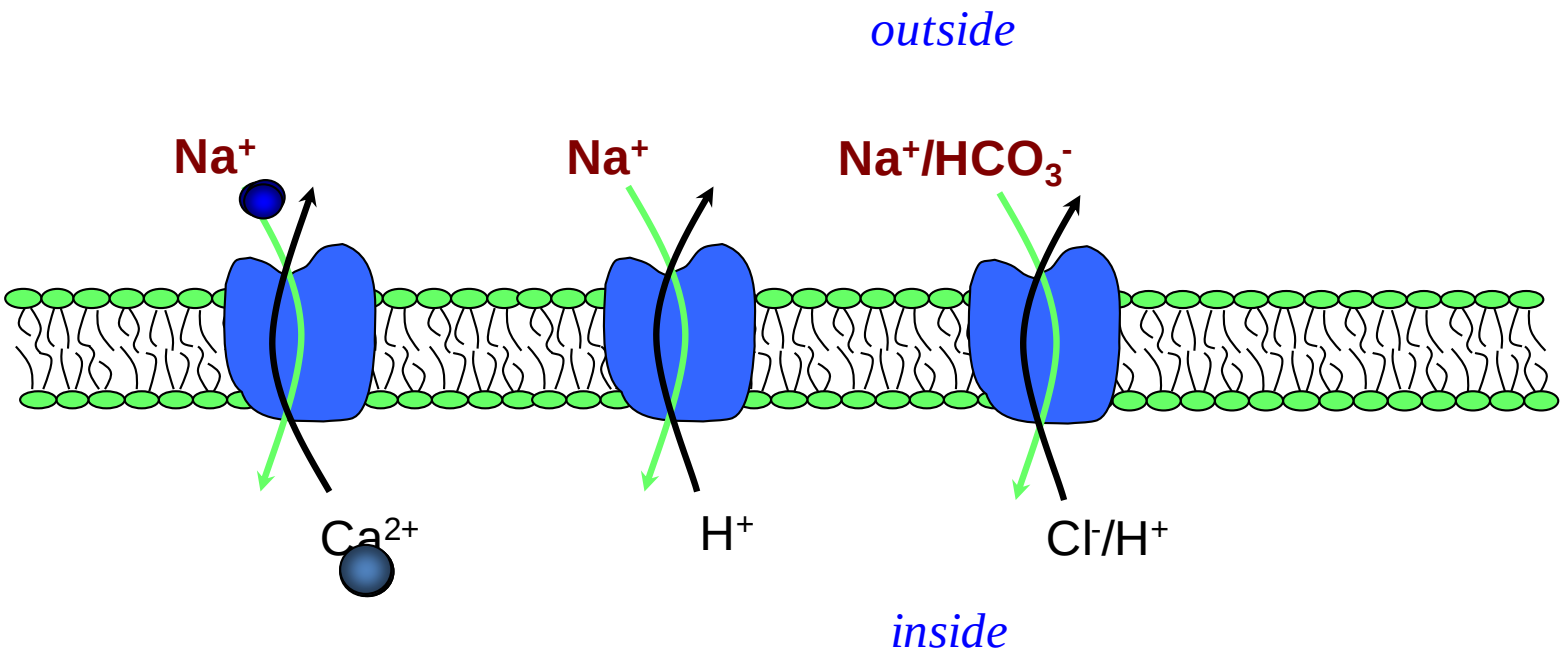
1. **Co-transport** *(co-porters)*: substance is transported in the same direction as the "driver" ion ($Na^+$)

*Examples:*



**2. Counter-transport *(anti-porters)*:** substance is transported in the opposite direction as the "driver" ion ($Na^+$)

*Examples:*

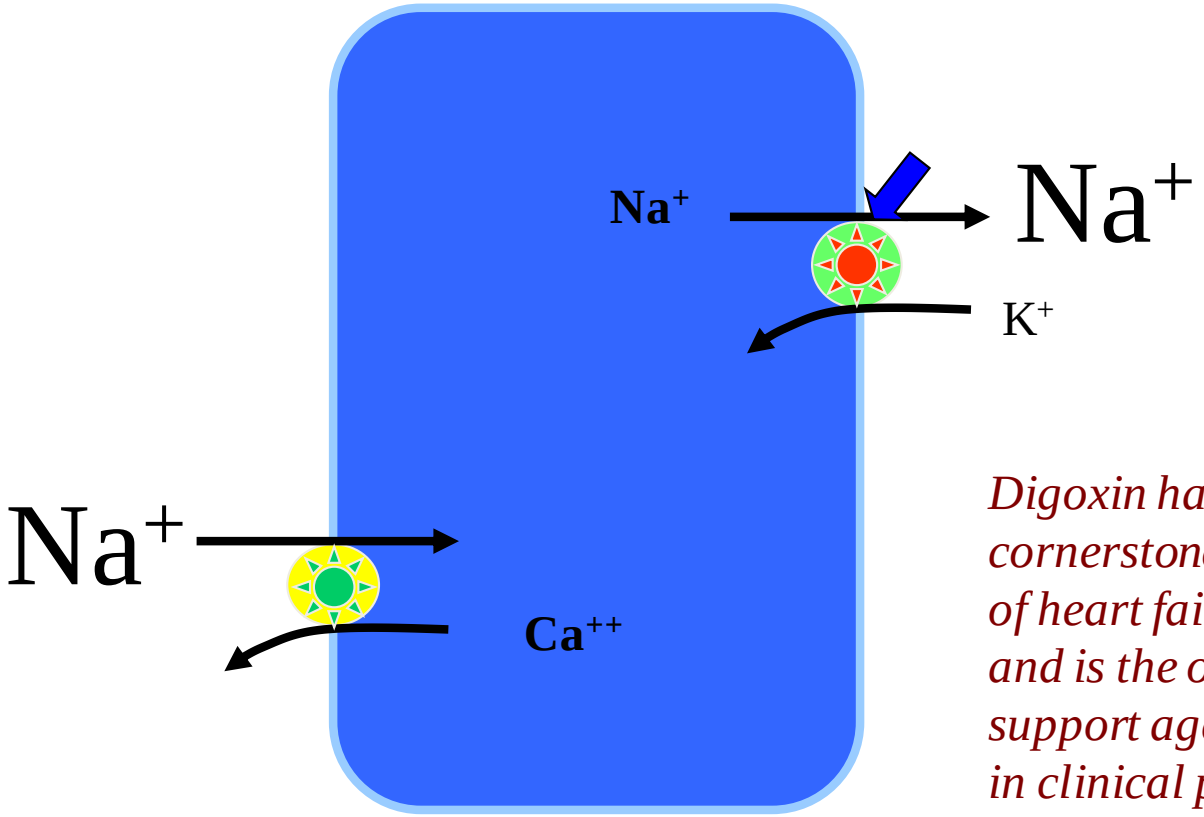


# Q: How do cardiac glycosides increase cardiac contractility?

Glycosides *(eg. digoxin)* inhibit the **Na/K ATPase**…

- increase intracellular $Na^+$
- decrease $Na^+$ gradient
- decrease $Na^+/Ca^{2+}$ counter-transport
- **increase intracellular $Ca^{2+}$**

# Q: How do cardiac glycosides increase cardiac contractility?

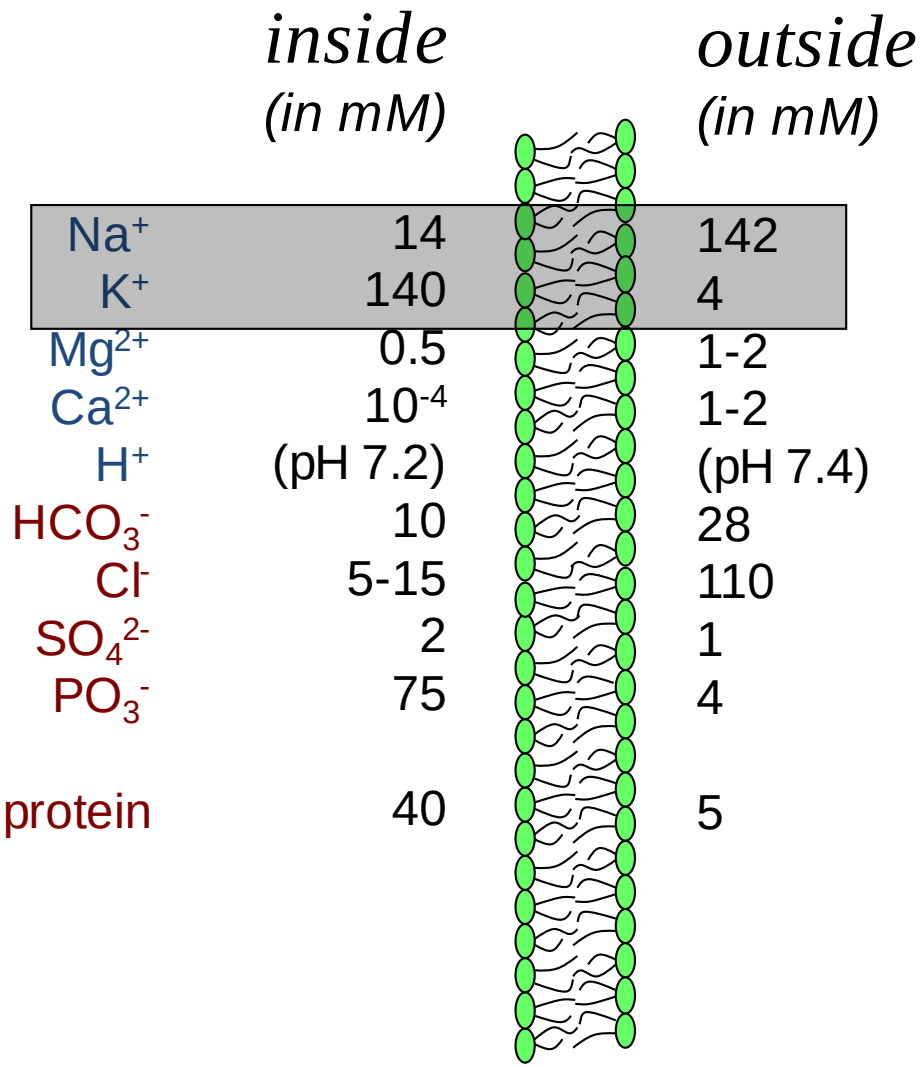



*Digoxin has been a cornerstone for the treatment of heart failure for decades and is the only oral inotropic support agent currently used in clinical practice.*

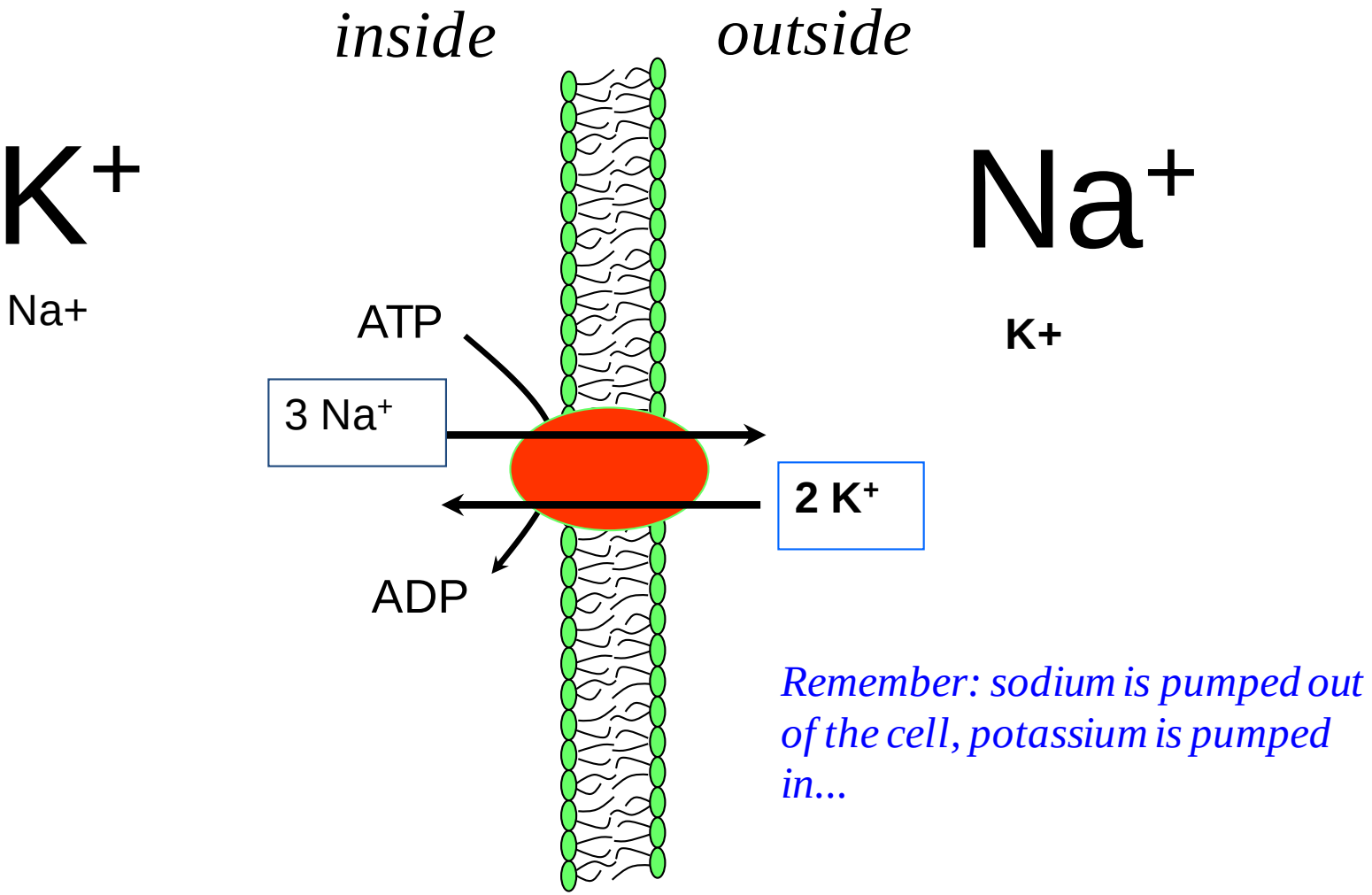
# Chapter 5:

Membrane Potentials and Action Potentials

- **Molecular Gradients**

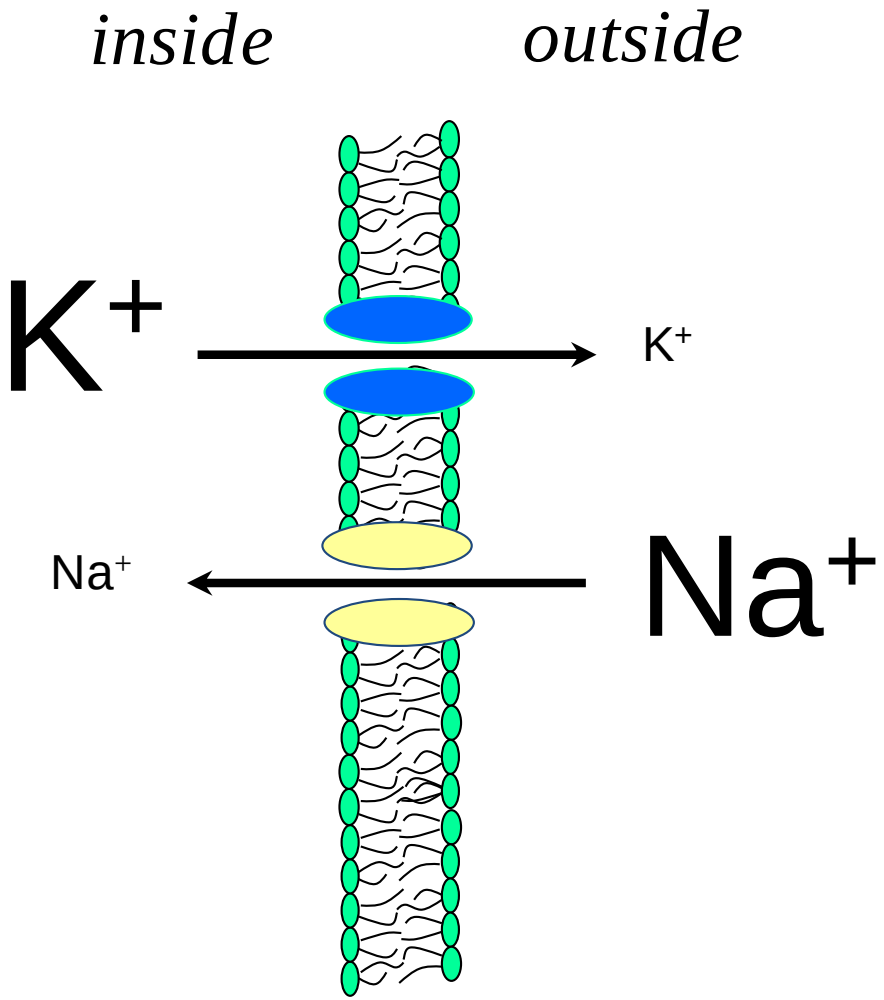


# Active Transport



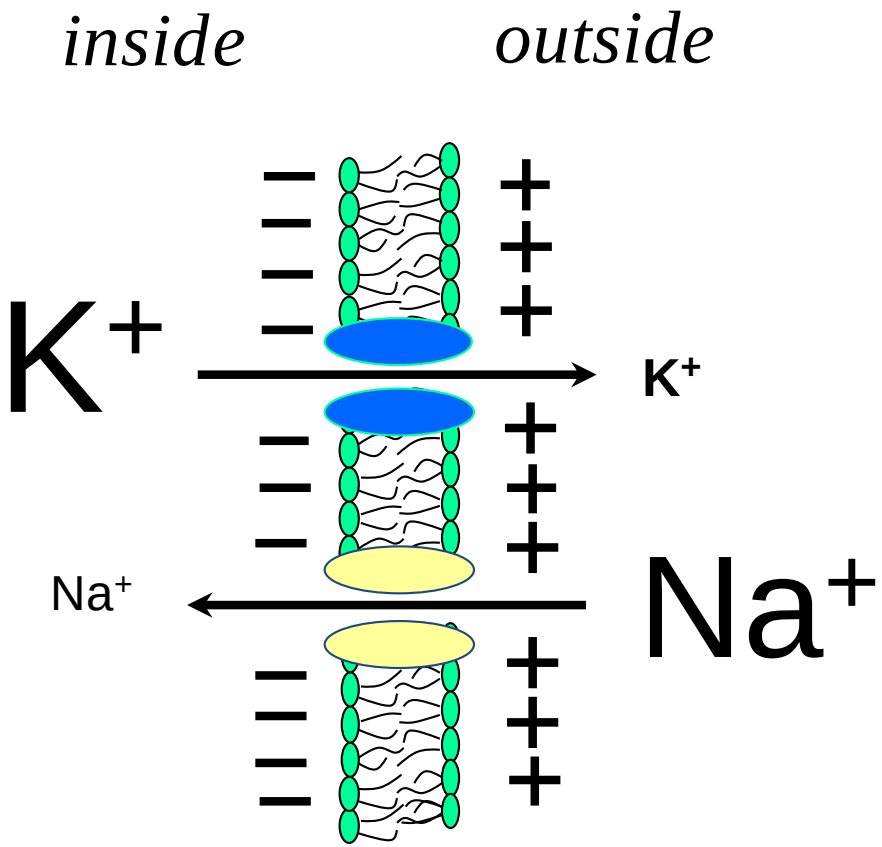

*Remember: sodium is pumped out of the cell, potassium is pumped in…*

- **Simple Diffusion**



- **Membrane Potential ($V_m$):**

  ***- charge difference across the membrane -***

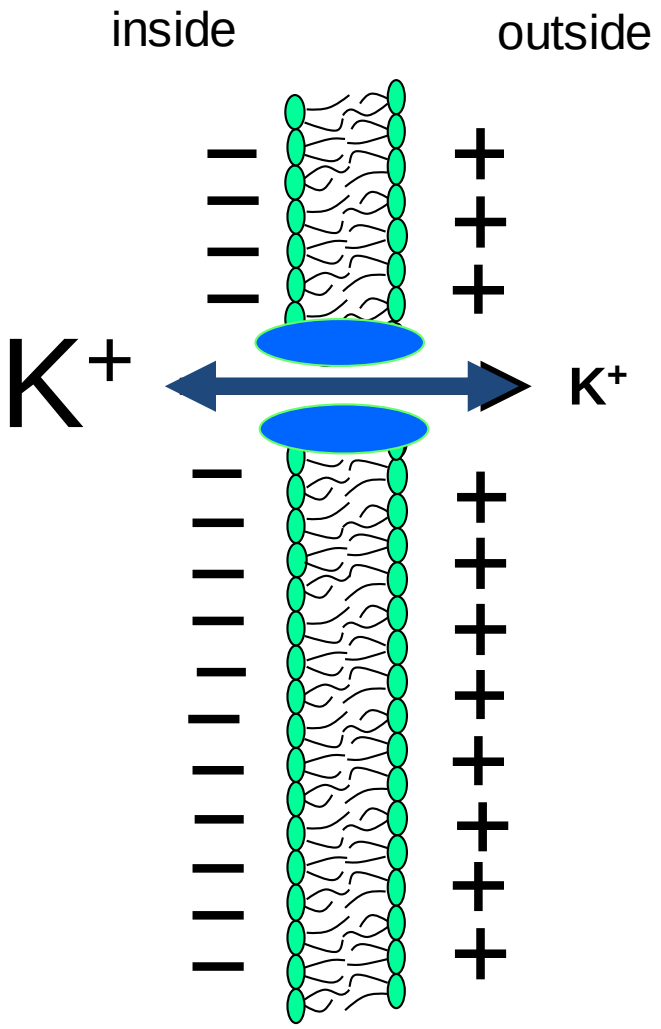



*...how can passive diffusion of potassium and sodium lead to development of negative membrane potential?*

# Simplest Case Scenario:

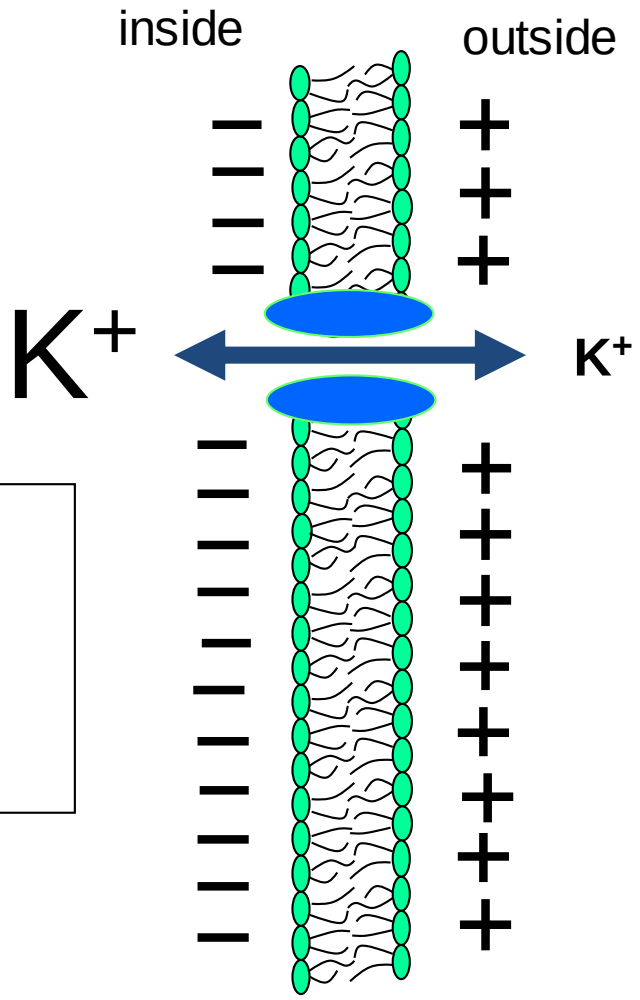
*If a membrane were permeable to only $K^+$ then…*

*$K^+$ would diffuse down its concentration gradient until the electrical potential across the membrane countered diffusion.*



# ➢ Simplest Case Scenario:

*If a membrane were permeable to only $K^+$ then…*




*The electrical potential that counters net diffusion of $K^+$ is called the $K^+$ equilibrium potential ($E_K$).*

# The Potassium Nernst Potential

*...also called the equilibrium potential*

$$E_K = -61 \log \frac{K_i}{K_o}$$

Example: If $K_o$ = 4 mM and $K_i$ = 140 mM

$E_K$ = -61 log(140/4)

$E_K$ = -61 log(35)

$E_K$ = -94 mV

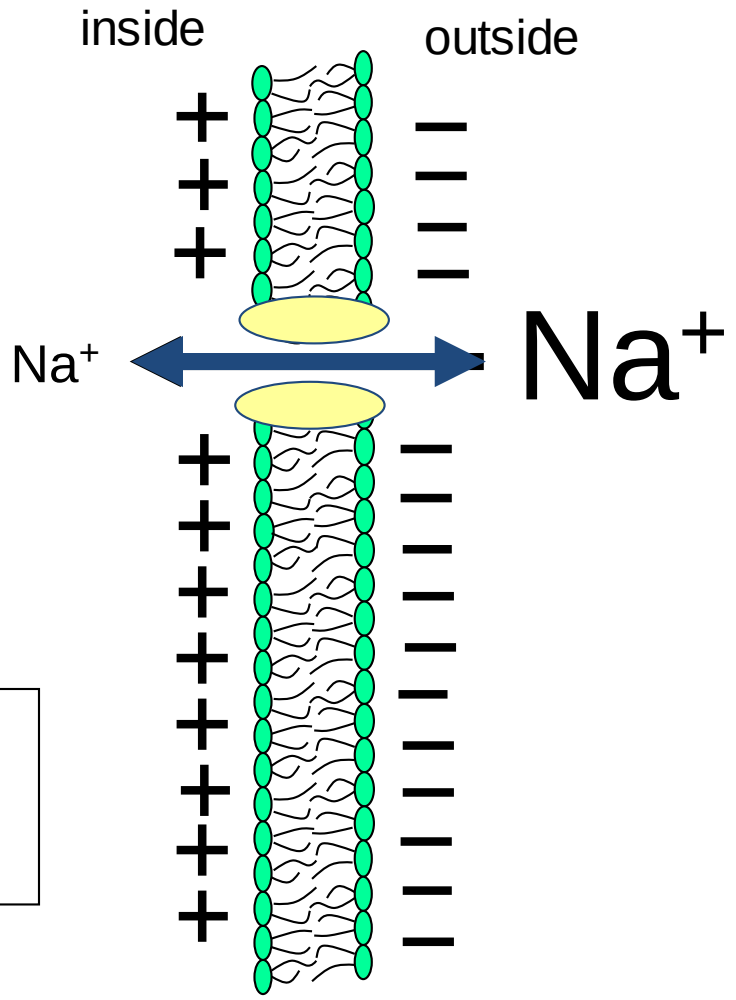
*So, if the membrane were permeable only to K+, Vm would be -94 mV*

# ➢ Simplest Case Scenario:

*If a membrane were permeable to only $Na^+$ then…*

$Na^+$ would diffuse down its concentration gradient until potential across the membrane countered diffusion.

The electrical potential that counters net diffusion of $Na^+$ is called the $Na^+$ equilibrium potential ($E_{Na}$).



# The Sodium Nernst Potential

$$E_K = -61 \log \frac{Na_i}{Na_o}$$

Example: If $Na_o$ = 142 mM and $Na_i$ = 14 mM

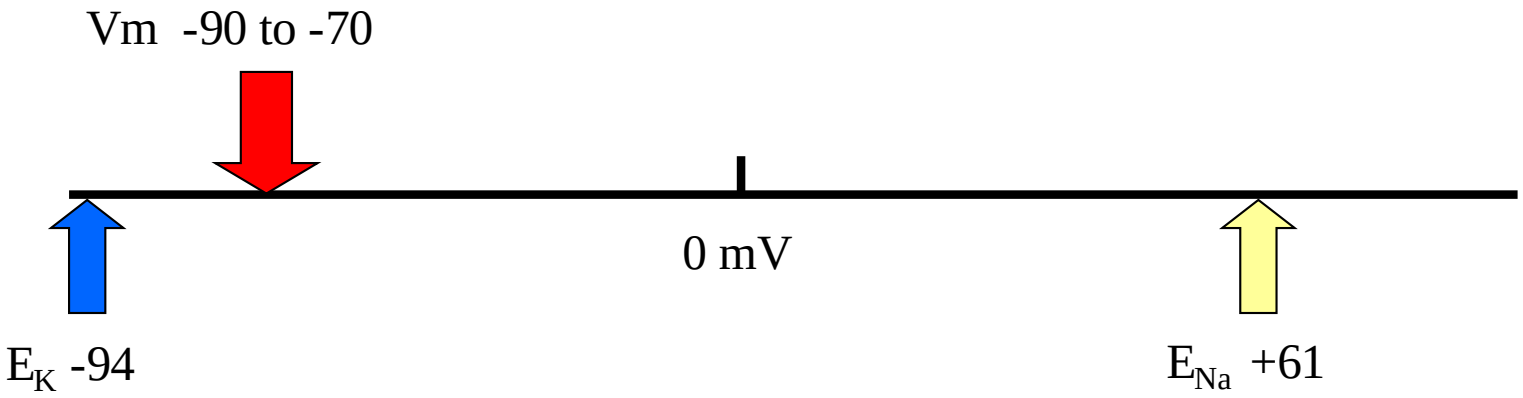
$E_K$ = -61 log(14/142)

$E_K$ = -61 log(0.1)

$E_K$ = +61 mV

*So, if the membrane were permeable only to $Na^+$, Vm would be +61 mV*

# Resting Membrane Potential




*Why is Vm so close to $E_K$?*
*Ans. The membrane is far more permeable to K than Na..*

# The Goldman-Hodgkin-Katz Equation

***(also called the Goldman Field Equation)***

*Calculates $V_m$ when more than one ion is involved.*

$$V_m = 61 \cdot \log \frac{p'_K [K^+]_o + p'_{Na} [Na^+]_o + p'_{Cl} [Cl^-]_i}{p'_K [K^+]_i + p'_{Na} [Na^+]_i + p'_{Cl} [Cl^-]_o}$$

*or*

$$V_m = -61 \cdot \log \frac{p'_K [K^+]_i + p'_{Na} [Na^+]_i + p'_{Cl} [Cl^-]_o}{p'_K [K^+]_o + p'_{Na} [Na^+]_o + p'_{Cl} [Cl^-]_i}$$

***NOTE:***
***P' = permeability***

# The Goldman-Hodgkin-Katz Equation

*Take home message…*

The resting membrane potential is closest to the equilibrium potential for the ion with the highest permeability!

# Resting Membrane Potential Summary

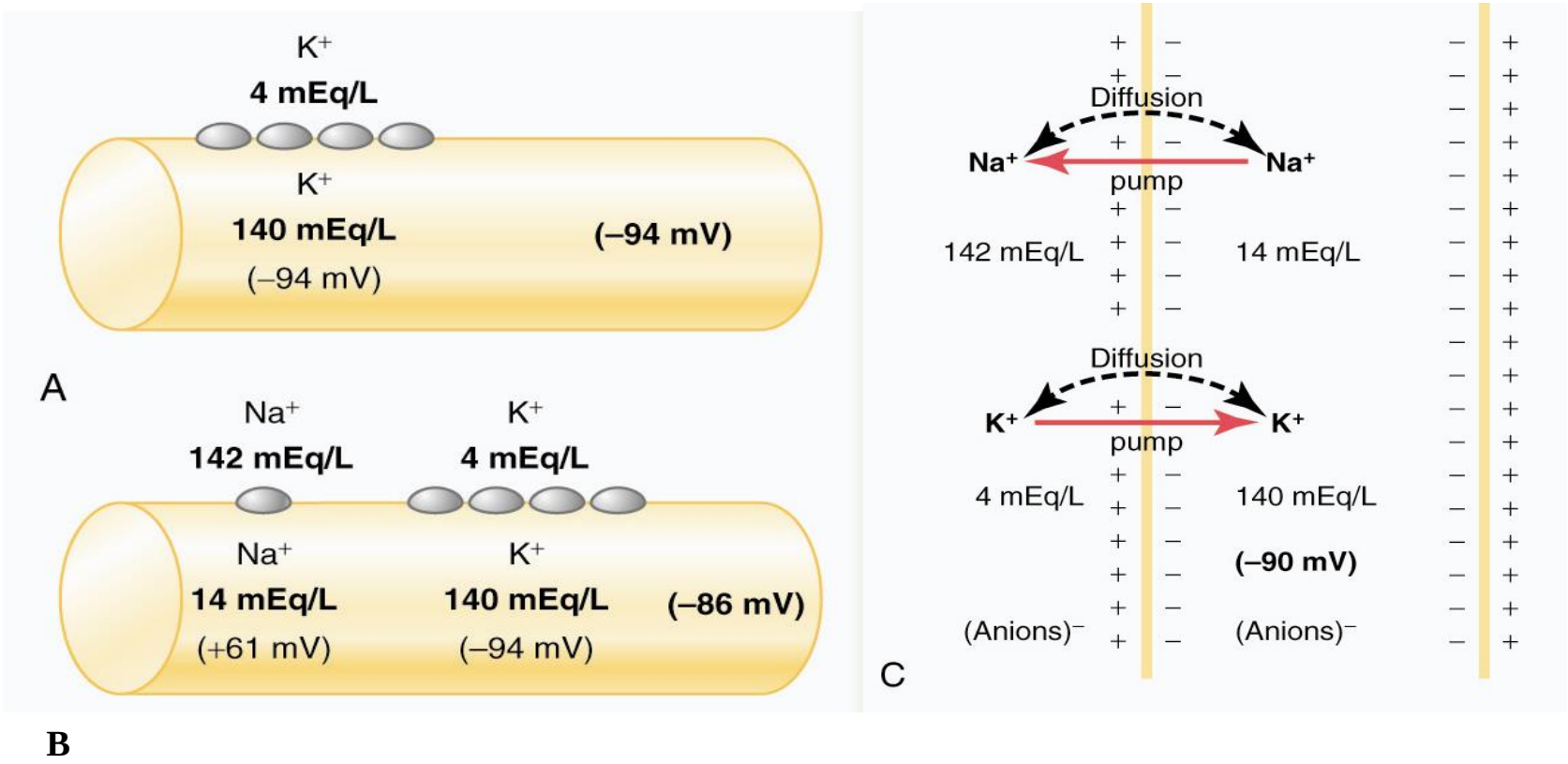
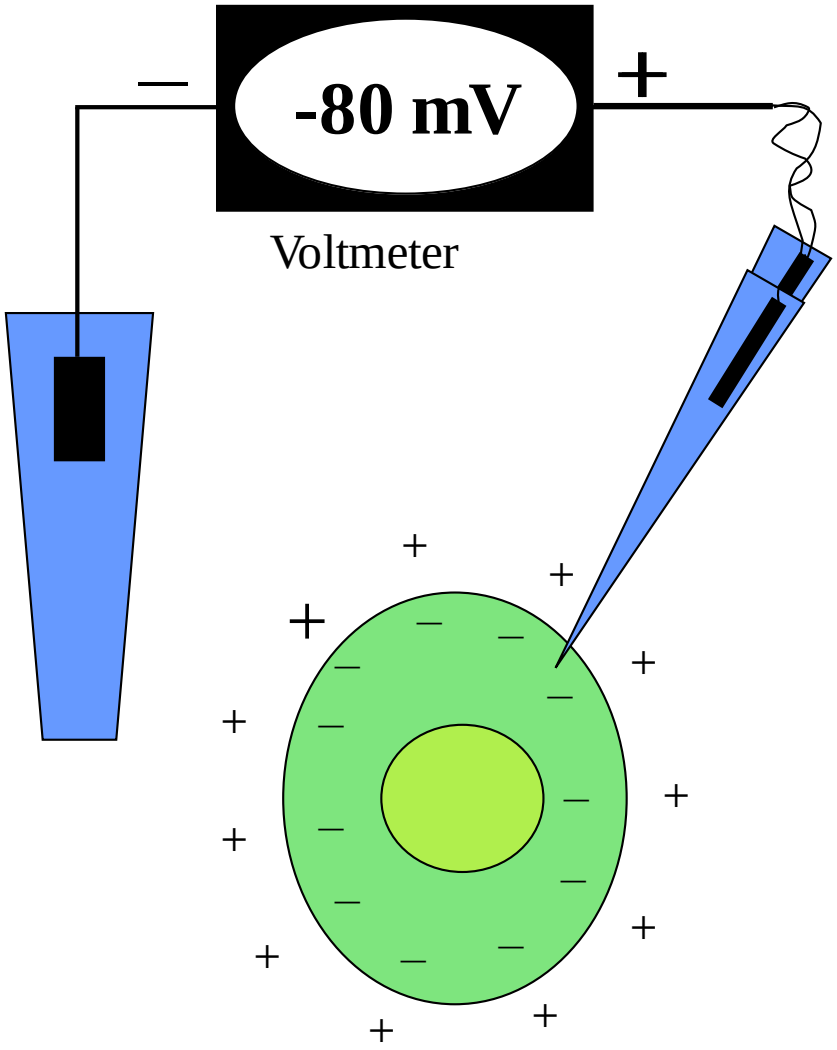



Figure5-5: Establishment of resting membrane potentials in nerve fibers under three conditions: A, when the membrane potential is caused entirely by potassium diffusion alone; B, when the membrane potential is caused by diffusion of both sodium and potassium ions; and C, when the membrane potential is caused by diffusion of both sodium and potassium ions plus pumping of both these ions by the Na+-K+ pump.

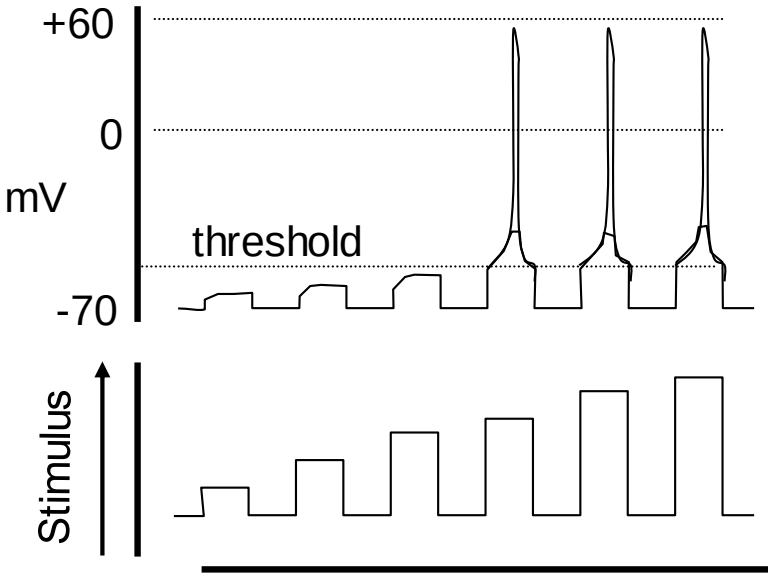
# Resting and action potentials

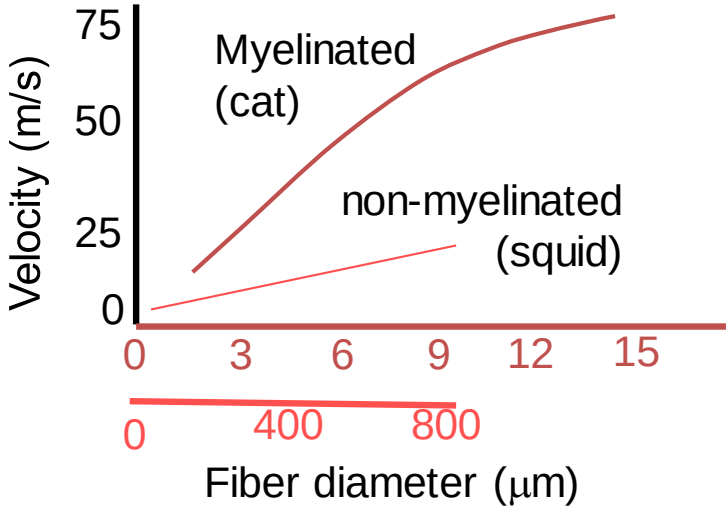
- Recall that cells:
  - contain high a $K^+$ concentration
  - have membranes that are essentially permeable to $K^+$ at rest
- Membrane electrical potential difference *(membrane potential)* is generated by diffusion of $K^+$ ions and charge separation
  - measured in mV (=1/1000$^{th}$ of 1V)
  - typically resting membrane potentials in neurons are -70 to -90 mV



# Properties of action potentials

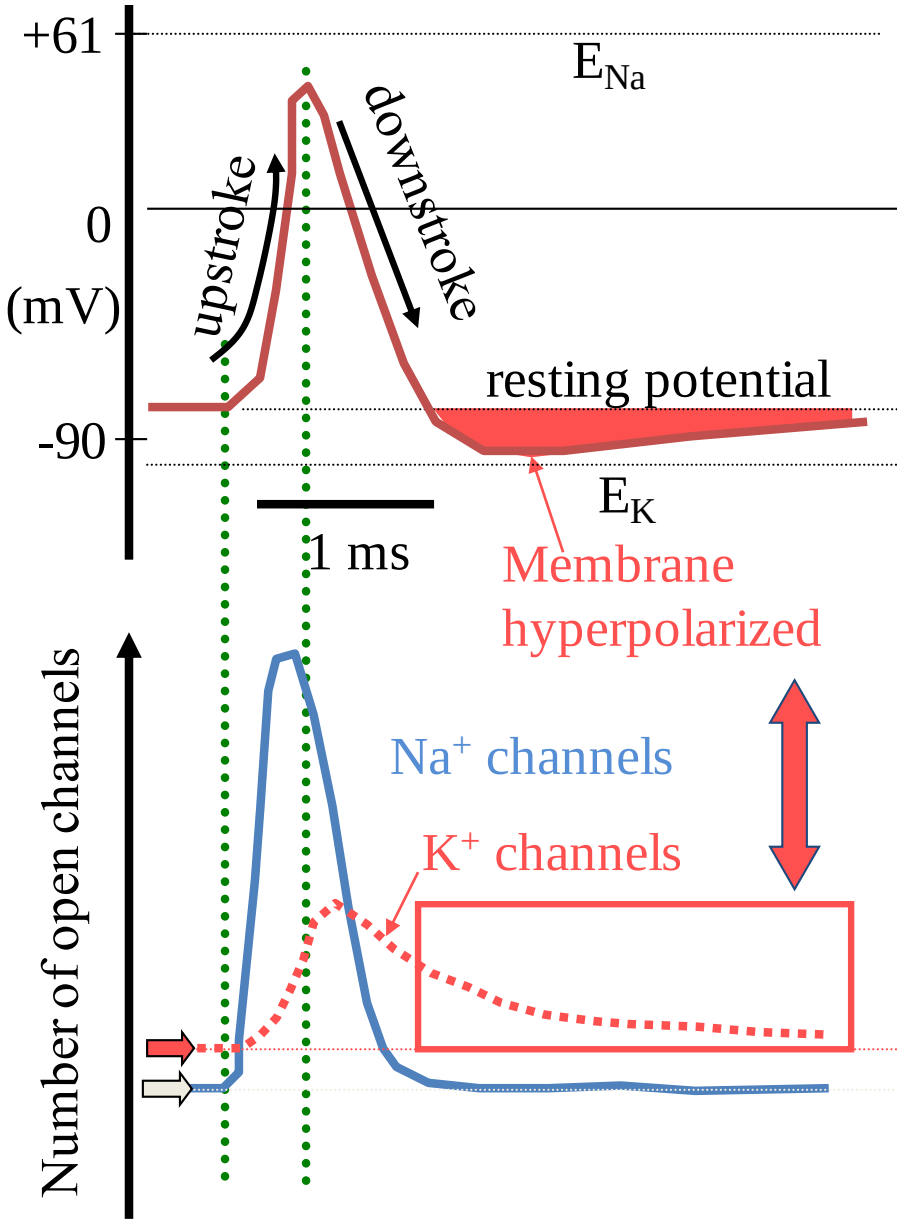
- Action potentials:
  - are all-or-none events
    - threshold voltage (usually 15 mV positive to resting potential)
  - are initiated by depolarization
    - action potentials can be induced in nerve and muscle by extrinsic (percutaneous) stimulation
  - have constant amplitude
    - APs do not summate - information is coded by frequency not amplitude.
  - have constant conduction velocity
    - True for given fiber. Fibers with large diameter conduct faster than small fibers.



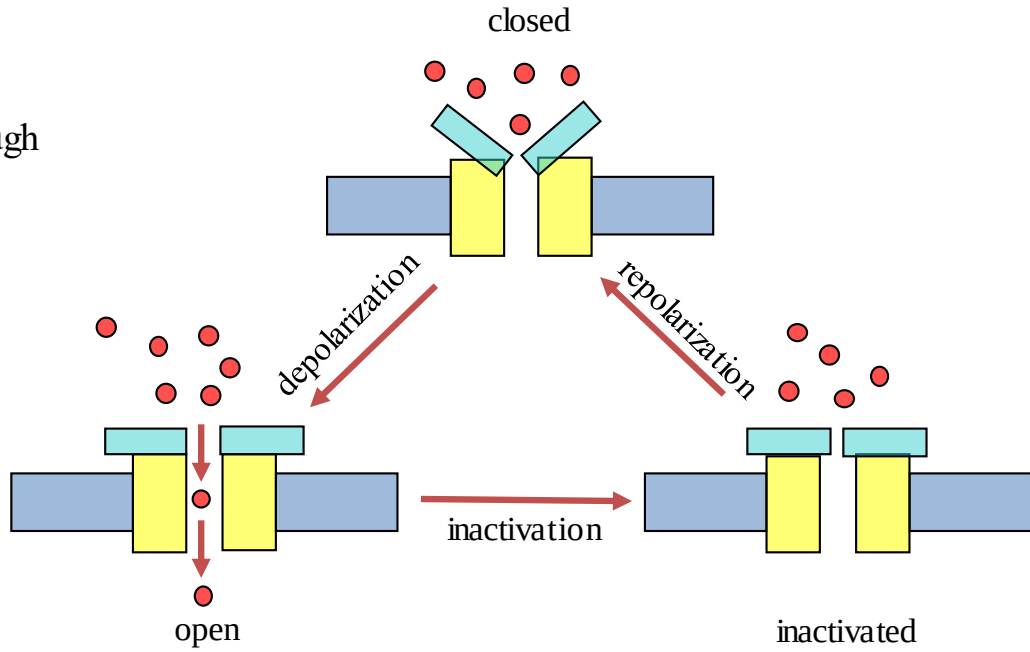
# The AP - membrane permeability

- During the upstroke of an action potential:
  - Na permeability increases
    - due to opening of $Na^+$ channels
      - memb. potential approaches $E_{Na}$
- During the downstroke of an action potential:
  - Na permeability decreases
    - due to inactivation of $Na^+$ channels
  - K permeability increases
    - due to opening of $K^+$ channels
      - mem. potential approaches $E_K$
- After hyperpolarization of membrane following an action potential:
  - not always seen!
  - There is increased $K^+$ conductance
    - due to delayed closure of $K^+$ channels



# ➢ Ion channels

- Ion channels - structure
  - ➢ proteins that span the membrane
  - ➢ have water filled channel that runs through protein
- Ion channel - properties
  - ➢ Have conducting states and non-conducting states
  - ➢ transition between states = 'gating'




- channels 'gate' in response to:
  - ➢ changes in membrane potential (usually depolarization)
    - voltage-gated channels. Action potential propagation relies on voltage-gated channels
  - ➢ occupation of receptor
    - ligand-gated or receptor operated channels (ROCs). These initiate action potentials

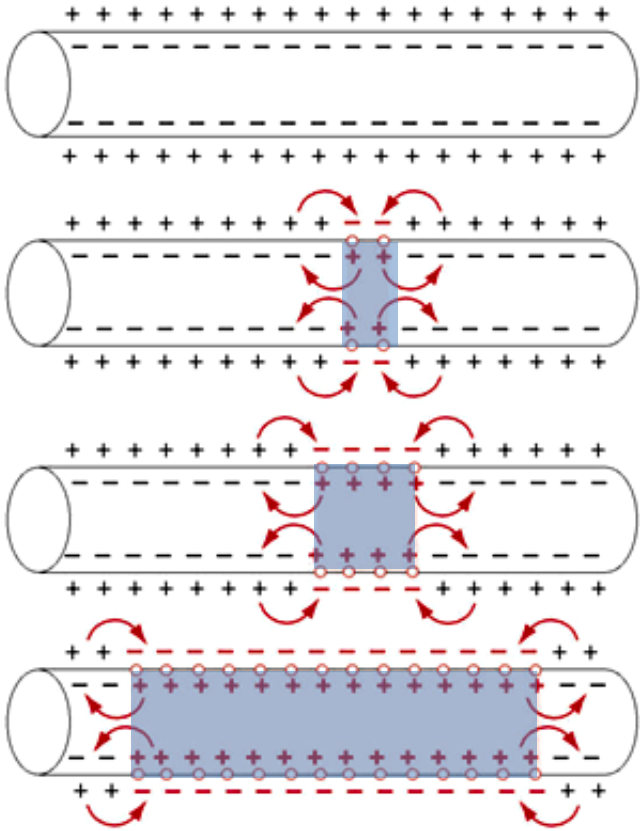
# Propagation:

Opening of $Na^+$ channels generates local current circuit that depolarizes adjacent membrane, opening more $Na^+$ channels…

**Rest**

**Stimulated**
(local depolarization)

**Propagation**
(current spread)



# Signal Transmission

## Myelination

- **Schwann cells** surround the nerve axon forming a myelin sheath

- Sphingomyelin decreases membrane capacitance and ion flow 5,000-fold

- Sheath is interrupted every 1-3 mm : **node of Ranvier**

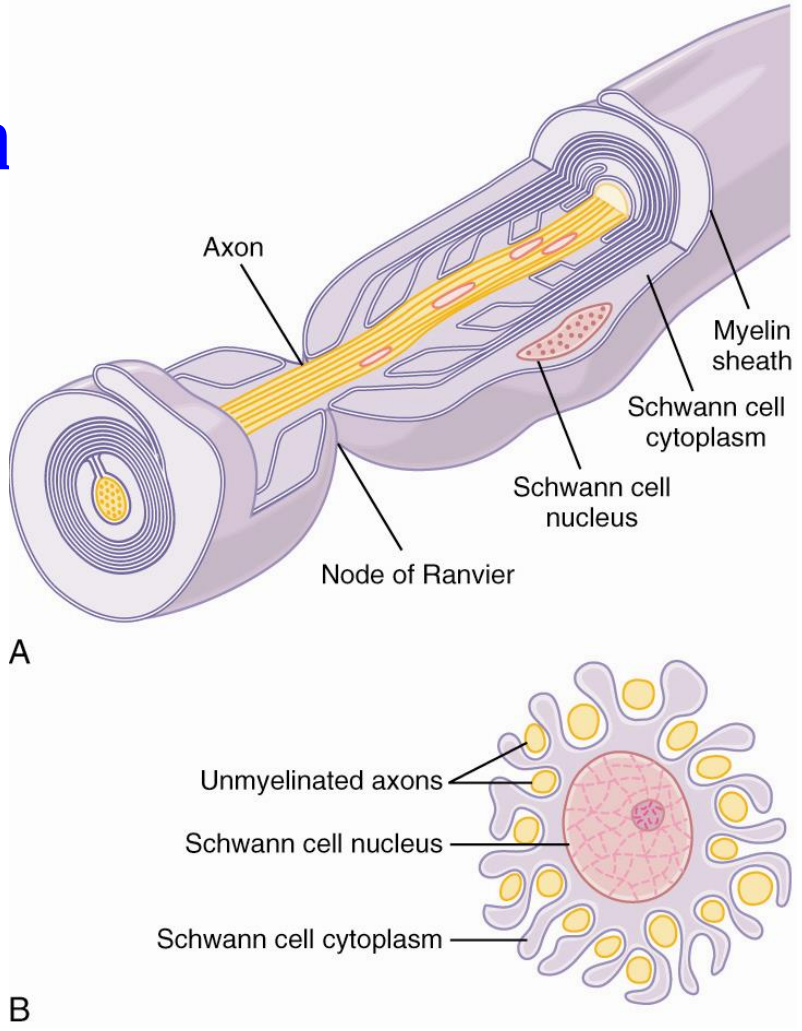



**Figure 5–16**
Function of the Schwann cell to insulate nerve fibers. A, Wrapping of a Schwann cell membrane around a large axon to form the myelin sheath of the myelinated nerve fiber. B, Partial wrapping of the membrane and cytoplasm of a Schwann cell around multiple unmyelinated nerve fibers (shown in cross section). (A, Modified from Leeson TS, Leeson R: Histology. Philadelphia: WB Saunders, 1979.)

# Saltatory Conduction

- AP's only occur at the nodes *(Na channels concentrated here!)*
- increased velocity
- energy conservation

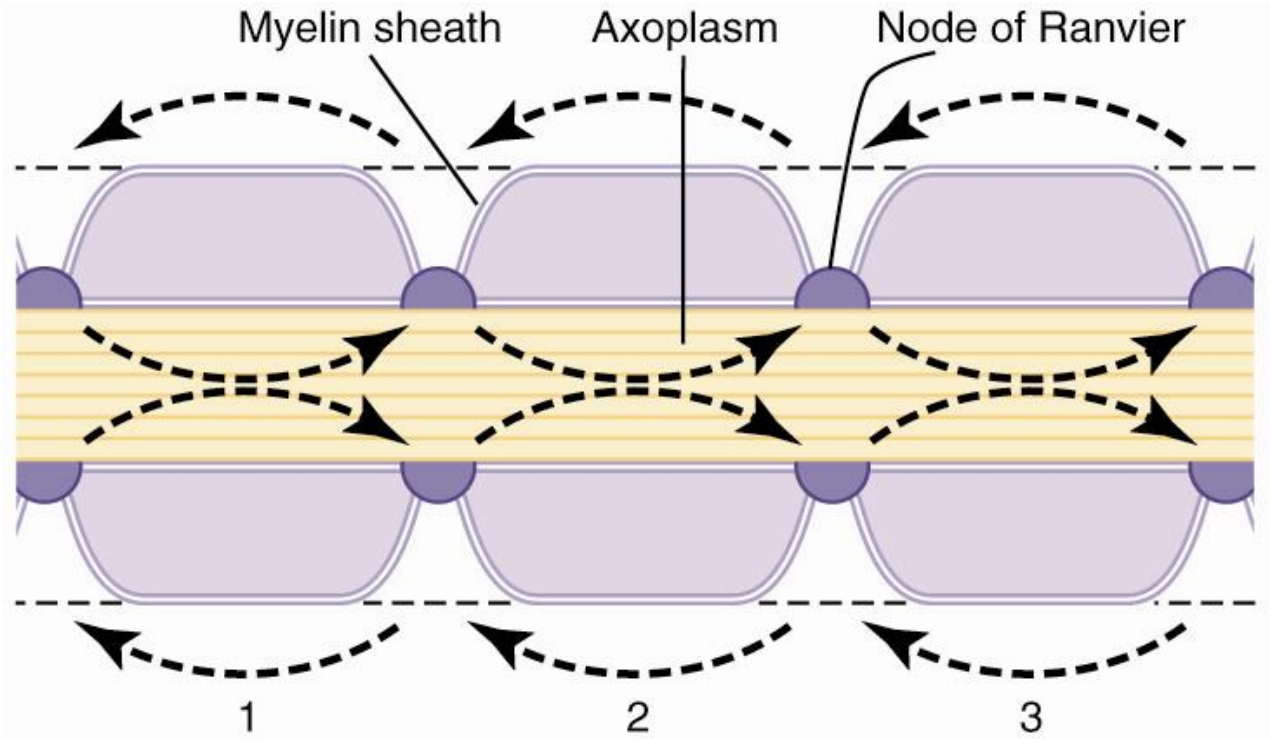
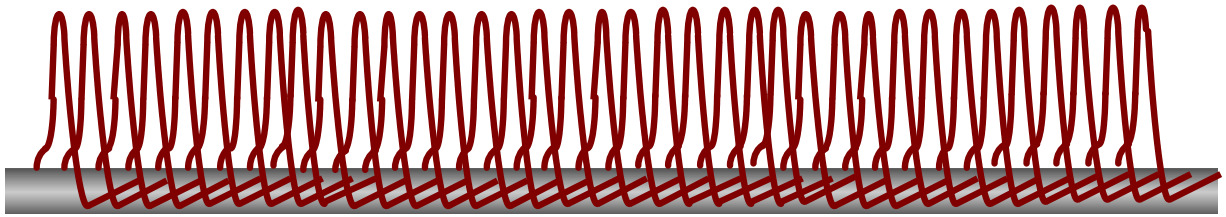


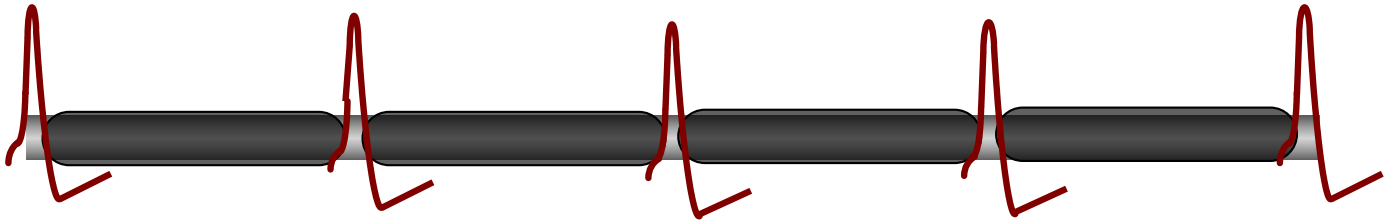

Figure 5-17; Saltatory conduction along a myelinated axon. Flow of electrical current from node to node is illustrated by the arrows.

# Conduction velocity

*- non-myelinated vs myelinated -*



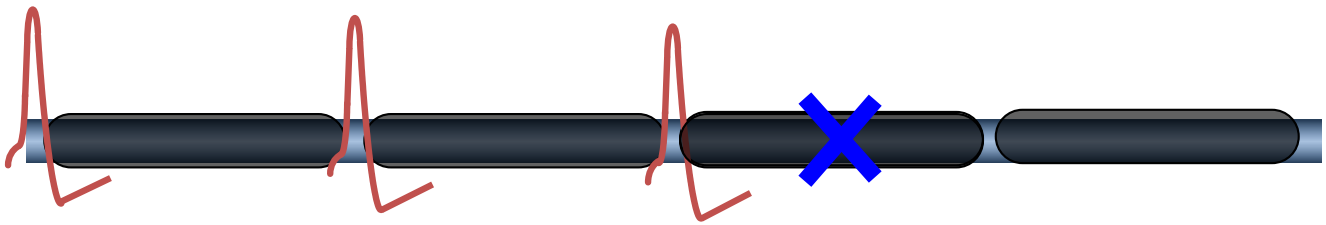
*non-myelinated*



*myelinated*

- The velocity of conduction in nerve fibers varies from as little as 0.25 m/sec in very small unmyelinated fibers to as great as 100 m/ sec (the length of a football field in 1 second) in very large myelinated fibers.

# Multiple Sclerosis



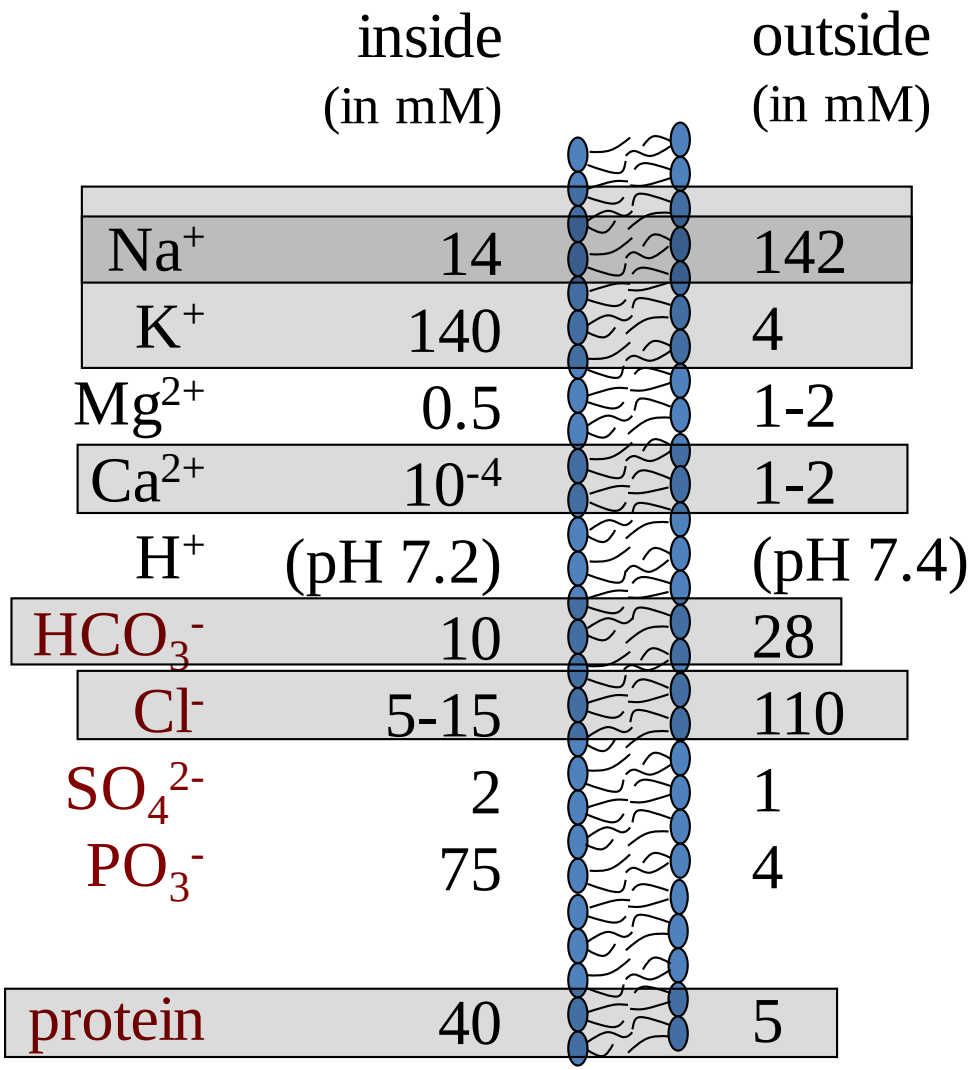
- MS is an immune-mediated inflammatory demyelinating disease of the CNS -

- About 1 person per 1000 in US is thought to have the disease - The female-to-male ratio is 2:1 - whites of northern European descent have the highest incidence

*Patients have a difficult time describing their symptoms. Patients may present with paresthesias of a hand that resolves, followed in a couple of months by weakness in a leg or visual disturbances. Patients frequently do not bring these complaints to their doctors because they resolve. Eventually, the resolution of the neurologic deficits is incomplete or their occurrence is too frequent, and the diagnostic dilemma begins.*

http://www.emedicine.com/pmr/topic82.htm

# Molecular Gradients



# Steady-state cell volume

is dependent upon the concentration of **impermeant** particles in the extracellular fluid (e.g. $Na^+$, $K^+$, $protein^-$)

**Permeant** particles cause only **transient** changes in cell volume (e.g. urea, glycerol)

**Time course** of the change in cell volume is dependent on the permeability of the particle

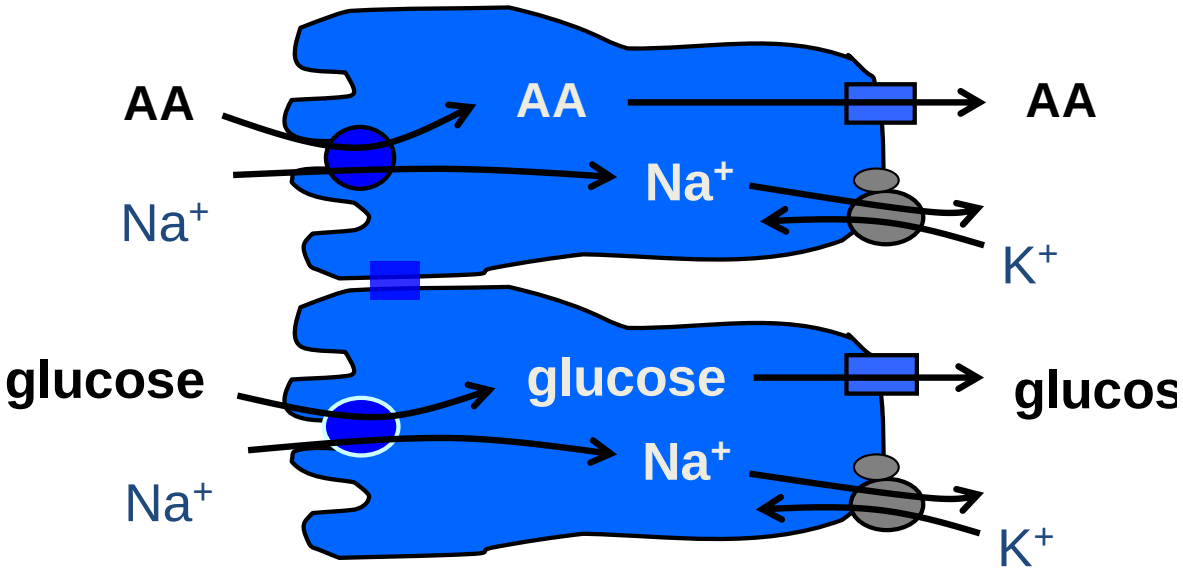
**higher permeability = more transient the change**

urea > glycerol

# Active Transport Through Cellular Sheets

- At many places in the body, substances must be transported all the way through a cellular sheet instead of simply through the cell membrane.
- The basic mechanism for transport of a substance through a cellular sheet is (1) active transport through the cell membrane on one side of the transporting cells in the sheet, and then (2) either simple diffusion or facilitated diffusion through the membrane on the opposite side of the cell.

➢ **Transcellular Transport of Glucose / AA**




**Examples:**

1. Intestinal epithelium
2. Renal tubular epithelium
3. Epithelium of exocrine glands
4. Epithelium of gallbladder
5. Membrane of choroid plexus of brain etc.