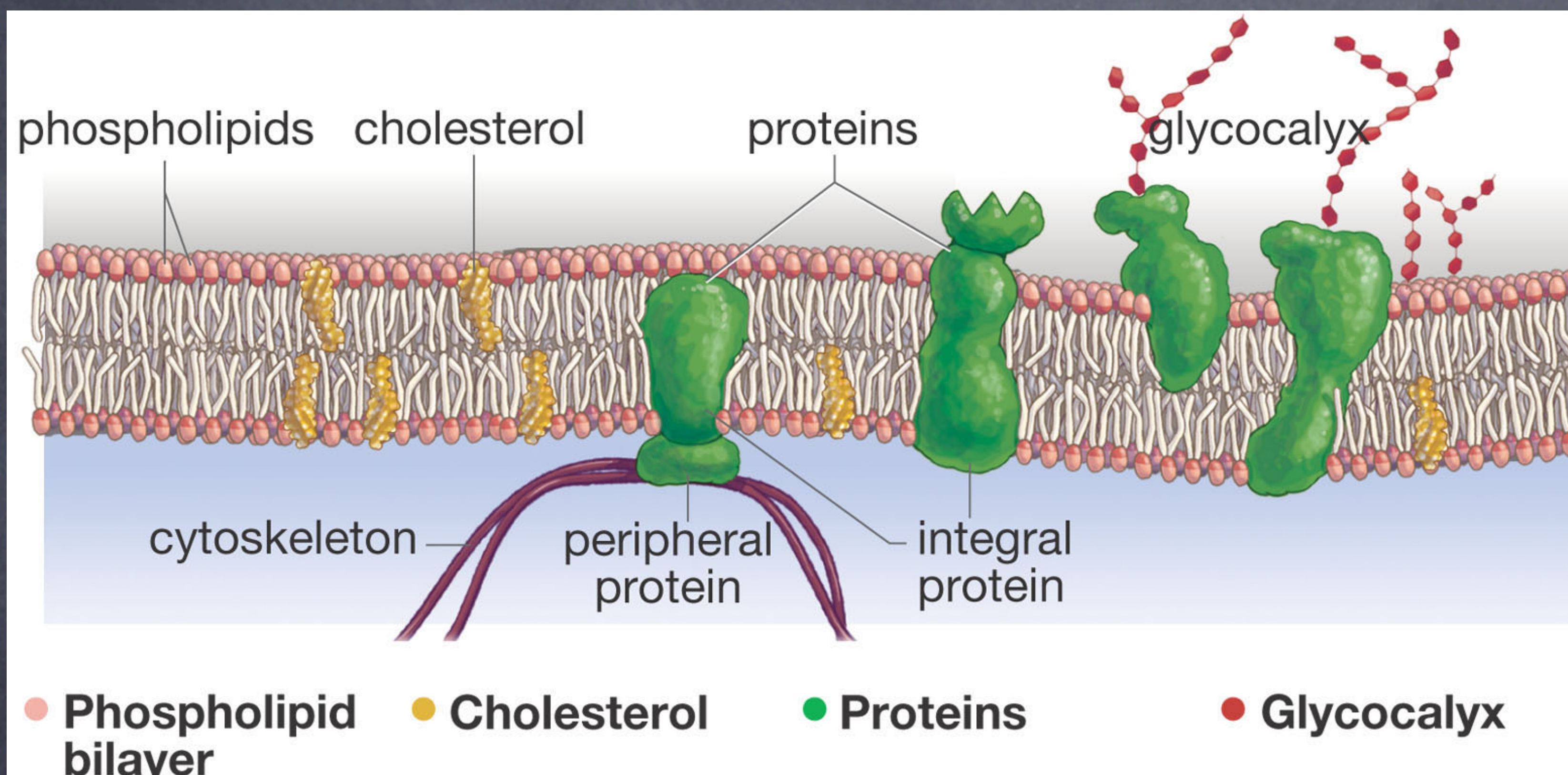
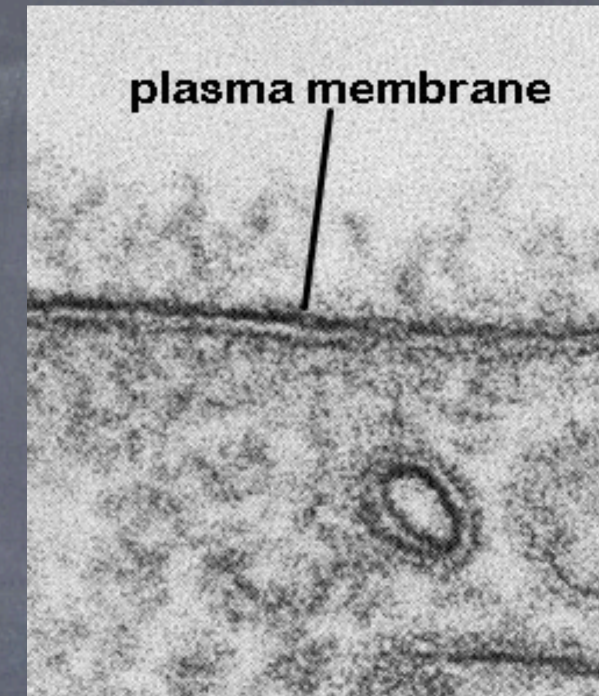
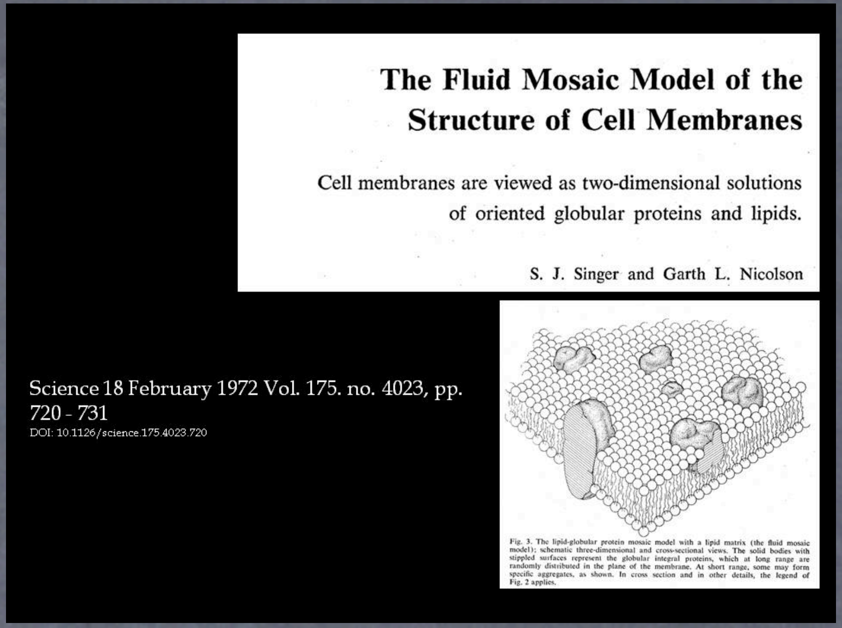
Cell Membrane



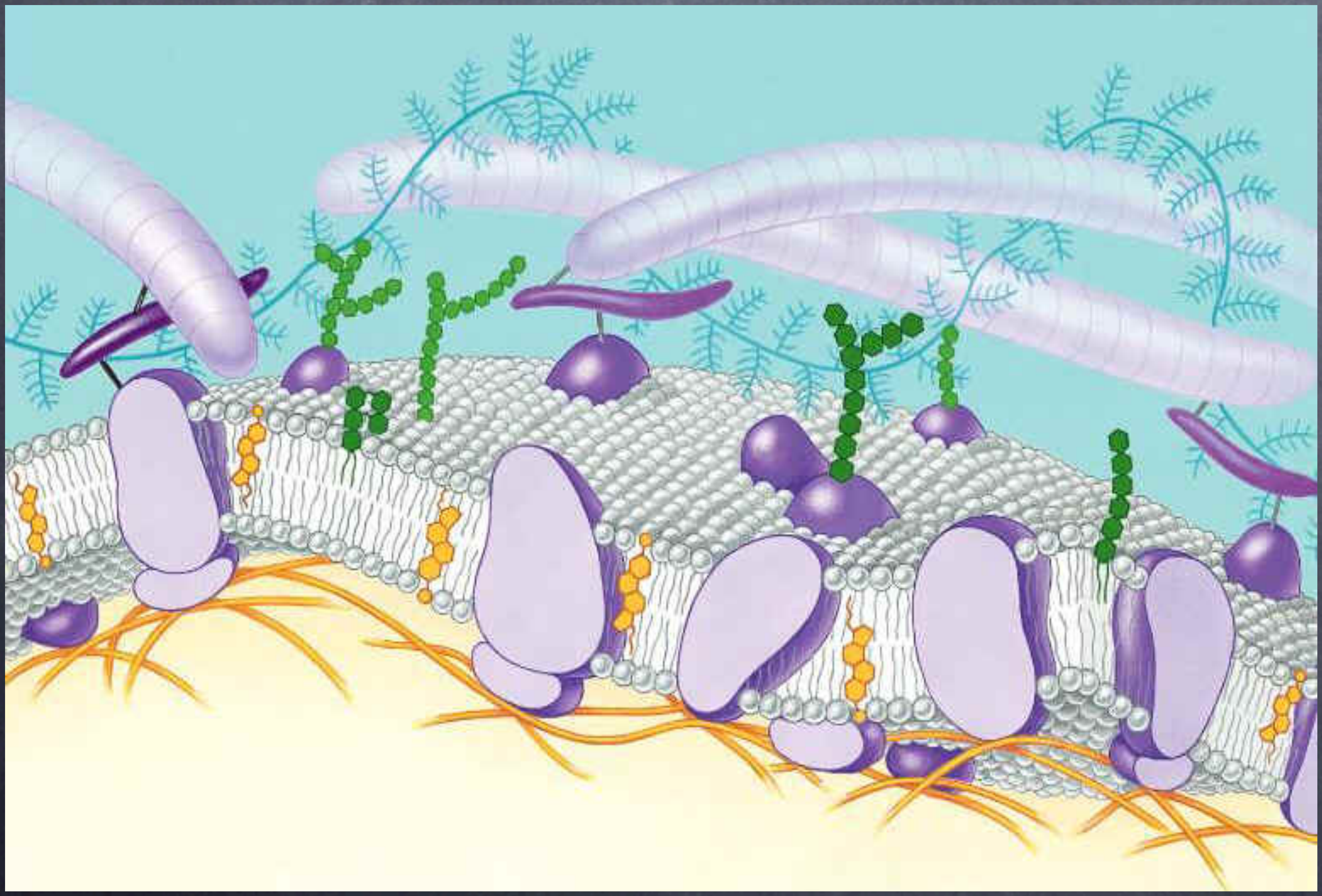


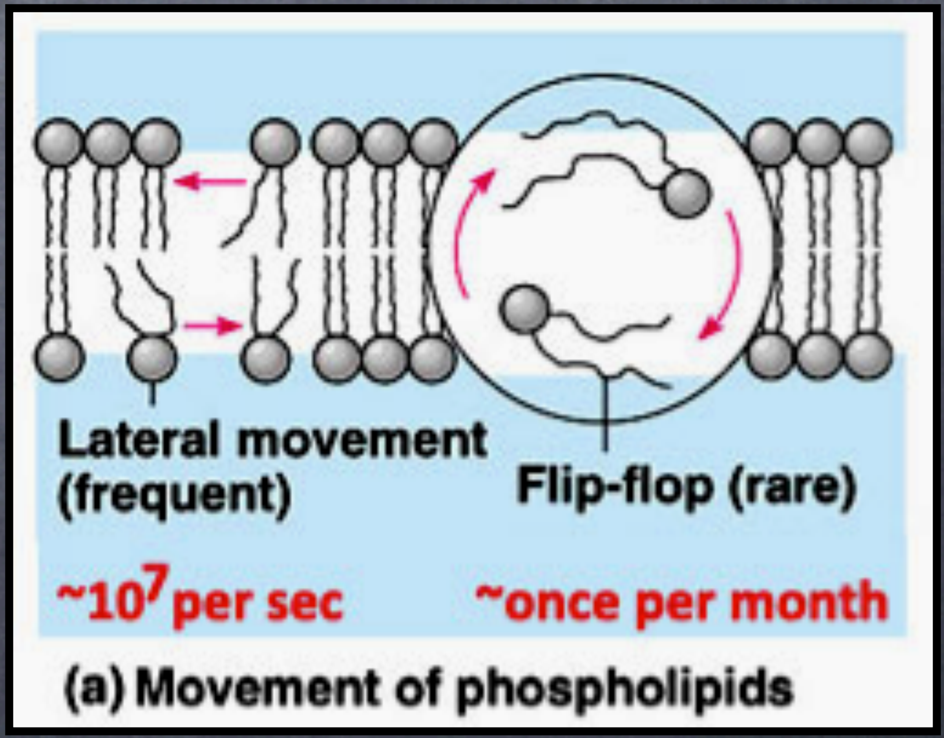
FLUID MOSAIC MODEL



FLUID- because individual phospholipids and proteins can move side-to-side within the layer, like it's a liquid.

MOSAIC- because of the pattern produced by the scattered protein molecules when the membrane is viewed from above.





Functions of Plasma Membrane

- ✓ Protective barrier
- ✓ Regulate transport in & out of cell (selectively permeable)
- ✓ Allow cell comunication and signaling
- ✓ Provide anchoring sites for extracellular matrix and cytoskeleton (cell adhesion, migration…)

Membranes separate different environments:

ASIMMETRY / GRADIENTS

maintained through energy consumption (OPEN SYSTEM)

COMPOSITION OF BODY FLUIDS

CATIONS (mmol/l)	Plasma	Interstitial	Intracellular
Na	142	139	14
K	4.2	4.0	140
Ca	1.3	1.2	0
Mg	0.8	0.7	20
ANIONS (mmol/l)			
Cl	108	108	4.0
HCO3	24.0	28.3	10
Protein	1.2	0.2	4.0
HPO4	2.0	2.0	11

	Concentration, mM		
Ion	Plasma	Cytosol	Seawater
Na^+	135~146	25~35	480
K^+	3.5~5.2	130~145	10.4
Mg^{2+}	0.8~1.4	4~20	54
Ca^{2+}	2.1~2.7	<0.01	10.6
Cl^-	98~108	50~60	559
HCO_3^-	23~31	4~12	54
PO_4^{2-}	0.7~1.4	90~110	<0.1

Physiol. Rev. 86(2006), 1049

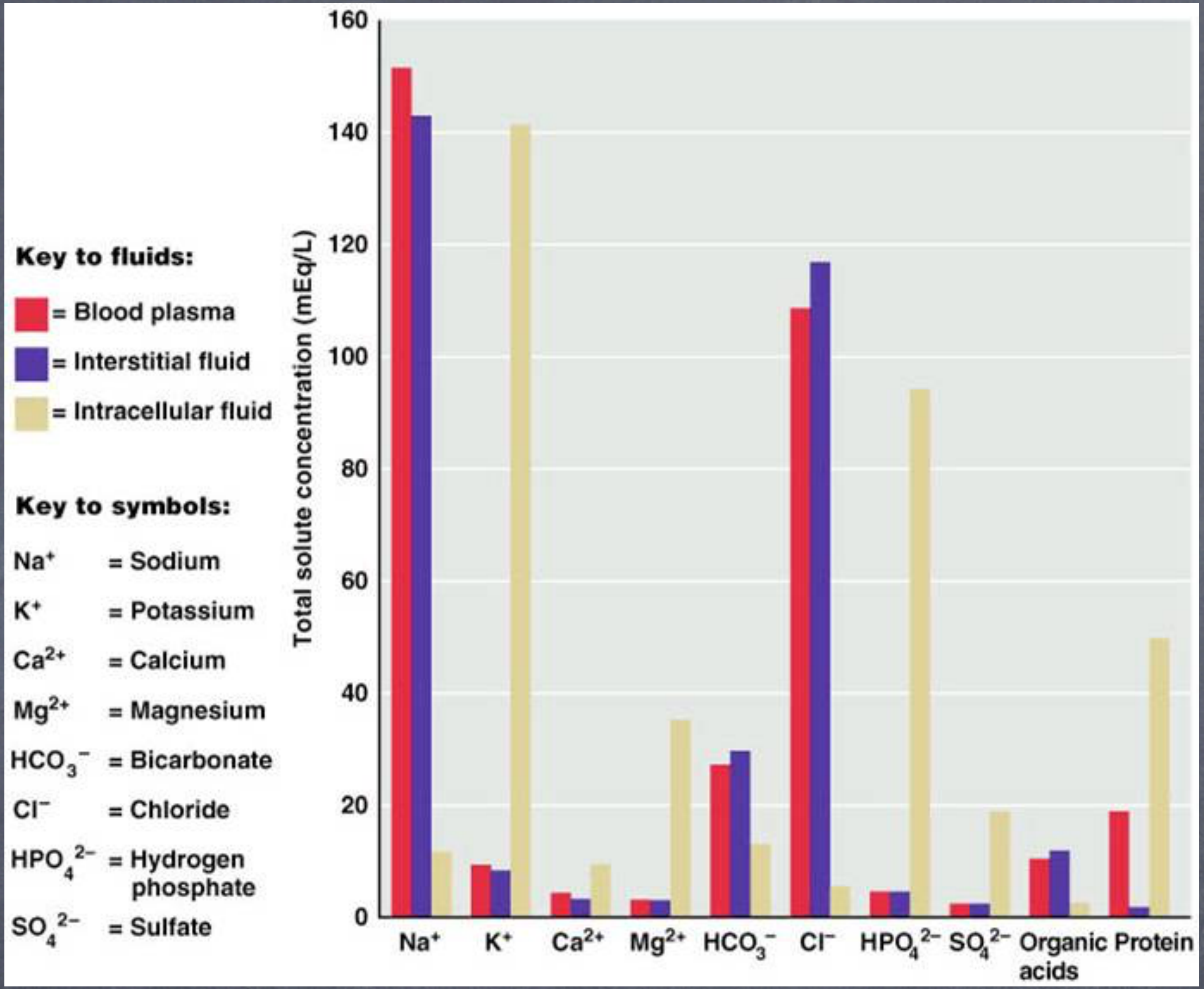
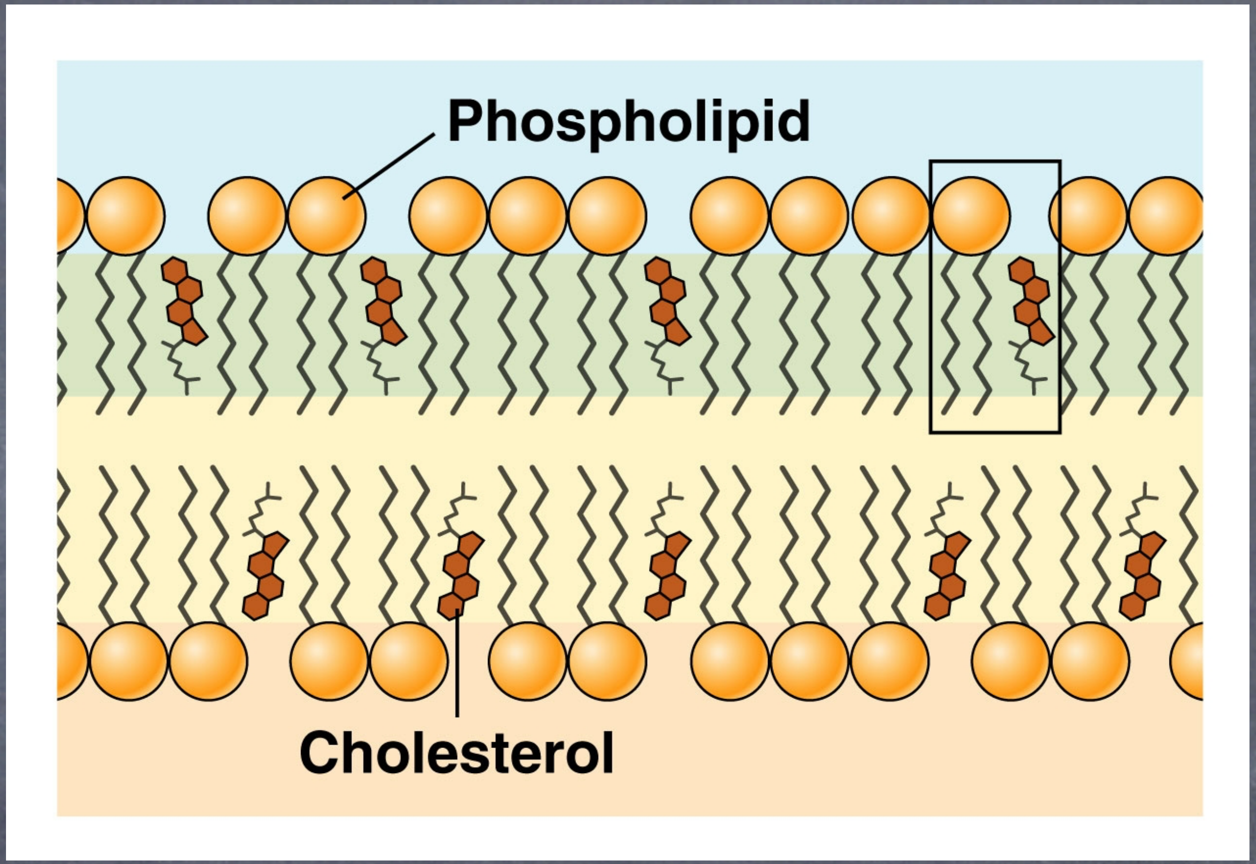


Table 1: Ionic Concentrations (mM) in SBF and Human Plasma.

	Na^{+}	K^{+}	Mg^{+2}	Ca^{+2}	Cl^{-}	HCO_3^{-}	HPO_4^{-2}	SO_4^{-2}
Plasma	142.0	5.0	1.5	2.5	103.0	27.0	1.0	0.5
SBF	142.0	5.0	1.5	2.5	147.8	4.2	1.0	0.5

Fluxes through the membranes are required (open system) but strictly **controlled**

Pure lipid bilayer



Polar heads are hydrophilic "water loving"

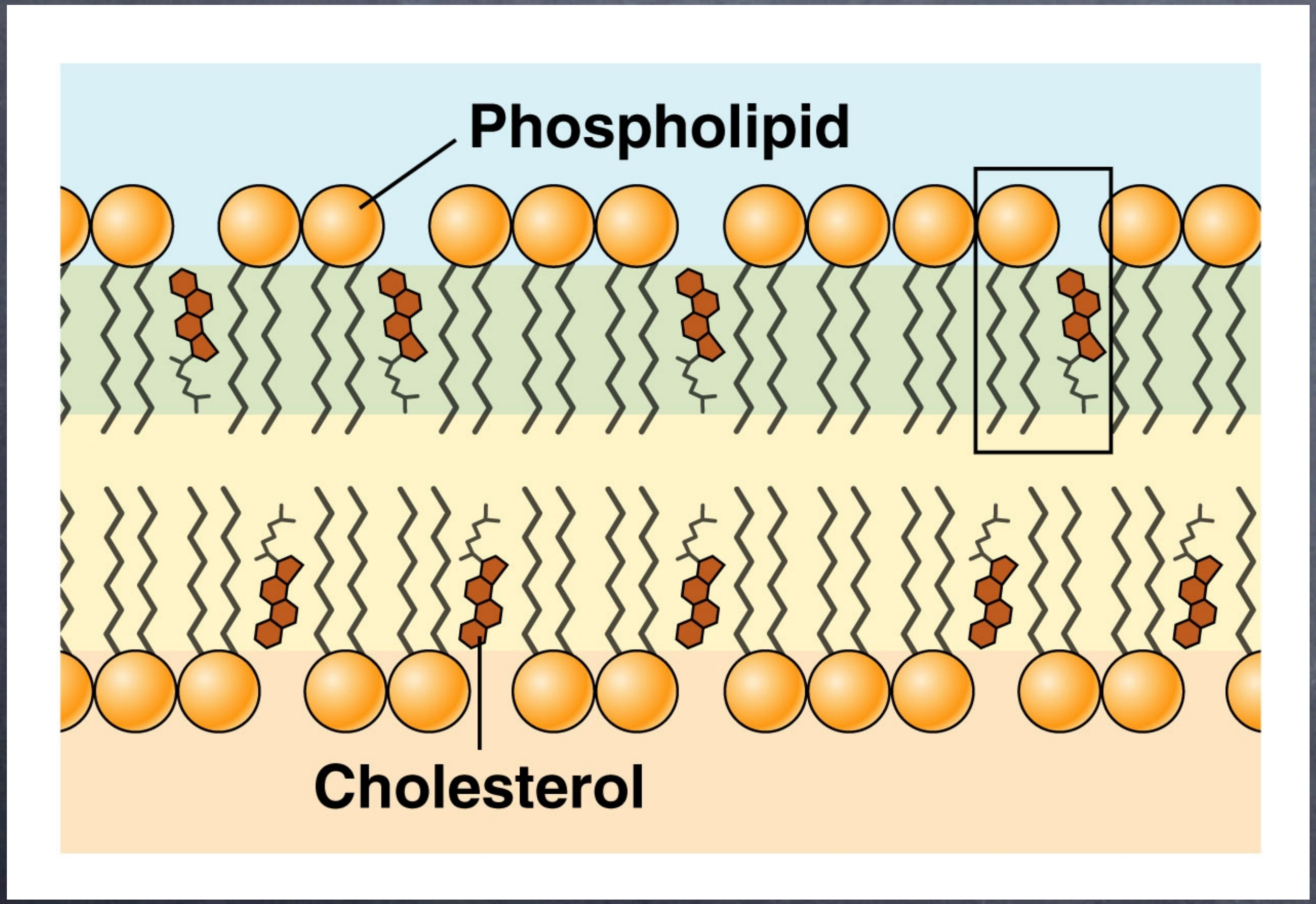
Nonpolar tails are hydrophobic "water fearing"

make membrane "Selective" in what crosses

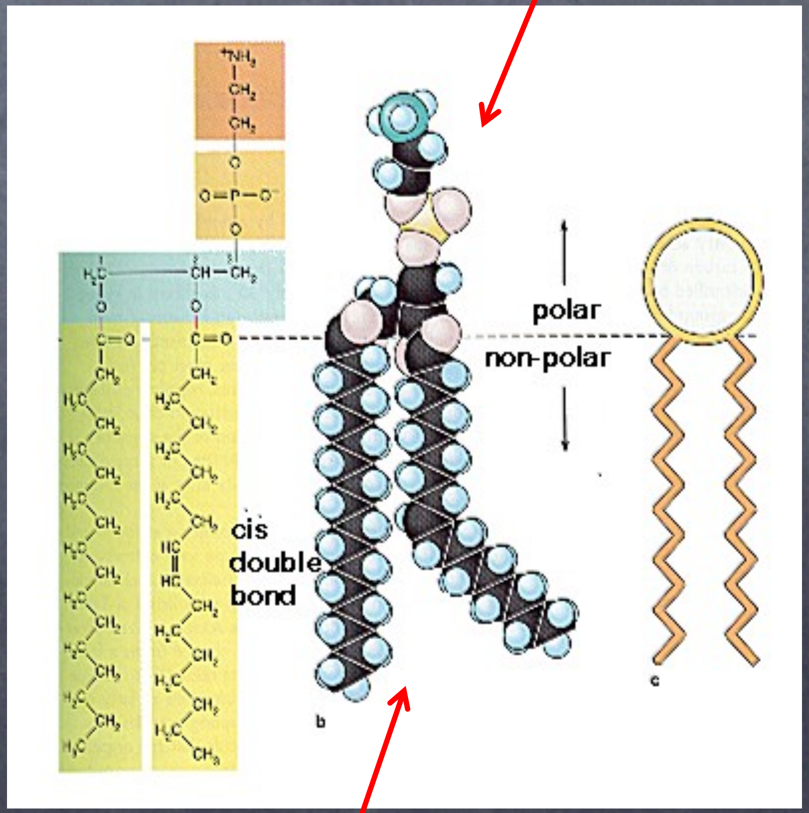
SELECTIVELY PERMEABLE:

Controls what comes **in and out** of the cell.

Does not let **large, charged** or **polar** things through without help.



Head is POLAR & contains a –PO_4 group & glycerol

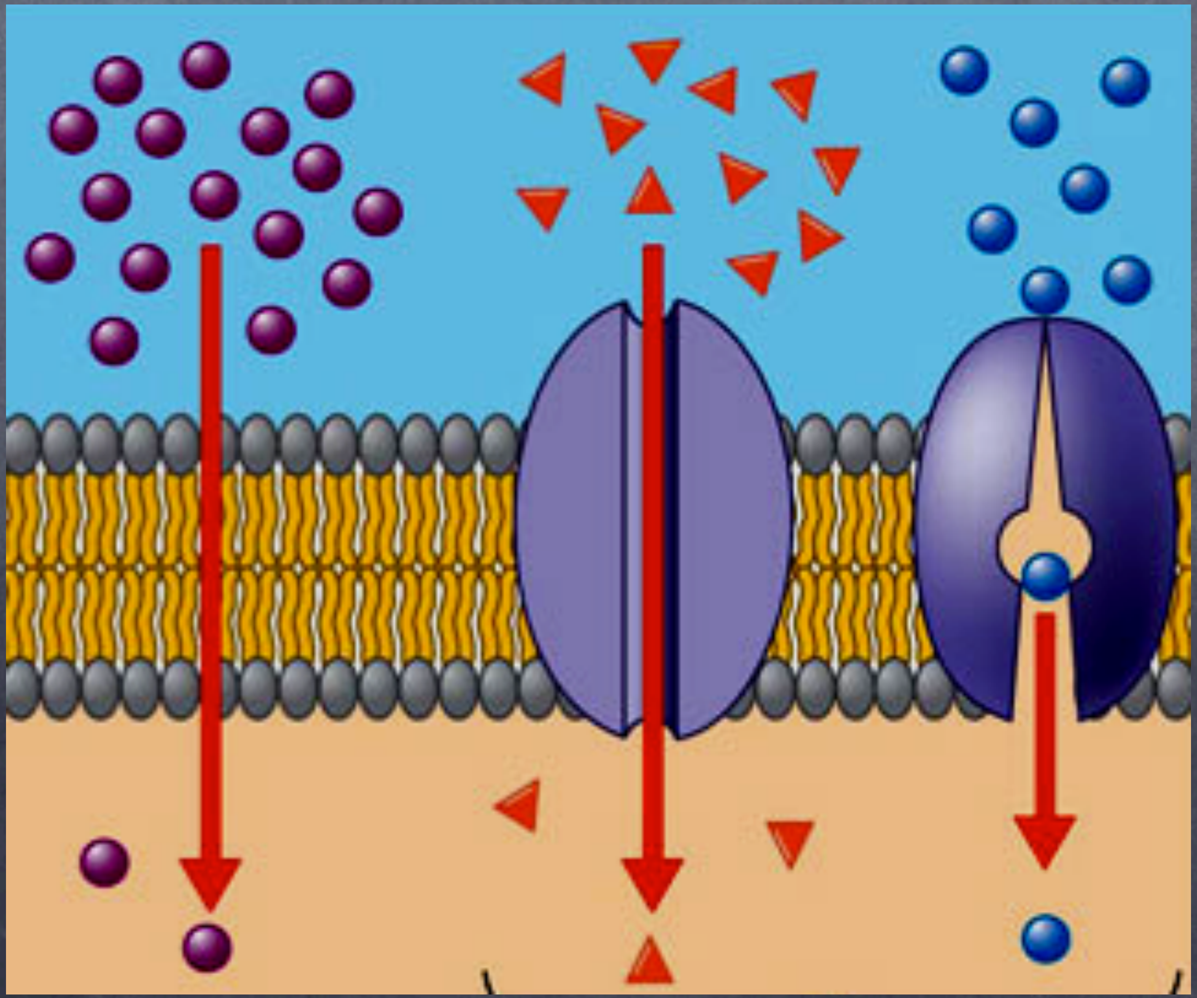


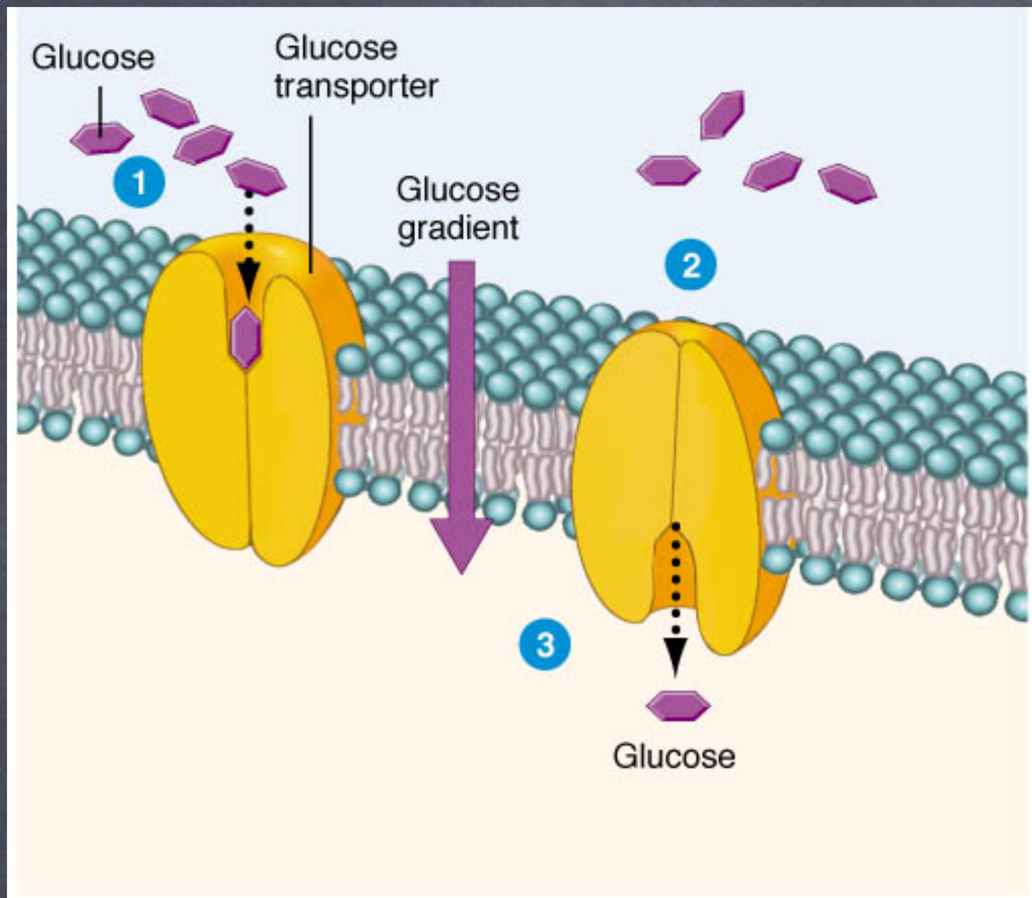
2 NONPOLAR fatty acid chains

Fluxes across the membranes depend on:

1. The gradient (the driving force)
   - chemical for uncharged particles (see Fick's laws)
   -electrochemical for ions (see Nernst's law)

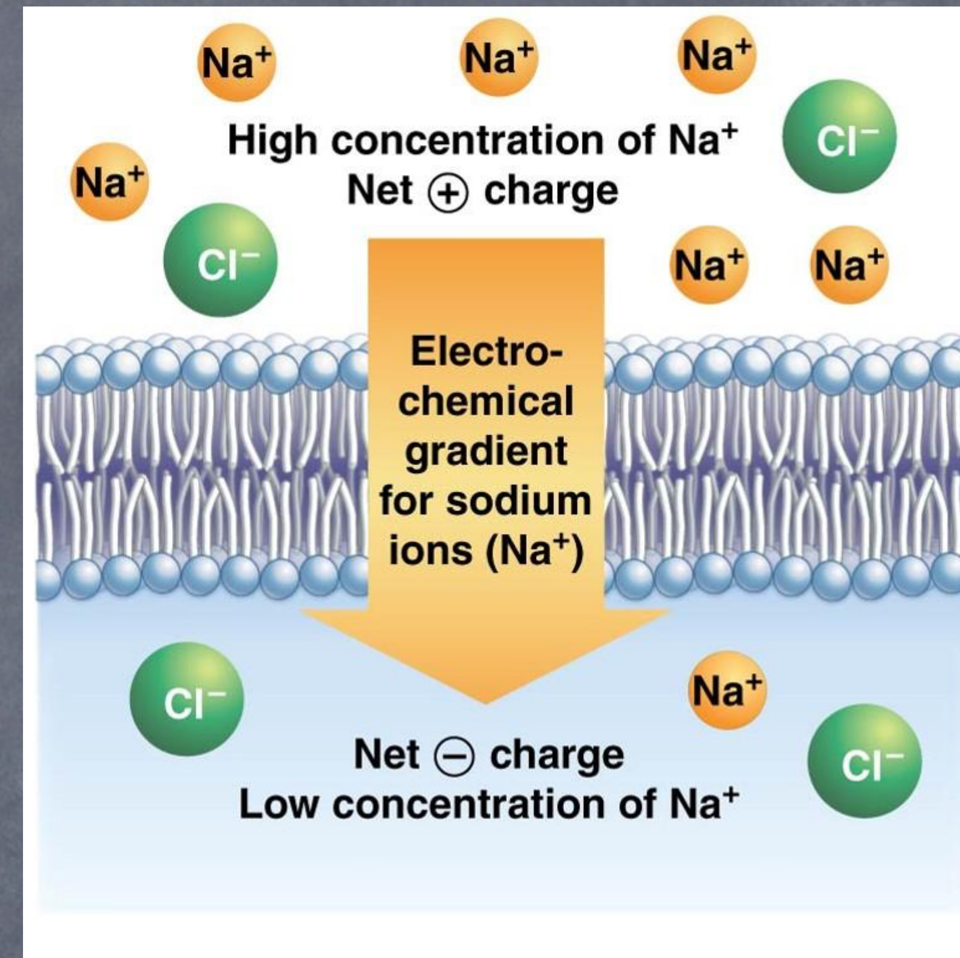
2. The membrane permeability





Outside cell

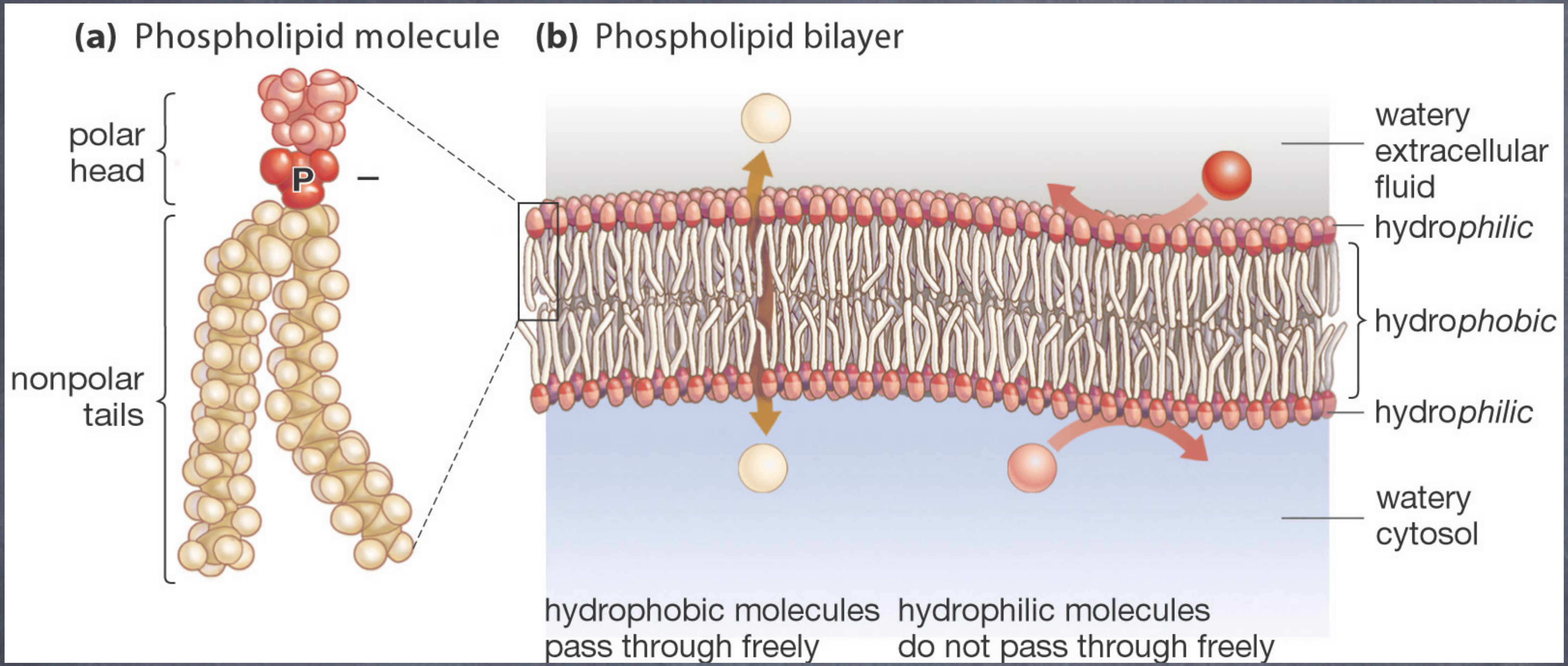
Inside cell



$$J = -D\frac{dc}{dx}$$ I FICK'S LAW

$$J = -D\left(\frac{dc}{dx} + c\frac{zF}{RT}\frac{d\varphi}{dx}\right)$$ NERNST-PLANCK

$$J = P_m \Delta c$$



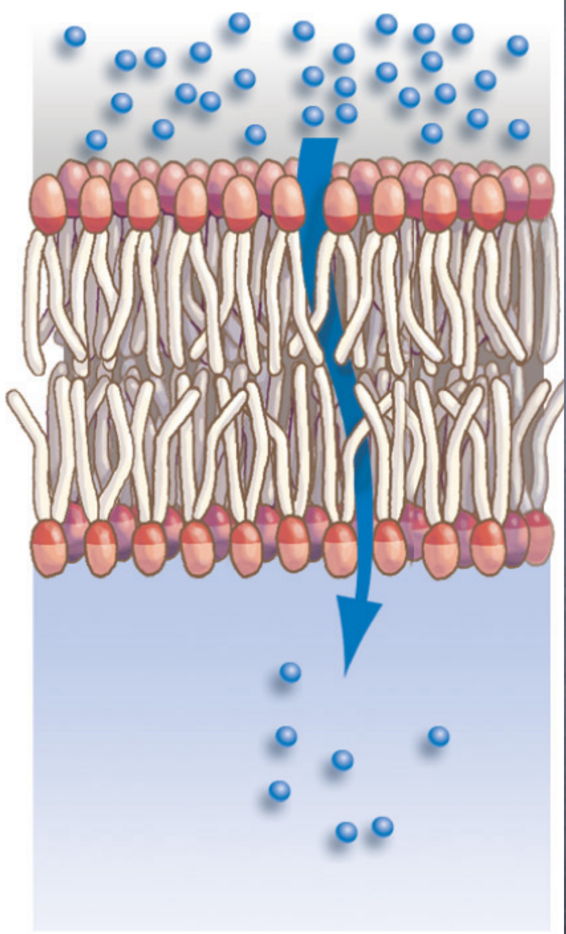
Small molecules and larger hydrophobic molecules move through easily.
e.g. O_2, CO_2, lipids…

Ions, hydrophilic molecules larger than water, and large molecules such as proteins do not move through the membrane on their own.

Three Forms of Transport Across the Membrane

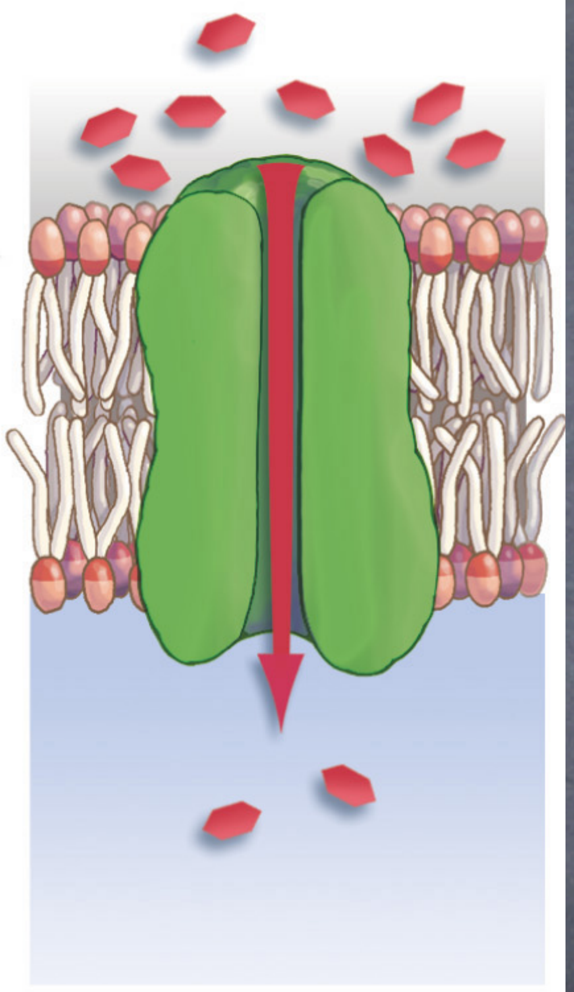
Passive transport

simple diffusion



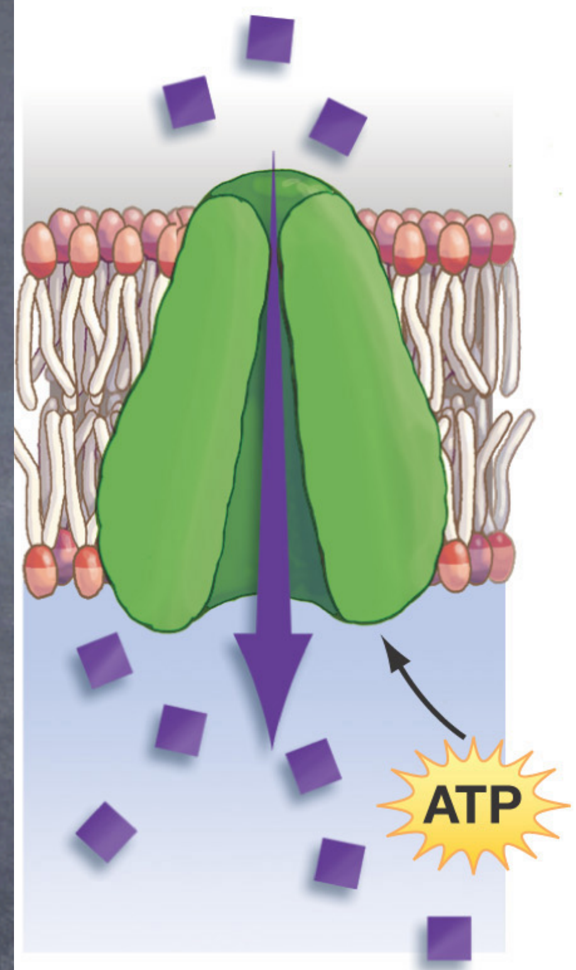
Materials move down their concentration gradient through the phospholipid bilayer.

facilitated diffusion



The passage of materials is aided both by a concentration gradient and by a transport protein.

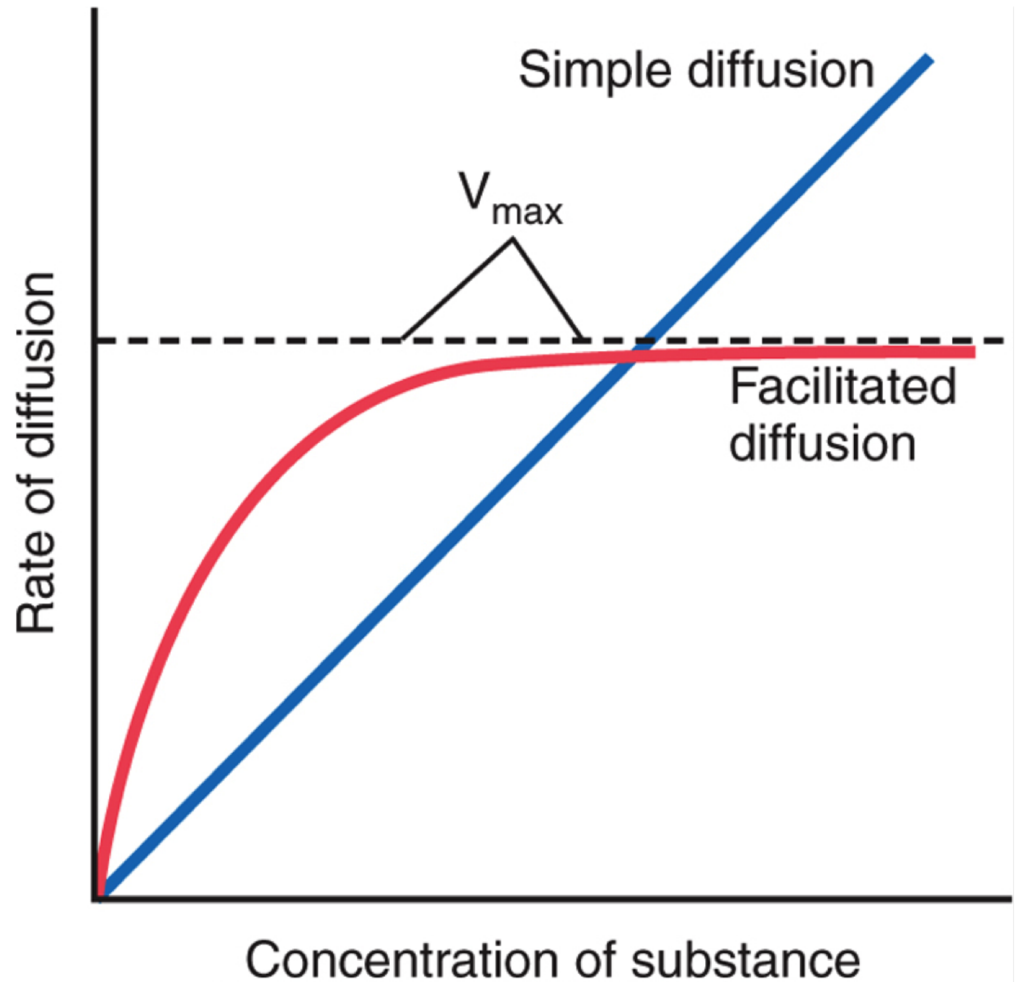
Active transport



Molecules again move through a transport protein, but now energy must be expended to move them against their concentration gradient.

- **Simple Diffusion** may occur through any part of the plasma membrane (e.g. N_2, O_2, CO_2, NO gas molecules)

- **Facilitated diffusion** uses protein transporters (e.g. glucose uniporter)



Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

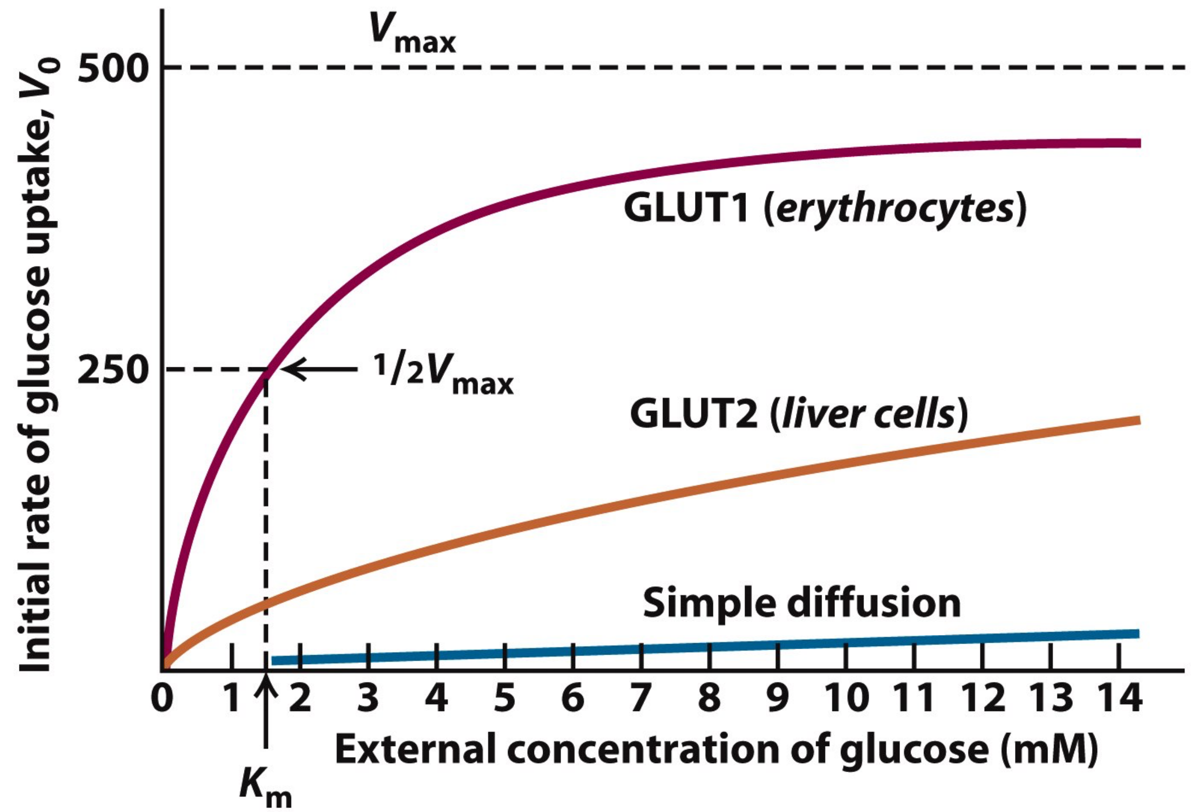


Figure 11-4
Molecular Cell Biology, Sixth Edition

Osmosis

- Diffusion of water across a membrane
- Moves from HIGH water potential (low solute) to LOW potential (high solute)

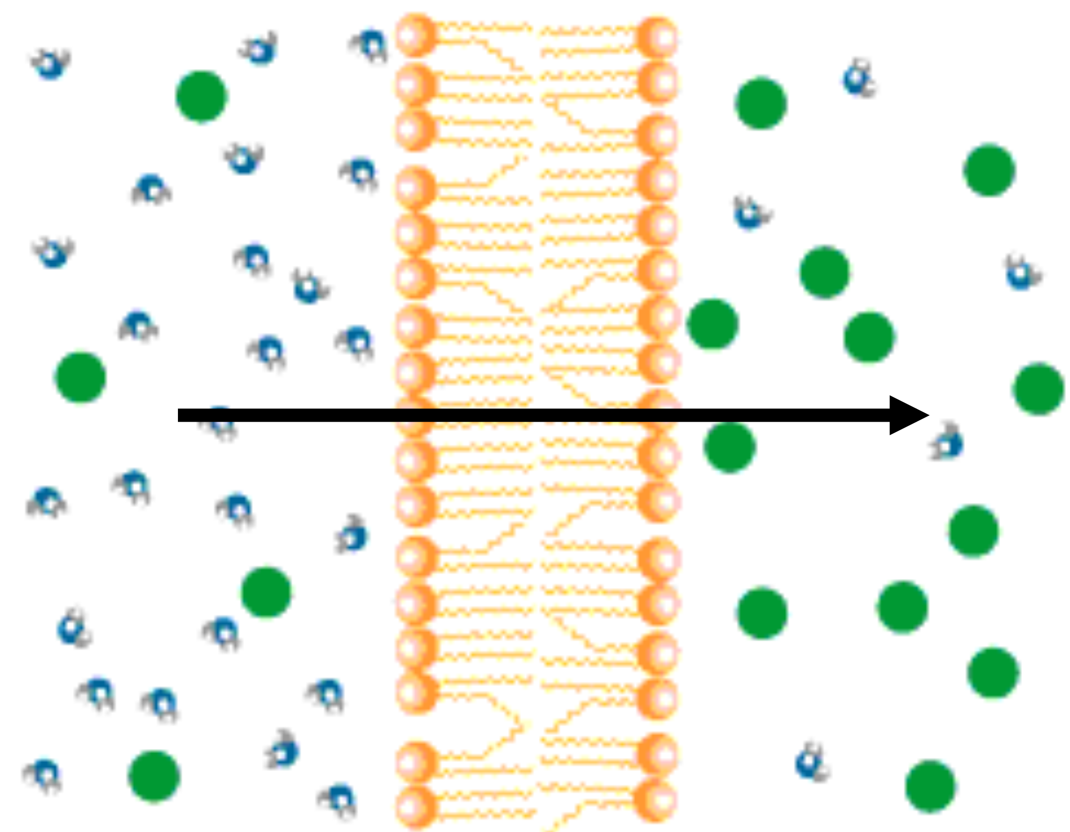
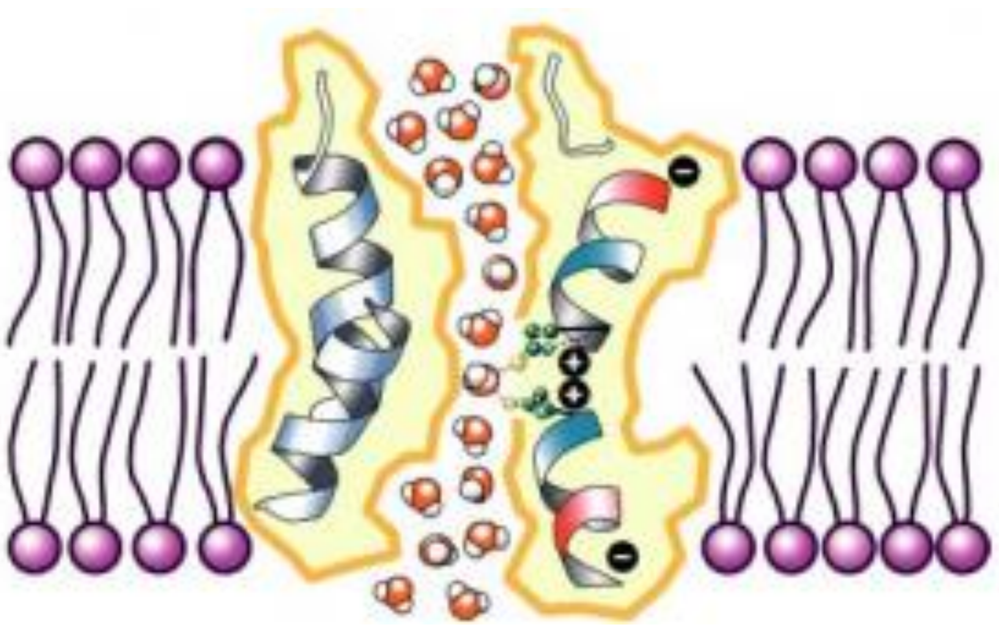


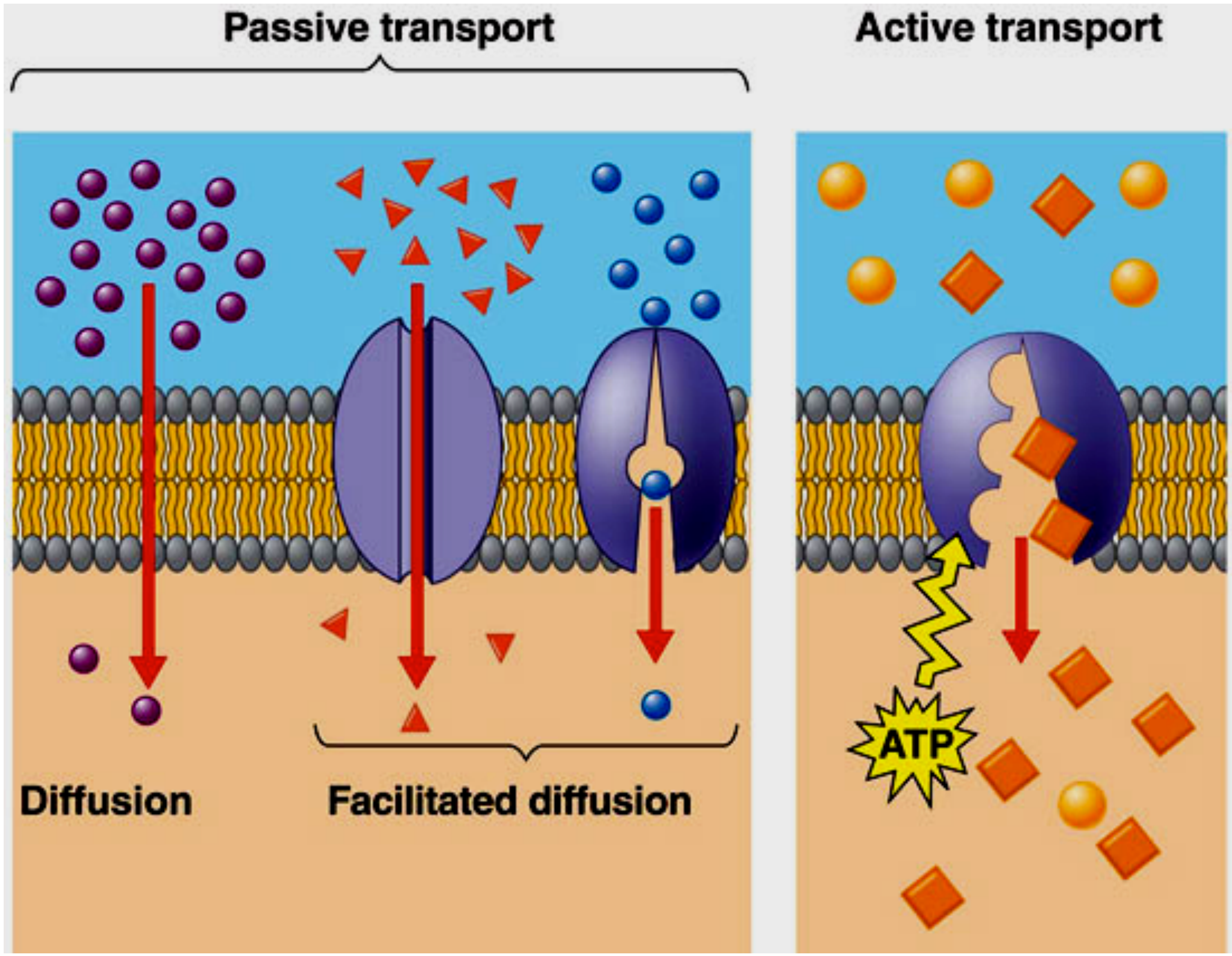
TABLE 5-1 ***Direction of Osmosis***

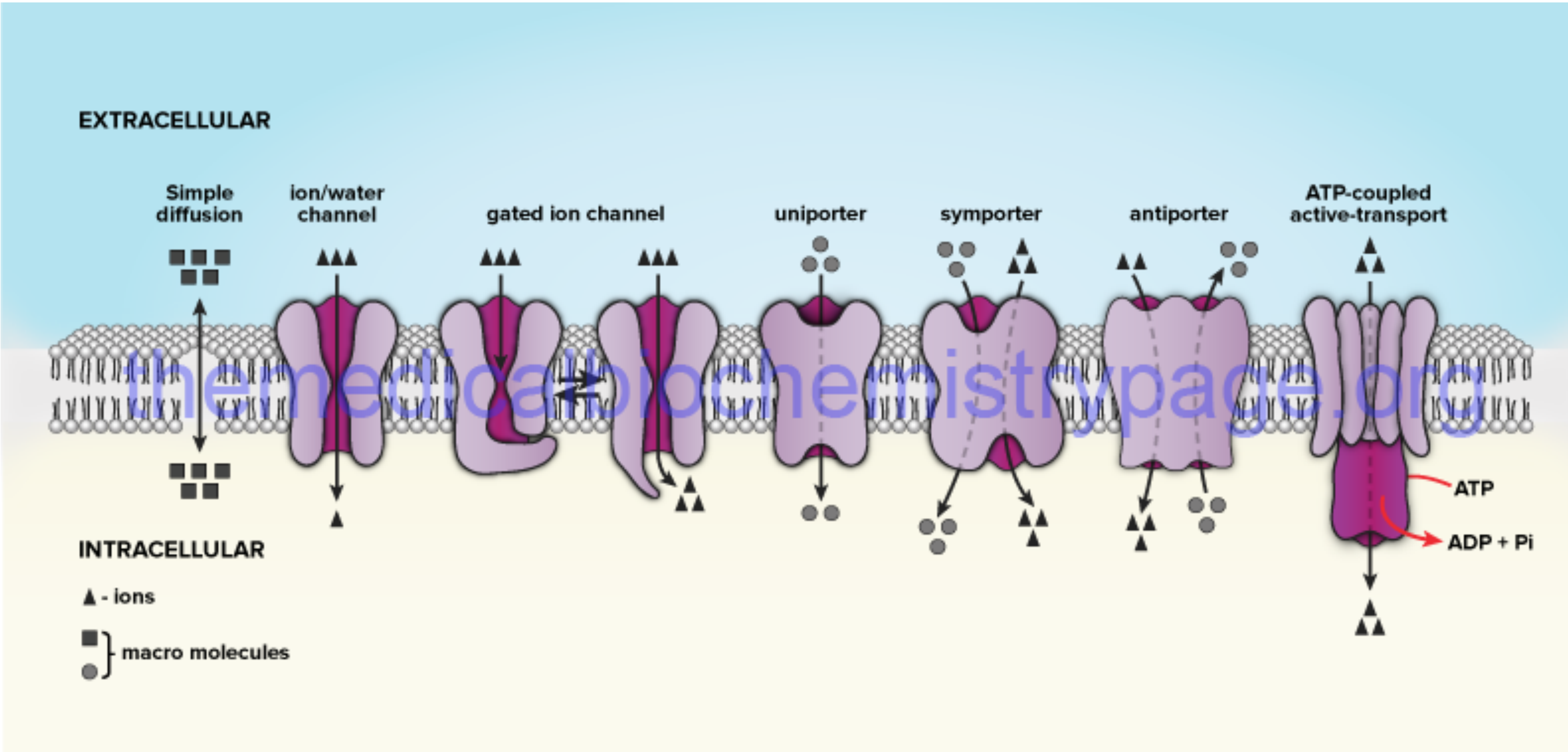
Condition	Net movement of water
External solution is hypotonic to cytosol	into the cell
External solution is hypertonic to cytosol	out of the cell
External solution is isotonic to cytosol	none



protein channels for water:
AQUAPORINS

MEMBRANE TRANSPORT PROTEINS





ATP-powered pump (10^0 – 10^3 ions/s)

Ion channel (10^7 – 10^8 ions/s)

Transporter (10^2 – 10^4 molecules/s)

Human Genome Organization: HUGO

The Human Genome Organization (HUGO) Nomenclature Committee Database has as a goal to make sure that **each symbol is unique**, and ensures that **each gene locus is only given one approved gene symbol**

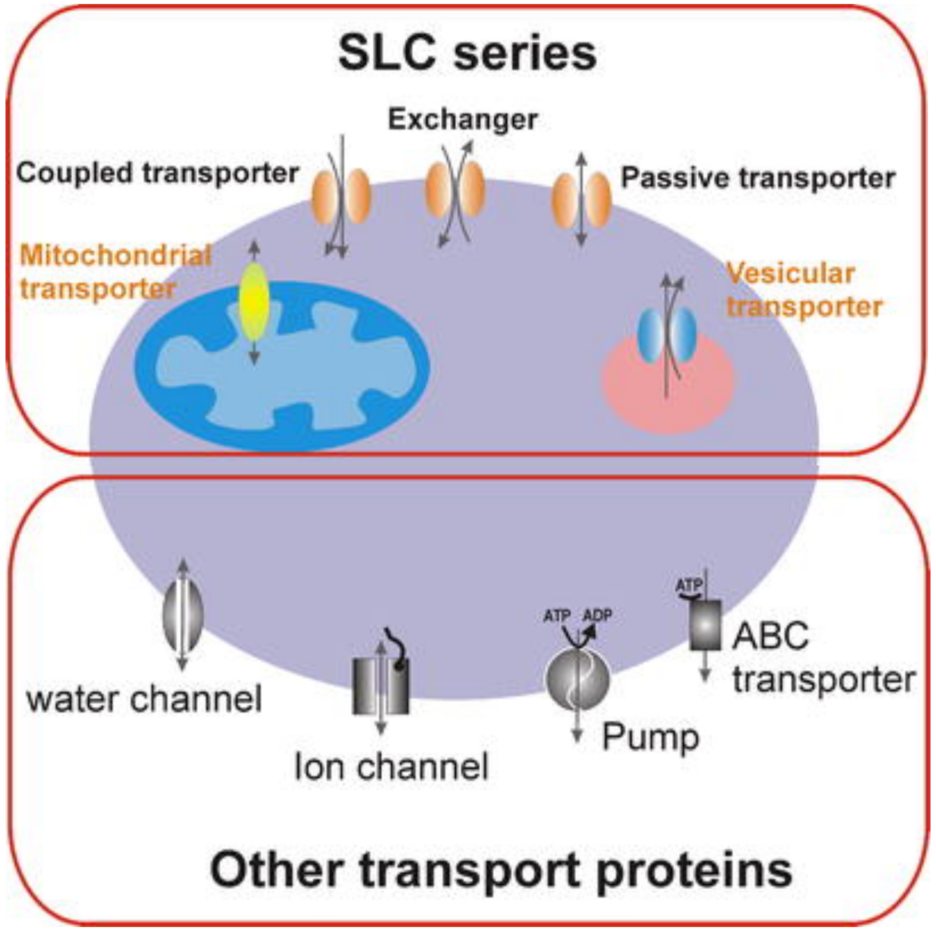
In HUGO Nomenclature Committee Database:

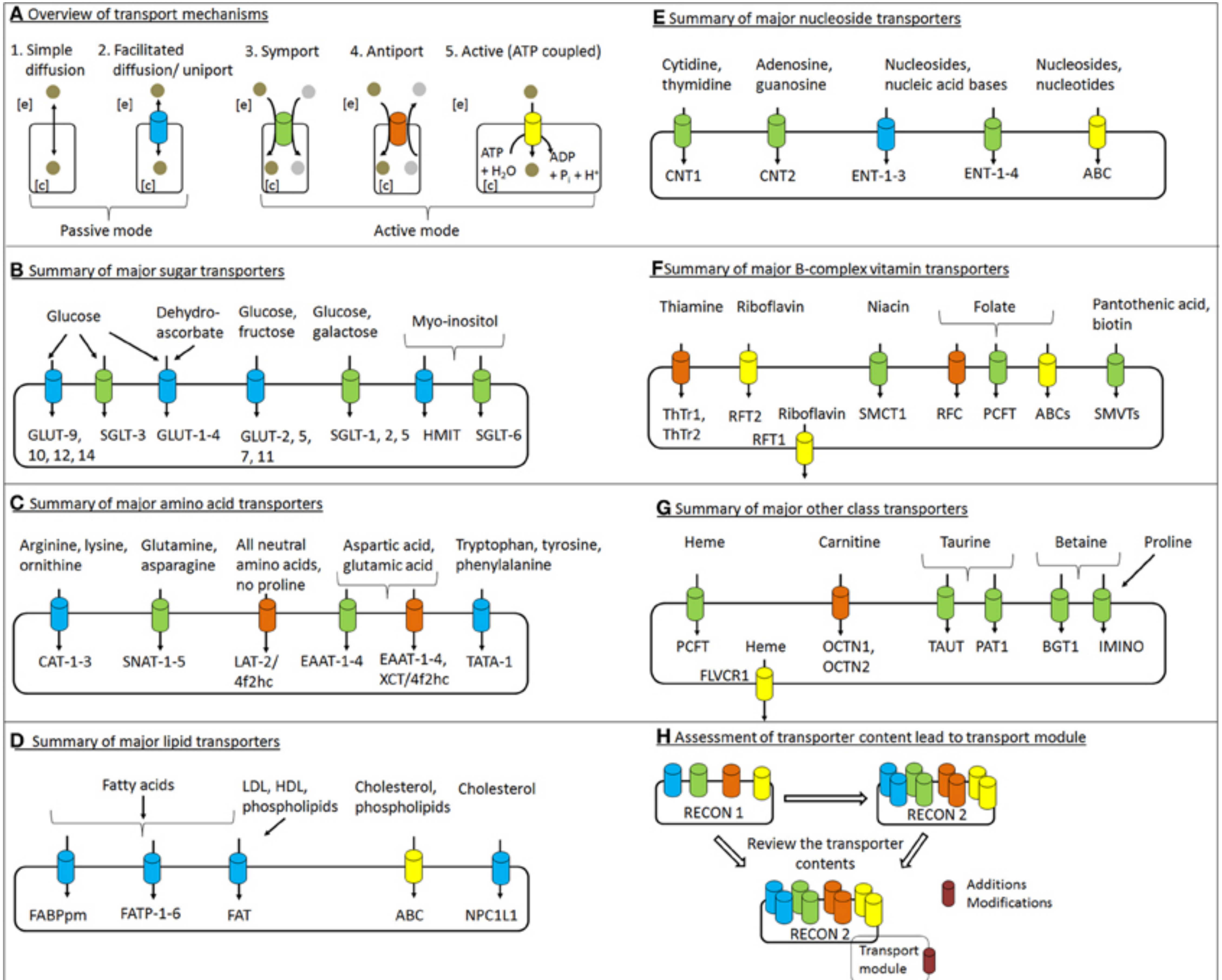
SOLUTE CARRIER FAMILY (SLC) series:

Currently 43 families and 298 transporter genes

Non-SLC human transport-related genes:

- ATP-driven transporters
- Channels
- Ionotropic receptors
- Aquaporins
- Transporter and channel subunits
- auxiliary/regulatory transport proteins



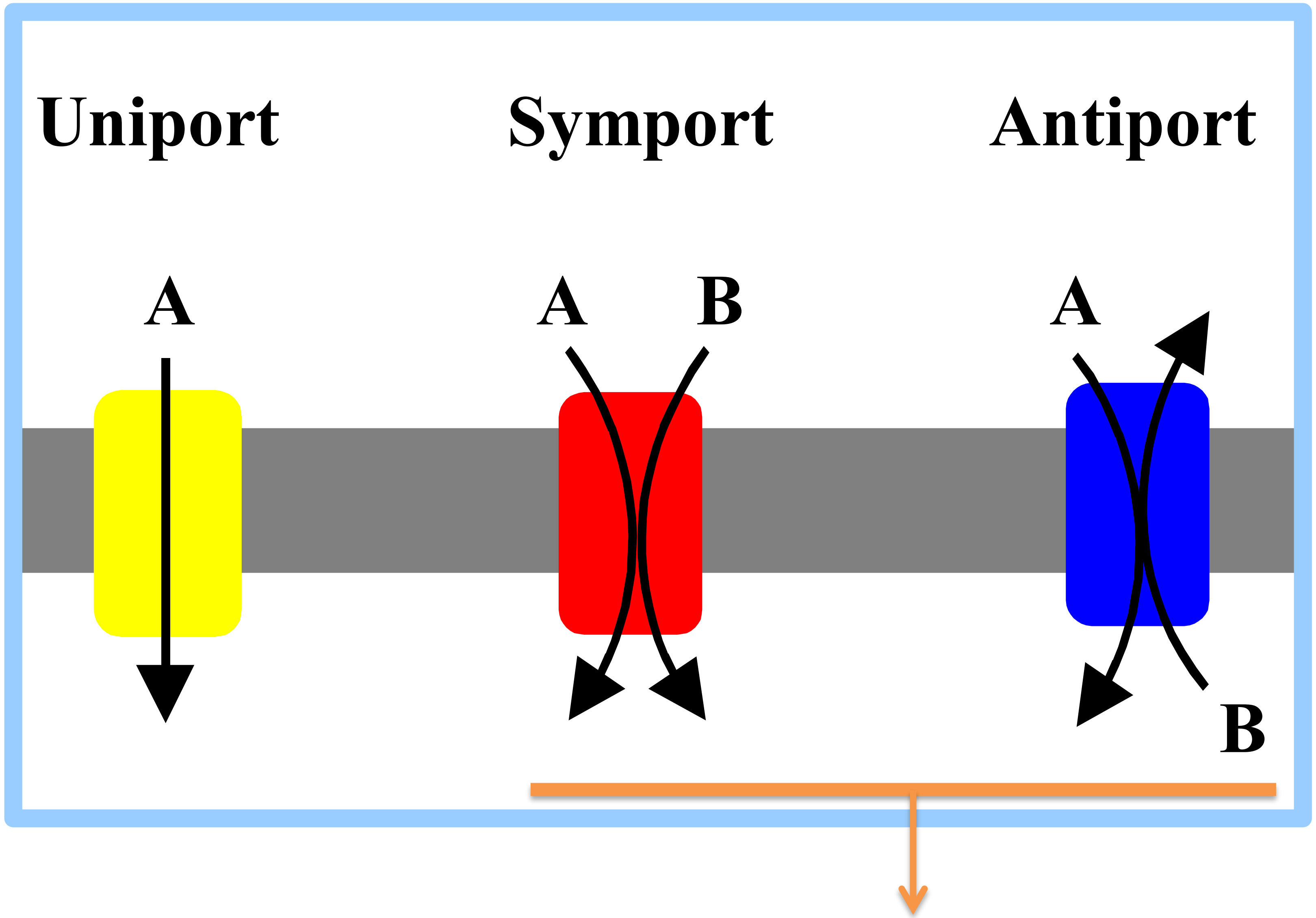

A Overview of transport mechanisms
1. Simple diffusion
2. Facilitated diffusion/ uniport
3. Symport
4. Antiport
5. Active (ATP coupled)
[e]
[c]
ATP + H_2O
ADP + P_i + H^+
Passive mode
Active mode
B Summary of major sugar transporters
Glucose
Dehydro-ascorbate
Glucose, fructose
Glucose, galactose
Myo-inositol
GLUT-9, 10, 12, 14
SGLT-3
GLUT-1-4
GLUT-2, 5, 7, 11
SGLT-1, 2, 5
HMIT
SGLT-6
C Summary of major amino acid transporters
Arginine, lysine, ornithine
Glutamine, asparagine
All neutral amino acids, no proline
Aspartic acid, glutamic acid
Tryptophan, tyrosine, phenylalanine
CAT-1-3
SNAT-1-5
LAT-2/ 4f2hc
EAAT-1-4
EAAT-1-4, XCT/4f2hc
TATA-1
D Summary of major lipid transporters
Fatty acids
LDL, HDL, phospholipids
Cholesterol, phospholipids
Cholesterol
FABPpm
FATP-1-6
FAT
ABC
NPC1L1
E Summary of major nucleoside transporters
Cytidine, thymidine
Adenosine, guanosine
Nucleosides, nucleic acid bases
Nucleosides, nucleotides
CNT1
CNT2
ENT-1-3
ENT-1-4
ABC
F Summary of major B-complex vitamin transporters
Thiamine
Riboflavin
Niacin
Folate
Pantothenic acid, biotin
ThTr1, ThTr2
RFT2
Riboflavin RFT1
SMCT1
RFC
PCFT
ABCs
SMVTs
G Summary of major other class transporters
Heme
Carnitine
Taurine
Betaine
Proline
PCFT
Heme FLVCR1
OCTN1, OCTN2
TAUT
PAT1
BGT1
IMINO
H Assessment of transporter content lead to transport module
RECON 1
RECON 2
Review the transporter contents
Additions Modifications
RECON 2
Transport module

Transport through cell membrane

Classification based on function

- Membrane transport
  - Passive
    - Simple diffusion
    - Facilitated
      - Via various transporters
      - Via Ion channels
  - Active Via mainly by ATP-driven transporters (pumps)
    - Primary Active transport
    - Secondary active transport

Classes of carrier proteins

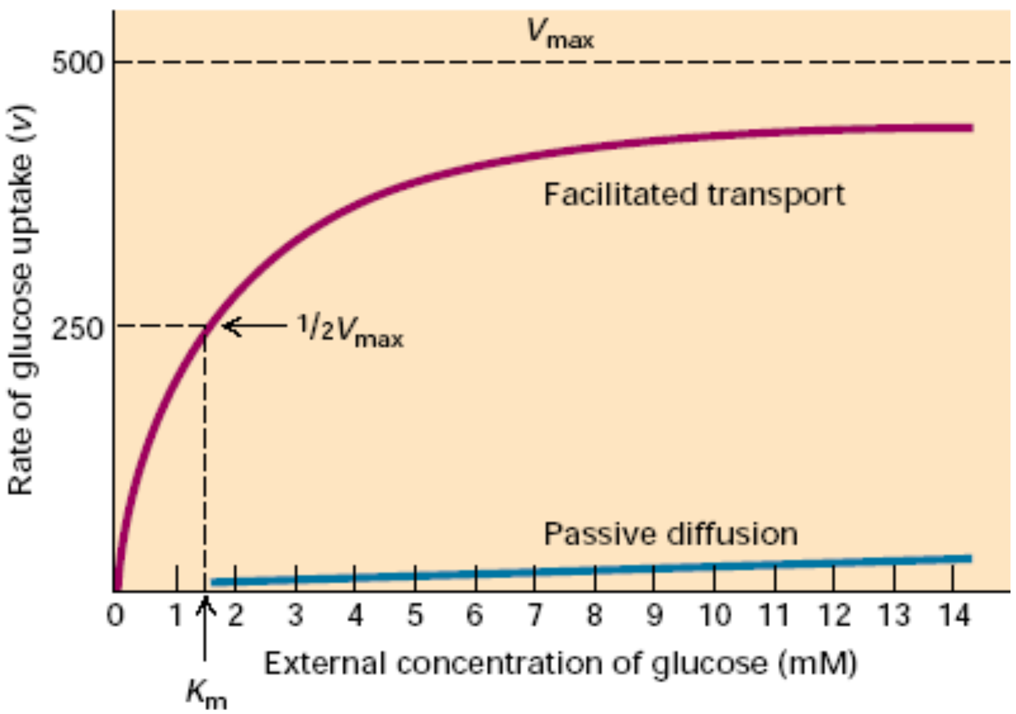


Transport of the two solutes is **obligatorily coupled**.

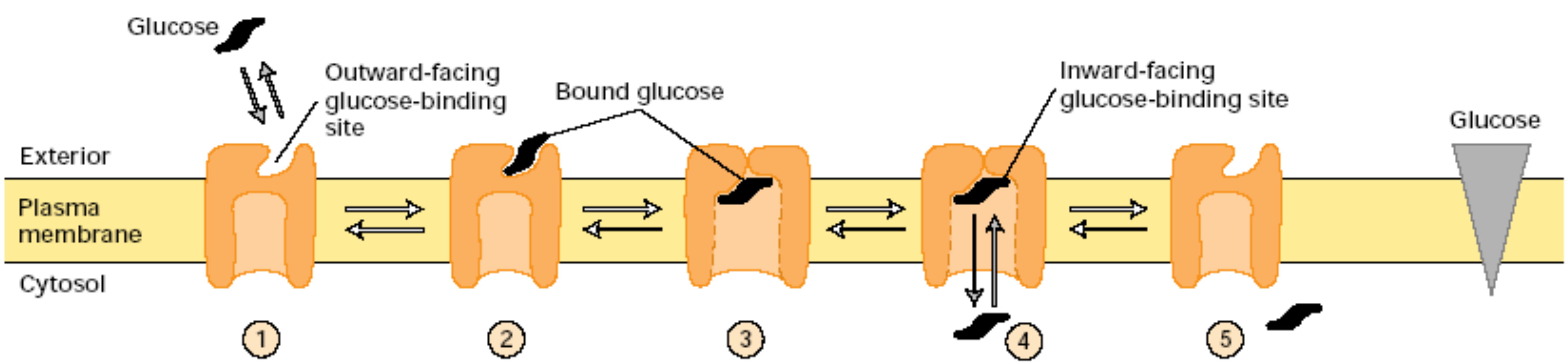
A gradient of one substrate, usually an ion, may drive uphill (against the gradient) transport of a co-substrate.

Uniporters: Example GLUT1

Facilitated vs. passive diffusion

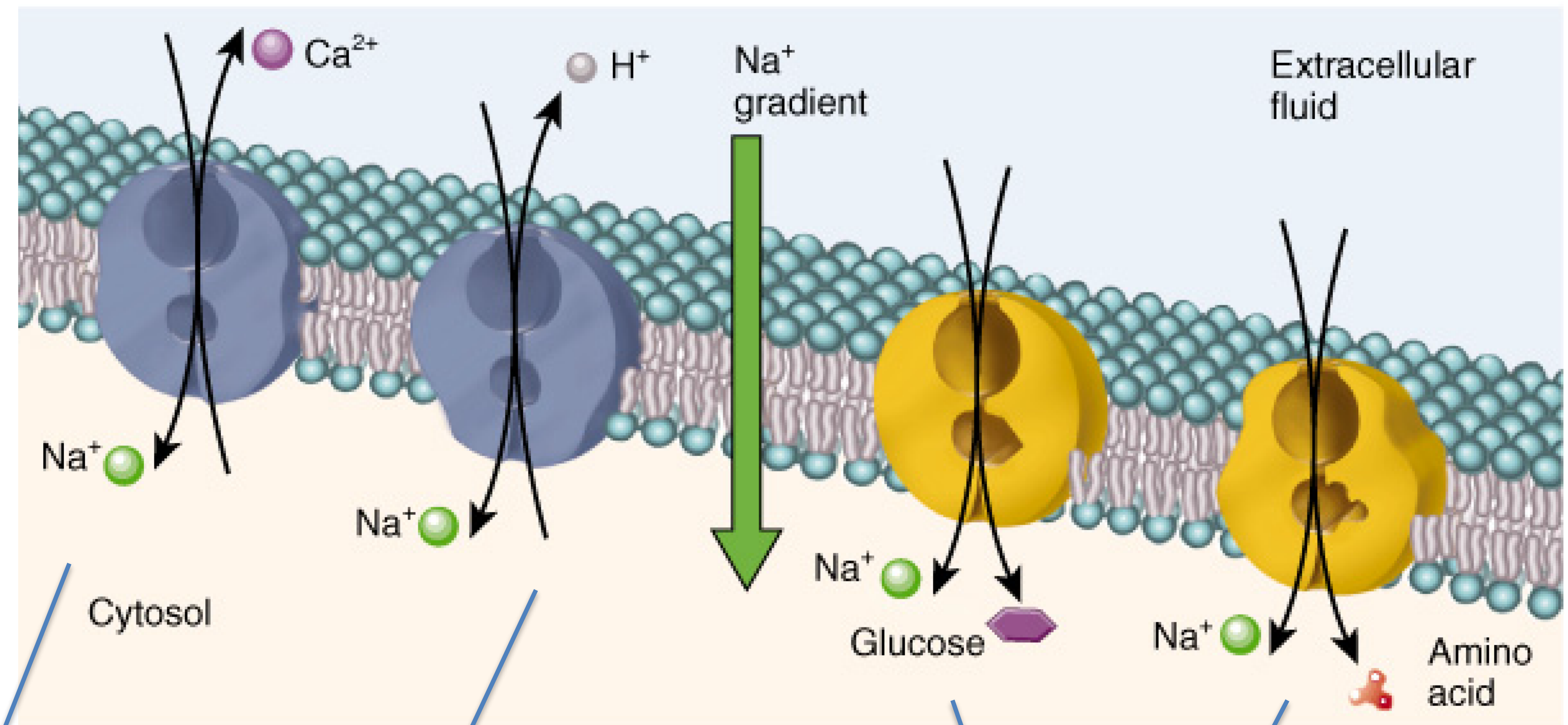


Mechanism of transport



Symporters and Antiporters (Exchangers): some examples

Sodium-coupled

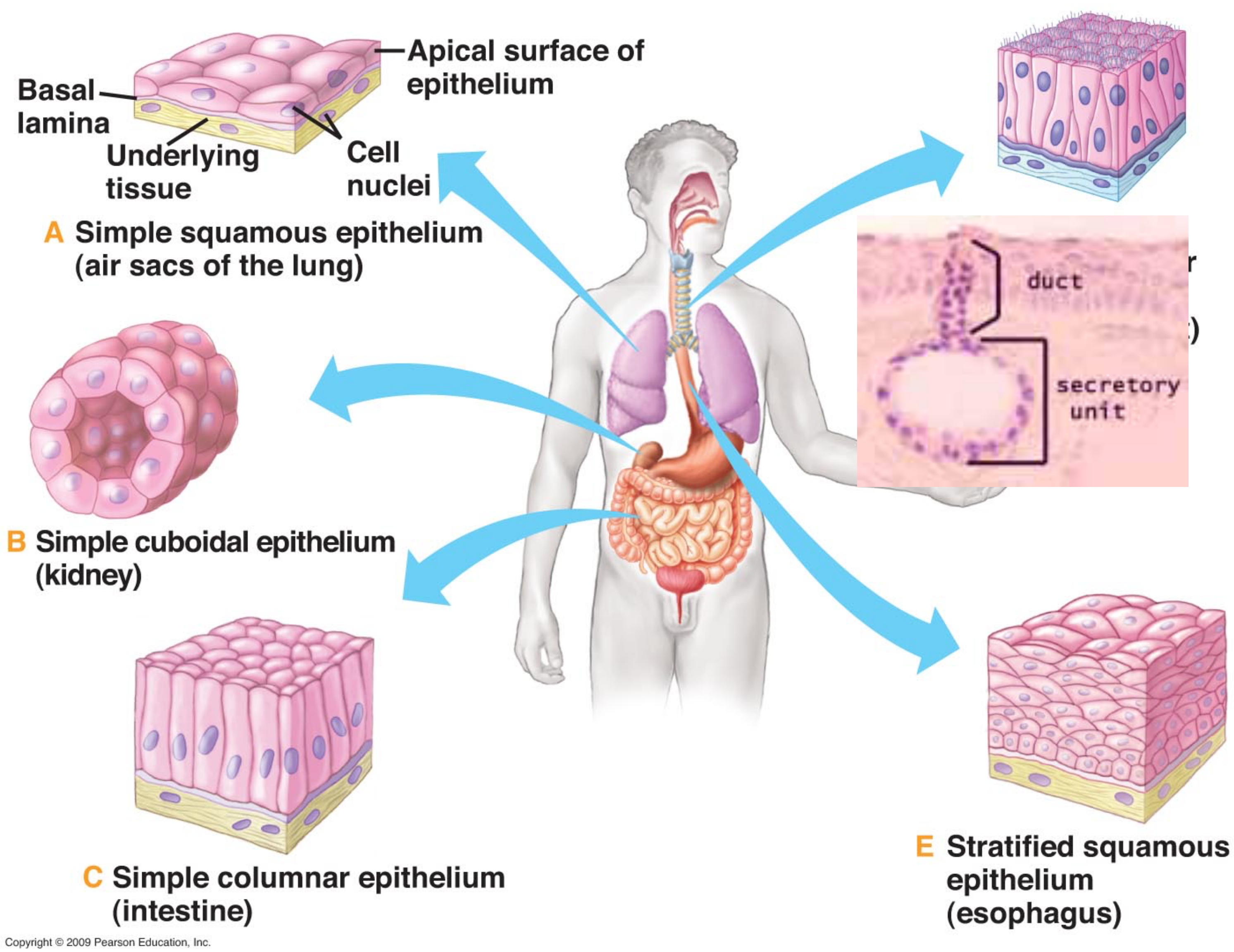


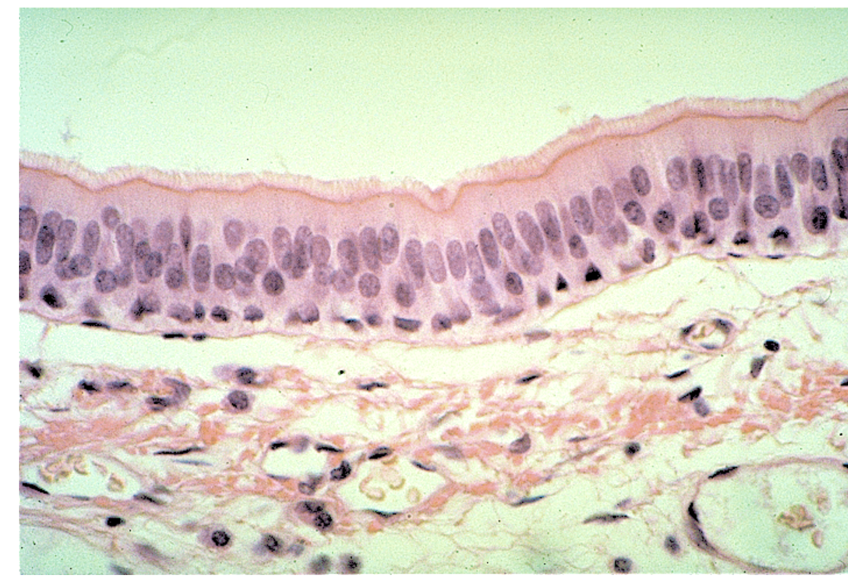
Calcium homeostasis

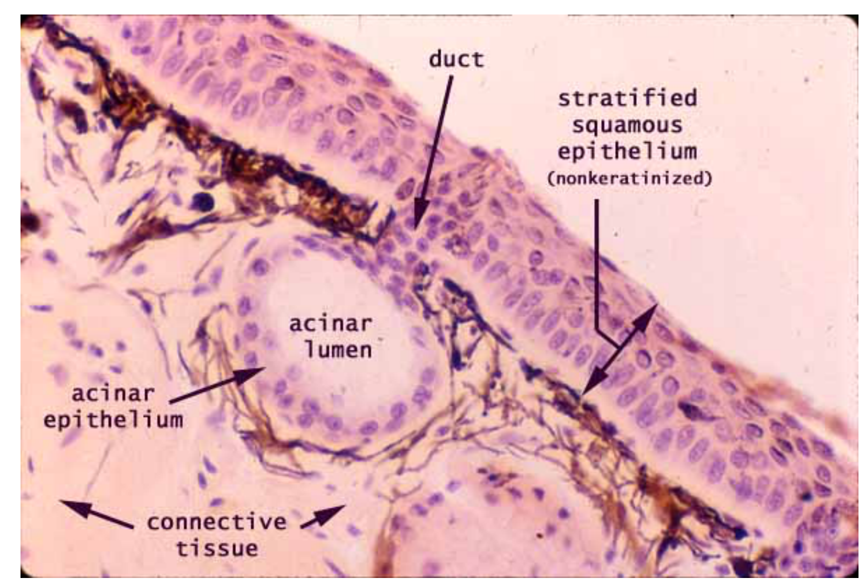
pH control

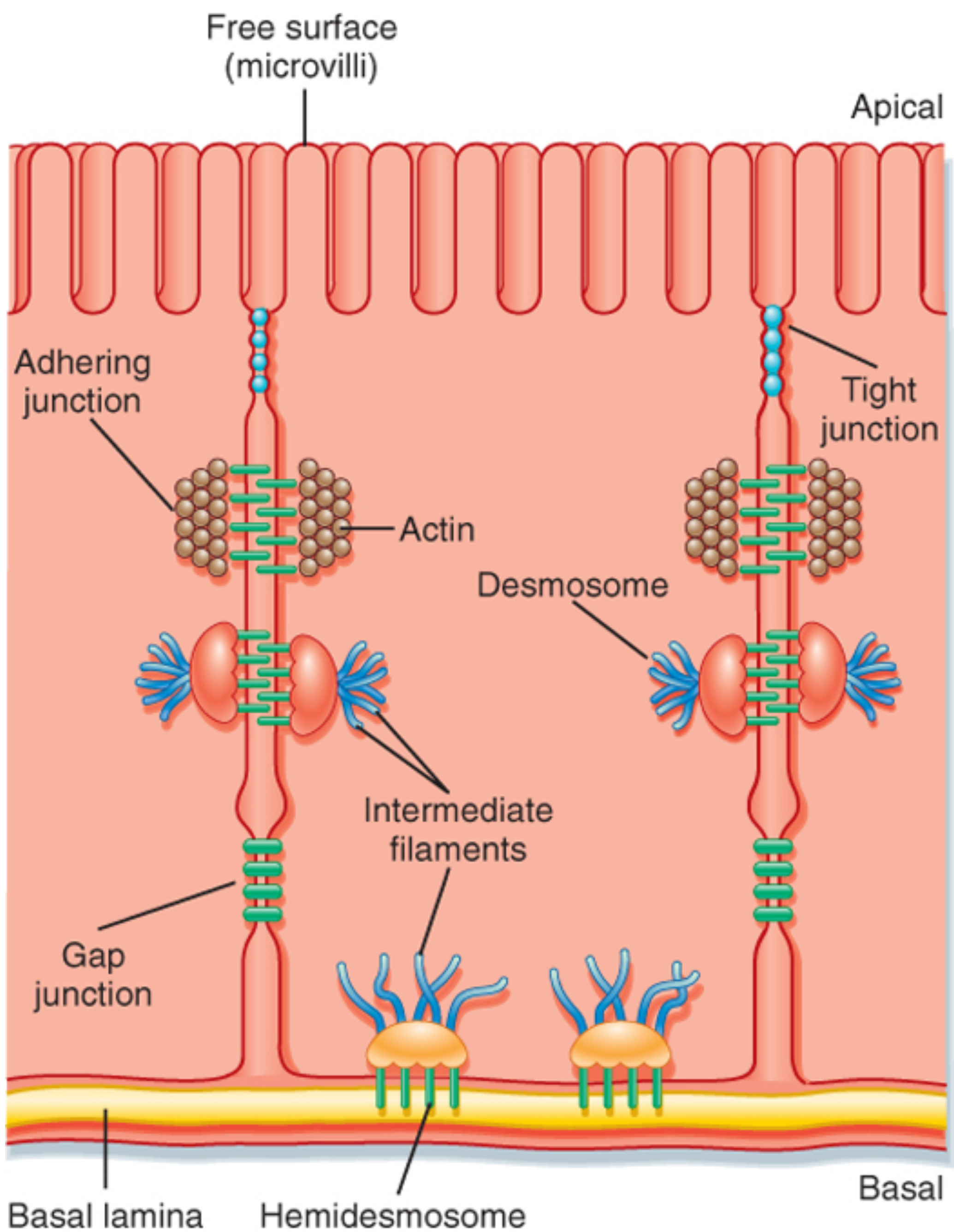
Glucose, aminoacid uptake

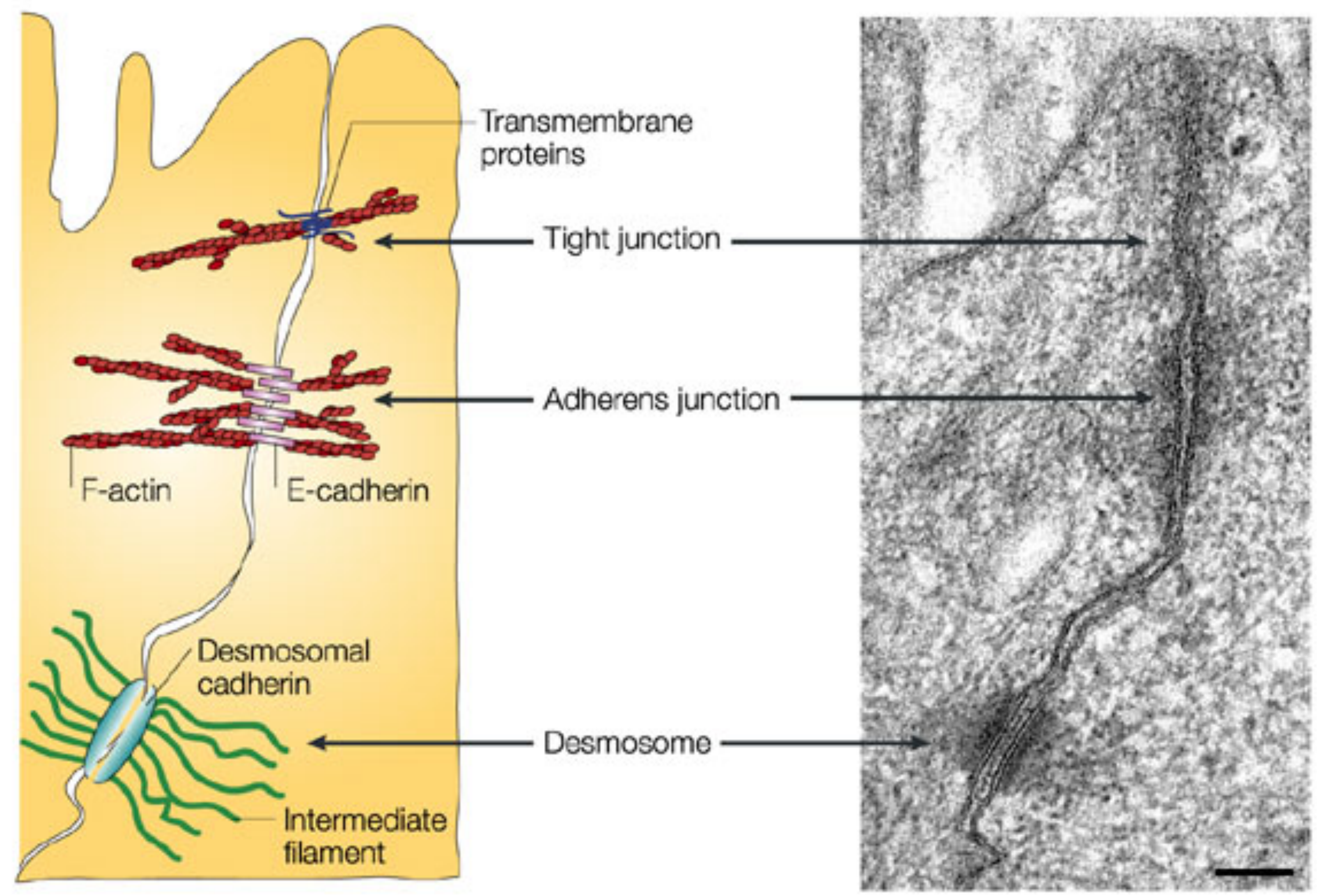
Complexity of membrane transport in epithelia: the importance of spatial organization



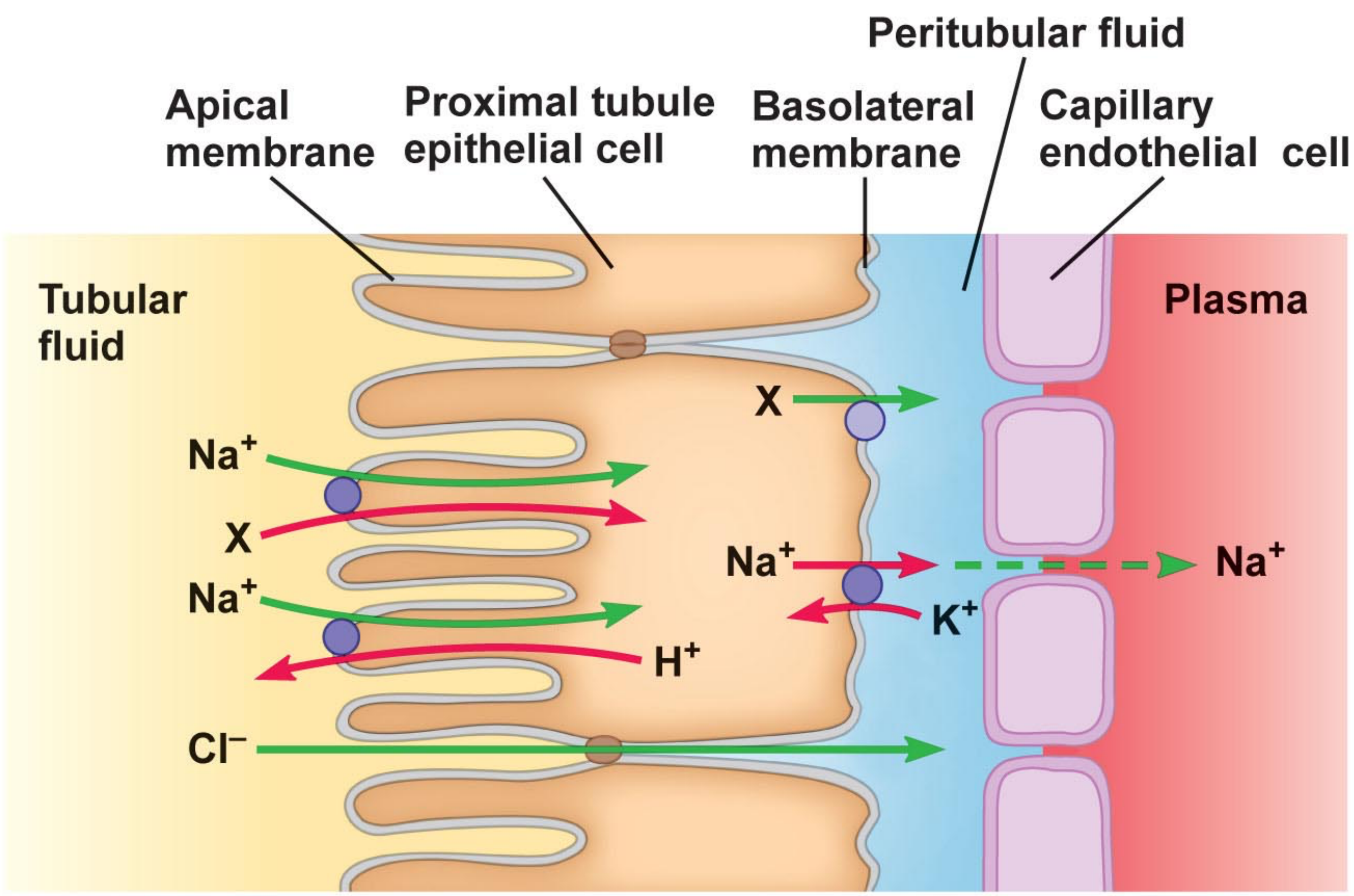




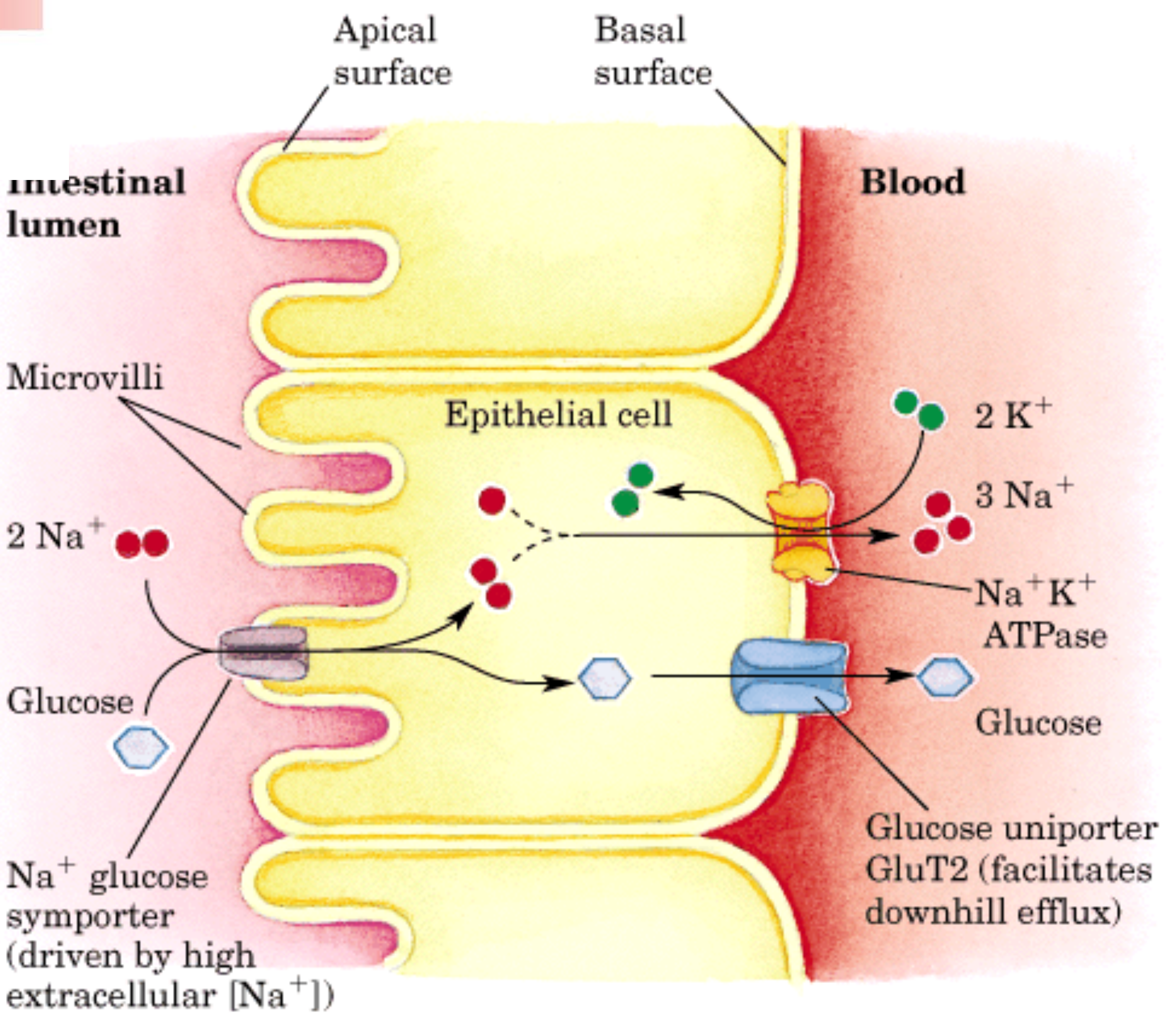


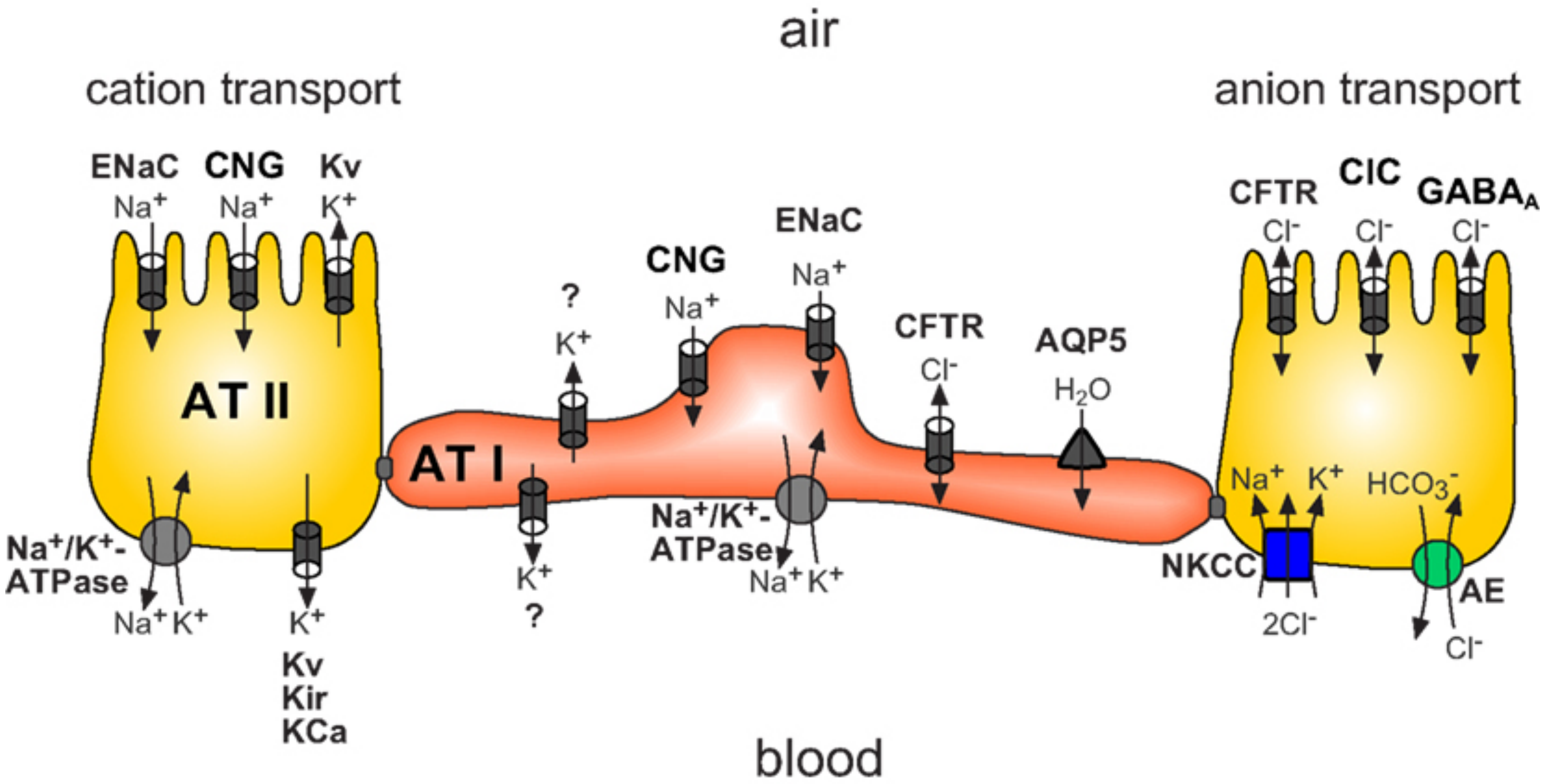


Nature Reviews | Molecular Cell Biology

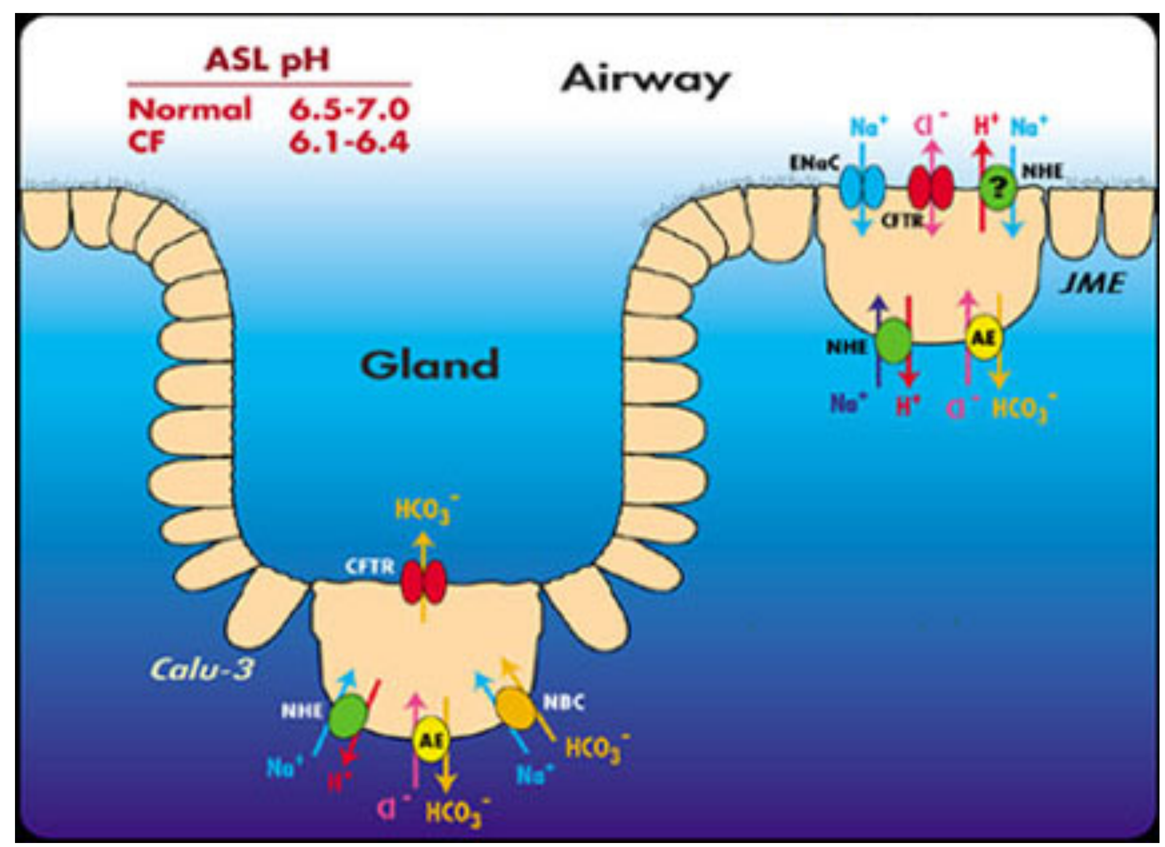


(a) Sodium reabsorption in the proximal tubule



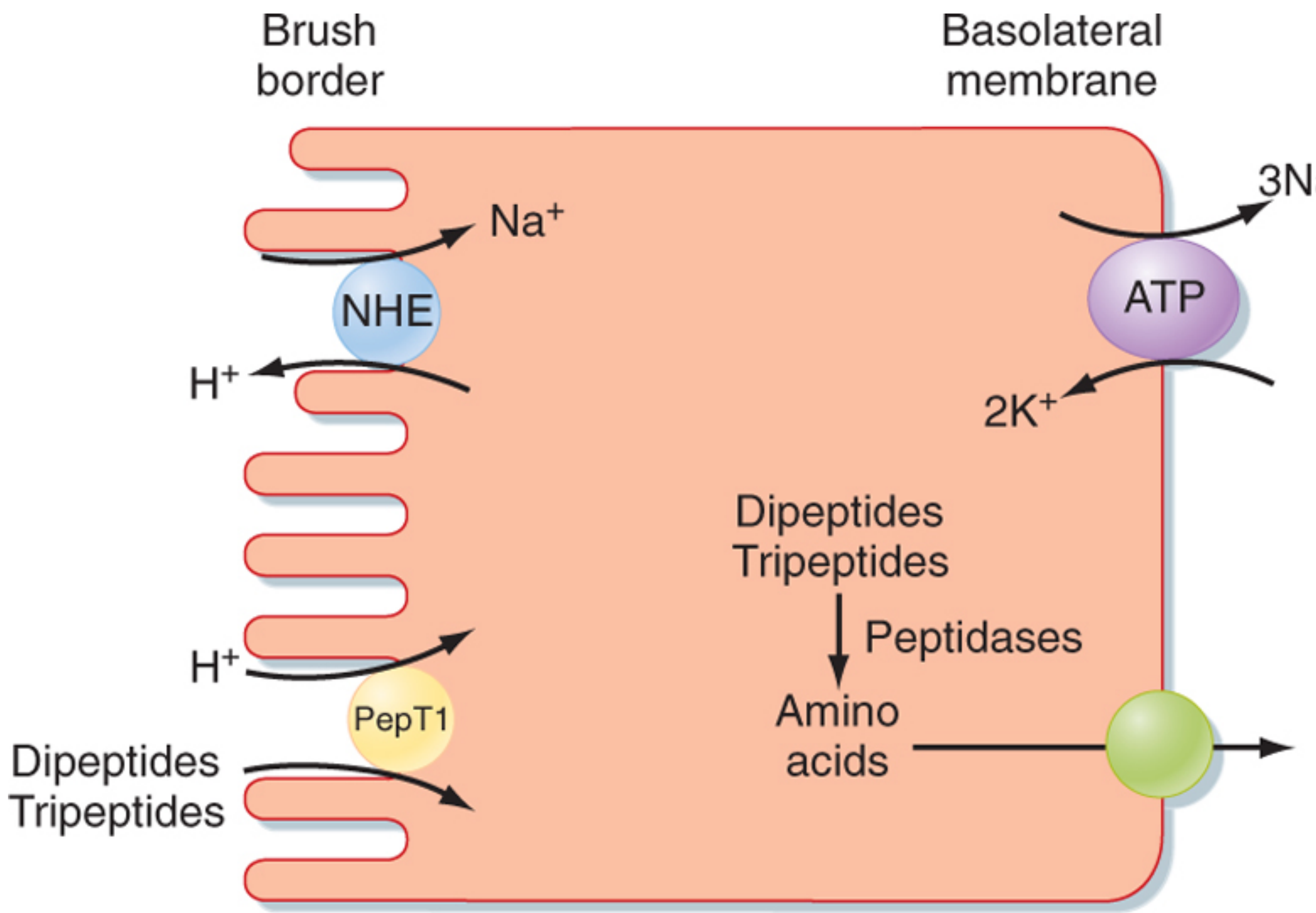


air
cation transport
anion transport
ENaC
CNG
Kv
Na+
K+
AT II
AT I
?
CFTR
ClC
GABA$_A$
Cl-
AQP5
H_2O
Na+/K+-ATPase
NKCC
2Cl-
HCO_3^-
AE
Kv
Kir
KCa
blood



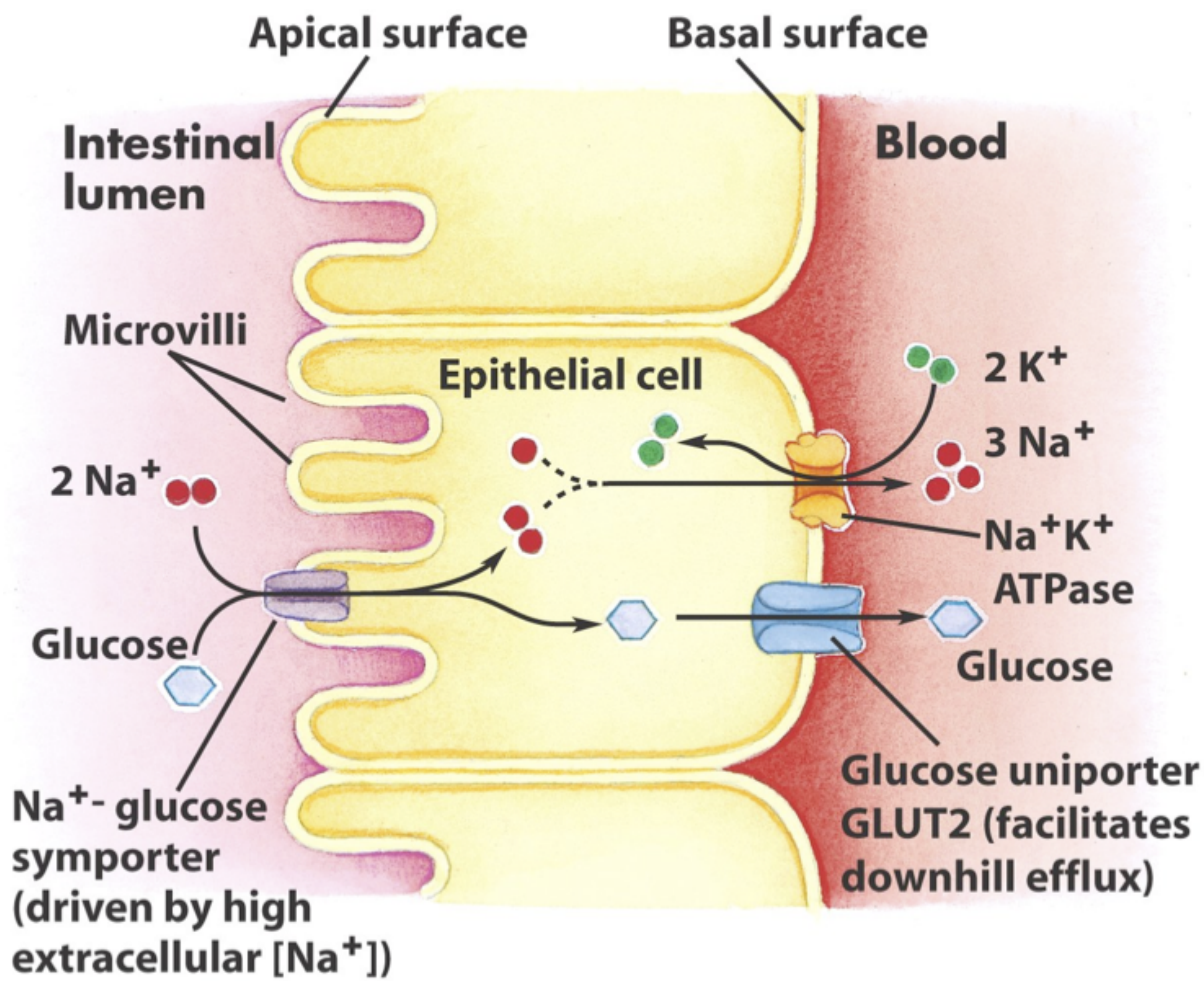
ASL pH
Normal 6.5-7.0
CF 6.1-6.4
Airway
Gland
ENaC
CFTR
NHE
JME
AE
Calu-3
NBC

Integrated example 1: epithelial absorption of peptides



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

Integrated example 2: epithelial absorption of glucose



Ion Channels

Three basic properties of ion channels:

- To conduct ions rapidly
- Exhibit high selectivity: only certain ion species flow while others are excluded
- Conduction be regulated by processes known as gating, i.e. ion conduction is turned on and off in response to specific environmental stimuli

Ion Channels Have Very High Turnover Ratios

Carrier	Substrate Turnover (s^{-1})
Valinomycin	3×10^4
Na-K-ATPase	5×10^2
Ca-ATPase	2×10^2
Glucose transporter	$0.1\text{-}1.3 \times 10^4$

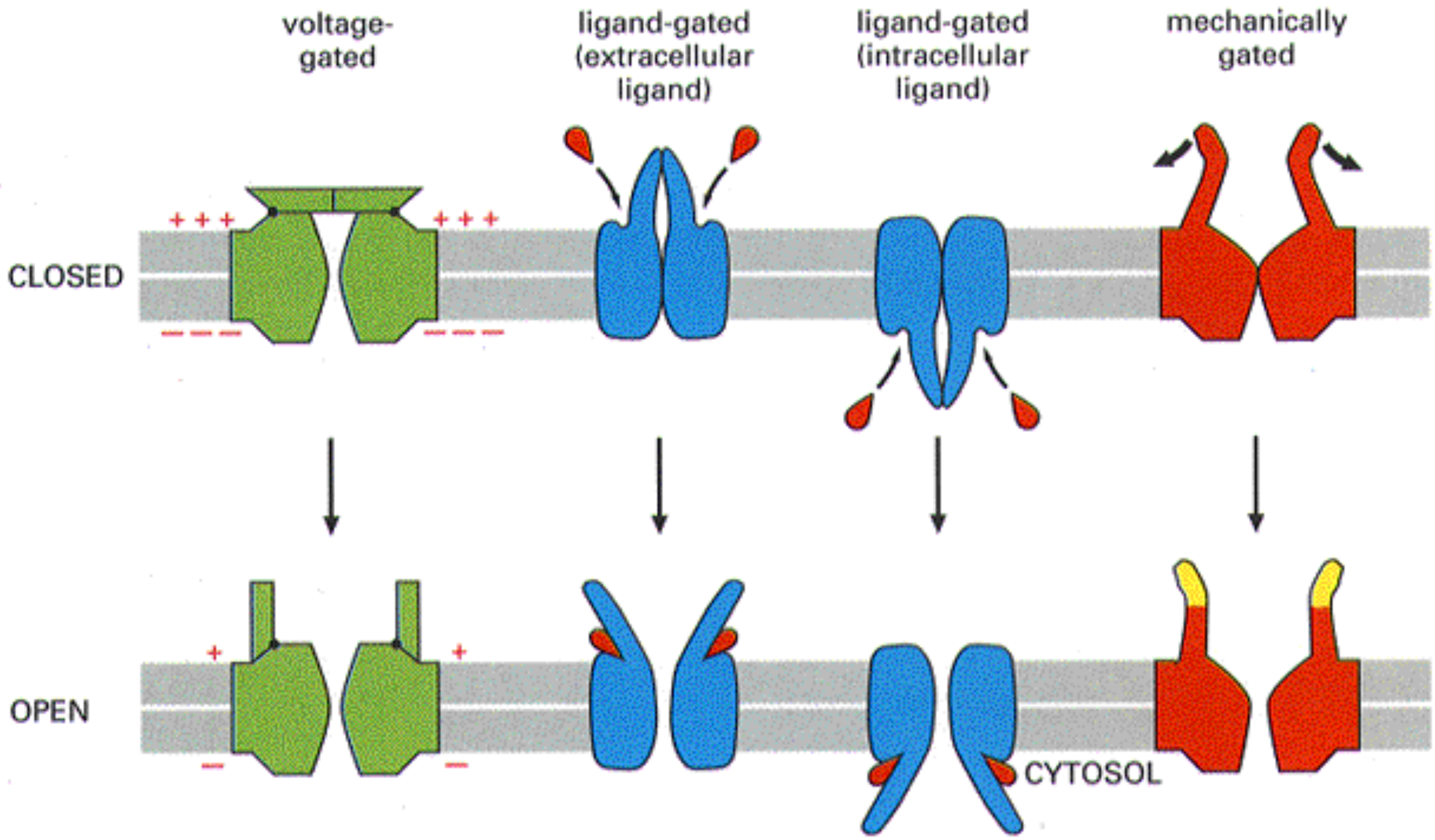
Channel	Substrate Turnover (s^{-1})
Na-channel (V)	7×10^6
Ca-channel (V)	1.9×10^6
K-channel (Ca, V)	$0.2\text{-}3 \times 10^7$
ACh receptor	2.3×10^7

As a comparison, the turnover ratio (maximum number of processed substrate molecules per active site, per second) serves as a good evidence for the physical concept of pore. The turnover rates for some known carriers or active transporters are compared to those of several ion channels

Also ...,

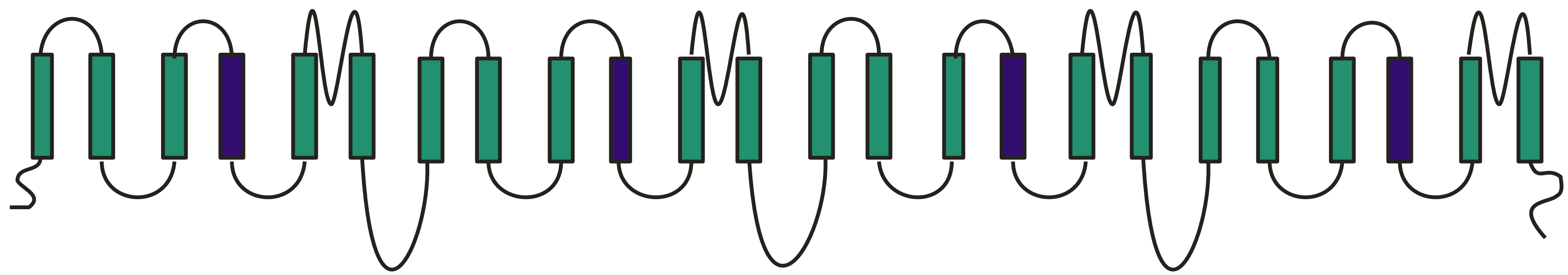
Very few ions are needed to generate a sizable transmembrane potential in cells

classification on the basis of gating mechanism



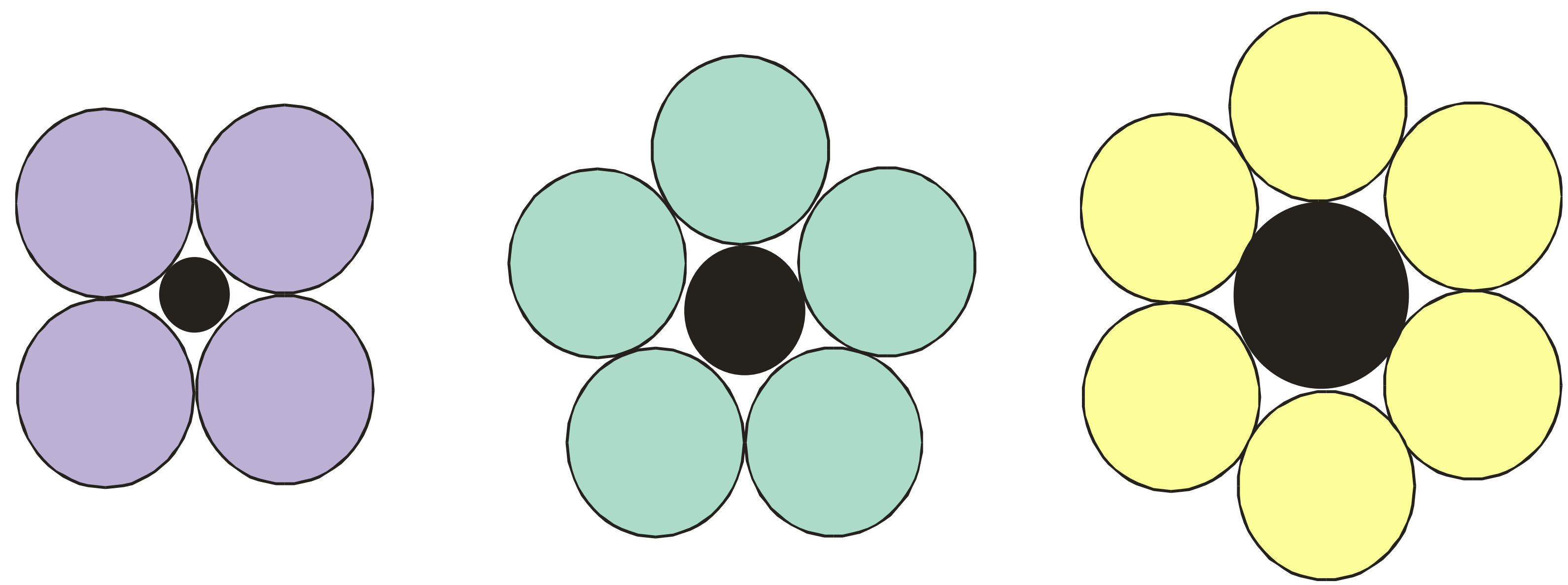
Unifying Themes in Ion Channel Structure

Polytopic Membrane Proteins



Oligomeric Arrangement
With Intrinsic Symmetry

Pore Size Correlates with the
Number of Subunits

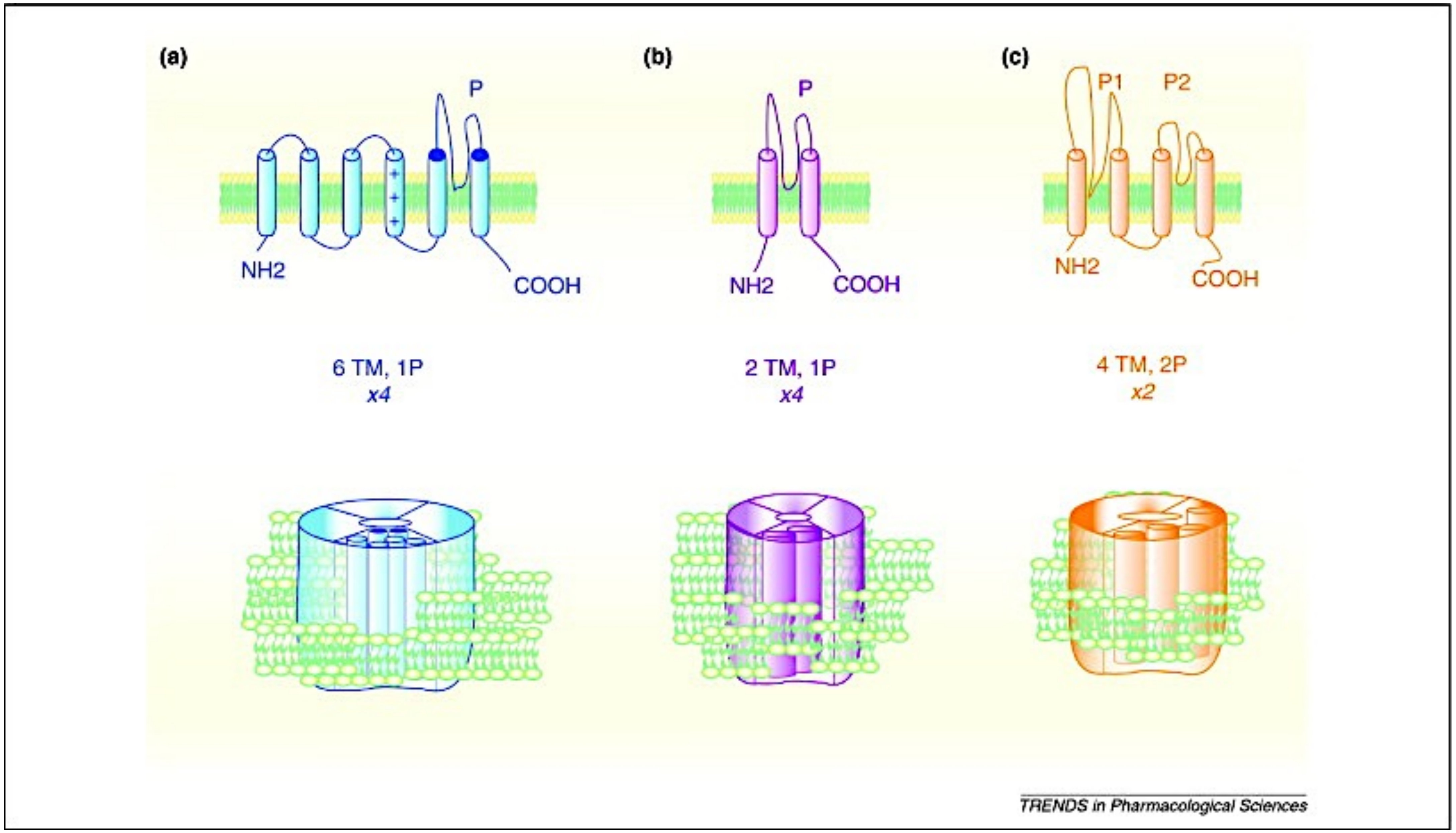


- Voltage-Dependent
  (Na^+, K^+, Ca^{++})
- Glutamate Receptors

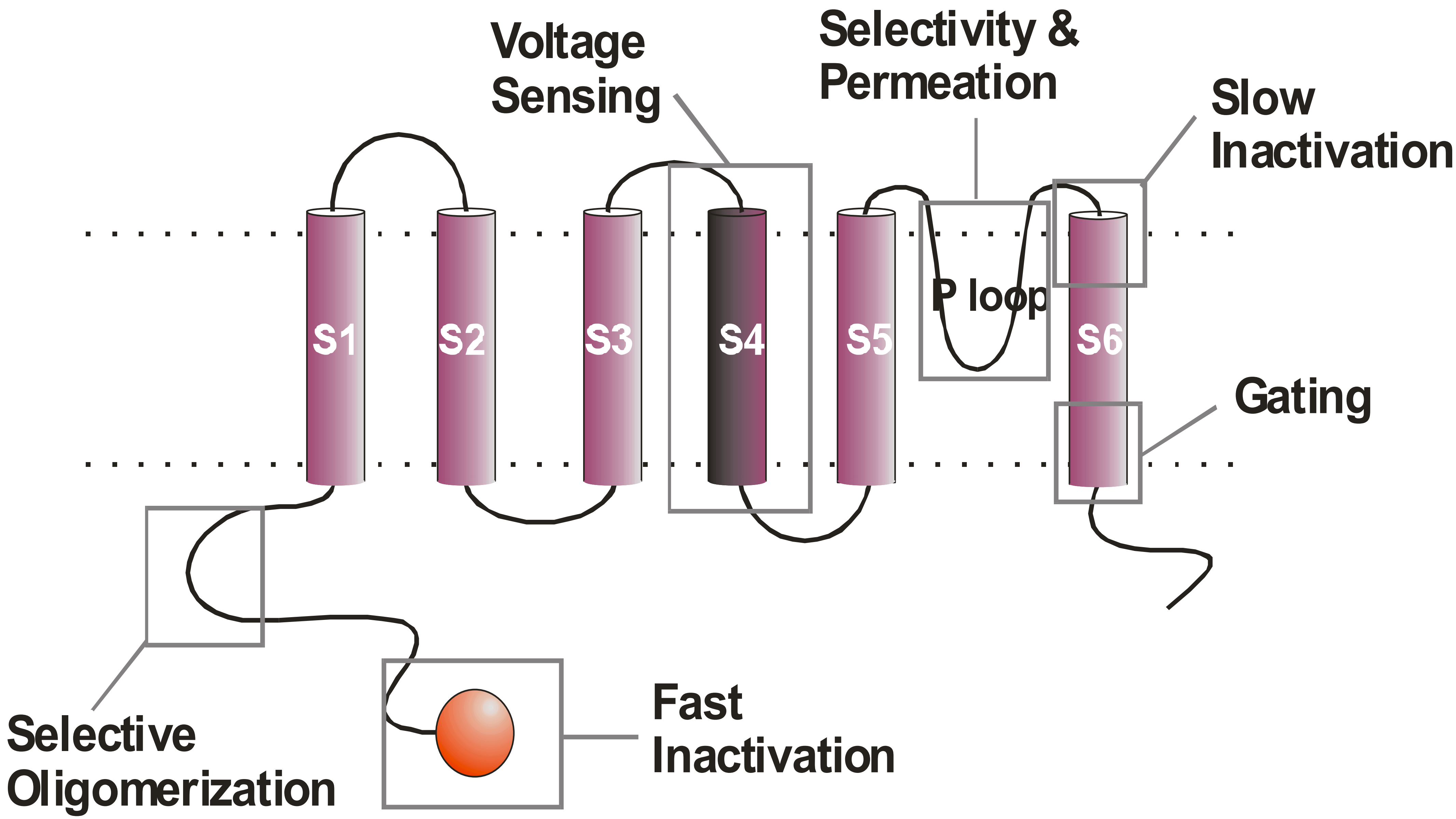
- Ligand-Gated
  (Ach, Gly, GABA,
  5-HT)
- Mechanosensitive

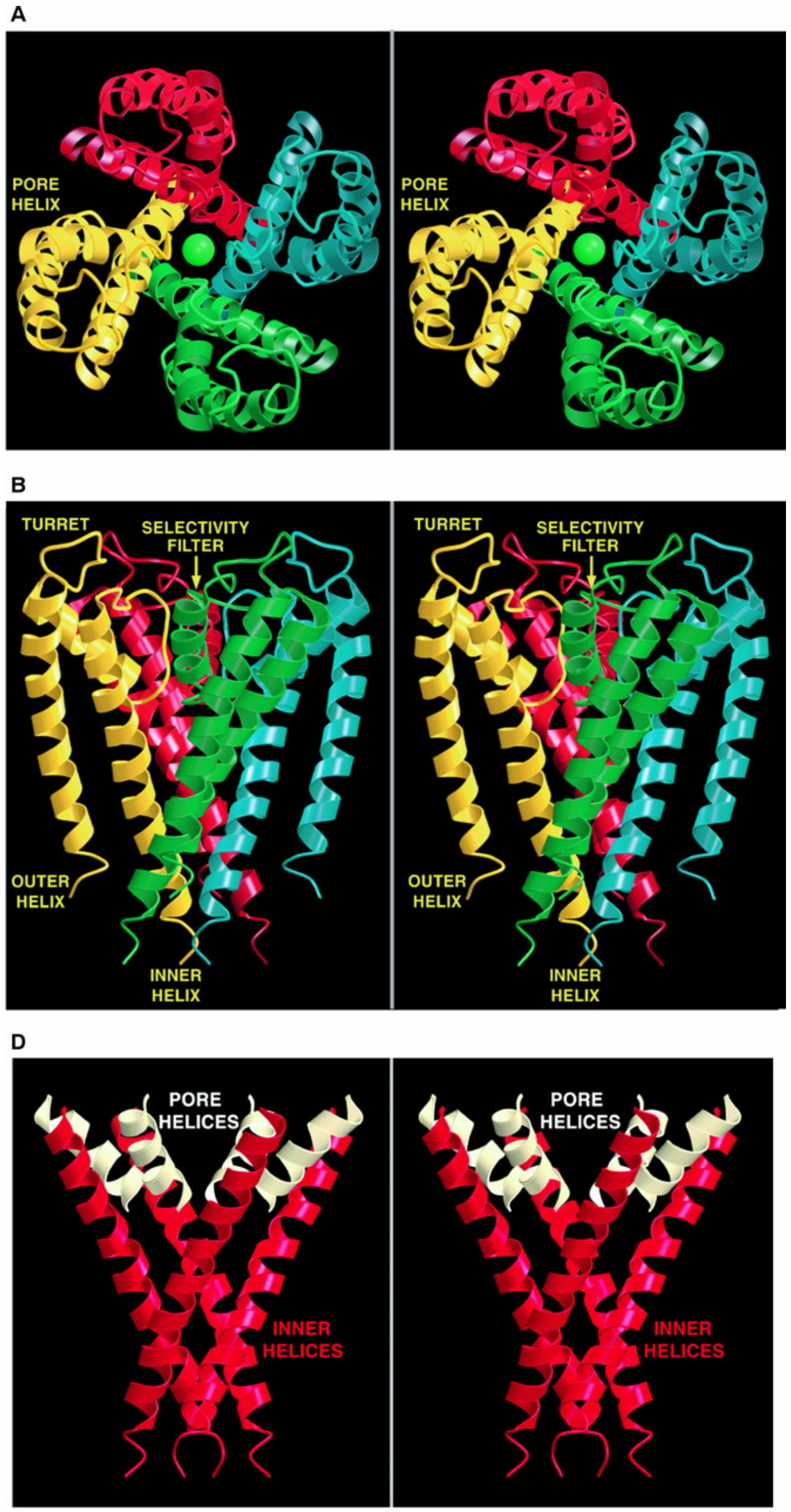
- Connexins
  (Gap Junctions)

Representative structures of potassium channels subunits



Structure-Function Relations in a Voltage-Dependent Channel



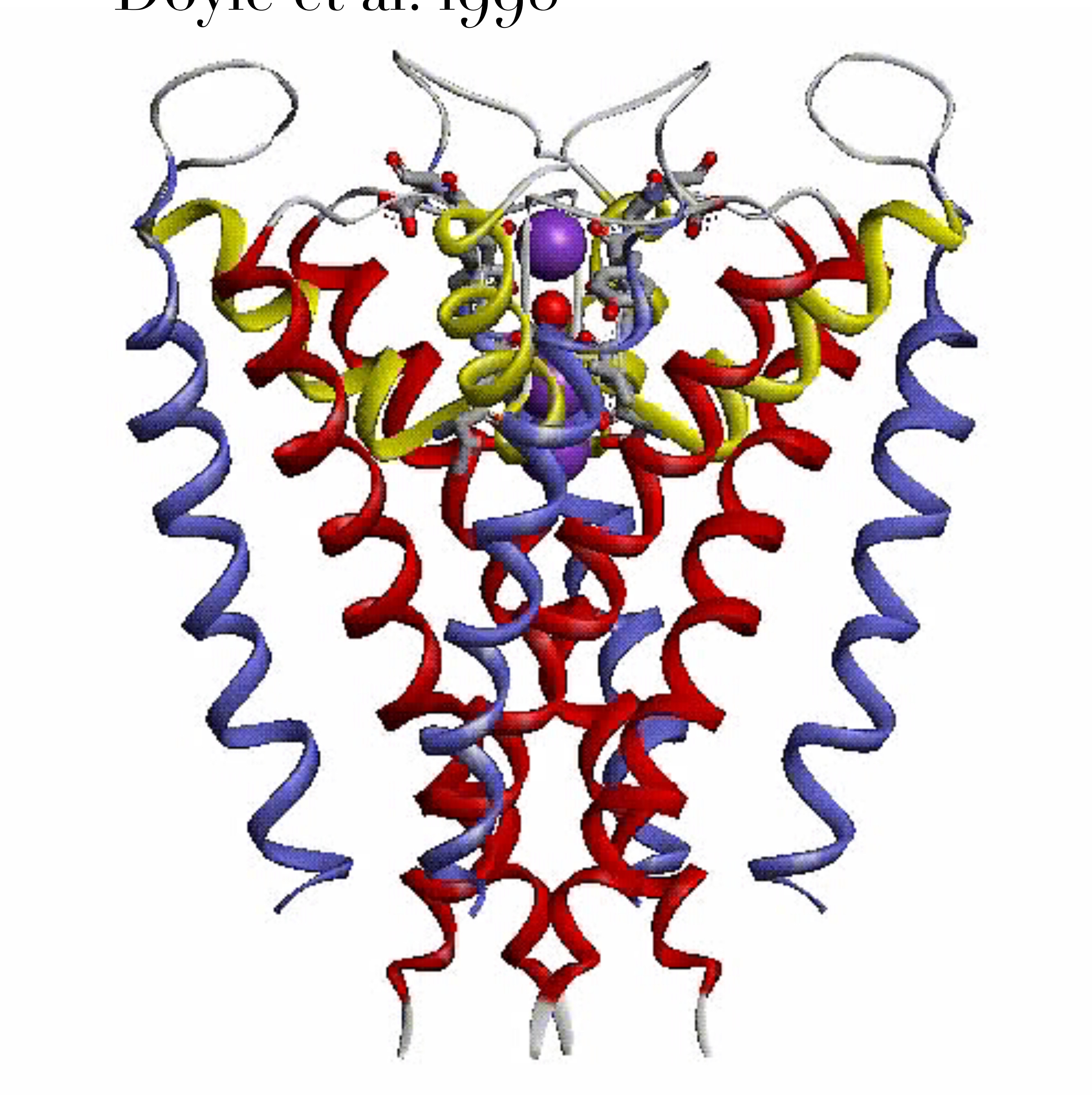


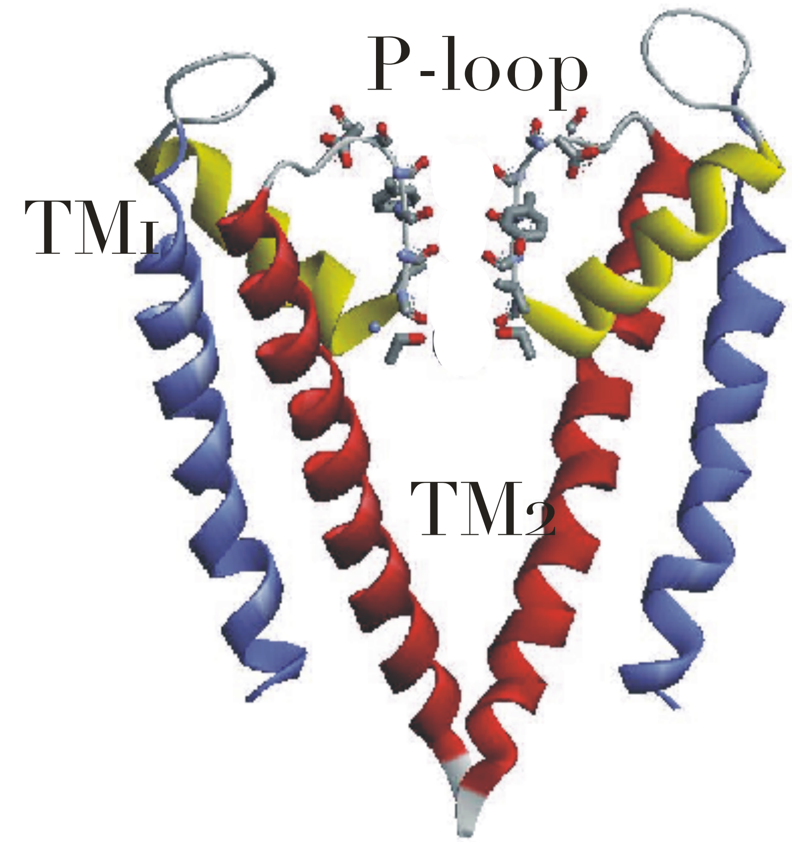
Structure

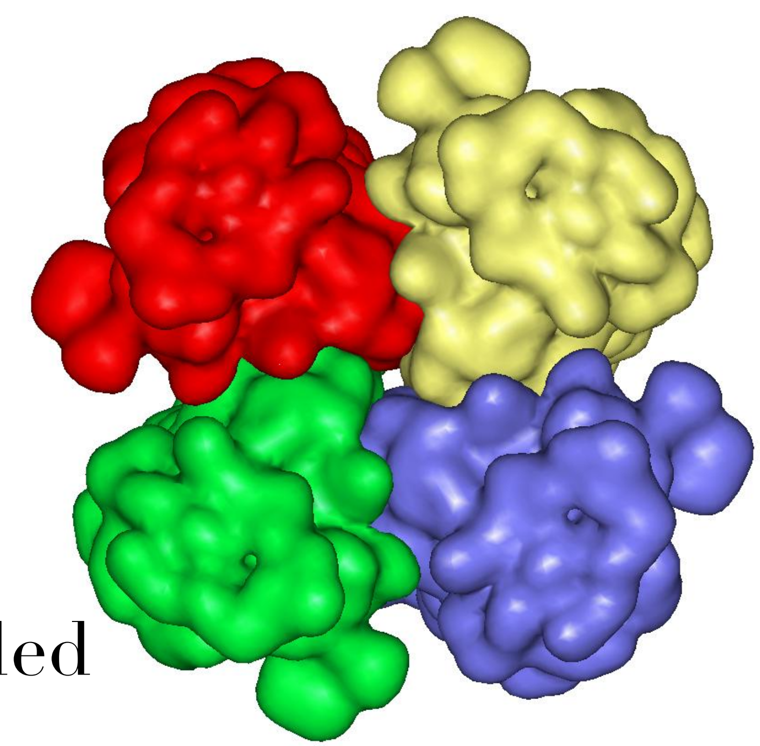
- Exists as a homo-tetramer with 4 identical subunits
- Each subunit is comprised of 3 alpha helices
- 2 helices are membrane spanning
- 1 inner helix is responsible for K^+ selectivity

Crystal Structure of the Streptomyces K⁺ Channel

Doyle et al. 1998



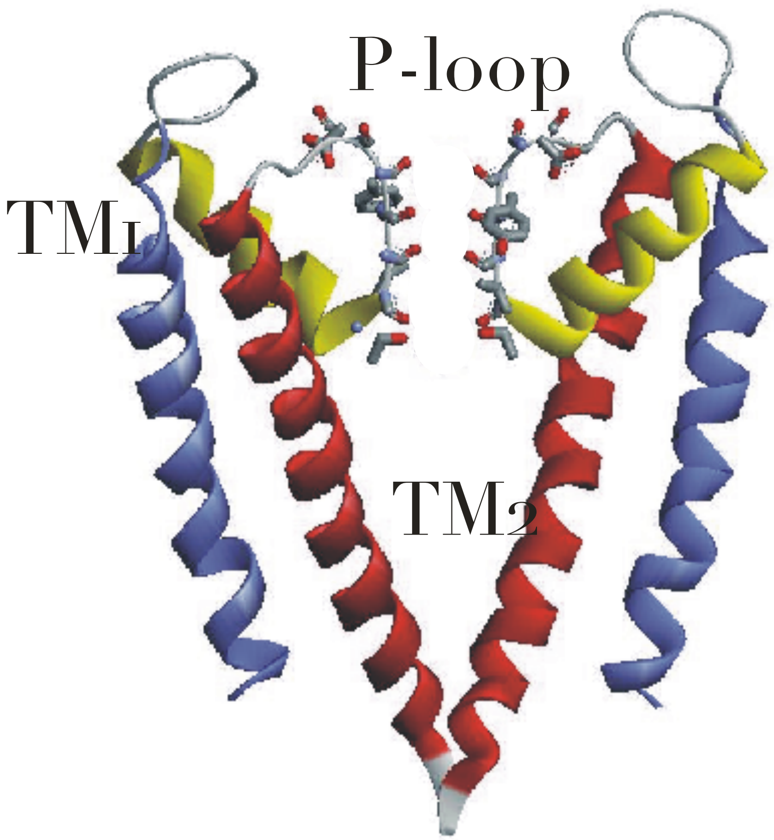




- *KcsA* is a homotetramer
- Each subunit contains two TM segments
- The selectivity filter is formed by an extended structure positioned by a short tilted helix

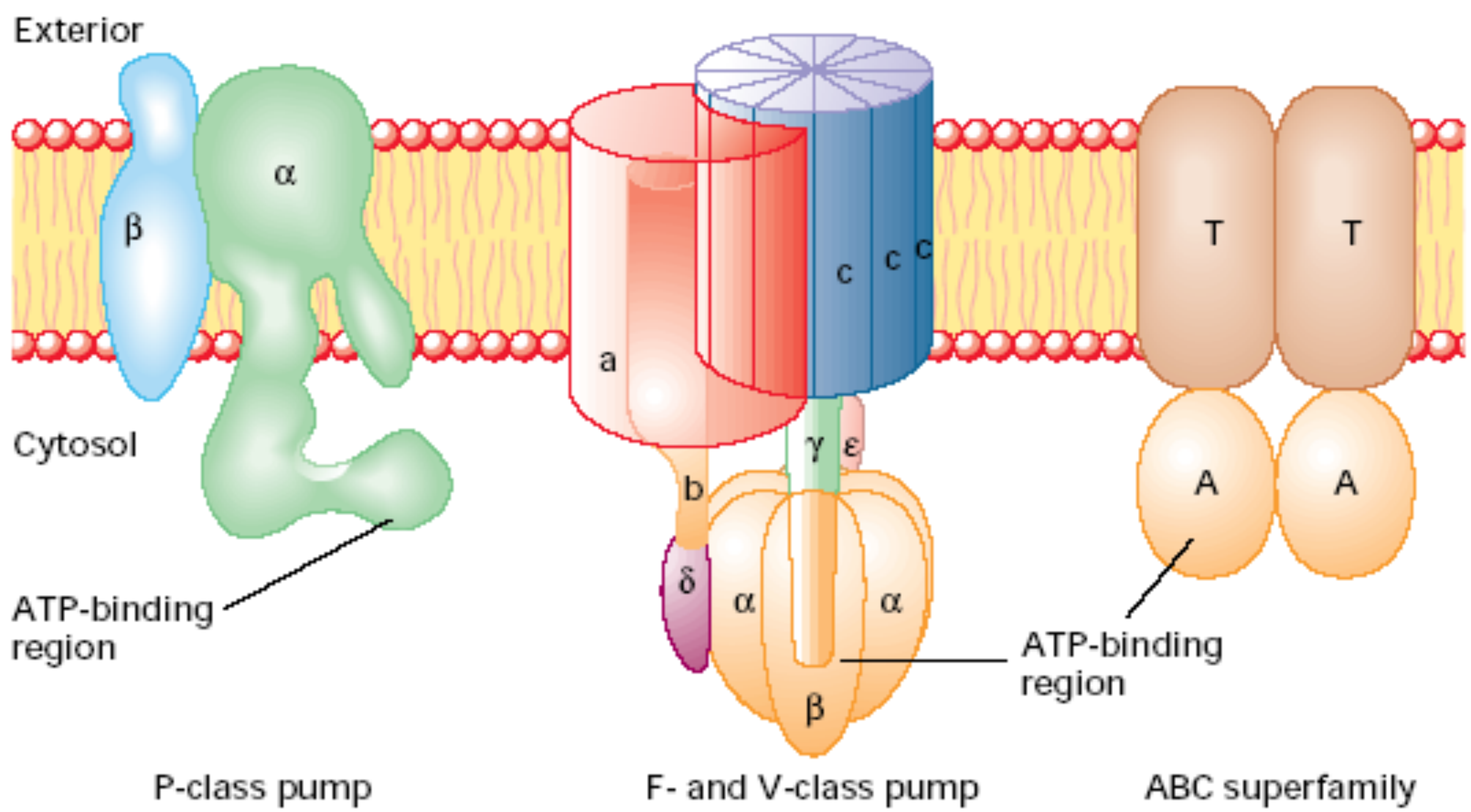
Selectivity Filter

How does K^+ channel distinguish K^+ from Na^+?

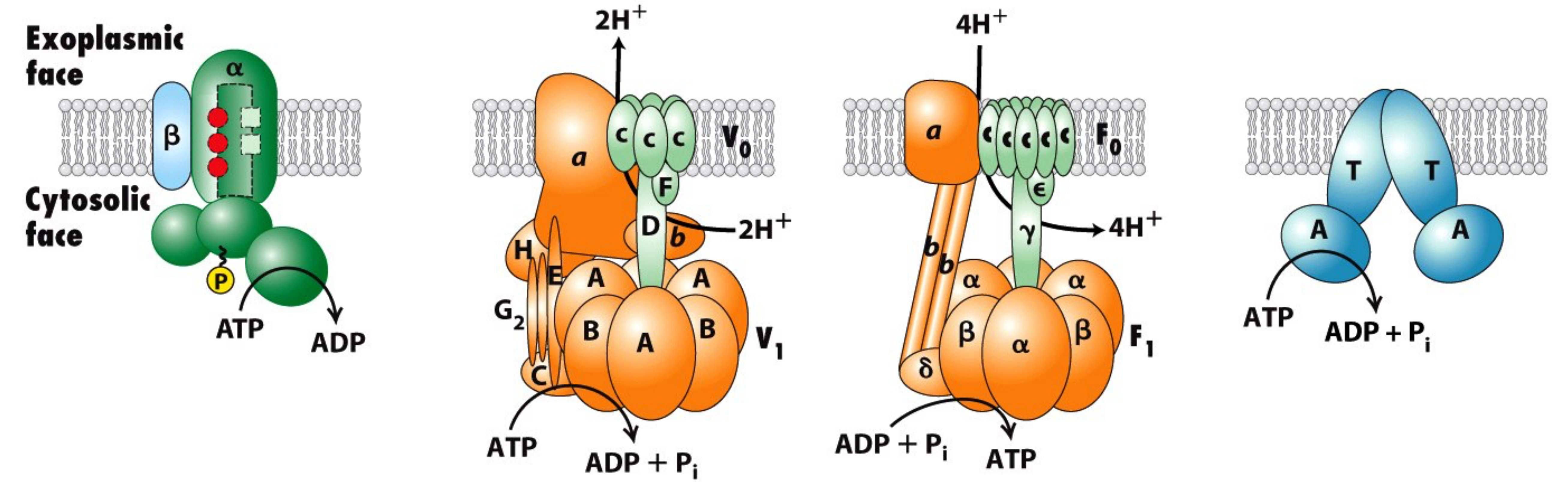


- Located in narrow region of the channel
- Contains Gly-Tyr-Gly AA residues
- Forces K+ to lose it's hydrating water molecules
- Carbonyl oxygen's in selectivity filter stabilize K+ ions
- Aromatic amino acids line the filter and act as springs to maintain appropriate channel width for K+
- This favorable interaction with the filter is not possible for Na+ because Na+ is too small to make contact with all the potential oxygen ligands of the carbonyl termini of the short alpha helices

Pumps



- Use the energy of ATP hydrolysis to move ions or small molecules across a membrane against a chemical concentration gradient or electric potential.
- Overall reaction—ATP hydrolysis and the "uphill" movement of ions or small molecules—is energetically favorable
- P, F, and V classes transport ions only, whereas the ABC superfamily class transports small molecules as well as ions.



P-class pumps

Plasma membrane of plants, fungi, bacteria (H^+ pump)

Plasma membrane of higher eukaryotes (Na^+/K^+ pump)

Apical plasma membrane of mammalian stomach (H^+/K^+ pump)

Plasma membrane of all eukaryotic cells (Ca^{2+} pump)

Sarcoplasmic reticulum membrane in muscle cells (Ca^{2+} pump)

V-class proton pumps

Vacuolar membranes in plants, yeast, other fungi

Endosomal and lysosomal membranes in animal cells

Plasma membrane of osteoclasts and some kidney tubule cells

F-class proton pumps

Bacterial plasma membrane

Inner mitochondrial membrane

Thylakoid membrane of chloroplast

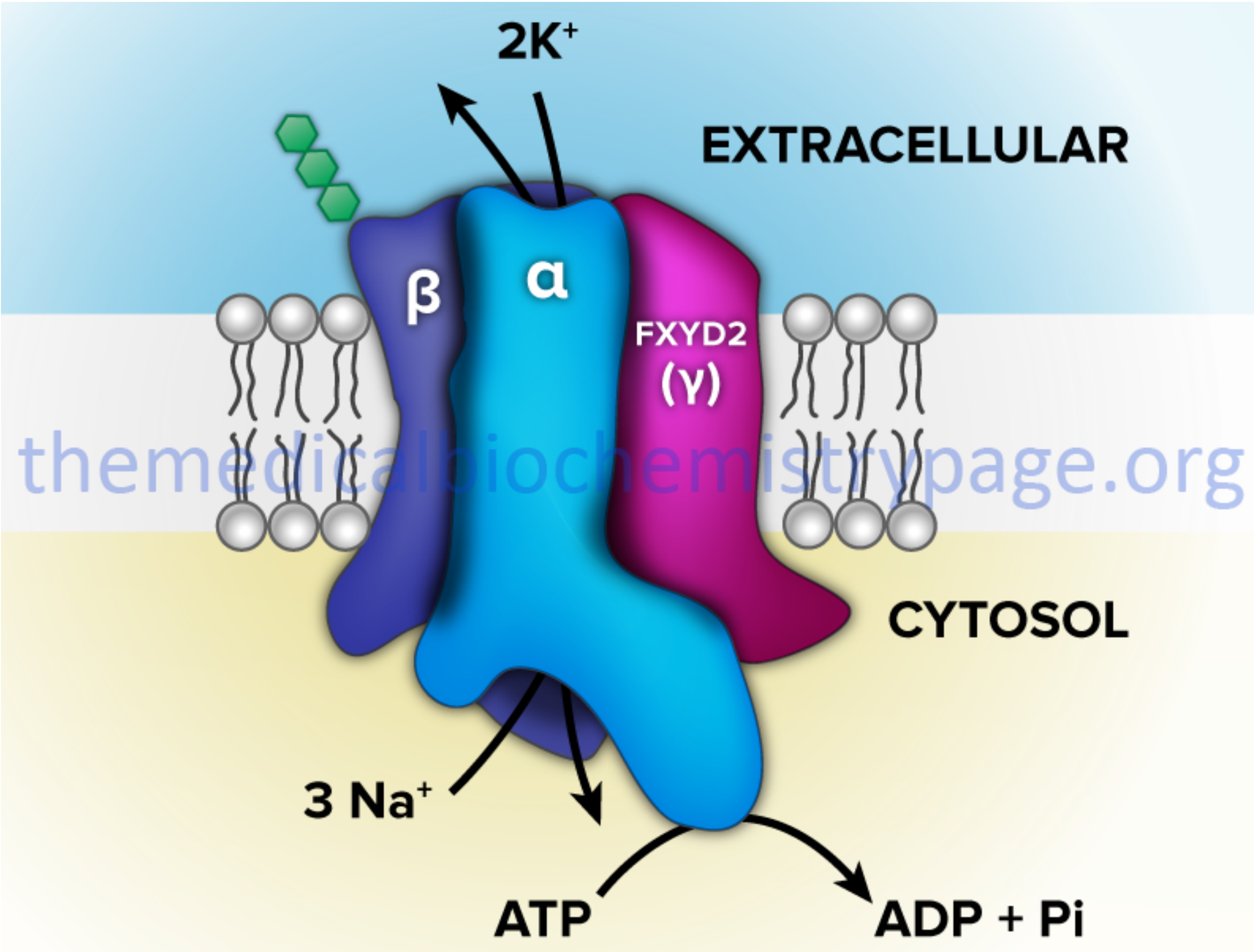
ABC superfamily

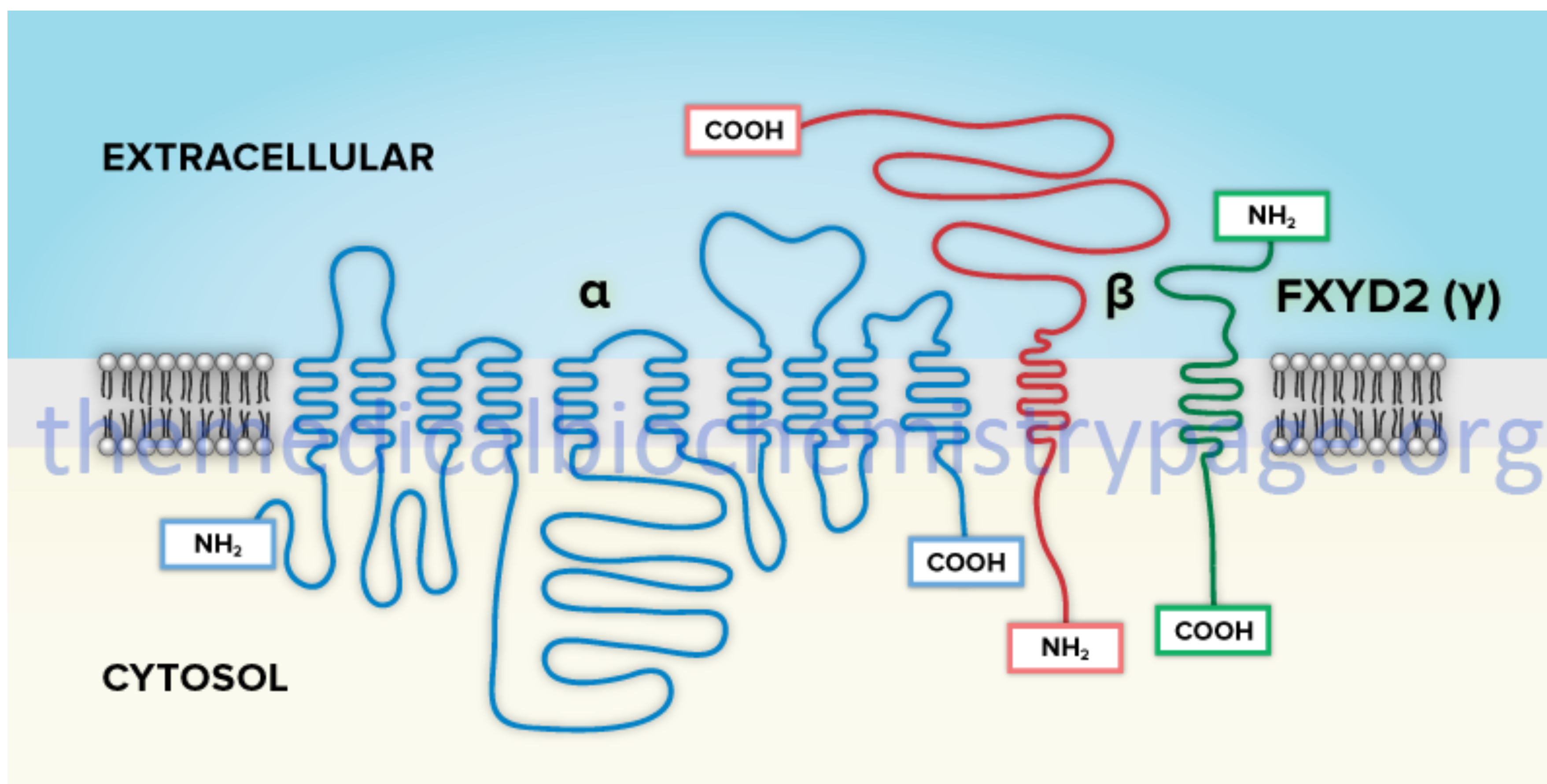
Bacterial plasma membranes (amino acid, sugar, and peptide transporters)

Mammalian plasma membranes (transporters of phospholipids, small lipophilic drugs, cholesterol, other small molecules)

Figure 11-9
Molecular Cell Biology, Sixth Edition

P Class	F Class	V Class	ABC Class
Substances Transported			
H^+, Na^+, K^+, Ca^{2+}	H^+ only	H^+ only	Ions and various small molecules
Structural and Functional Features			
Large catalytic α subunits (often two) become phosphorylated during solute transport; smaller β subunits may regulate transport.	Multiple transmembrane and cytosolic subunits generally function to synthesize ATP on β cytosolic subunits powered by movement of H^+ down an electrochemical gradient.	Multiple transmembrane and cytosolic subunits generally use energy released by ATP hydrolysis to pump H^+ ions from cytosol to organelle lumens, acidifying them.	Two transmembrane domains form the pathway for solute; two cytosolic ATP-binding domains couple ATP hydrolysis to solute movement. Domains may be in one or separate subunits.
Location of Specific Pumps			
Plasma membrane of plants, fungi, bacteria (H^+ pump)	Bacterial plasma membranes	Vacuolar membranes in plants, yeast, other fungi	Bacterial plasma membranes (amino acid, sugar, and peptide transporters)
Plasma membrane of higher eukaryotes (Na^+/K^+ pump)	Inner mitochondrial membrane	Endosomal and lysosomal membrane in animal cells	Mammalian endoplasmic reticulum (transporters of peptides associated with antigen presentation by MHC proteins)
Apical plasma membrane of mammalian stomach cells (H^+/K^+ pump)	Thylakoid membrane of chloroplast	Plasma membrane of certain acid-secreting animal cells (e.g., osteoclasts and some kidney tubule cells)	
Plasma membrane of all eukaryotic cells (Ca^{2+} pump)			Mammalian plasma membranes (transporters of small molecules, phospholipids, small lipidlike drugs)
Sarcoplasmic reticulum membrane in muscle cells (Ca^{2+} pump)			


2K+
EXTRACELLULAR
β
α
FXYD2
(γ)
themedicalbiochemistrypage.org
CYTOSOL
3 Na+
ATP
ADP + Pi


EXTRACELLULAR
COOH
NH2
α
β
FXYD2 (γ)
themedicalbiochemistrypage.org
NH2
COOH
NH2
COOH
CYTOSOL