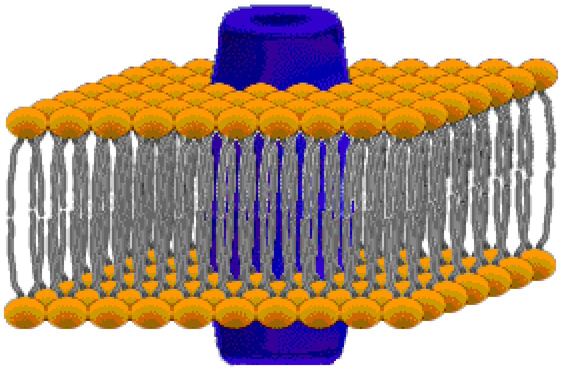
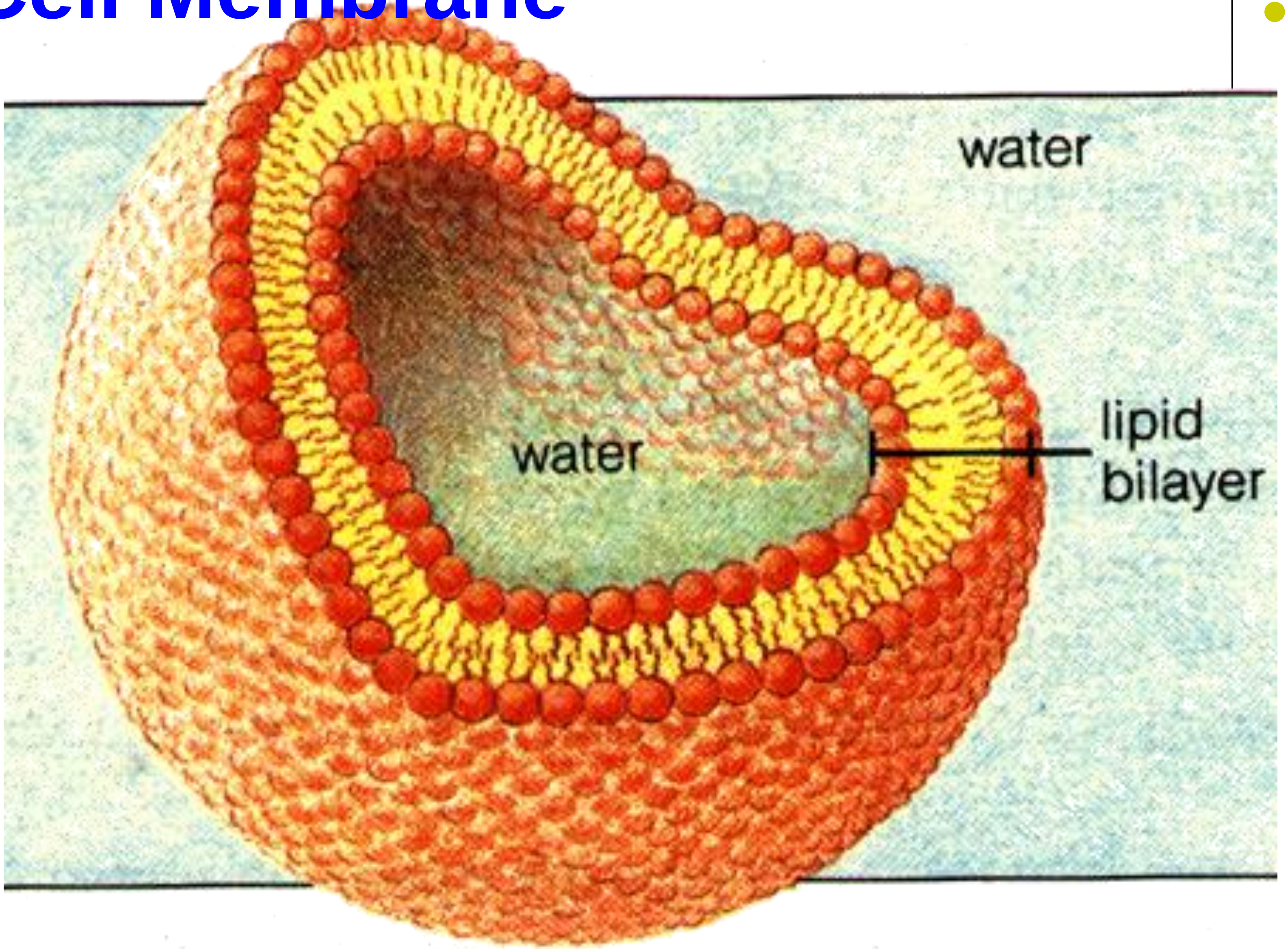
Transport of small molecules across membranes



Dr. S. K. Maurya

Cell Membrane

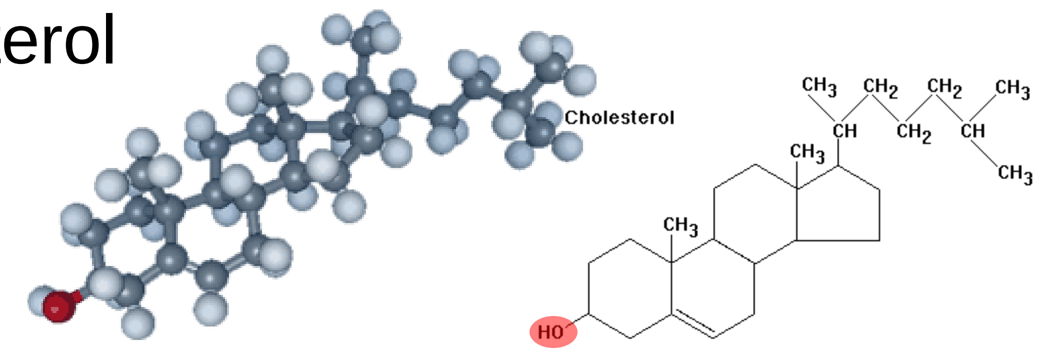


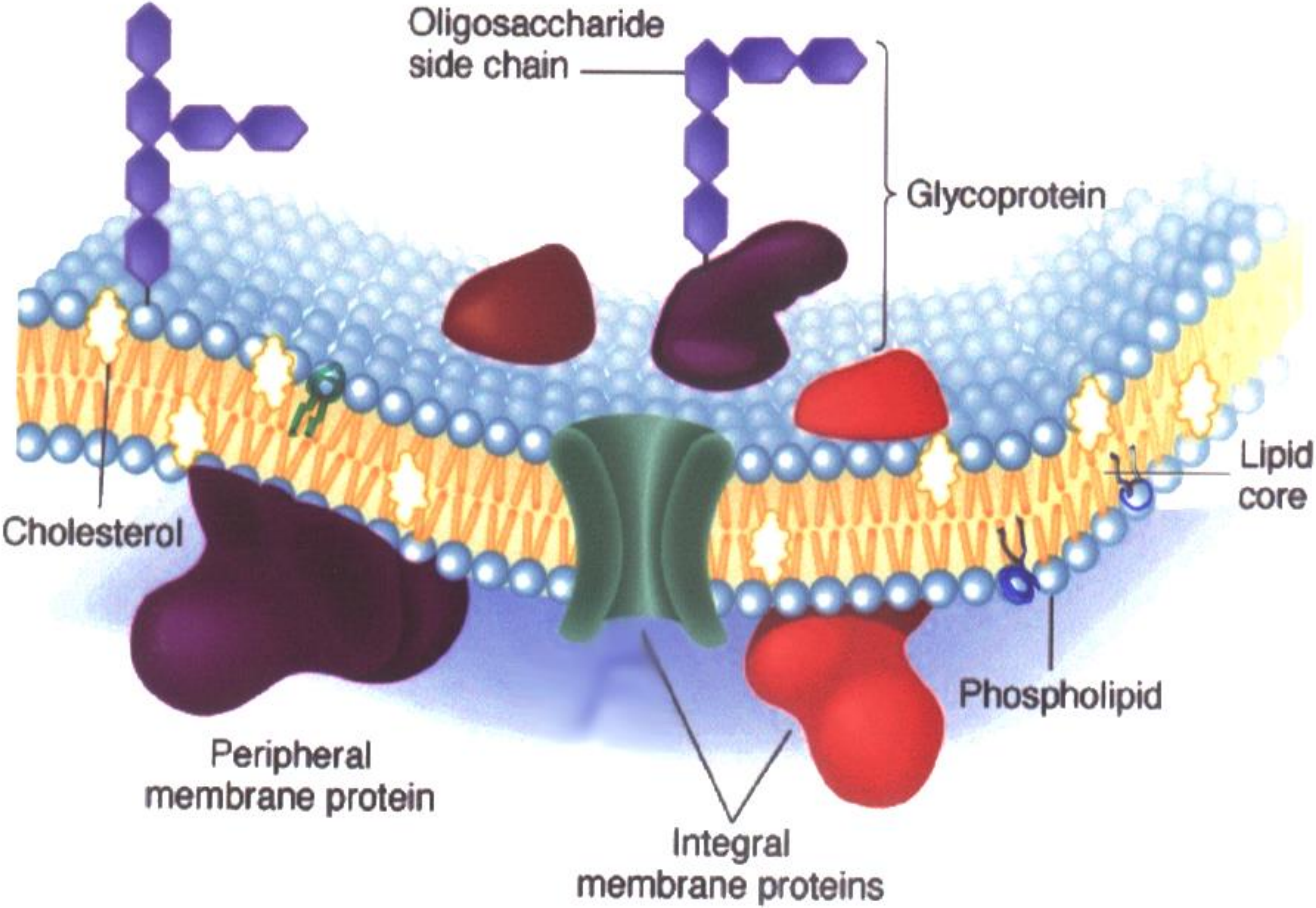
Cell Membrane Composition

- Plasma membrane encloses cell and cell organelles
- Made of hydrophobic and hydrophillic components
  - Semi-permeable and fluid-like
  - “lipid bilayer”

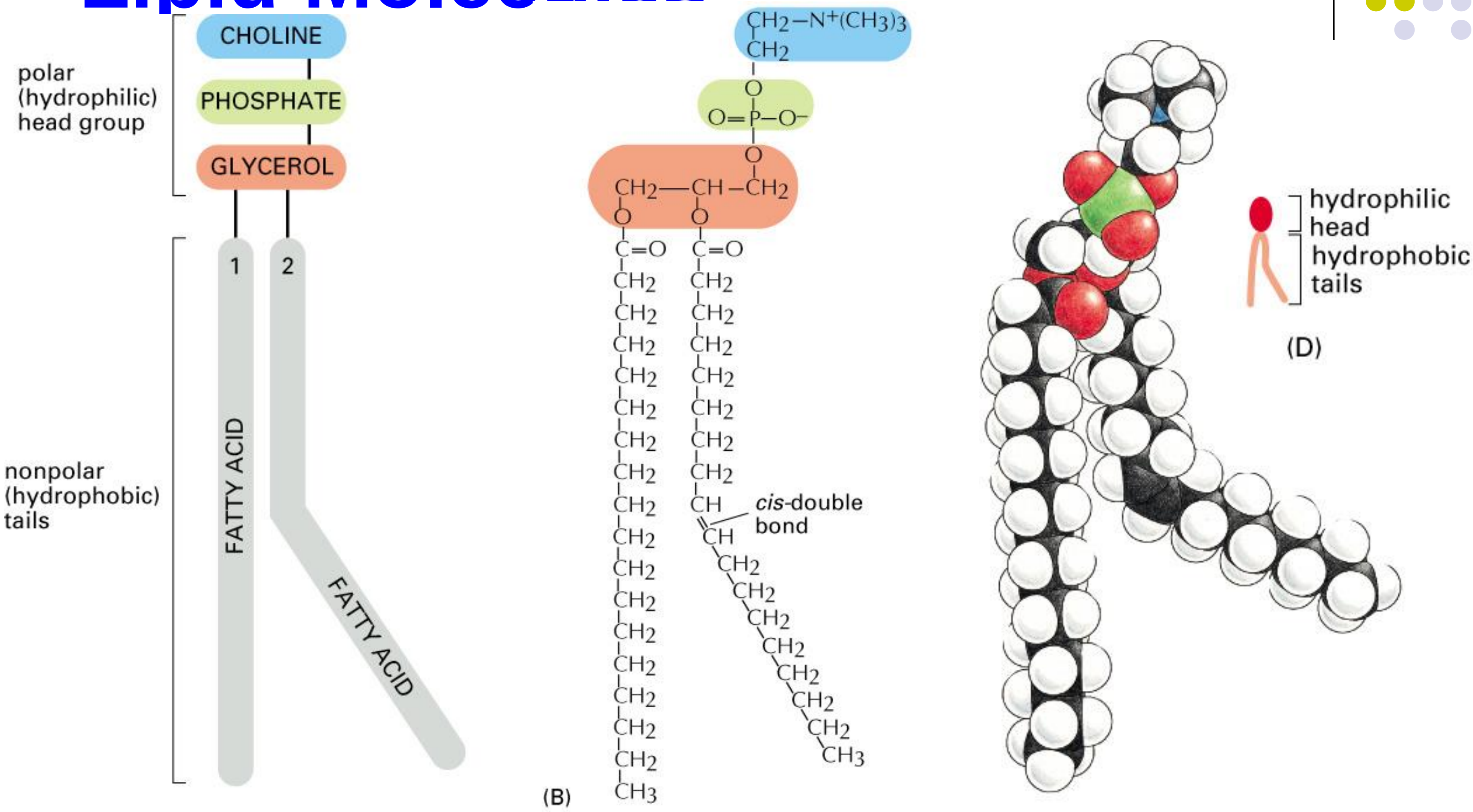
Cell Membrane Composition

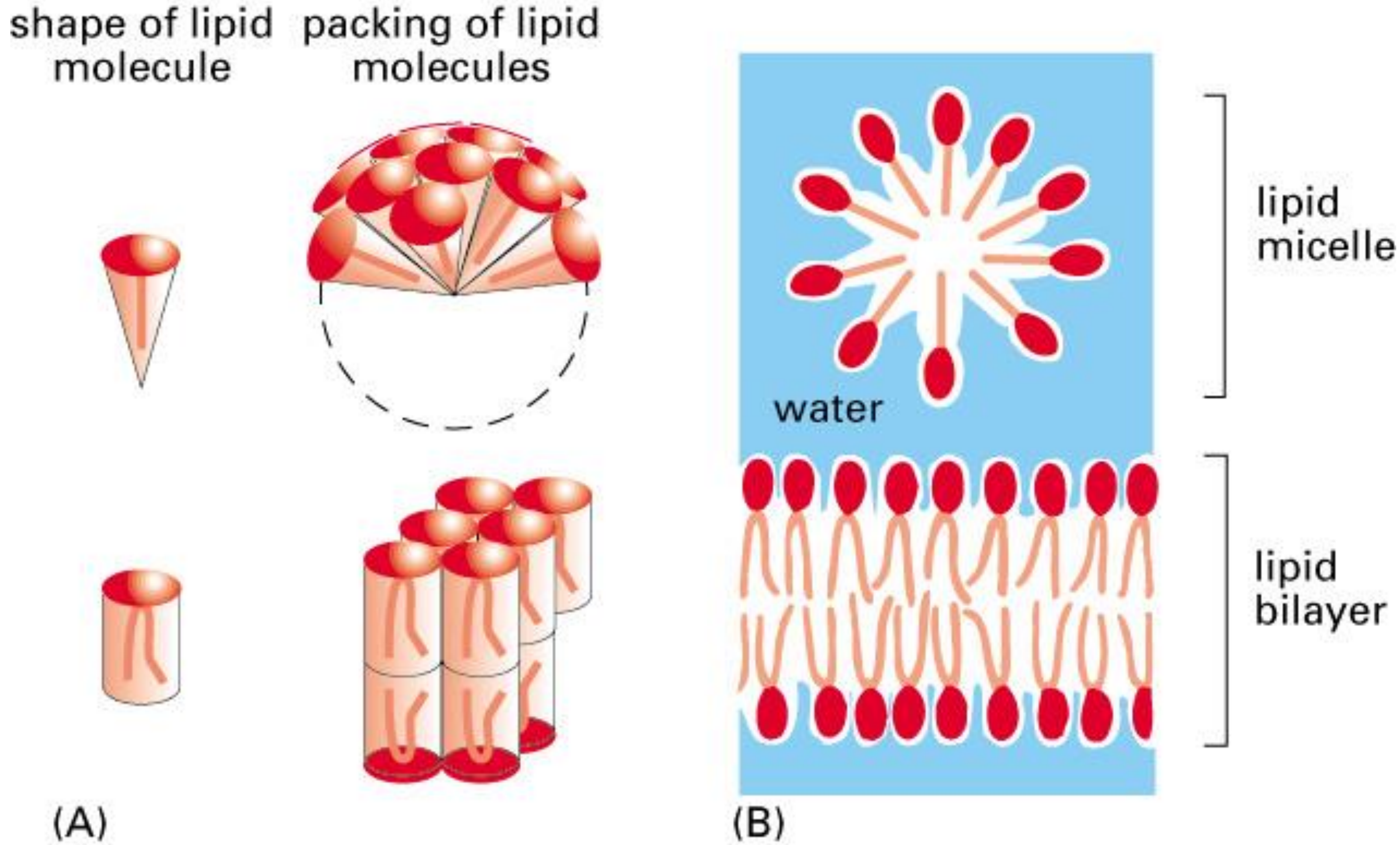
- Integral proteins interact with “lipid bilayer”
  - Passive transport pores and channels
  - Active transport pumps and carriers
  - Membrane-linked enzymes, receptors and transducers
- Sterols stabilize the lipid bilayer
  - Cholesterol

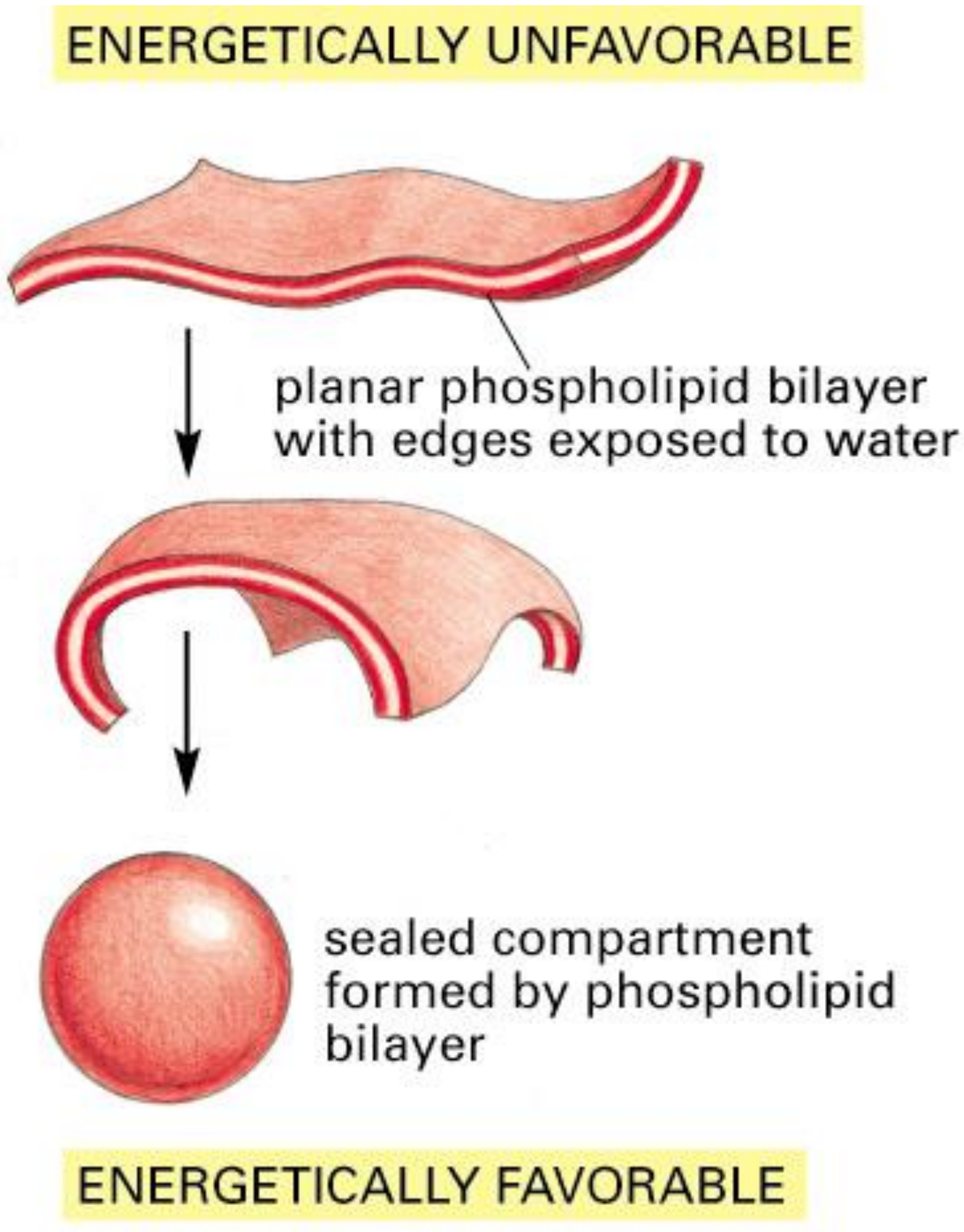



Oligosaccharide
side chain
Glycoprotein
Lipid
core
Cholesterol
Phospholipid
Peripheral
membrane protein
Integral
membrane proteins

Lipid Molecules




shape of lipid molecule
packing of lipid molecules
water
lipid micelle
lipid bilayer
(A)
(B)

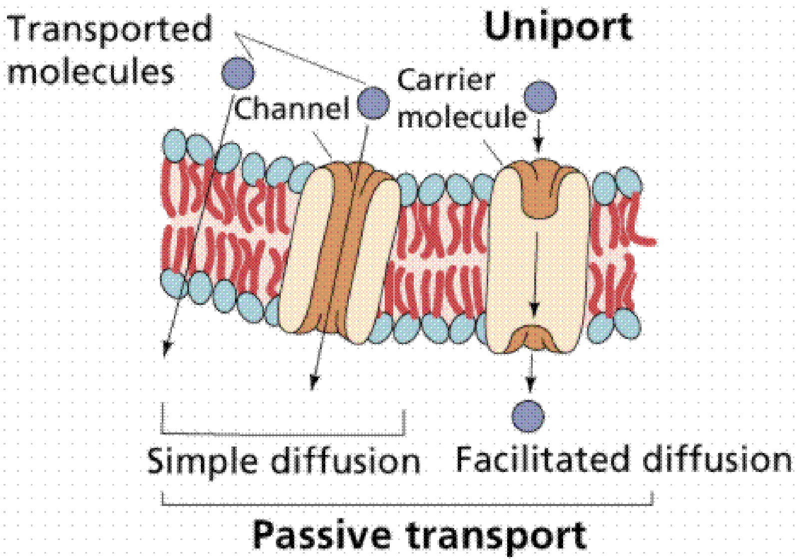

ENERGETICALLY UNFAVORABLE
planar phospholipid bilayer
with edges exposed to water
sealed compartment
formed by phospholipid
bilayer
ENERGETICALLY FAVORABLE

TRANSPORT

Two major modes

- ***Passive transport*** and
- ***Active transport***

PASSIVE TRANSPORT



I. Simple (Passive)Diffusion

no carriers is involved

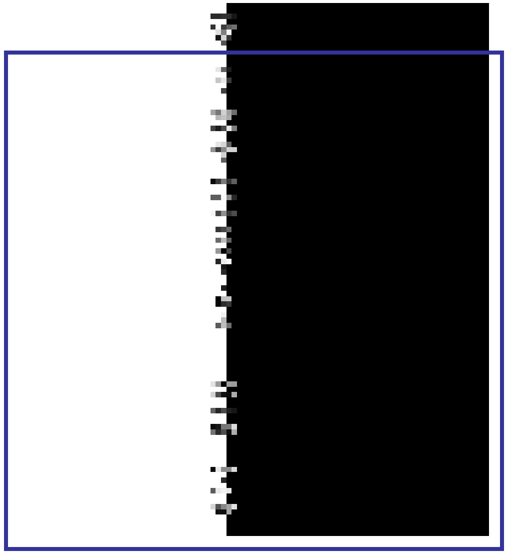
•Molecules that are transported through the cell membrane via simple diffusion include organic molecules, such as benzene and small uncharged molecules, such as H_2O, O_2, N_2, urea, glycerol,and CO_2

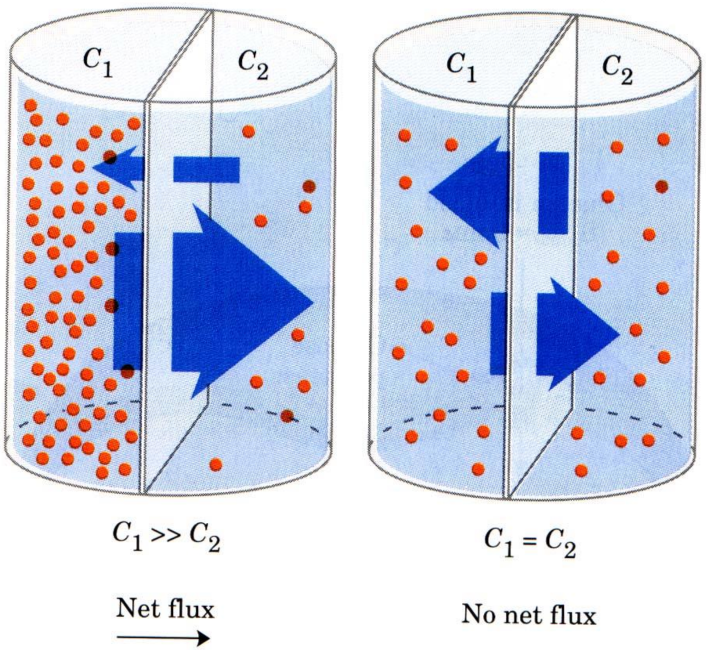
II. Mediated Diffusion

is carried out by proteins, peptides, and small molecular weight carriers

(ions, uncharged organic compounds, peptides, and even proteins can be transported)

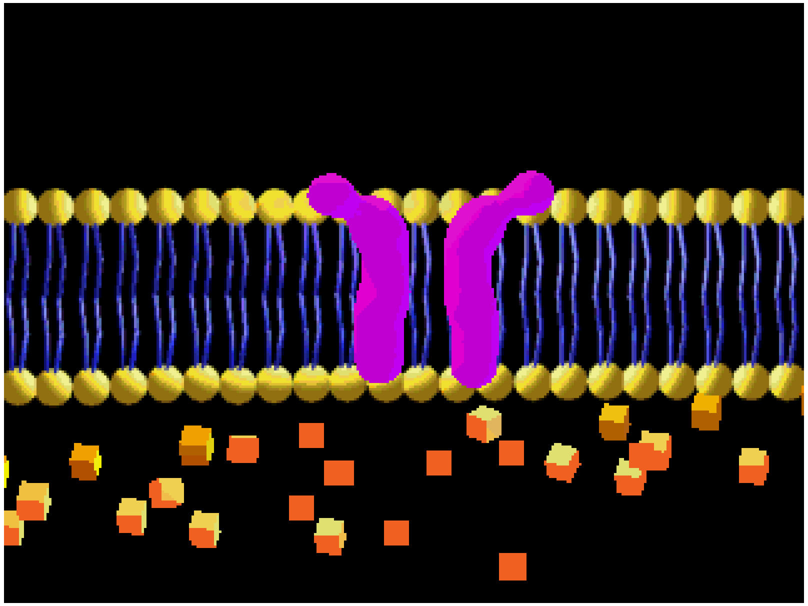
Simple (passive) diffusion
is a non-mediated and non-saturable transport





- Molecules that are transported through the cell membrane via simple diffusion include small organic molecules, H_2O, O_2, N_2, urea, glycerol,and CO_2
- Applications of simple diffusion: drugs delivery, analysis of membrane topology using membrane-permeable and impermeable reagents, regulation of osmotic pressure, etc.

Passive transport (facilitated diffusion)
energy independent, down the concentration gradient

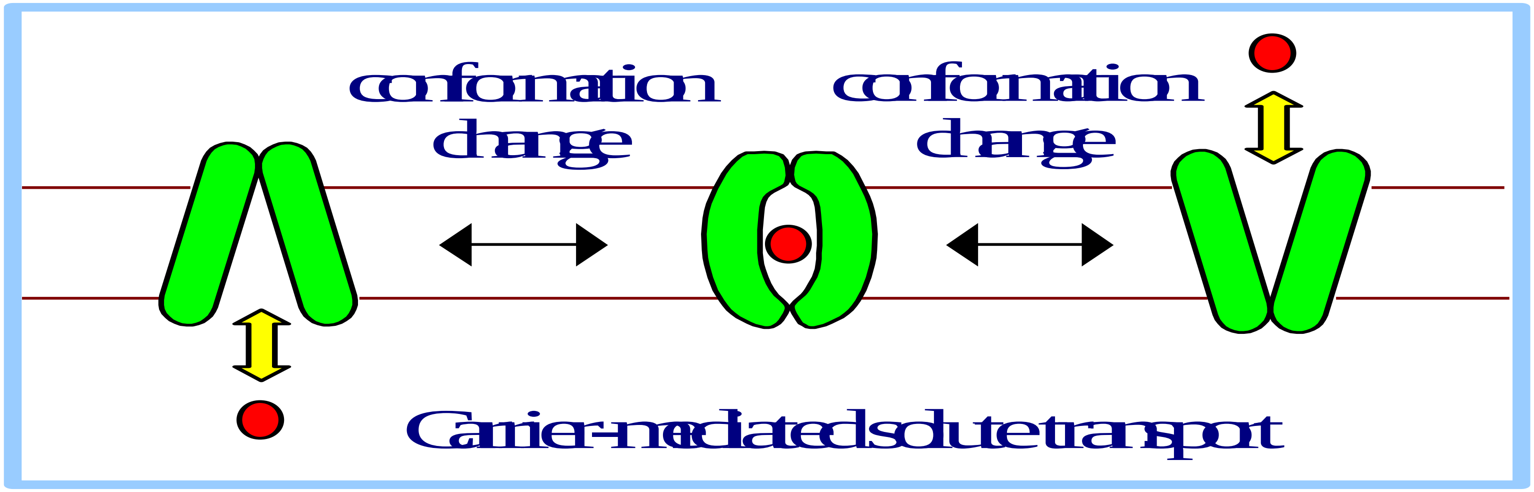


- *Mobile carriers* -ionophores (valinomycin, nigericin, dinitrophenol, etc)
- *Protein-translocators* - (Band 3, porins, erythrocyte glucose transporter)
- *Channels* - channels-forming ionophores (gramicidin)
  - voltage-gated channels (Na^+-, K^+- and Ca^{2+} -channels)
  - ligand-gated channels
  - mechanosensitive channels

Transporters/ Carrier proteins

- About 10% of **all** proteins function in **transport**
- In E.coli –427 transporters
- In eucaryotic cells, **2/3** of cellular energy at rest is used to transport ions (H+, K+, Na+, Ca++)
- About 200 families of transporters are recognized
- The largest family: ABC (ATP Binding Cassette) transporters

- **Proteins** that act as **carriers** are too large to move across the membrane.
- They are transmembrane proteins, with **fixed topology**.
- An example is the **GLUT1** glucose carrier, in plasma membranes of various cells, including erythrocytes.
- GLUT1 is a large integral protein, that include 12 transmembrane α-helices.

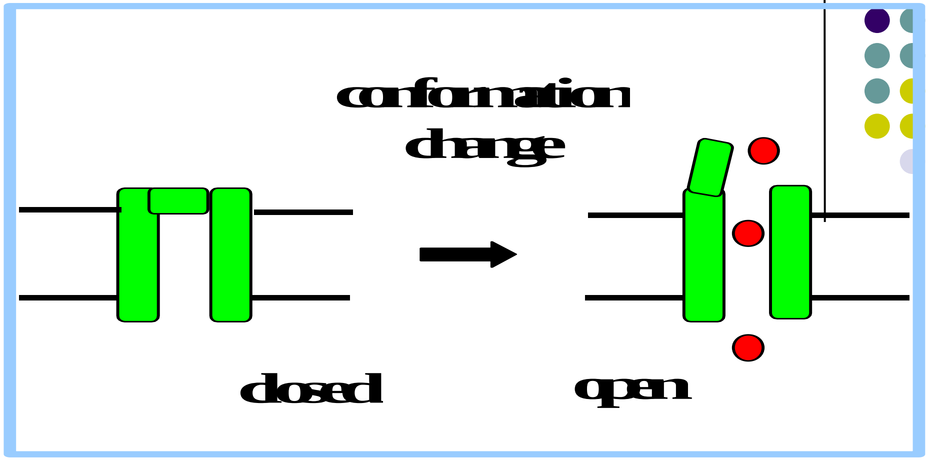


Carrier proteins cycle between conformations in which a solute binding site is accessible on one side of the membrane or the other.

There may be an intermediate conformation in which a bound substrate is inaccessible to either aqueous phase.

With **carrier** proteins, there is **never an open channel** all the way through the membrane.

Ion Channels



Channels cycle between open & closed conformations.

When open, a channel provides a **continuous pathway through the bilayer**, allowing flux of many ions.

Gramicidin is an example of a channel.

Channels that are proteins

Cellular channels usually consist of large protein complexes with multiple transmembrane α-helices.

Control of channel gating is a form of **allosteric** regulation. Conformational changes associated with channel opening may be regulated by:

- **Voltage** (opens in response to a change in potential)
- **Binding of a ligand** (a regulatory molecule)
- **Membrane stretch** (e.g., via link to cytoskeleton)

Active transport

- energy-dependent, against concentration gradient

ATP-dependent ion pumps are grouped into **classes** based on transport mechanism, as well as genetic & structural homology.

Examples include:

- **P-class** pumps: This family of ion pumps functions to establish and maintain ion gradients across membranes
- **F-class** (e.g., F_1F_o-ATPase): The function of this family of ion pumps is to synthesize ATP from existing proton gradients.
- related **V-class** pumps.

ABC (ATP binding cassette) **transporters**, which catalyze transmembrane movements of various organic compounds including amphipathic lipids and drugs.

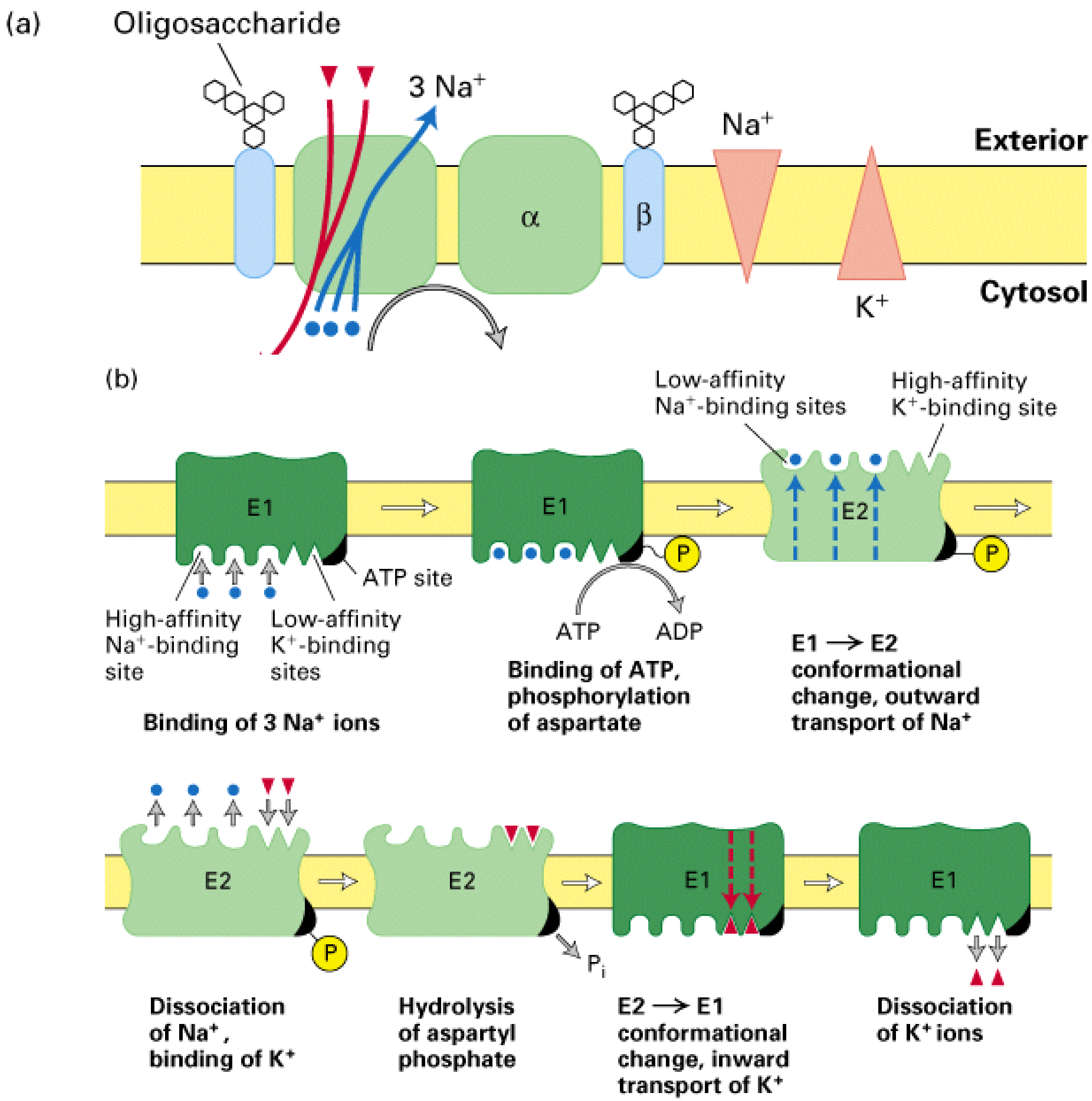
P-class ion pumps are a gene family exhibiting sequence homology. They include:

- **Na^+,K^+-ATPase**, in plasma membranes of most animal cells is an antiport pump.

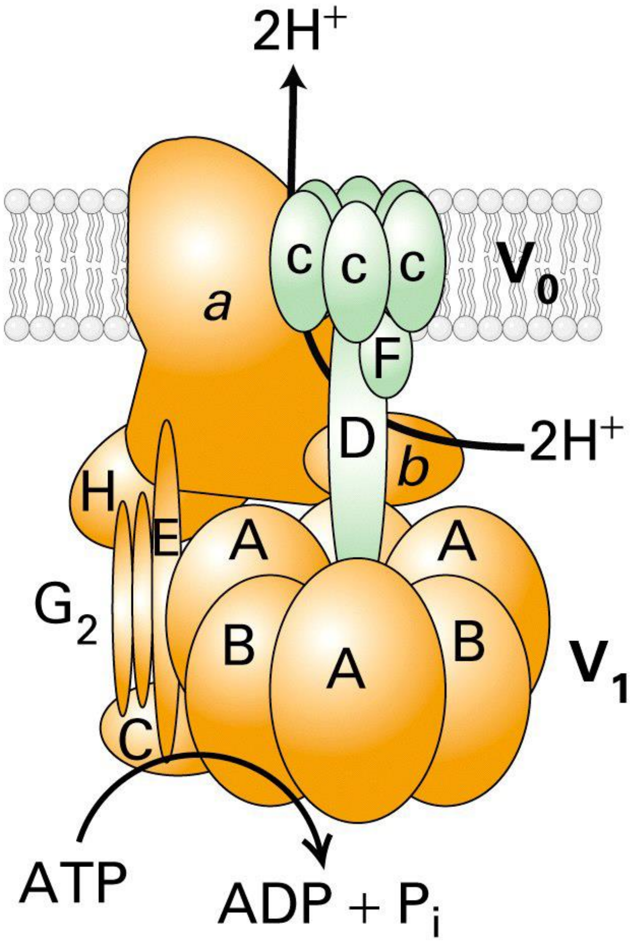
  It catalyzes ATP-dependent transport of Na^+ out of a cell in exchange for K^+ entering.

- **(H^+, K^+)-ATPase**, involved in acid secretion in the stomach is an antiport pump.

  It catalyzes transport of H^+ out of the gastric parietal cell (toward the stomach lumen) in exchange for K^+ entering the cell.


(a)
Oligosaccharide
3 Na+
α
β
Na+
K+
Exterior
Cytosol
(b)
E1
ATP site
High-affinity Na+-binding site
Low-affinity K+-binding sites
Binding of 3 Na+ ions
E1
P
ATP
ADP
Binding of ATP, phosphorylation of aspartate
Low-affinity Na+-binding sites
High-affinity K+-binding site
E2
P
E1 → E2 conformational change, outward transport of Na+
E2
P
Dissociation of Na+, binding of K+
E2
Pi
Hydrolysis of aspartyl phosphate
E1
E2 → E1 conformational change, inward transport of K+
E1
Dissociation of K+ ions

V Class: transpost H+ only



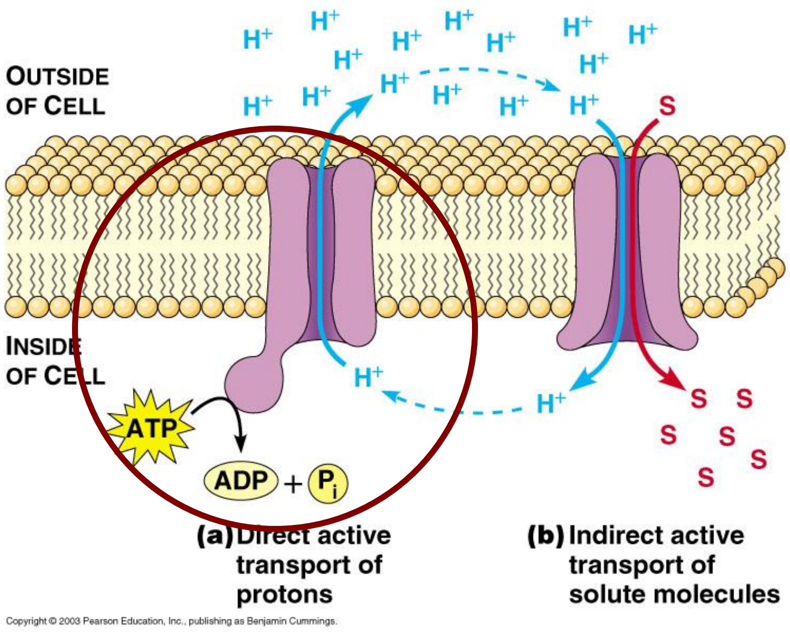
V-class proton pumps

Vacuolar membranes in plants, yeast, other fungi

Endosomal and lysosmal membranes in animal cells

Plasma membrane of osteoclasts and some kidney tubule cells

Primary Active Transport - **utilizes energy of ATP hydrolysis**

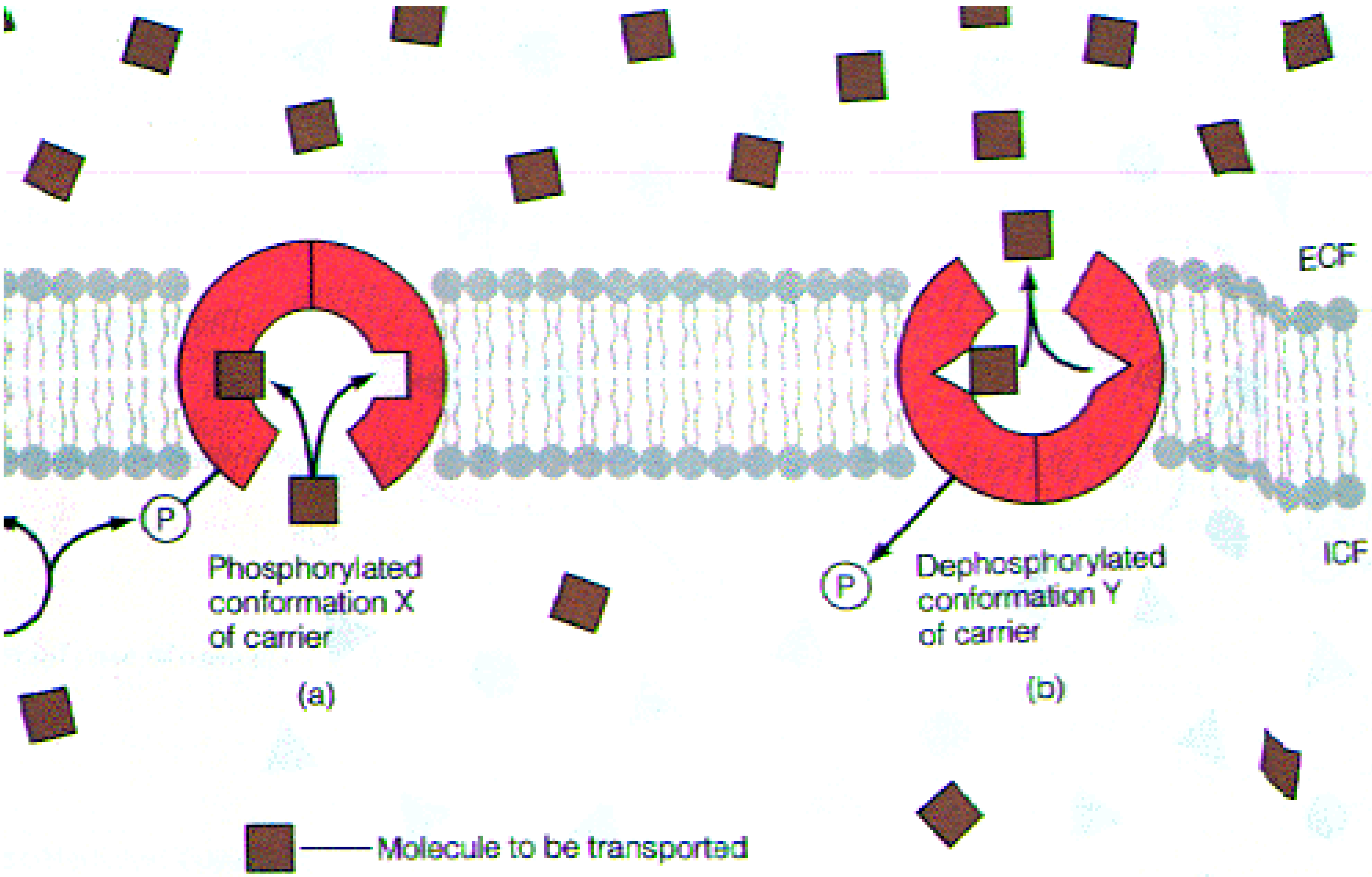


–P-type ATPases (Na,K-ATPase, H,K-ATPases, Ca-ATPase, Zn^{2+}/Pb^{2+}transporting ATPase of bacteria)

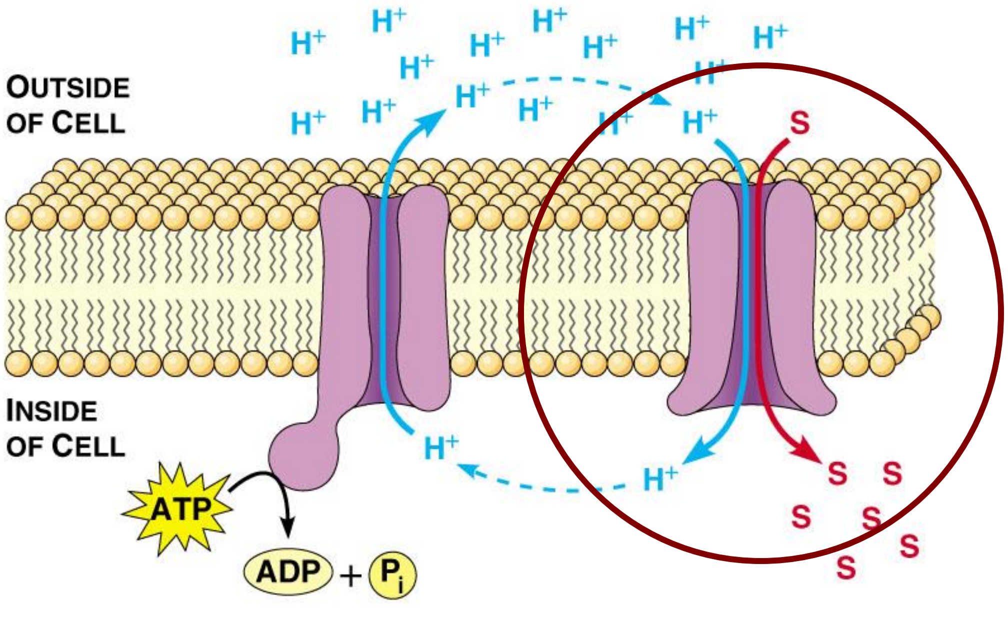
–V-type ATPases and F_1F_0-ATPases (Na+-ATPase and H+-ATPase)

–ATPases that transport peptides and drugs (multidrug-resistance protein, P-glycoprotein, yeast α-factor transporter

ACTIVE TRANSPORT



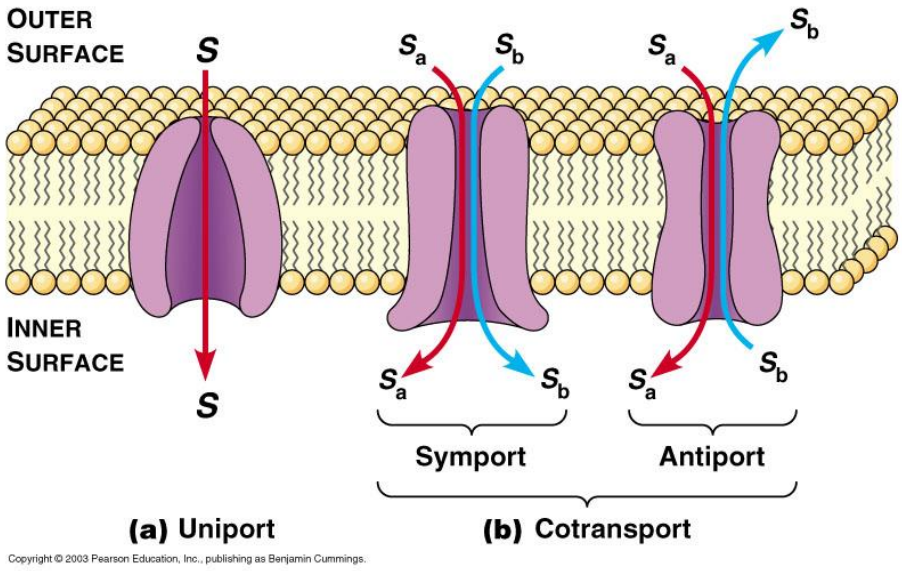
Secondary Active (Coupled) Transport **- utilizes ion-gradients generated by primary transporters**



(a) Direct active transport of protons

(b) Indirect active transport of solute molecules

Types of Secondary Transporters

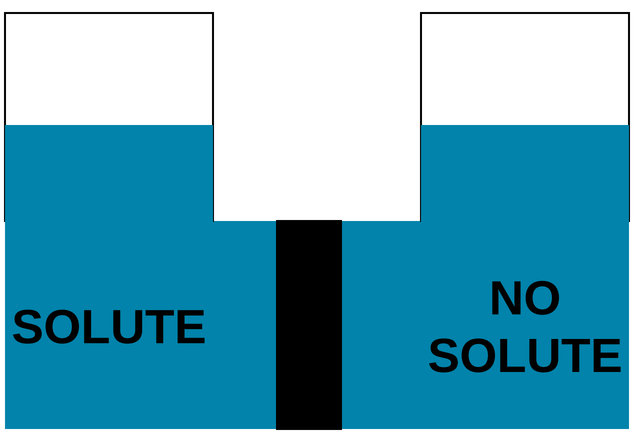


- Symporters (two solutes move in same direction) Lac- permease, Na^+/glucose transporter)
- Antiporters (two solutes move in opposite directions Na^+/Ca^{2+} exchanger)
- Uniporters (mitochondrial Ca^{2+} uniporter and NH^+_4-transporter in plants require H^+ gradient)

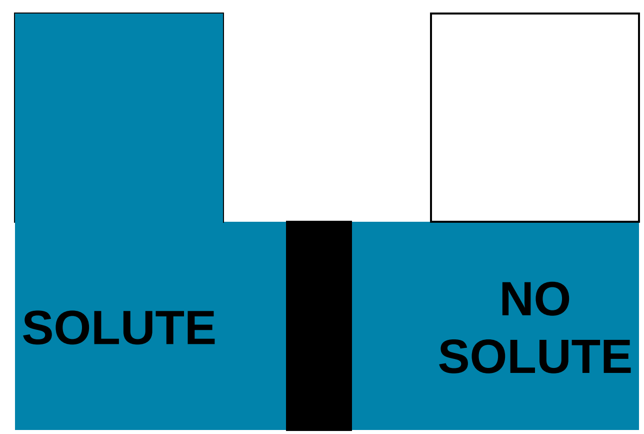
Osmosis

Water moves across a semi-permeable membrane to the side where the solute is most concentrated

- Before:



After:



Endo and Exocytosis

- Exocytosis

  - membrane vesicle fuses with cell membrane, releases enclosed material to extracellular space.

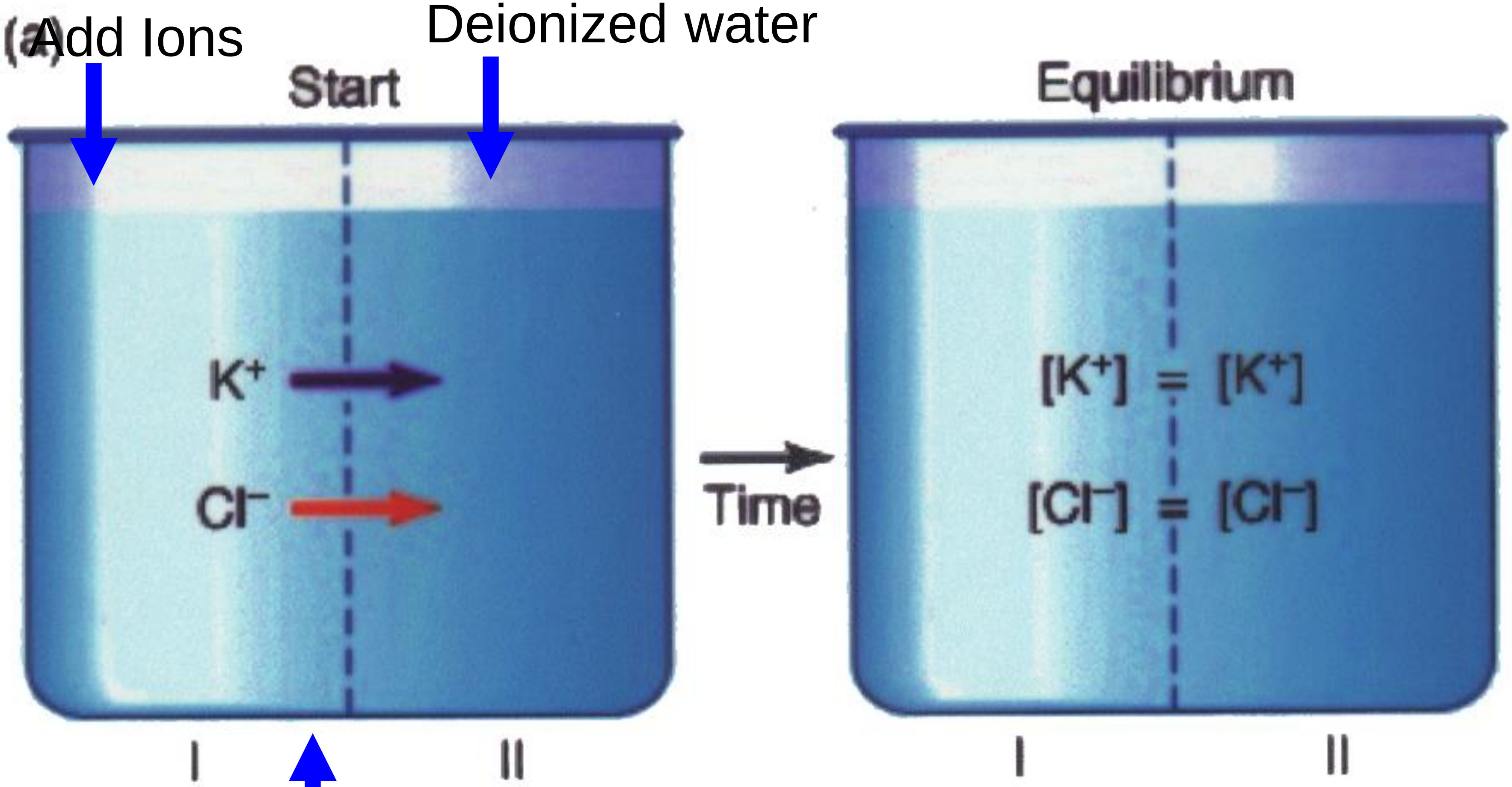
- Endocytosis

  - cell membrane invaginates, pinches in, creates vesicle enclosing contents

Donnan Equilibrium

Add Ions

Deionized water

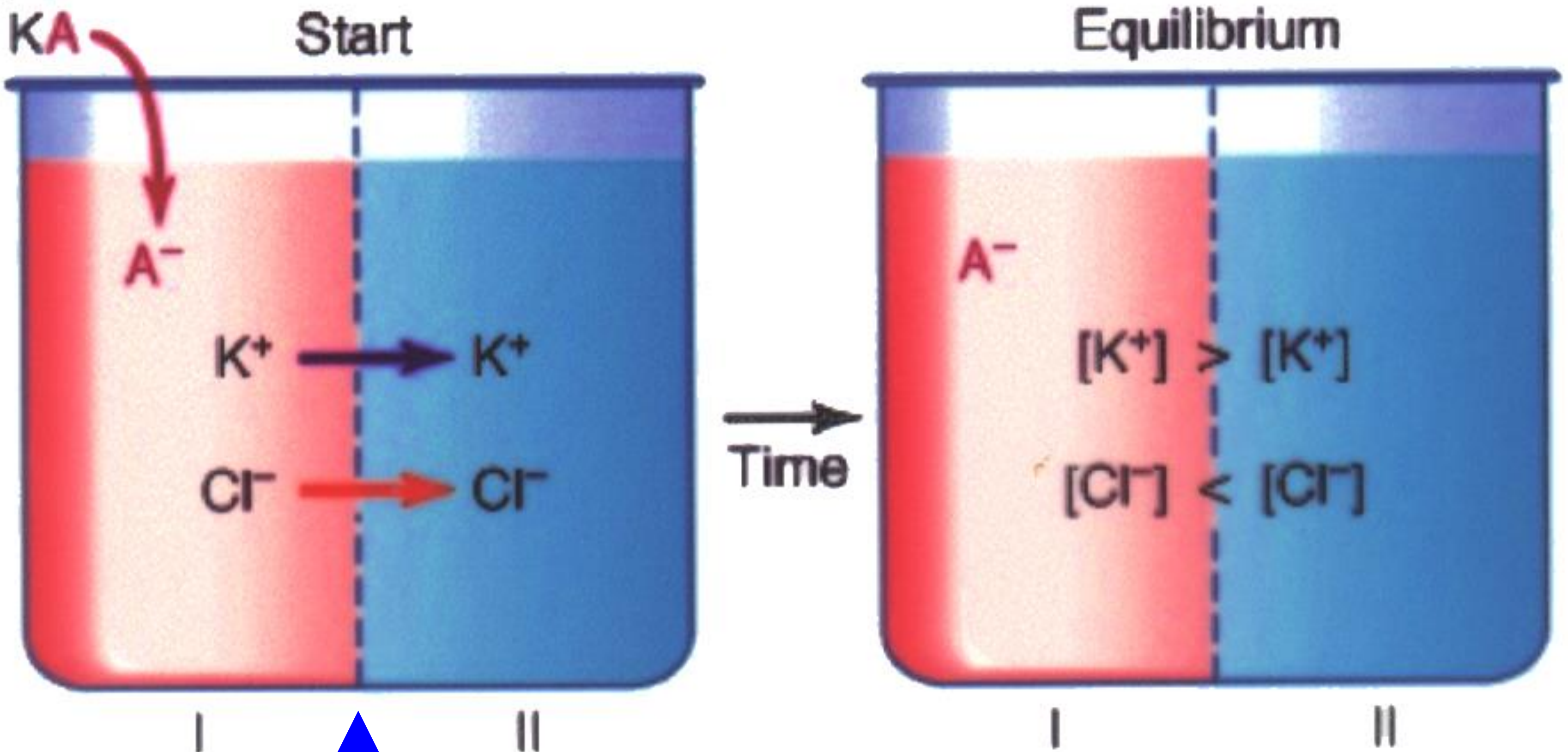


Semi-permeable membrane

Balanced charges among both sides

Donnan Equilibrium

(b) Add anion

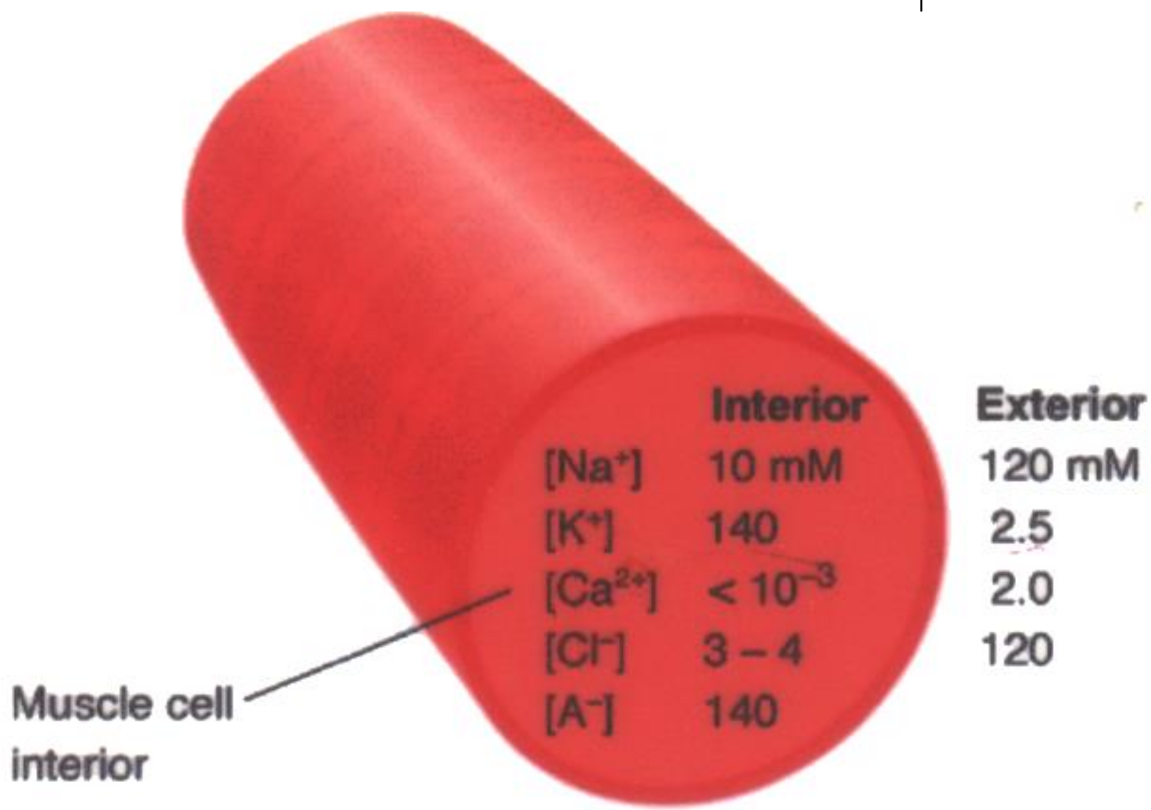


Diffusion

More Cl^- leaves I to balance charges

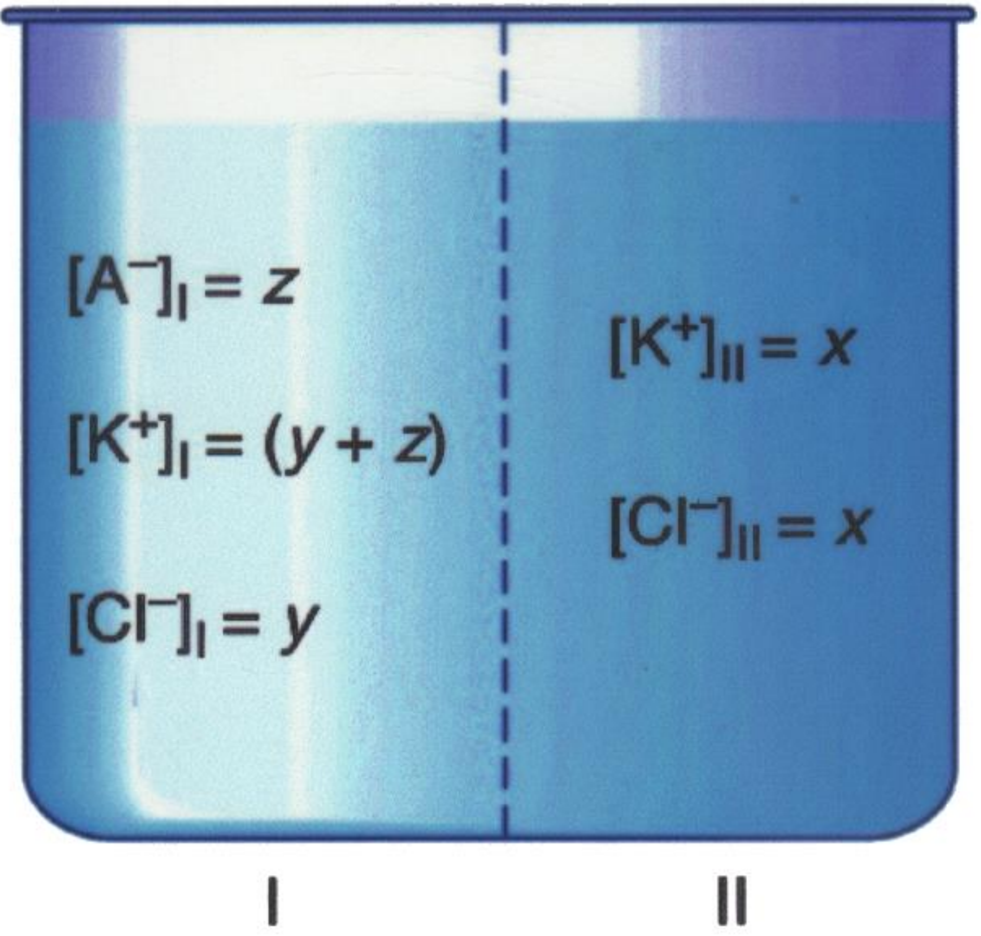
Ionic Steady State

- Potaasium cations most abundant inside the cell
- Chloride anions ions most abundant outside the cell
- Sodium cations most abundant outside the cell



$[A^-]$ = molar equivalent of negative charges carried by other molecules and ions.

Donnan equilibrium



$$\frac{[K^+]_i}{[K^+]_{ii}} \qquad \frac{[Cl^-]_{ii}}{[Cl^-]_i}$$

The End