11 Biological Membranes and Transport

P1 Principle 1 (1 of 3)

The biological membrane is a lipid bilayer with proteins of various functions (enzymes, transporters) embedded in or associated with the bilayer. The hydrophobic effect stabilizes structures (lipid bilayers and vesicles) in which lipids with some polar and some nonpolar regions can protect their nonpolar regions from interaction with the very polar solvent, water. Membrane proteins are associated with the lipid bilayer more or less tightly, and proteins and lipids are both allowed limited lateral motion in the plane of the bilayer.

P2 Principle 2 (1 of 8)

All of the internal membranes of cells are part of an interconnected, functionally specialized, and dynamic endomembrane system. Proteins and lipids synthesized in the endoplasmic reticulum move through the Golgi apparatus, and they are targeted to the membranes of organelles or to the plasma membrane, where they provide the essential properties of these structures. During this membrane trafficking, some proteins are covalently altered, and some lipids are segregated into different organelles or are concentrated in one of the bilayer leaflets. Rafts are functionally specialized regions with unique lipid and protein compositions.

P3 Principle 3 (1 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

11.1 The Composition and Architecture of Membranes

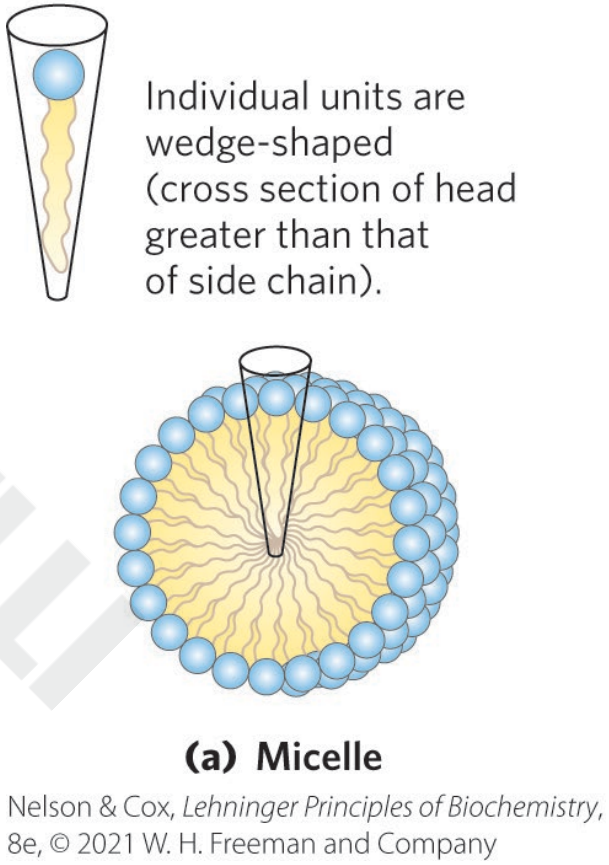
The Lipid Bilayer Is Stable in Water

- glycerophospholipids, sphingolipids, and sterols:
  - virtually insoluble in water
  - spontaneously form microscopic lipid aggregates when mixed with water

- **hydrophobic interactions =** the clustering of hydrophobic molecule surfaces in an aqueous environment to find the lowest-energy environment by reducing the hydrophobic surface area exposed to water

Micelle Formation

- **micelles** = spherical structures containing amphipathic molecules arranged with hydrophobic regions in the interior and hydrophilic head groups on the exterior
  - favored when the cross-sectional area of the head group is greater than that of the acyl side chain(s)



(a) Micelle

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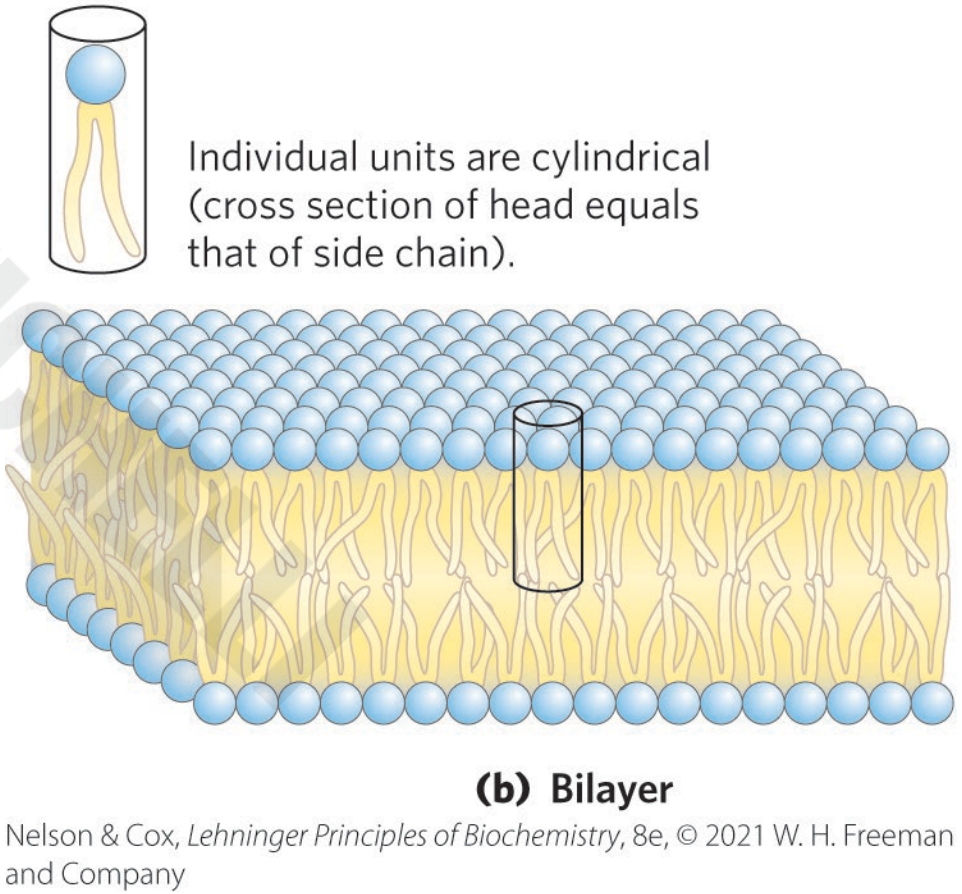
Bilayer Formation

- **bilayer** = lipid aggregate in which two lipid monolayers (leaflets) form a two-dimensional sheet
  - favored when the cross-sectional areas of the head group and acyl side chain(s) are similar



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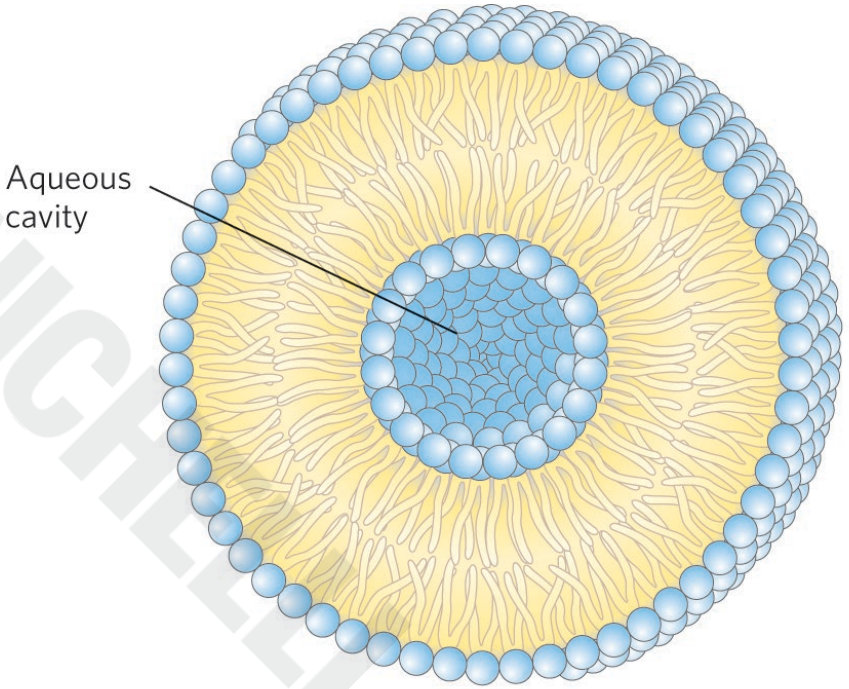
Vesicle Formation

- **vesicle** (liposome) = forms spontaneously when a bilayer sheet folds back on itself to form a hollow sphere



(c) Vesicle

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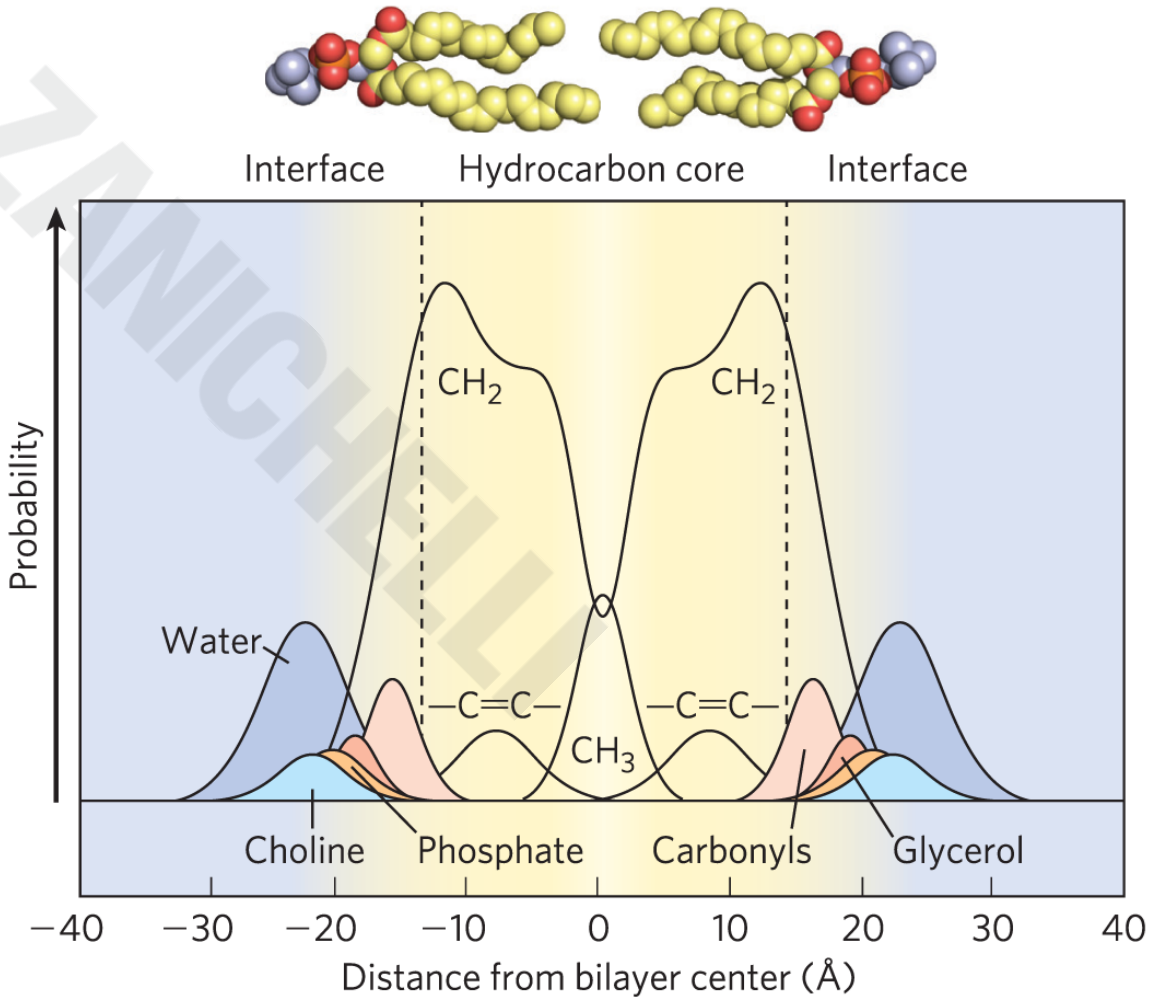
Distribution of Membrane Lipids in an Artificial Membrane

- hydrocarbon core of the bilayer = ~30 Å
- biological membranes (including protruding proteins) = ~50 – 80 Å



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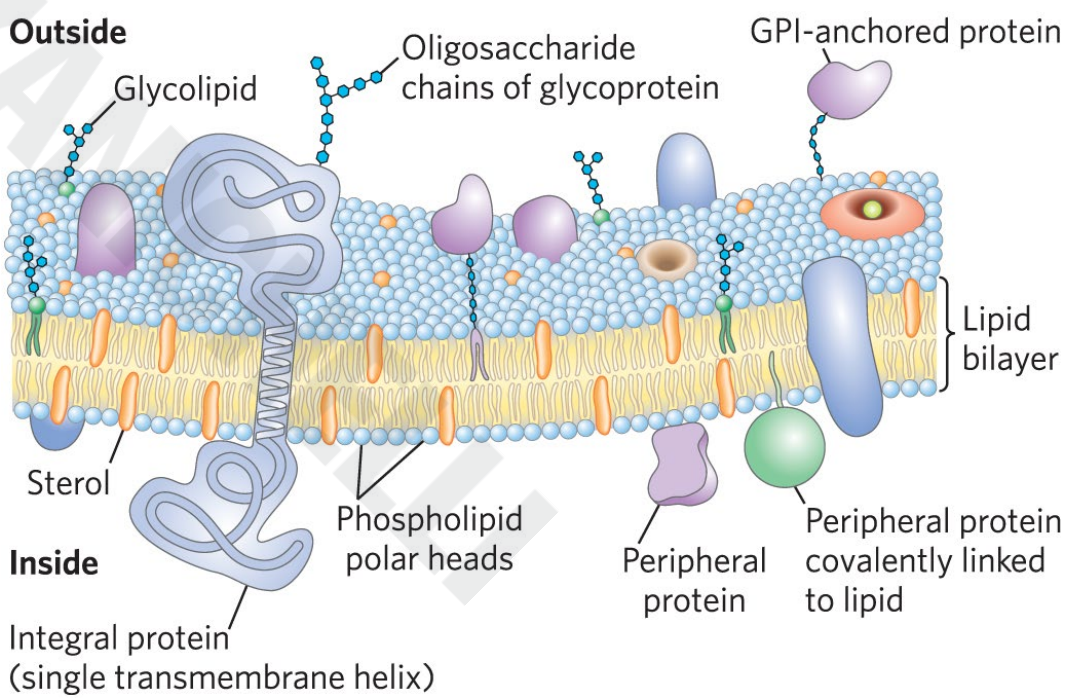
P1 Principle 1 (2 of 3)

The biological membrane is a lipid bilayer with proteins of various functions (enzymes, transporters) embedded in or associated with the bilayer. The hydrophobic effect stabilizes structures (lipid bilayers and vesicles) in which lipids with some polar and some nonpolar regions can protect their nonpolar regions from interaction with the very polar solvent, water. Membrane proteins are associated with the lipid bilayer more or less tightly, and proteins and lipids are both allowed limited lateral motion in the plane of the bilayer.

Bilayer Architecture Underlies the Structure and Function of Biological Membranes

- **fluid mosaic** = pattern formed by individual lipid and protein units in a membrane
  - pattern can change while maintaining the permeability membrane



Functions of Biological Membranes

- permit shape changes that accompany cell growth and movement
- permit exocytosis, endocytosis, and cell division
- serve as molecular gatekeepers

Proteins and Enzymes In and On Membranes

- transporters = move specific organic solutes and inorganic ions across the membrane
- receptors = sense extracellular signals and trigger molecular changes in the cell
- ion channels = mediate electrical signaling between cells
- adhesion molecules = hold neighboring cells together

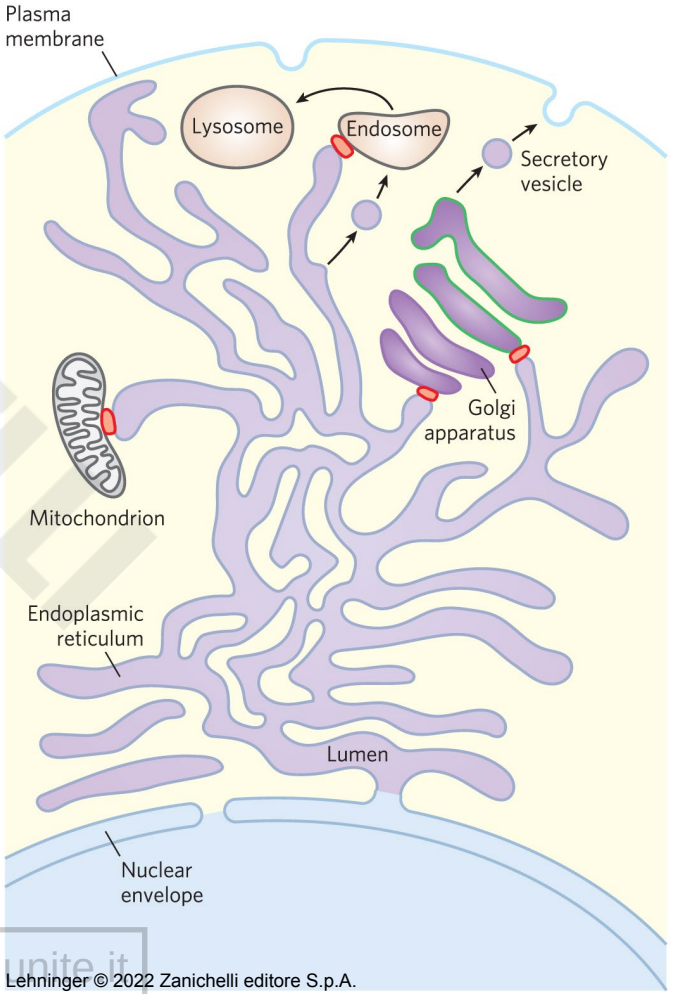
P2 Principle 2 (2 of 8)

All of the internal membranes of cells are part of an interconnected, functionally specialized, and dynamic endomembrane system. Proteins and lipids synthesized in the endoplasmic reticulum move through the Golgi apparatus, and they are targeted to the membranes of organelles or to the plasma membrane, where they provide the essential properties of these structures. During this membrane trafficking, some proteins are covalently altered, and some lipids are segregated into different organelles or are concentrated in one of the bilayer leaflets. Rafts are functionally specialized regions with unique lipid and protein compositions.

The Endomembrane System Is Dynamic and Functionally Differentiated

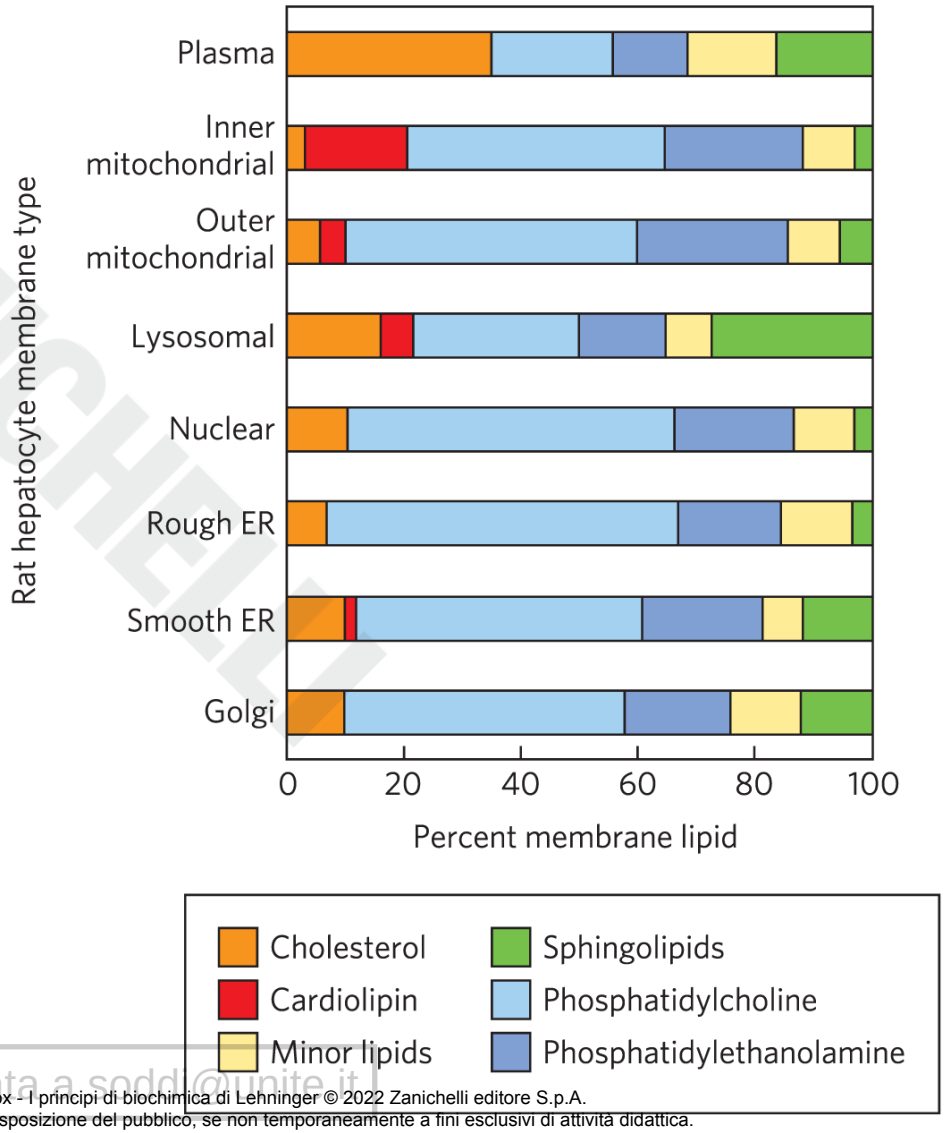
- single membrane surrounds:
  - endoplasmic reticulum (ER)
  - Golgi apparatus
  - lysosomes
  - various small vesicles

- double membrane surrounds:
  - nucleus
  - mitochondrion
  - chloroplasts (in plants)



Lipid Composition of the Plasma and Organelle Membranes

- the functional specialization of each membrane type is reflected in its unique lipid composition



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Membrane Trafficking

- membrane trafficking = process by which membrane lipids and proteins that are synthesized in the ER move to their destination organelles or to the plasma membrane

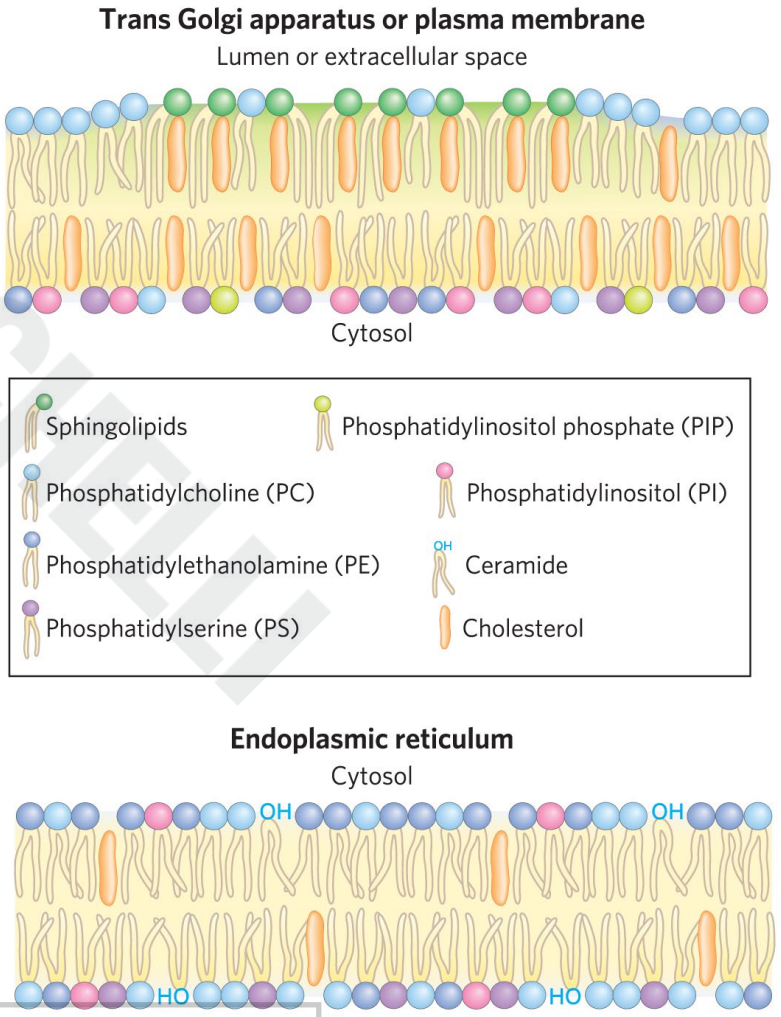
- lipids and proteins undergo covalent modifications in the Golgi apparatus
  - dictates the eventual location of the mature protein

P2 Principle 2 (3 of 8)

All of the internal membranes of cells are part of an interconnected, functionally specialized, and dynamic endomembrane system. Proteins and lipids synthesized in the endoplasmic reticulum move through the Golgi apparatus, and they are targeted to the membranes of organelles or to the plasma membrane, where they provide the essential properties of these structures. During this membrane trafficking, some proteins are covalently altered, and some lipids are segregated into different organelles or are concentrated in one of the bilayer leaflets. Rafts are functionally specialized regions with unique lipid and protein compositions.

Changes in Lipid Composition During Membrane Trafficking

- sphingolipids and cholesterol largely replace phosphatidylcholine
- plasma membrane lipids are asymmetrically distributed between the two leaflets of the bilayer



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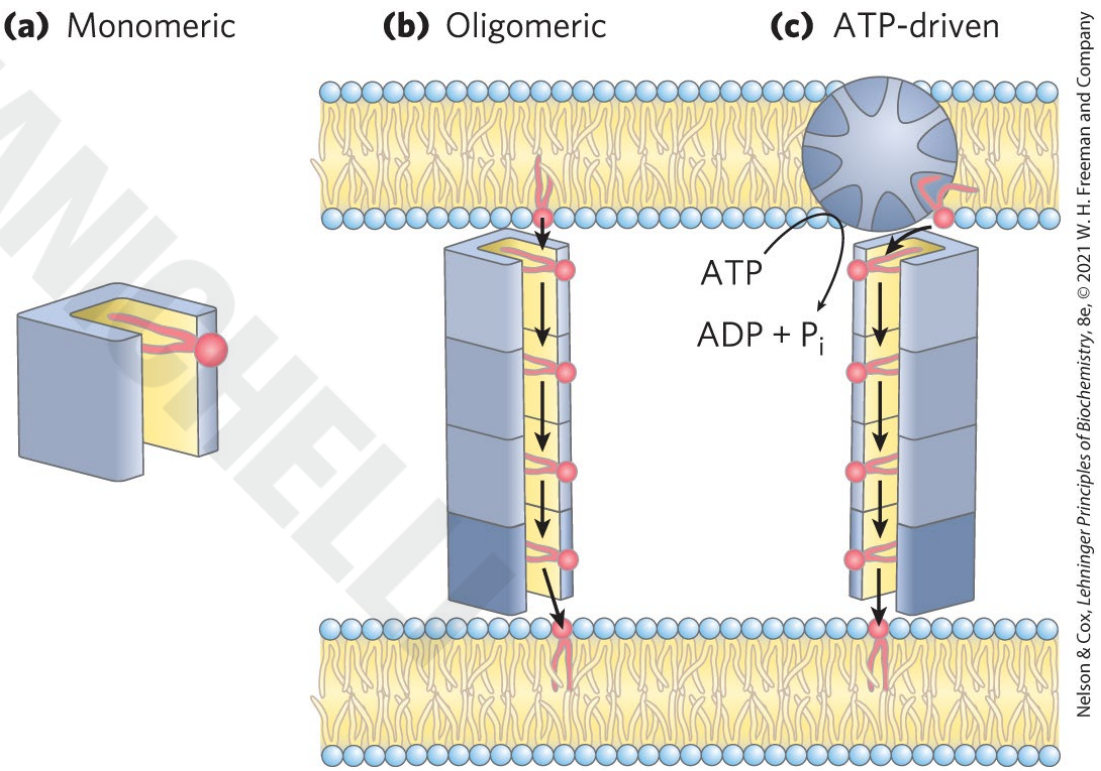
Lipid Transfer Proteins (LTPs)

- **lipid transfer proteins (LTPs)** = soluble proteins that contain a hydrophobic lipid-binding pocket to carry a lipid from one membrane to another
  - can be bispecific



P2 Principle 2 (4 of 8)

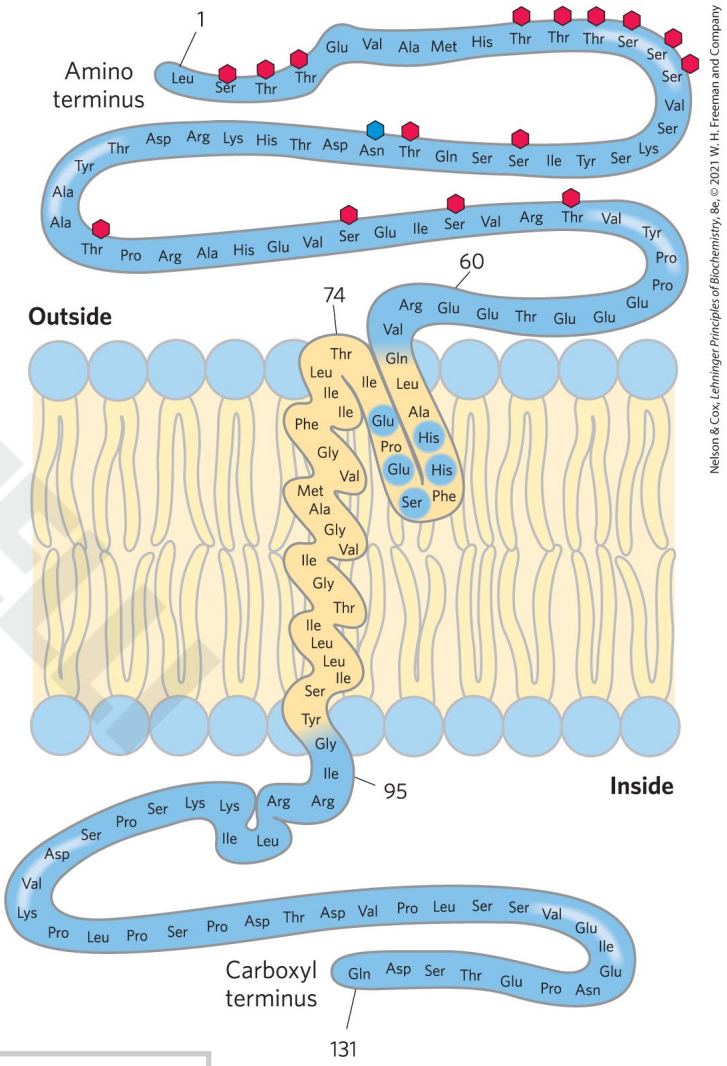
All of the internal membranes of cells are part of an interconnected, functionally specialized, and dynamic endomembrane system. Proteins and lipids synthesized in the endoplasmic reticulum move through the Golgi apparatus, and they are targeted to the membranes of organelles or to the plasma membrane, where they provide the essential properties of these structures. During this membrane trafficking, some proteins are covalently altered, and some lipids are segregated into different organelles or are concentrated in one of the bilayer leaflets. Rafts are functionally specialized regions with unique lipid and protein compositions.

Membrane Proteins Are Receptors, Transporters, and Enzymes

- groups of membrane proteins:
  - receptors for extracellular signals
  - transporters to carry specific polar or charged compounds across the plasma membrane or between organelles
  - enzymes

Posttranslational Modification of Membrane Proteins

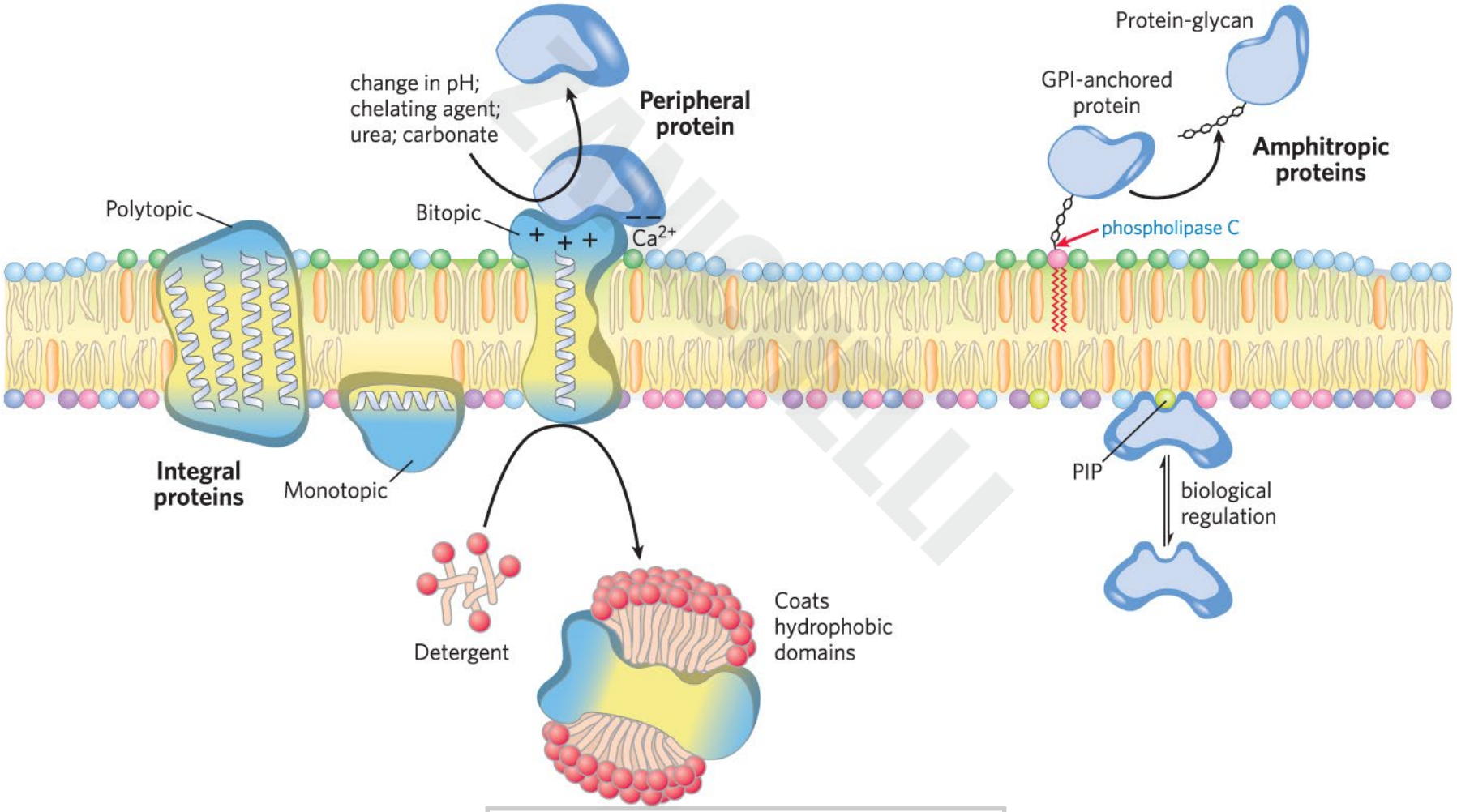
- glycosylation = attachment of oligosaccharides to proteins
  - typically on the outer face of the plasma membrane
- attachment of 1+ lipids = serve as hydrophobic anchors or targeting tags



Membrane Proteins Differ in the Nature of Their Association with the Membrane Bilayer

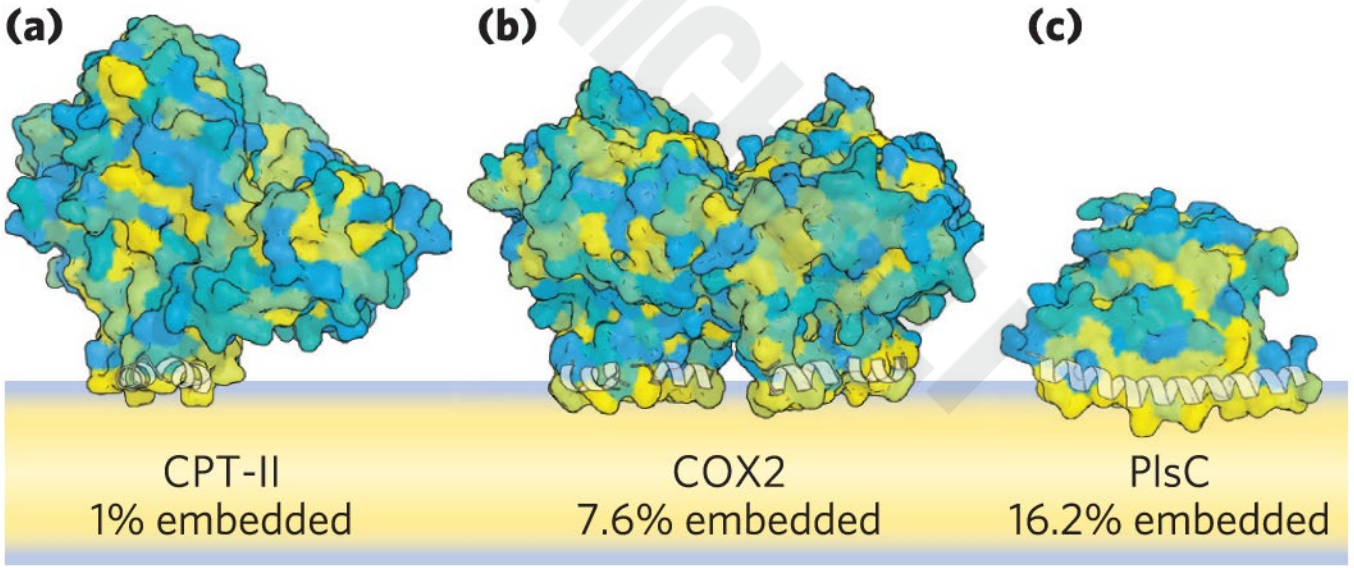
- **integral membrane proteins** = firmly embedded within the lipid bilayer
- **peripheral membrane proteins** = associate with the membrane through electrostatic interactions and hydrogen bonding
- **amphitropic proteins** = associate reversibly with membranes
  - found in both membranes and the cytosol

Integral, Peripheral, and Amphitropic Proteins



Monotopic Proteins

- **monotopic** = have small hydrophobic domains that interact with only a single leaflet of the membrane



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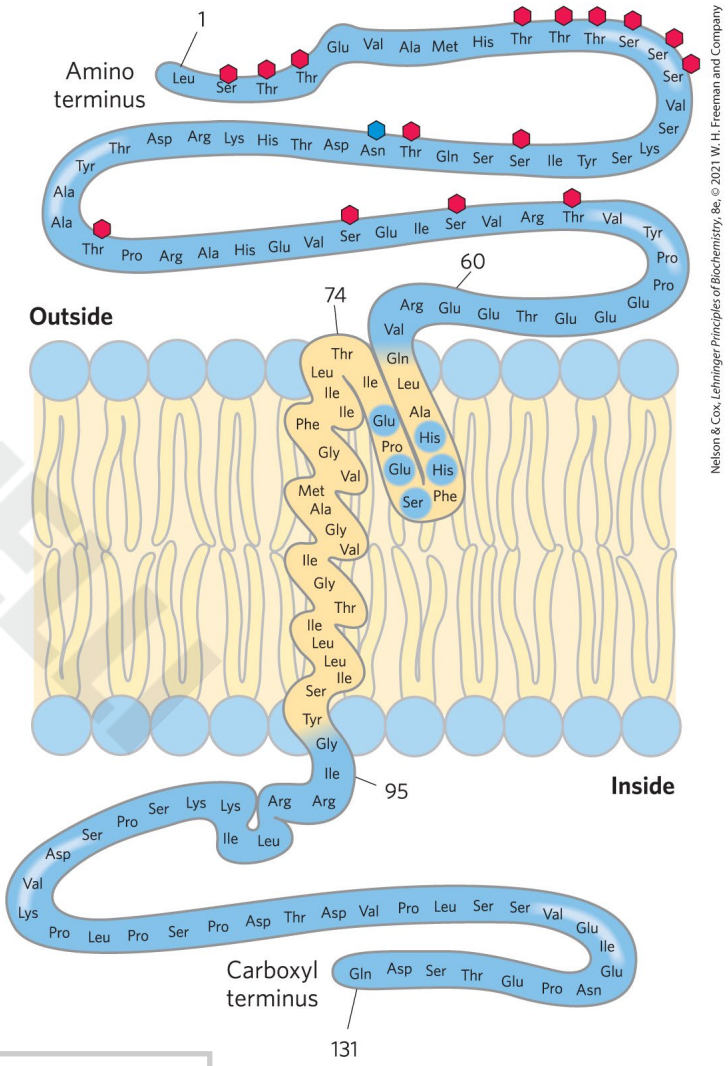
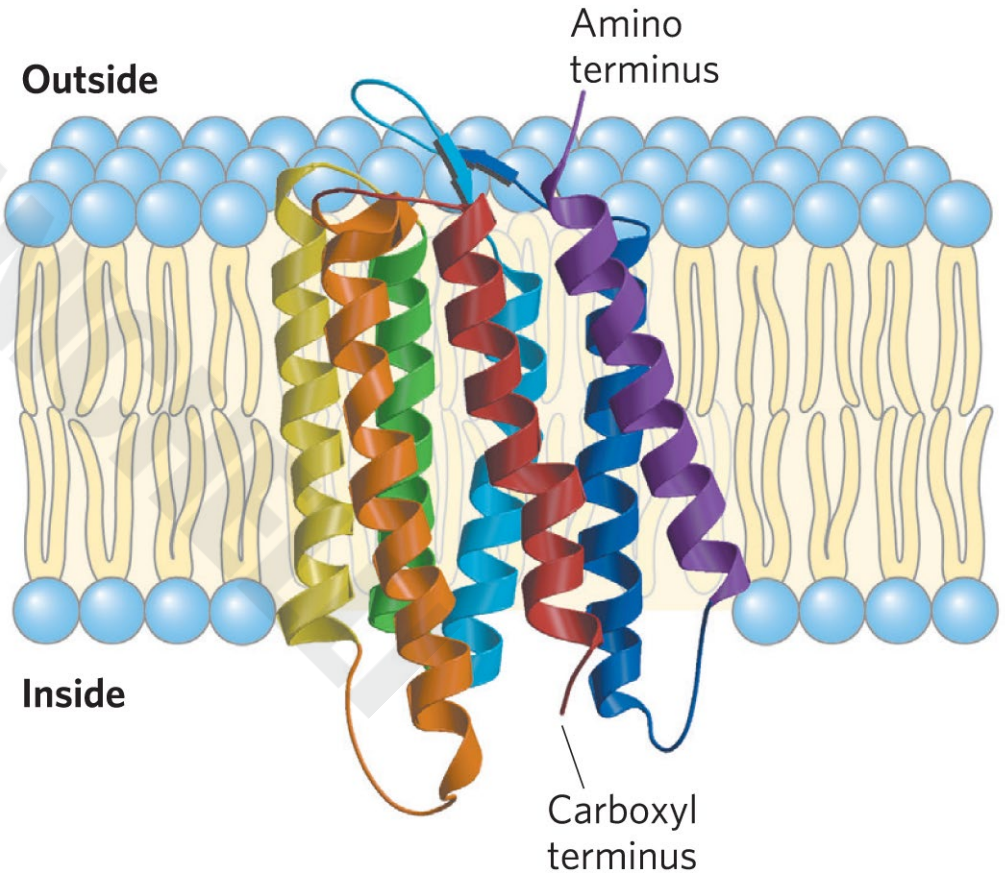
Bitopic Proteins

- **bitopic** = span the bilayer once, extending on either surface
  - have a single hydrophobic sequence somewhere in the molecule



Polytopic Proteins

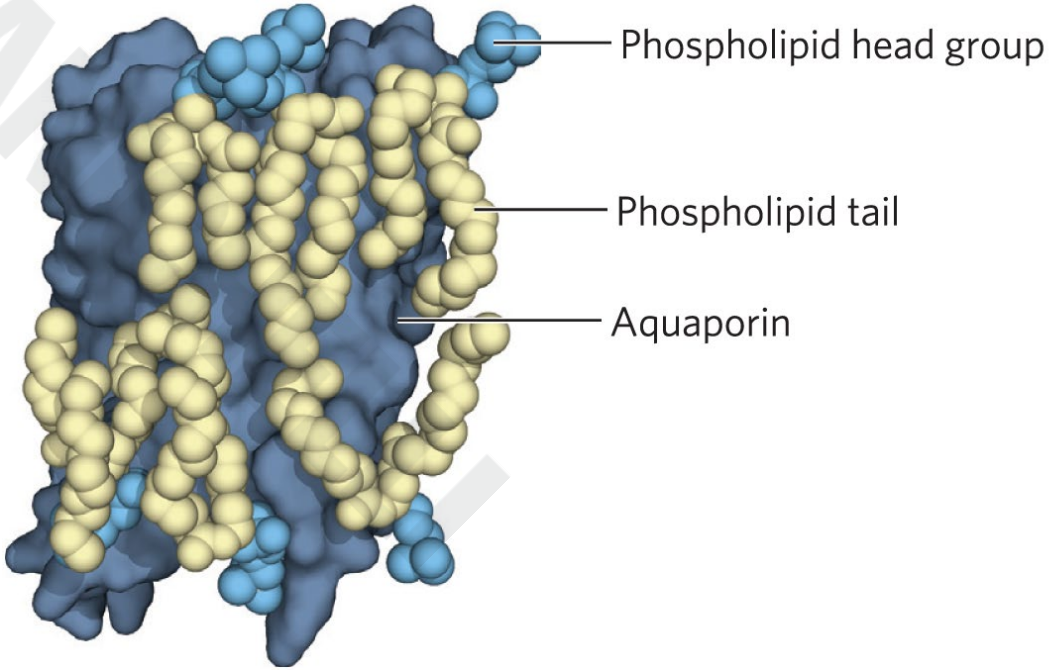
- **polytopic** = cross the membrane several times
  - have multiple hydrophobic sequences of ~20 residues that each cross the membrane when in the *α*-helical conformation



bacteriorhodopsin

Many Membrane Proteins Co-Crystallize with Phospholipid Molecules

- phospholipids lie:
  - on the protein surface
  - at interfaces between monomers of multisubunit proteins, forming a “grease seal”



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The Topology of an Integral Membrane Protein Can Often Be Predicted from Its Sequence

- an *α*-helical sequence of 20-25 residues (each 1.5 Å) is just long enough to span the thickness (30 Å) of the lipid bilayer
  - stabilized by intrachain hydrogen bonding and the hydrophobic effect

- in many organisms, 20-30% of proteins are integral proteins

Hydropathy Index

- **hydropathy index** = expresses the free-energy change associated with the movement of an amino acid side chain from a hydrophobic environment to water
  - ranges from highly exergonic to highly endergonic

- overall hydropathy index = estimated by summing the free energies of transfer for the residues in the sequence

Hydropathy Index for the 20 Common Amino Acids

TABLE 3-1 Properties and Conventions Associated with the Common Amino Acids Found in Proteins

Amino acid	Abbreviation/ symbol	M_r[a]	pK'_a values: pK'_1 (—COOH)	pK'_2 ($—NH_3^+$)	pK'_R (R group)	pI	Hydropathy index[b]	Occurrence in proteins (%)[c]		
Nonpolar, aliphatic R groups										
Glycine	Gly G	75	2.34	9.60		5.97	−0.4	7.2	7.3	7.3
Alanine	Ala A	89	2.34	9.69		6.01	1.8	7.8	9.4	7.2
Proline	Pro P	115	1.99	10.96		6.48	−1.6[d]	5.2	4.4	4.2
Valine	Val V	117	2.32	9.62		5.97	4.2	6.6	7.1	8.2
Leucine	Leu L	131	2.36	9.60		5.98	3.8	9.1	10.6	9.9
Isoleucine	Ile I	131	2.36	9.68		6.02	4.5	5.3	6.0	7.6
Methionine	Met M	149	2.28	9.21		5.74	1.9	2.3	2.2	2.2
Aromatic R groups										
Phenylalanine	Phe F	165	1.83	9.13		5.48	2.8	3.9	4.0	4.5
Tyrosine	Tyr Y	181	2.20	9.11	10.07	5.66	−1.3	3.2	3.0	3.9
Tryptophan	Trp W	204	2.38	9.39		5.89	−0.9	1.4	1.3	1.1
Polar, uncharged R groups										
Serine	Ser S	105	2.21	9.15		5.68	−0.8	6.8	6.1	5.7
Threonine	Thr T	119	2.11	9.62		5.87	−0.7	5.9	5.4	4.5
Cysteine[e]	Cys C	121	1.96	10.28	8.18	5.07	2.5	1.9	1.2	0.8
Asparagine	Asn N	132	2.02	8.80		5.41	−3.5	4.3	3.7	3.4
Glutamine	Gln Q	146	2.17	9.13		5.65	−3.5	4.2	4.5	2.0
Positively charged R groups										
Lysine	Lys K	146	2.18	8.95	10.53	9.74	−3.9	5.9	4.7	6.8
Histidine	His H	155	1.82	9.17	6.00	7.59	−3.2	2.3	2.4	1.6
Arginine	Arg R	174	2.17	9.04	12.48	10.76	−4.5	5.1	5.6	5.9
Negatively charged R groups										
Aspartate	Asp D	133	1.88	9.60	3.65	2.77	−3.5	5.3	5.1	5.0
Glutamate	Glu E	147	2.19	9.67	4.25	3.22	−3.5	6.3	6.0	8.2

[a] M_r values reflect the structures as shown in Figure 3-5. The elements of water (M_r 18) are deleted when the amino acid is incorporated into a polypeptide.

[b] A scale combining hydrophobicity and hydrophilicity of R groups. The values reflect the free energy (ΔG) of transfer of the amino acid side chain from a hydrophobic environment to water. This transfer is favorable ($\Delta G < 0$; negative value in the index) for charged or polar amino acid side chains, and it is unfavorable ($\Delta G > 0$; positive value in the index) for amino acids with nonpolar or more hydrophobic side chains. See Chapter 11. Source: Data from J. Kyte and R. F. Doolittle, *J. Mol. Biol.* 157:105, 1982.

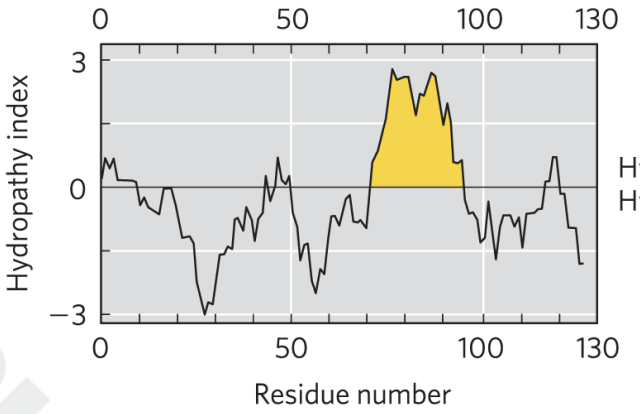
[c] The first value in each row is the average occurrence in more than 1,150 proteins. Source: Data from R. F. Doolittle, in *Prediction of Protein Structure and the Principles of Protein Conformation* (G. D. Fasman, ed.), p. 599, Plenum Press, 1989. The second and third values are, respectively, from the complete proteomes of nine mesophilic bacterial species and seven thermophilic bacterial species. Mesophiles grow at commonly encountered temperatures, whereas thermophiles grow at elevated temperatures up to and beyond the boiling point of water. The decline in glutamine occurrence in thermophiles may reflect a tendency of this amino acid to deaminate at high temperatures. Source: Data from A. C. Singer and D. A. Hickey, *Gene* 317:39, 2003.

[d] As originally composed, the hydropathy index takes into account the frequency with which an amino acid residue appears on the surface of a protein. As proline often appears on the surface in β turns, it has a lower score than its chain of methylene groups would suggest.

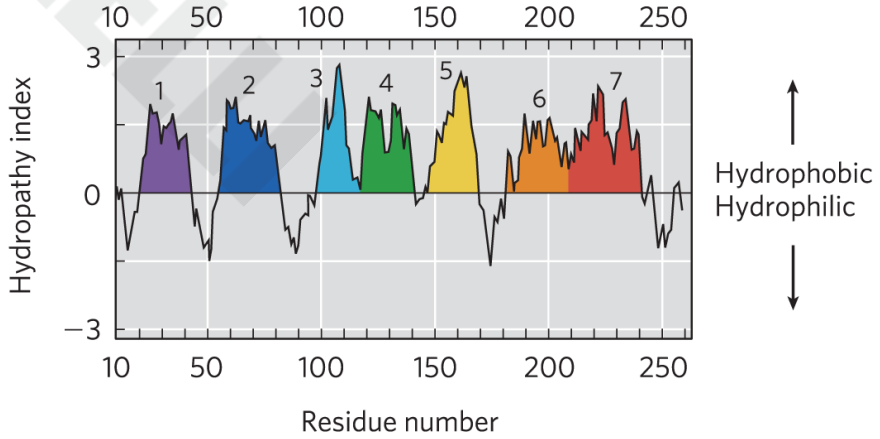
[e] Cysteine is generally classified as polar, despite having a positive hydropathy index. This reflects the ability of the sulfhydryl group to act as a weak acid and to form a weak hydrogen bond with oxygen or nitrogen.

Hydropathy Plots

- hydropathy plot = average hydropathy index plotted against residue number
  - window = segment of given length
  - hydropathy index (*y*-axis) = average hydropathy for a window
  - residue number (*x*-axis) = the residue in the middle of the window



(a) Glycophorin



(b) Bacteriorhodopsin

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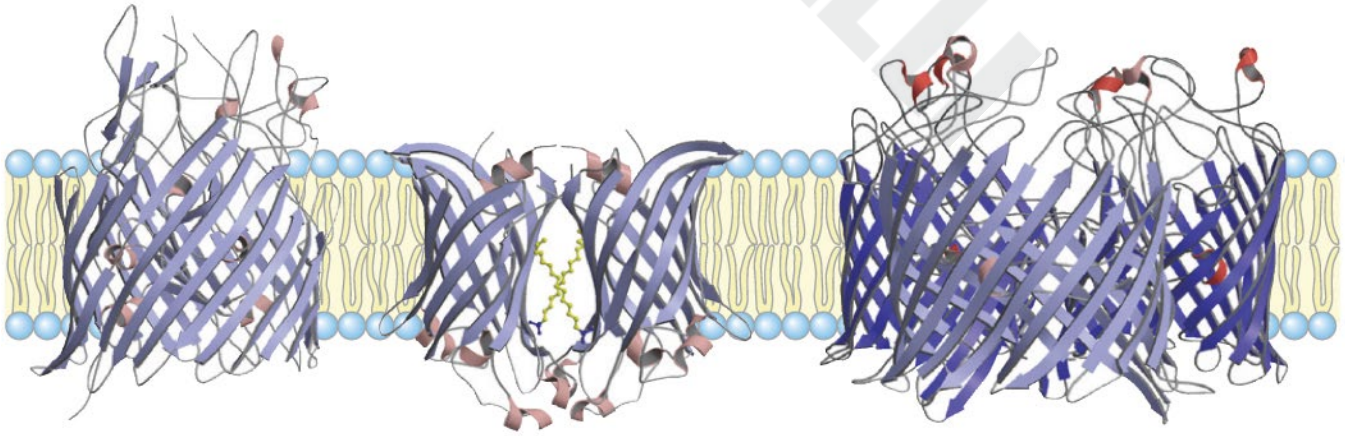
β Barrel

- ***β barrel*** = structural motif in which 20+ transmembrane segments form β sheets that line a cylinder
  - stabilized by intrachain hydrogen bonds

- **porins** = proteins that allow certain polar solutes to cross the outer membrane of gram-negative bacteria
  - have β barrels lining the transmembrane passage



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β Strands of Membrane Proteins

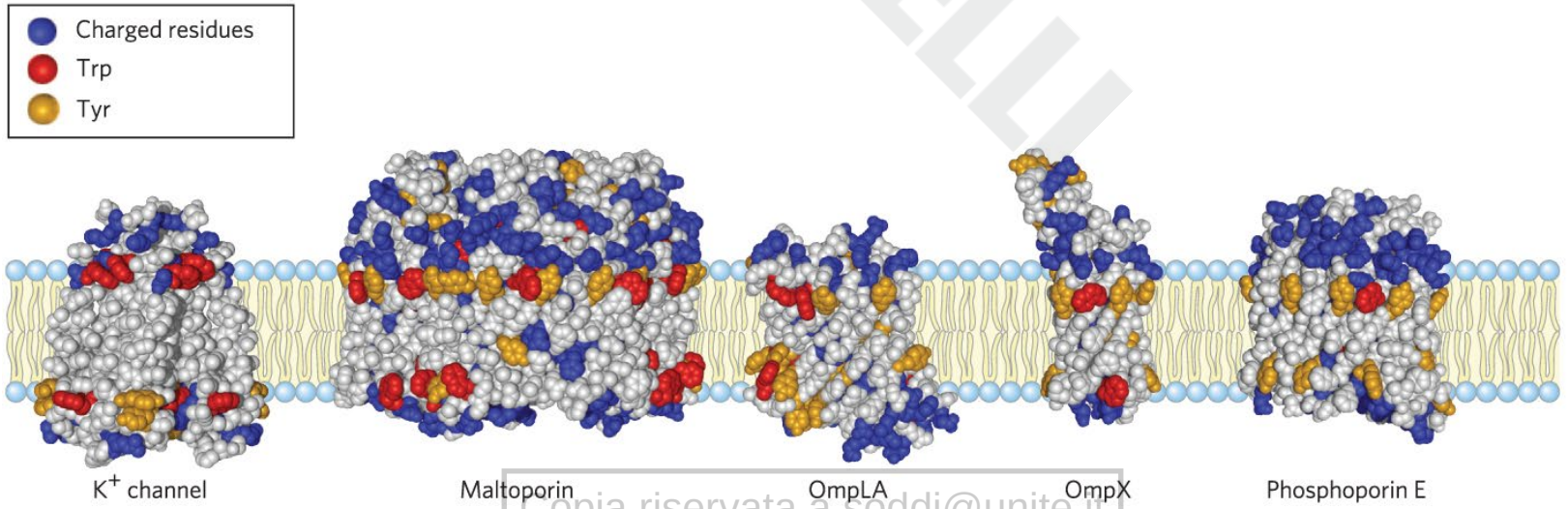
- in β conformation:
  - seven to nine residues are needed to span a membrane
  - alternating side chains project above and below the sheet

- in β strands of membrane proteins:
  - every second residue in the membrane-spanning segment is hydrophobic and interacts with the lipid bilayer
  - aromatic side chains are commonly found at the lipid-protein interface

Amino Acid Locations Relative to the Bilayer

- Tyr and Trp side chains serve as membrane interface anchors

- **positive-inside rule** = positively charged Lys and Arg residues in the extramembrane loop of membrane proteins occur more commonly on the cytoplasmic face



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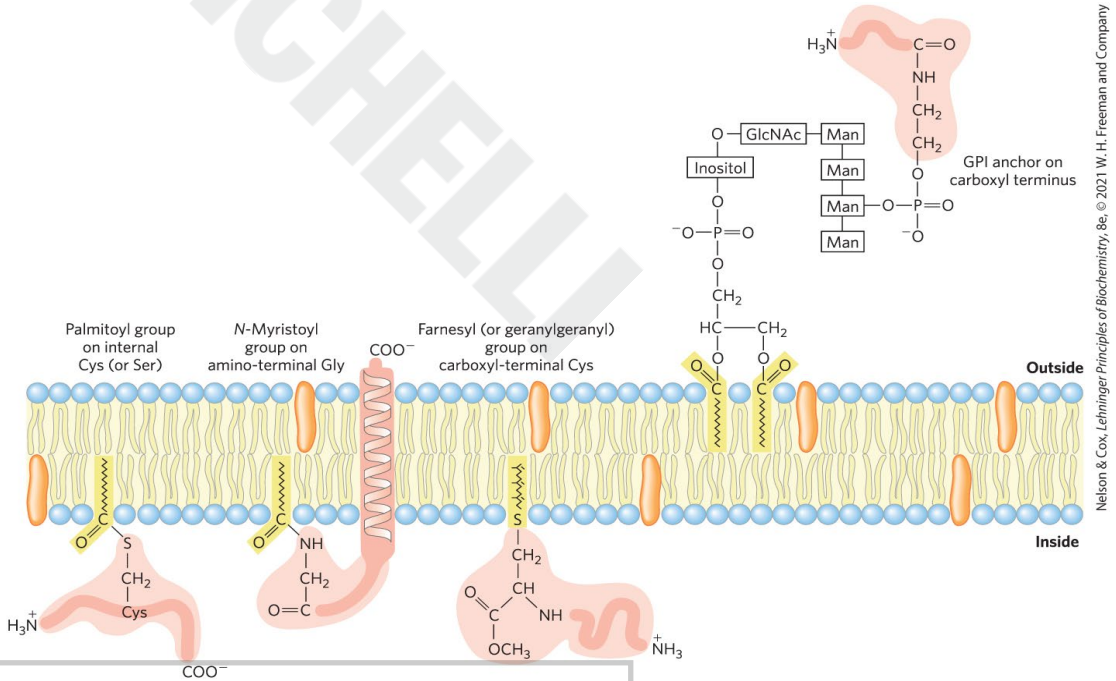
Covalently Attached Lipids Anchor or Direct Some Membrane Proteins

- **GPI-anchored protein** = exclusively on the outer face and are clustered in certain regions



Ionic Attractions Can Add to the Anchoring Effect of a Covalently Bound Lipid

- ionic attractions between positively charged residues in the protein and negatively charged lipid head groups add to the protein's affinity for the membrane
  - example: the plasma membrane protein MARCKS (*m*yristoylated *a*lanine-*r*ich *C*-*k*inase *s*ubstrate)

11.2 Membrane Dynamics

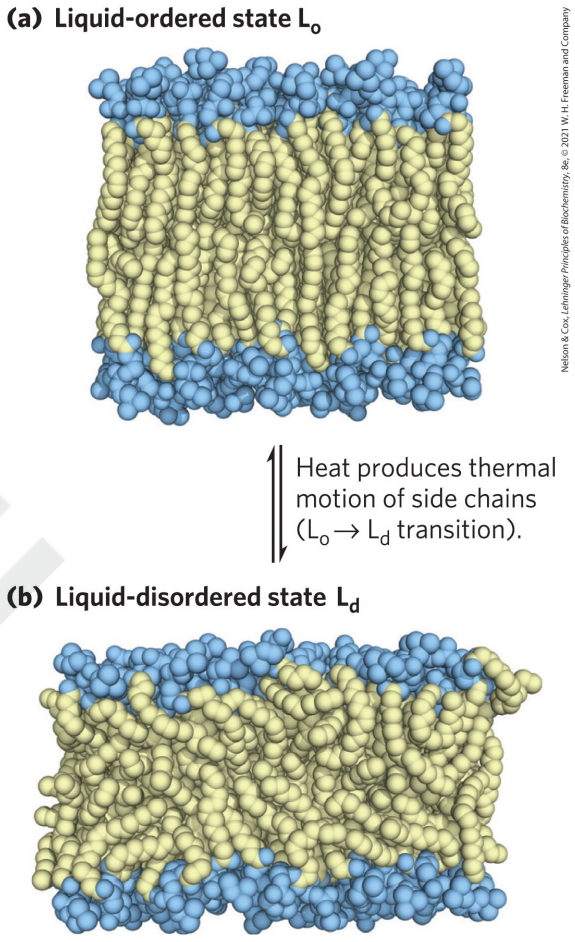
P1 Principle 1 (3 of 3)

The biological membrane is a lipid bilayer with proteins of various functions (enzymes, transporters) embedded in or associated with the bilayer. The hydrophobic effect stabilizes structures (lipid bilayers and vesicles) in which lipids with some polar and some nonpolar regions can protect their nonpolar regions from interaction with the very polar solvent, water. Membrane proteins are associated with the lipid bilayer more or less tightly, and proteins and lipids are both allowed limited lateral motion in the plane of the bilayer.

Acyl Groups in the Bilayer Interior Are Ordered to Varying Degrees

- **liquid-ordered (L_o) state** = gel-like state in which all types of motion of individual molecules are strongly constrained

- **liquid-disordered (L_d) state** = state in which individual hydrocarbon chains are in constant motion (lateral and rotational)



Fatty Acid Composition Affects Membrane Fluidity

- at physiological temperatures:
  - long-chain saturated fatty acids tend to pack into an L_o phase
  - kinks in unsaturated fatty acids interfere with packing, favoring the L_d state
  - shorter-chain fatty acyl groups favor the L_d state

Sterol Content Affects Membrane Fluidity

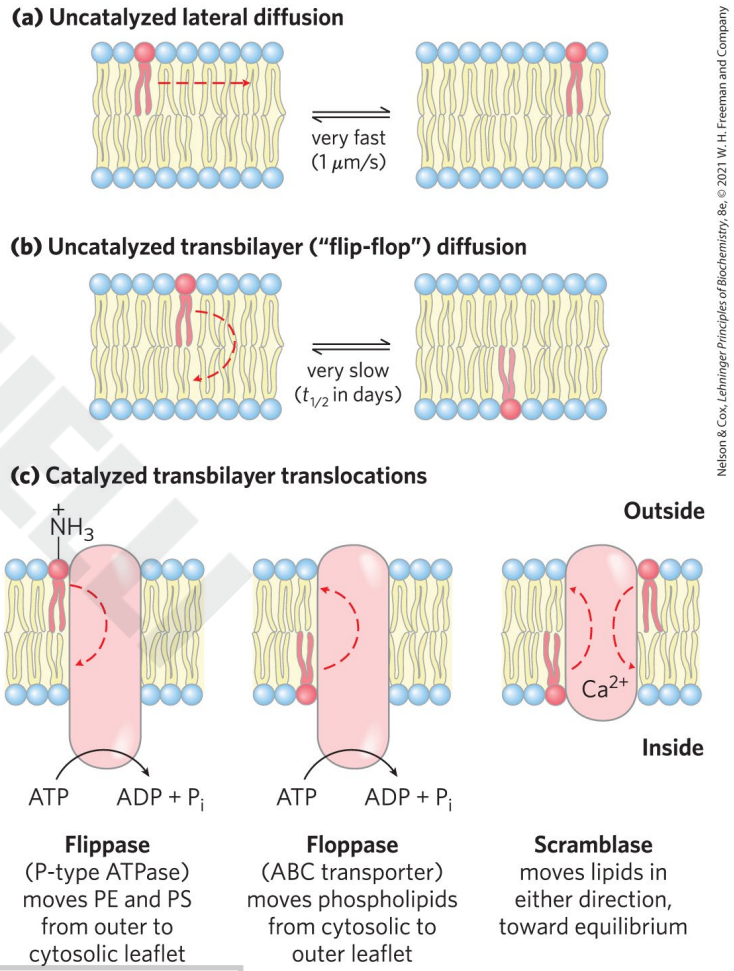
- sterols have paradoxical effects on bilayer fluidity:
  - they interact with phospholipids containing unsaturated fatty acyl chains, compacting them and constraining their motion
  - they associate with sphingolipids and phospholipids having long, saturated fatty acyl chains, making the bilayer fluid

P2 Principle 2 (5 of 8)

All of the internal membranes of cells are part of an interconnected, functionally specialized, and dynamic endomembrane system. Proteins and lipids synthesized in the endoplasmic reticulum move through the Golgi apparatus, and they are targeted to the membranes of organelles or to the plasma membrane, where they provide the essential properties of these structures. During this membrane trafficking, some proteins are covalently altered, and some lipids are segregated into different organelles or are concentrated in one of the bilayer leaflets. Rafts are functionally specialized regions with unique lipid and protein compositions.

Transbilayer Movement of Lipids Requires Catalysis

- transbilayer ("flip-flop") movement has a large, positive free-energy change
- membrane proteins facilitate the translocation of individual lipid molecules



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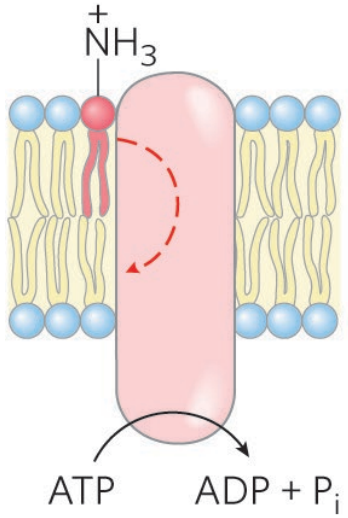
Flippases

- **flippases** = catalyze translocation of the *amino*- phospholipids phosphatidylethanolamine (PE) and phosphatidylserine (PS) from the extracellular to the cytoplasmic leaflet of the plasma membrane
  - consume ~1 ATP per molecule of phospholipid translocated
  - related to the P-type ATPases (active transporters)



Flippase (P-type ATPase) moves PE and PS from outer to cytosolic leaflet

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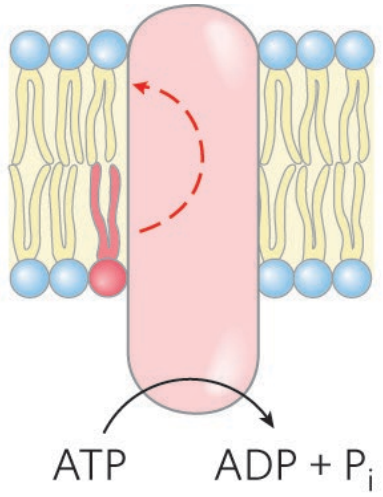
Floppases

- **floppases** = move plasma membrane phospholipids and sterols from the cytoplasmic leaflet to the extracellular leaflet
  - are ATP-dependent
  - members of the ABC transporter family
  - each specializes in movement of specific lipids



Floppase (ABC transporter) moves phospholipids from cytosolic to outer leaflet

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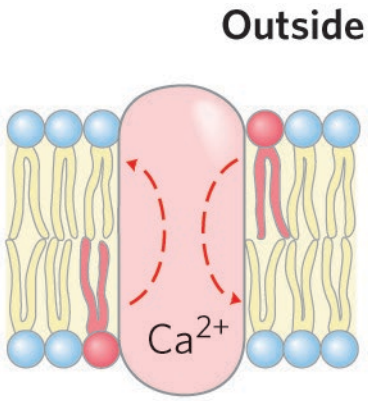
Scramblases

- **scramblases** = move any membrane phospholipid across the bilayer down its concentration gradient
  - not dependent on ATP; some require Ca^{2+}
  - lead to controlled randomization of the head-group composition on the two faces of the bilayer



Scramblase moves lipids in either direction, toward equilibrium

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Phosphatidylinositol Transfer Proteins

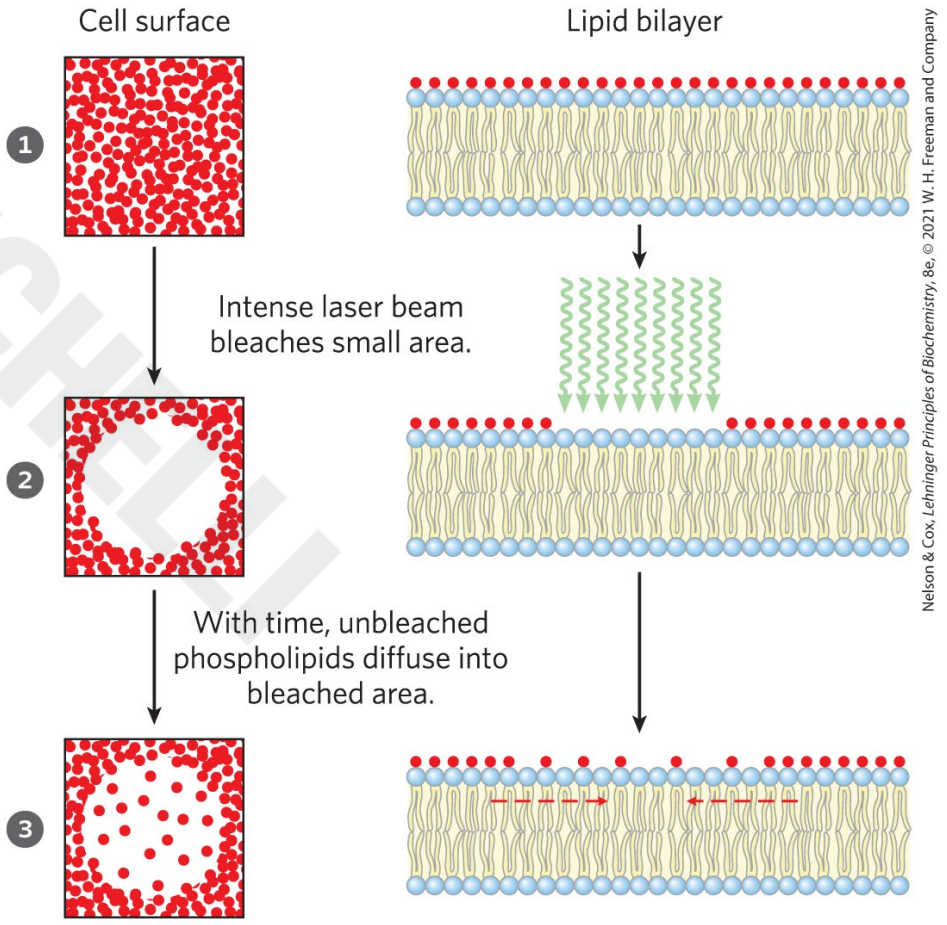
- **phosphatidylinositol transfer proteins** = move phosphatidylinositol lipids across lipid bilayers
  - believed to have roles in lipid signaling and membrane trafficking

P2 Principle 2 (6 of 8)

All of the internal membranes of cells are part of an interconnected, functionally specialized, and dynamic endomembrane system. Proteins and lipids synthesized in the endoplasmic reticulum move through the Golgi apparatus, and they are targeted to the membranes of organelles or to the plasma membrane, where they provide the essential properties of these structures. During this membrane trafficking, some proteins are covalently altered, and some lipids are segregated into different organelles or are concentrated in one of the bilayer leaflets. Rafts are functionally specialized regions with unique lipid and protein compositions.

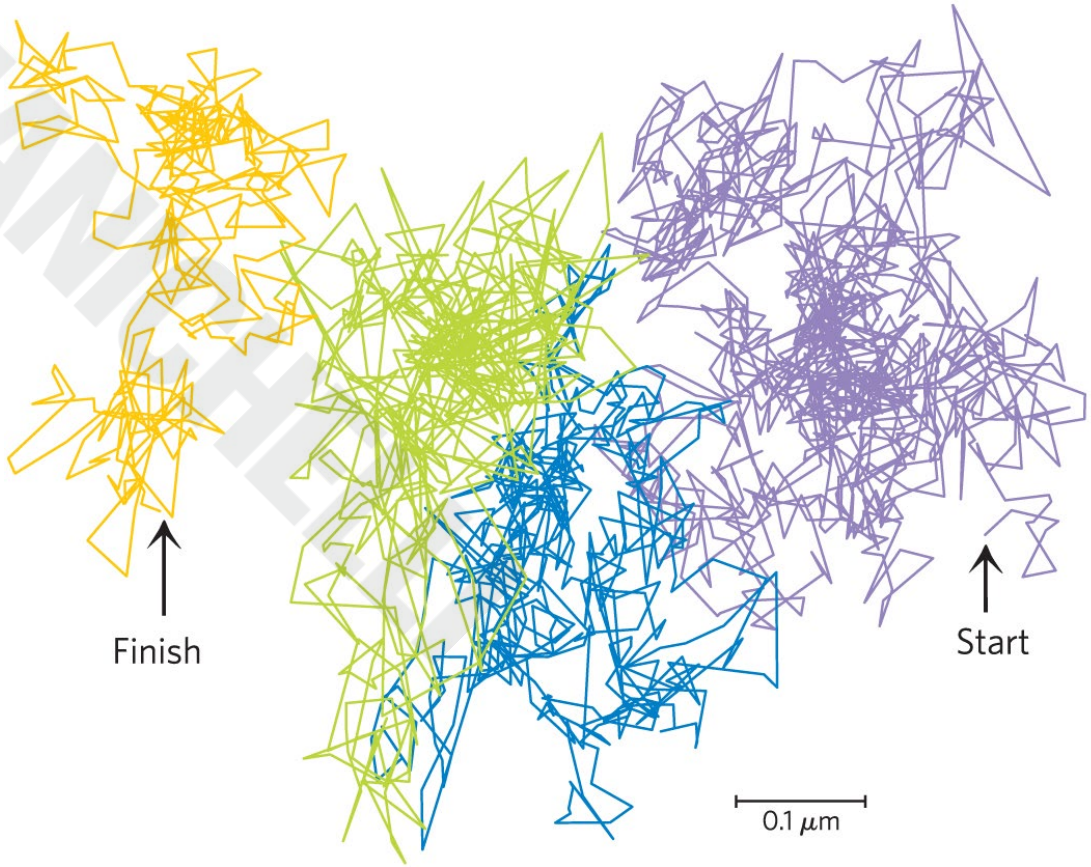
Lipids and Proteins Diffuse Laterally in the Bilayer

- individual lipid molecules undergo Brownian movement
- **FRAP** = fluorescence recovery after photobleaching
  - rate is a measure of the rate of lateral diffusion of the lipids



Hop Diffusion of Individual Lipid Molecules

- single particle tracking confirms lipid molecules diffuse laterally within small regions
- movement from one region to another (“hop diffusion”) is rarer



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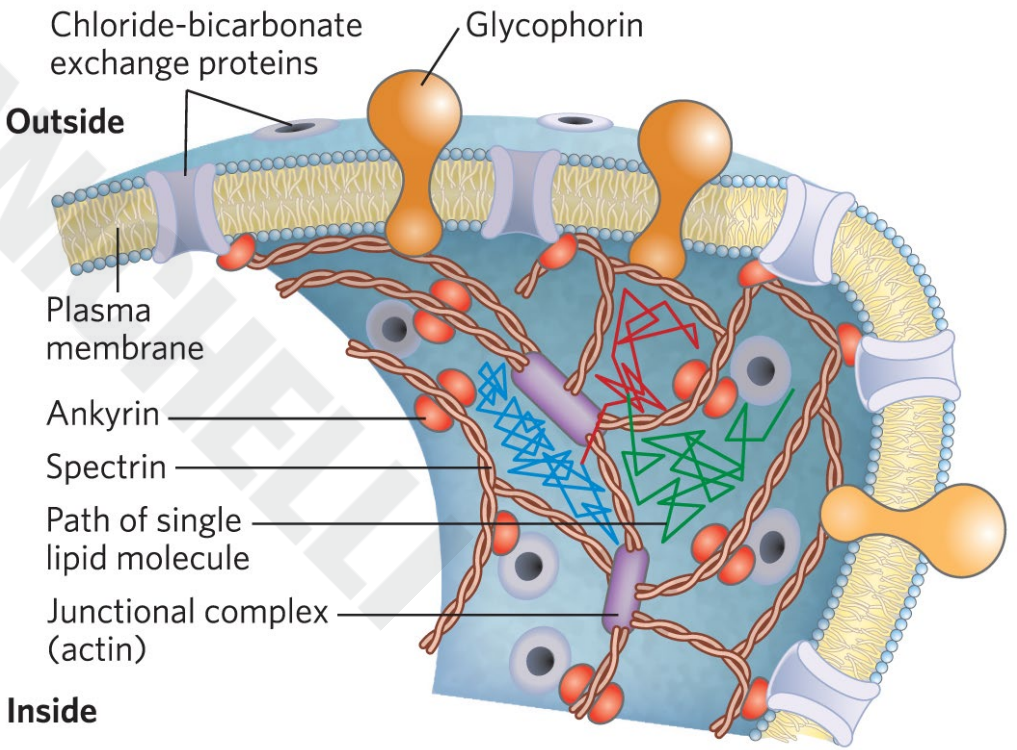
Some Membrane Proteins Are Free to Diffuse, Whereas Others Are Not

- membrane proteins are limited in movement by:
  - associating to form large aggregates (“patches”)
  - anchoring to internal structures



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P2 Principle 2 (7 of 8)

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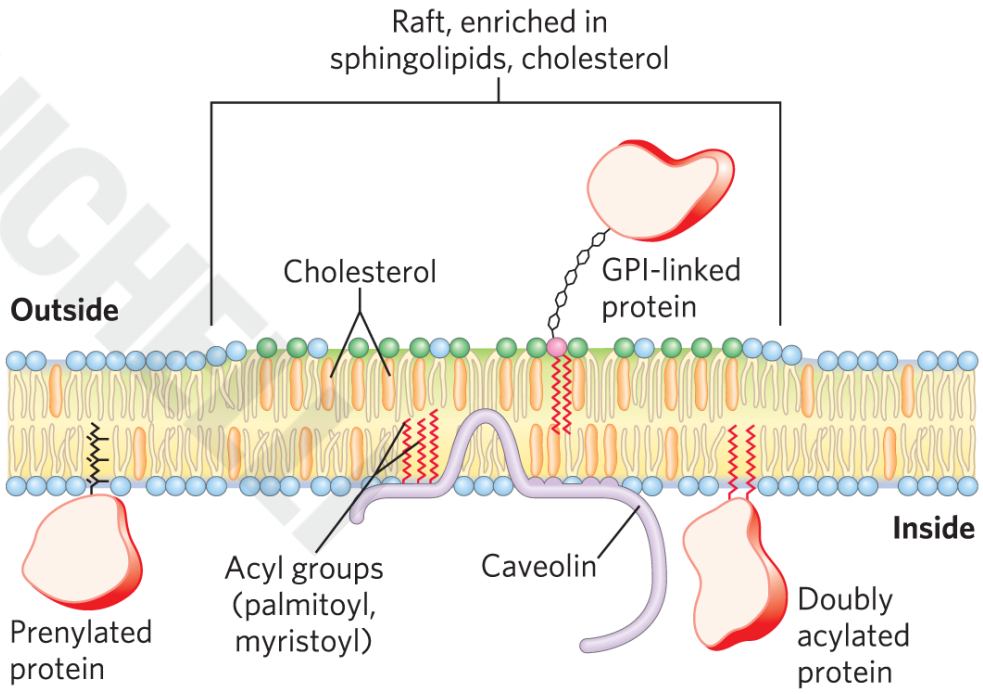
Sphingolipids and Cholesterol Cluster Together in Membrane Rafts

- **microdomains (rafts)** = clusters of cholesterol and sphingolipids that make the bilayer slightly thicker and more ordered than neighboring, phospholipid-rich regions
  - can be up to 50% of the cell surface



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Proteins and Lipid Rafts

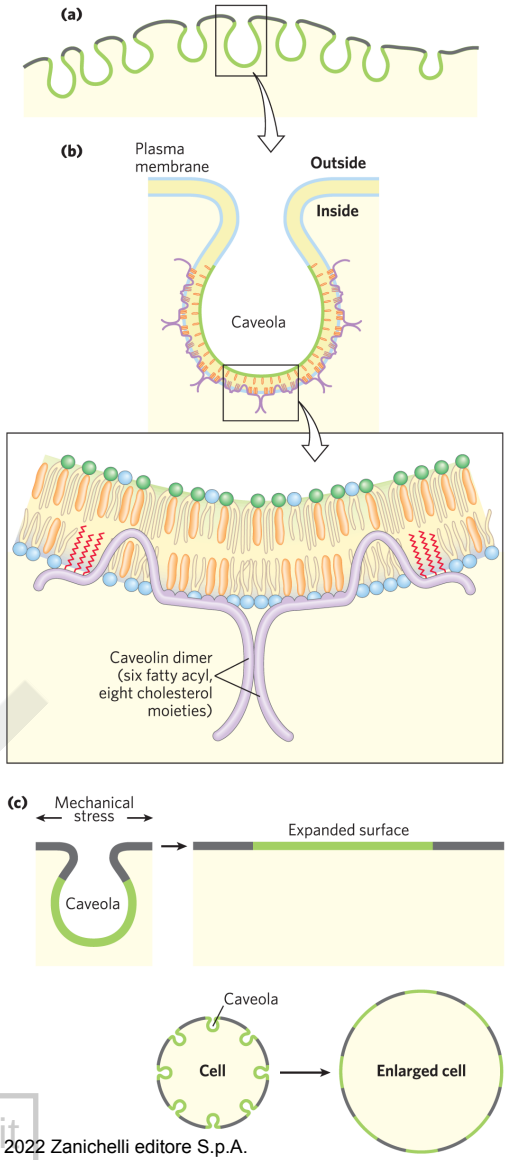
- proteins must have hydrophobic helical sections long enough to segregate into the thicker bilayer regions of rafts

- lipid rafts are enriched in:
  - proteins that have two long-chain saturated fatty acids covalently attached through Cys residues
  - GPI-anchored proteins

Caveolae and Caveolin

- **caveolae** (“little caves”) = specialized rafts

- **caveolin** = integral protein that binds to the cytoplasmic leaflet of the plasma membrane
  - forms dimers
  - associates with cholesterol-rich membrane regions
  - forces the bilayer to curve inward to form caveolae



P2 Principle 2 (8 of 8)

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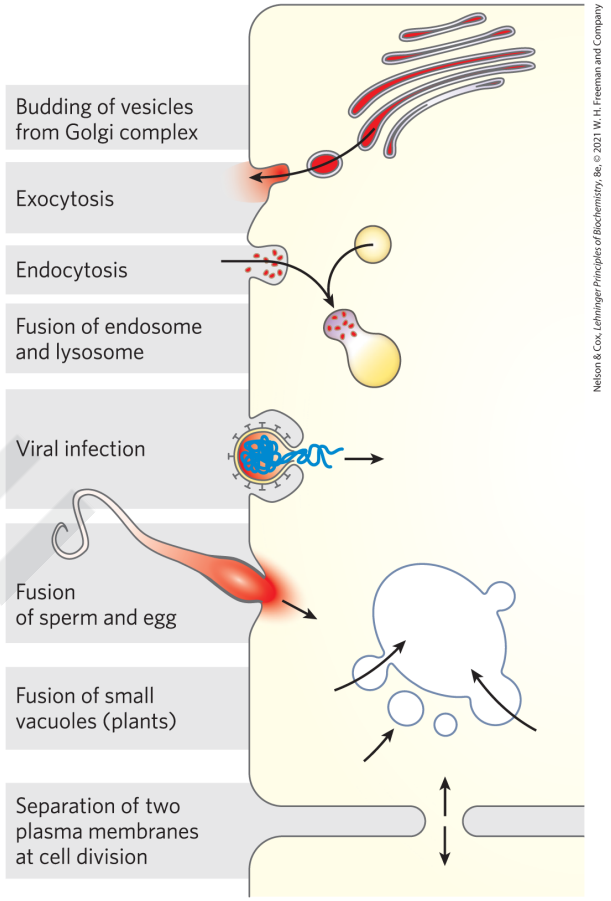
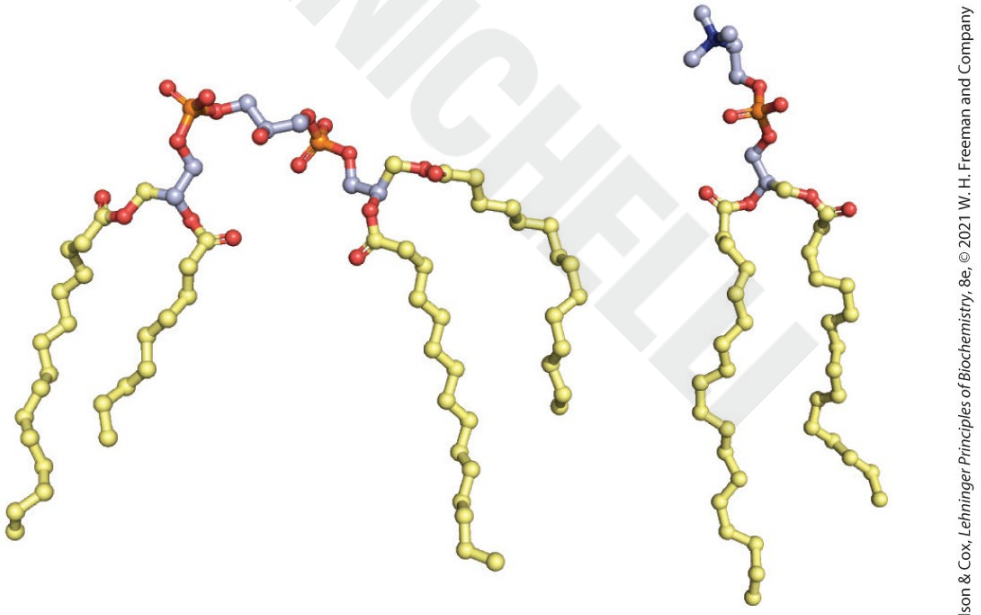
Membrane Curvature and Fusion Are Central to Many Biological Processes

- curvature changes are central to the ability of biological membranes to undergo fusion with other membranes without losing continuity



Cardiolipid

- cardiolipin = can create or recognize membrane curvature
  - located in mitochondrial and bacterial membranes



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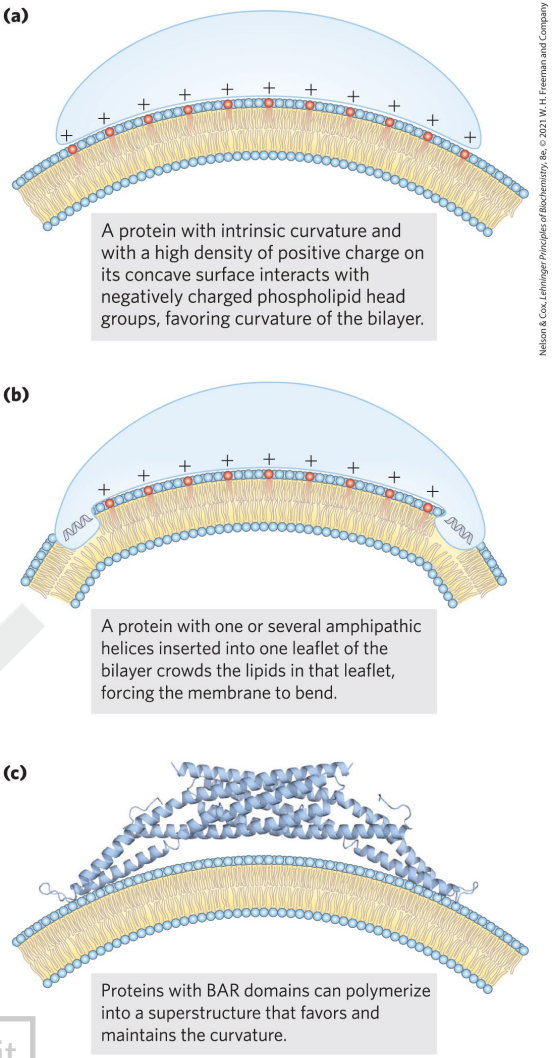
Protein-Induced Curvature of Membranes

- **BAR domains** = domains consisting of coiled coils that form long, thin, curved dimers with a positively charged concave surface

- BAR domain proteins assemble into crescent-shaped scaffolds and favor membrane curvature



Septins

- **septins** = family of GTP-binding proteins that polymerize at curved regions of the plasma membrane
  - participate in cell division, exocytosis, phagocytosis, and apoptosis
  - have an amphipathic helix that is important in vesicle trafficking and neurotransmitter release

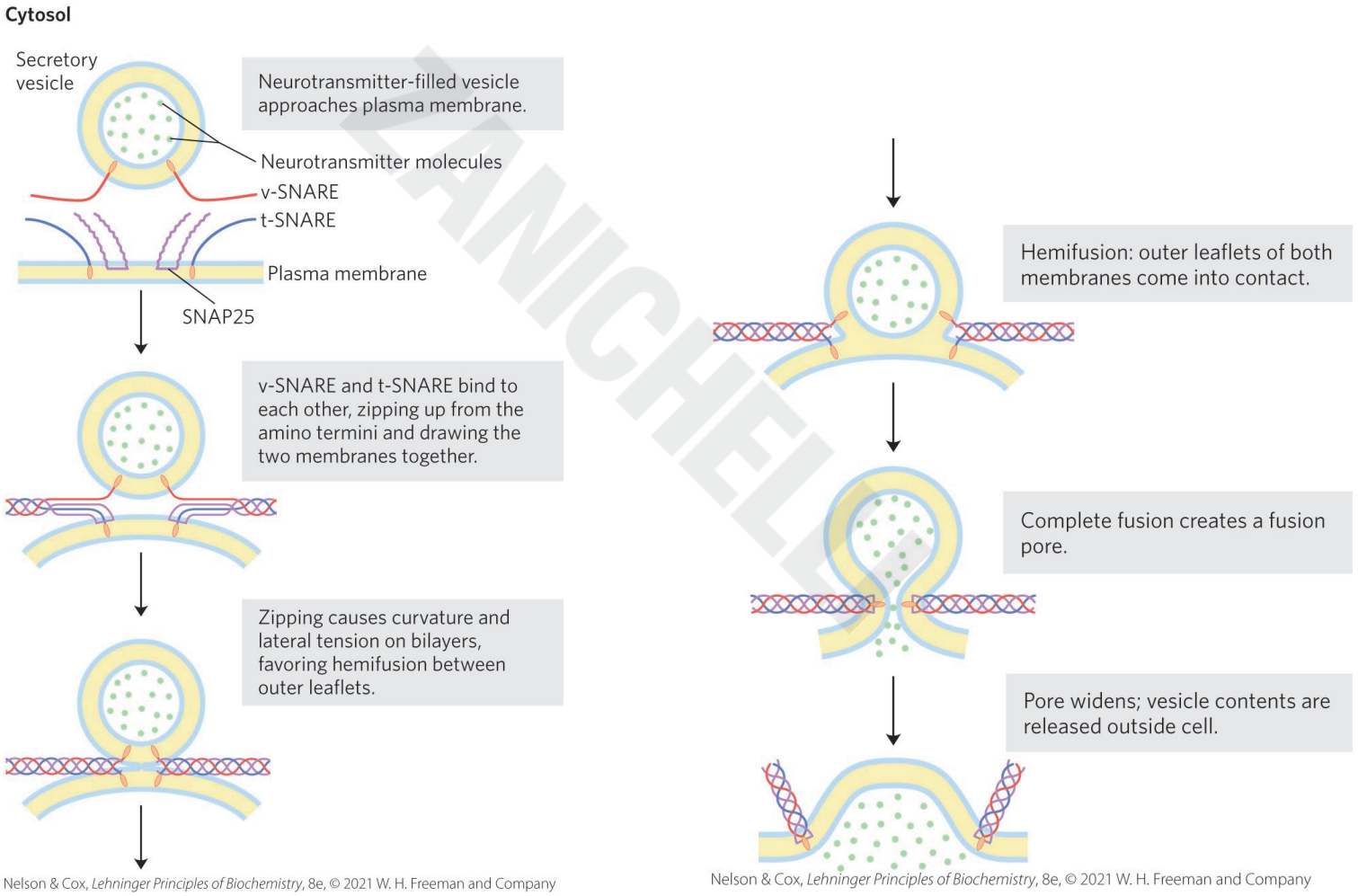
Fusion Proteins

- **fusion proteins** = mediate specific fusion of two membranes by bringing about specific recognition and a transient local distortion of the bilayer structure

SNARE Proteins

- SNAREs (*sna*p *re*ceptors) = family of proteins
- **v-SNAREs** = SNAREs in the cytoplasmic face of the intracellular vesicle
- **t-SNAREs** = SNAREs in the target membrane with which the vesicle fuses

Membrane Fusion During Neurotransmitter Release



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Integral Proteins of the Plasma Membrane Are Involved in Surface Adhesion, Signaling, and Other Cellular Processes

- **integrins** = surface adhesion proteins that mediate a cell's interaction with the extracellular matrix and with other cells
  - carry signals in both directions across the plasma membrane
  - heterodimeric proteins composed of two unlike subunits, α and β

Cadherins and Selectins

- **cadherins** = involved in surface adhesion
  - undergo homophilic interactions with identical cadherins in an adjacent cell

- **selectins** = have extracellular domains that bind specific polysaccharides on the surface of an adjacent cell
  - require Ca^{2+}
  - essential part of the blood-clotting process

11.3 Solute Transport across Membranes

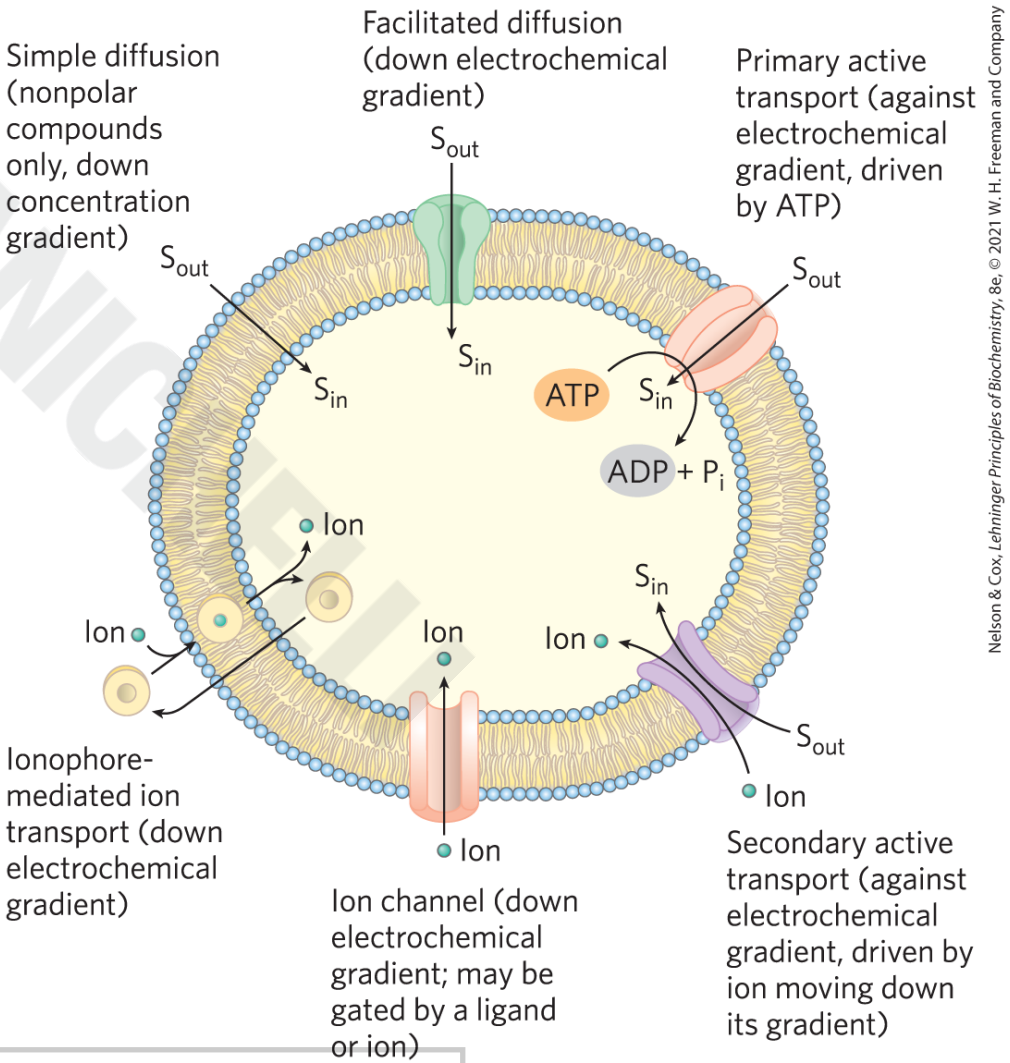
P3 Principle 3 (2 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

Summary of Transport Types

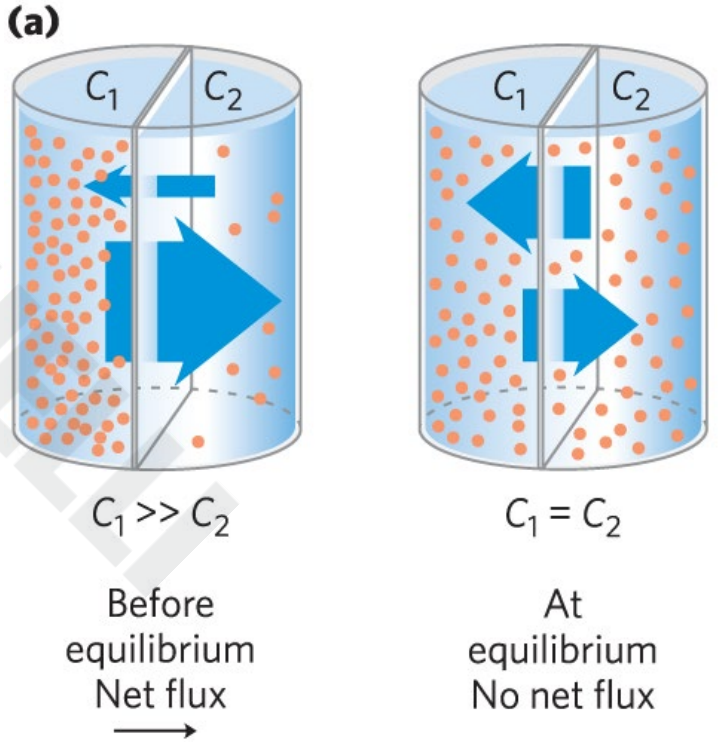
- nonpolar compounds can dissolve in the lipid bilayer and cross a membrane unassisted

- polar compounds and ions require a specific membrane protein carrier



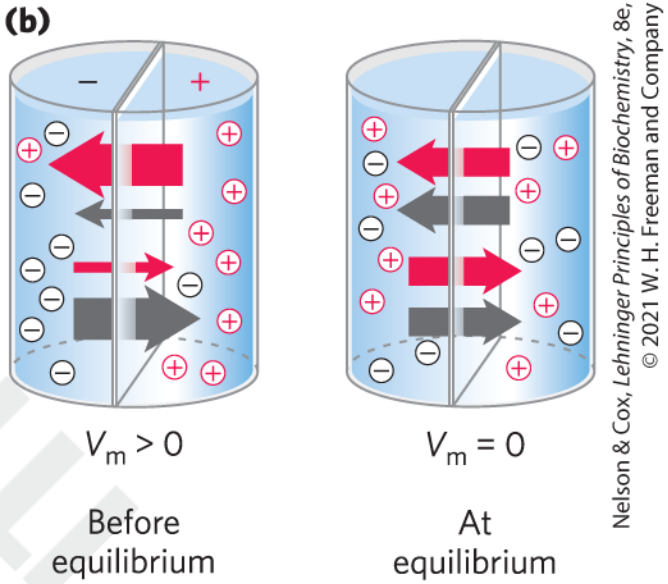
Transport May Be Passive or Active

- **simple diffusion** = movement of a solute from the region of higher concentration to the region of lower concentration



Membrane Potential, V_m

- **membrane potential, V_m** = a transmembrane electrical gradient that occurs when ions of opposite charge are separated by a permeable membrane
  - produces a force that:
    - opposes ion movements that increase V_m
    - drives movements that reduce V_m



P3 Principle 3 (3 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

Electrochemical Gradient

- **electrochemical gradient (electrochemical potential)** = determines the direction in which a charged solute moves across a membrane
  - composed of:
    - the chemical gradient
    - the electrical gradient (V_m)

P3 Principle 3 (4 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

Passive and Active Transporters

- **passive transporters** = facilitate movement down a concentration gradient, increasing the transport rate
  - process is called **passive transport** or **facilitated diffusion**

- **active transporters** = move substrates across a membranes against a concentration gradient or an electrical potential
  - process is called **active transport**

Types of Active Transporters

- **primary active transporters** = use energy provided directly by a chemical reaction

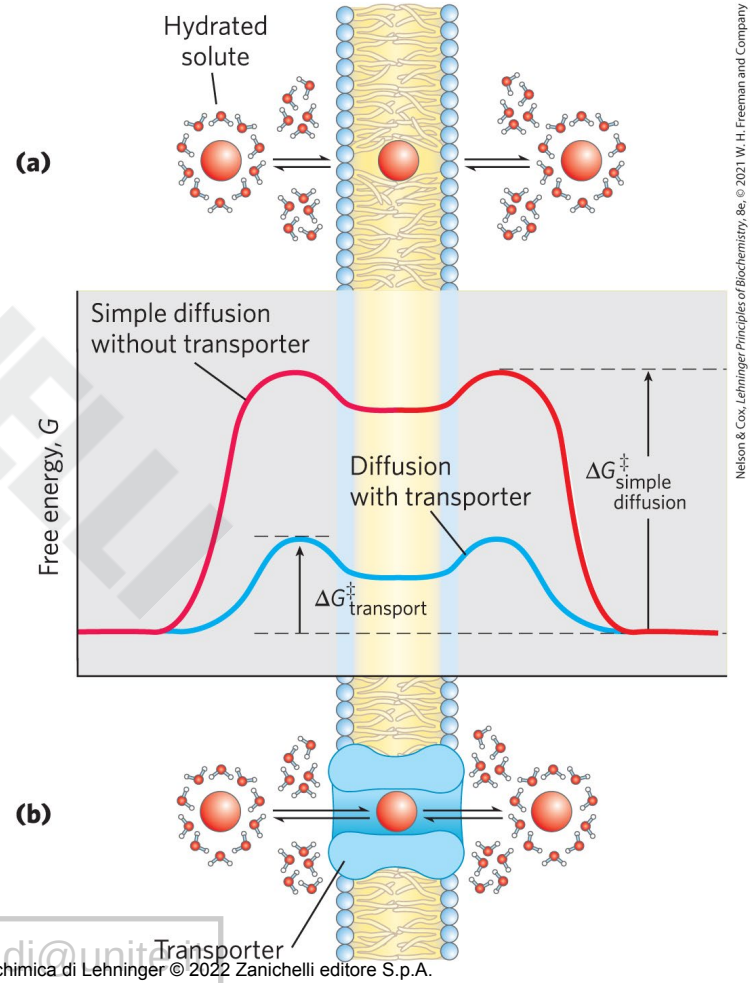
- **secondary active transporters** = couple uphill transport of one substrate with downhill transport of another

P3 Principle 3 (5 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

Transporters and Ion Channels Share Some Structural Properties but Have Different Mechanisms

- transporter proteins reduce the energy of activation ($\Delta G^{\ddagger}$) for diffusion by:
  - forming noncovalent interactions with the dehydrated solute
  - providing a hydrophilic transmembrane pathway



P3 Principle 3 (6 of 11)

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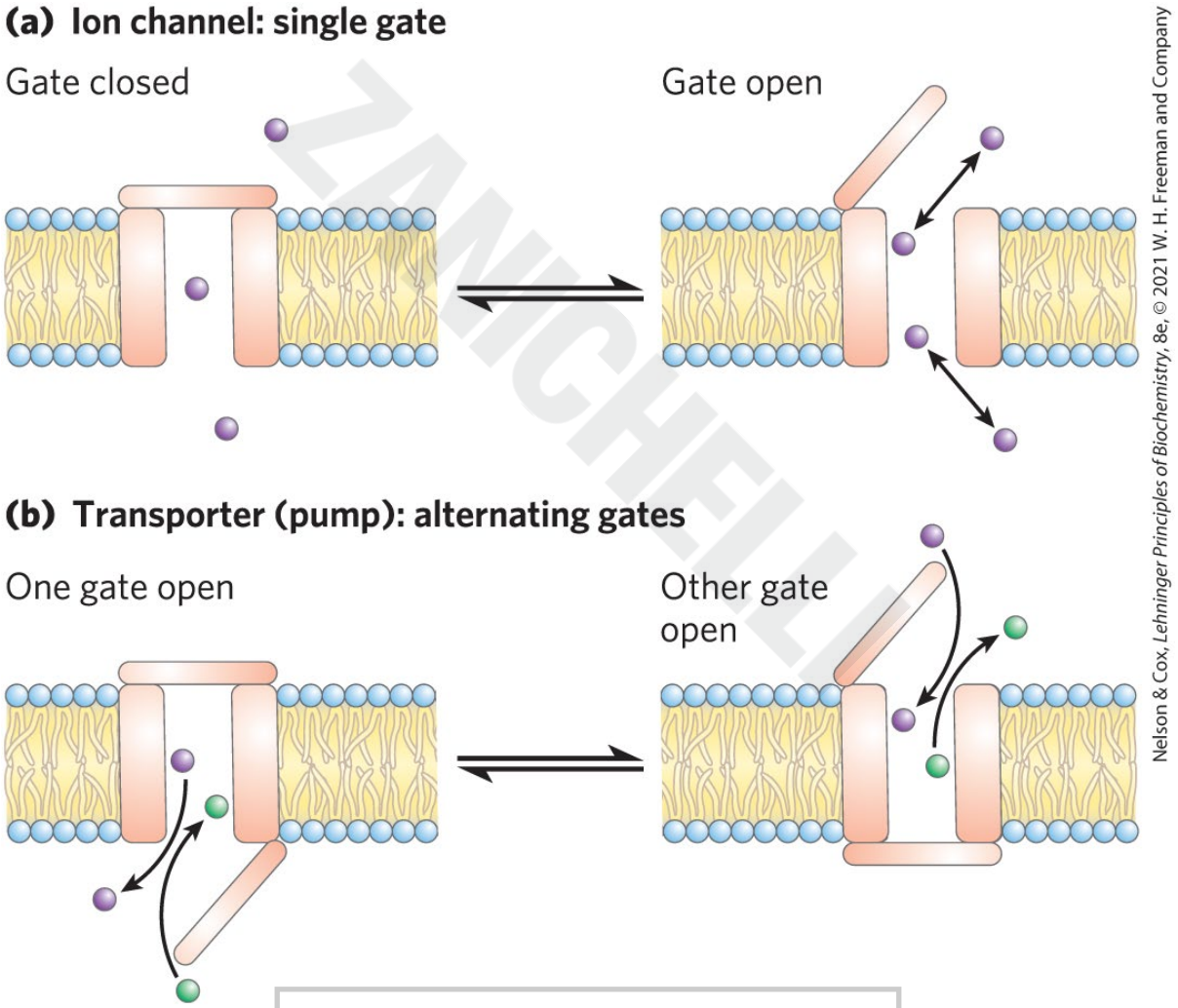
Ion Channels

- **ion channels =** provide an aqueous path across the membrane through which inorganic ions can diffuse at very high rates
  - most have a “gate” regulated by a biological signal
  - typically show some specificity for an ion
  - are not saturable with their ion substrate
  - flow stops either when the gate is closed or when there is no longer an electrochemical gradient

Differences Between Ion Channels and Transporters



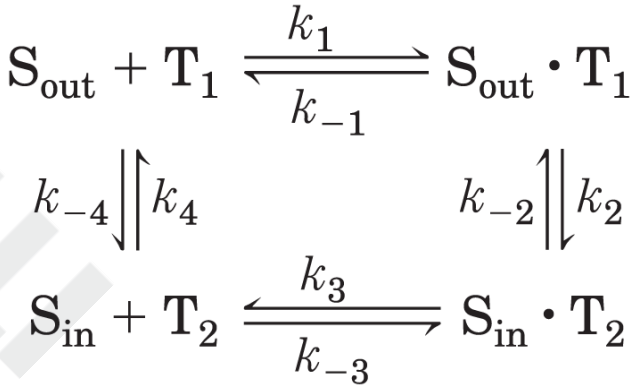
P3 Principle 3 (7 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

The Glucose Transporter of Erythrocytes Mediates Passive Transport

- glucose enters the erythrocyte by passive transport via GLUT1

- analogous with an enzymatic reaction where:
  - glucose (“substrate”) outside is S_{out}
  - glucose (“product”) inside is S_{in}
  - transporter (“enzyme”) is T



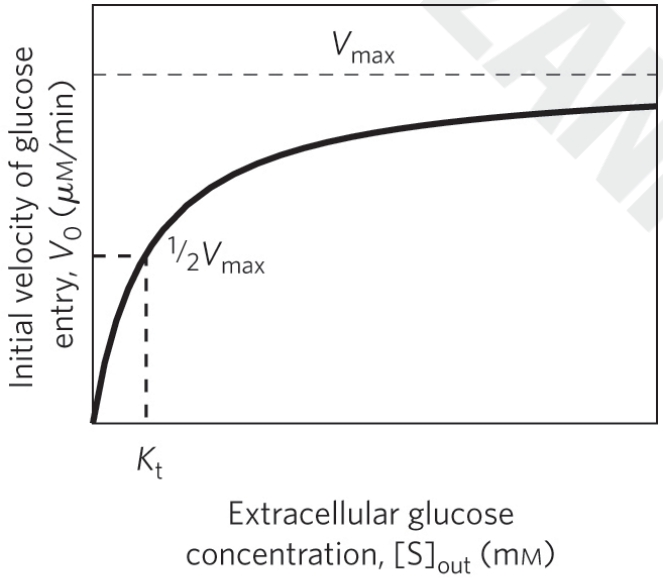
Rate Equations for Glucose Transport

- analogous to the Michaelis-Menten equation:

$$V_0 = \frac{V_{max}[S]_{out}}{K_t + [S]_{out}} \qquad (11\text{-}1)$$

where V_0 is the initial velocity of accumulation of glucose inside the cell, $[S]_{out}$ is the concentration of glucose in the surrounding medium, and $\boldsymbol{K_t}$ **(**$\boldsymbol{K_{transport}}$**)** is a constant analogous to the Michaelis constant

Kinetics of Glucose Transport into Erythrocytes



(a)

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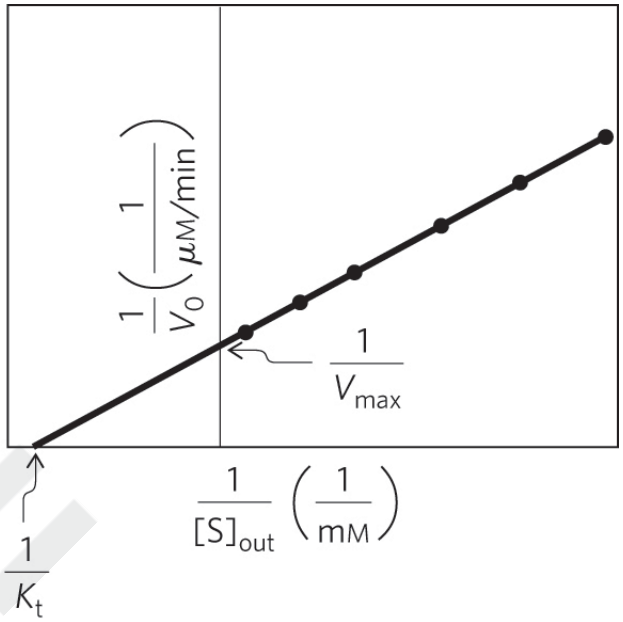

(b)

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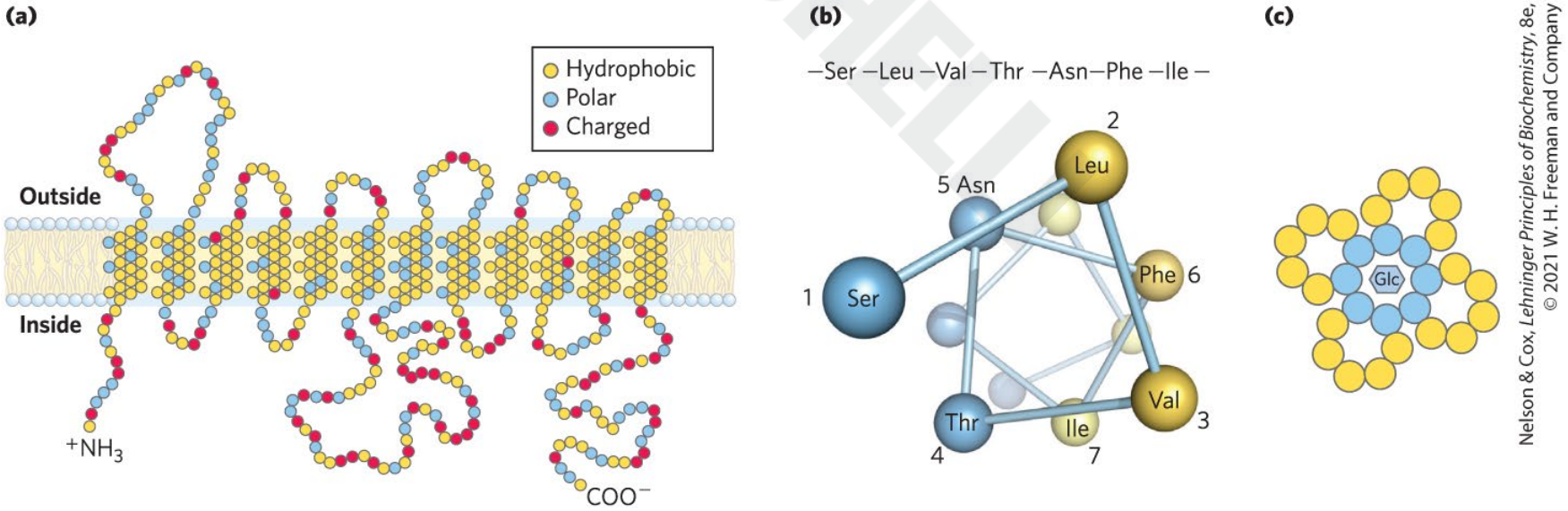
Membrane Topology of GLUT1

- GLUT1 = integral membrane protein with 12 hydrophobic segments that form 12 membrane-spanning helices
  - helices are **amphipathic** (resides are nonpolar on one side and polar on the other side)



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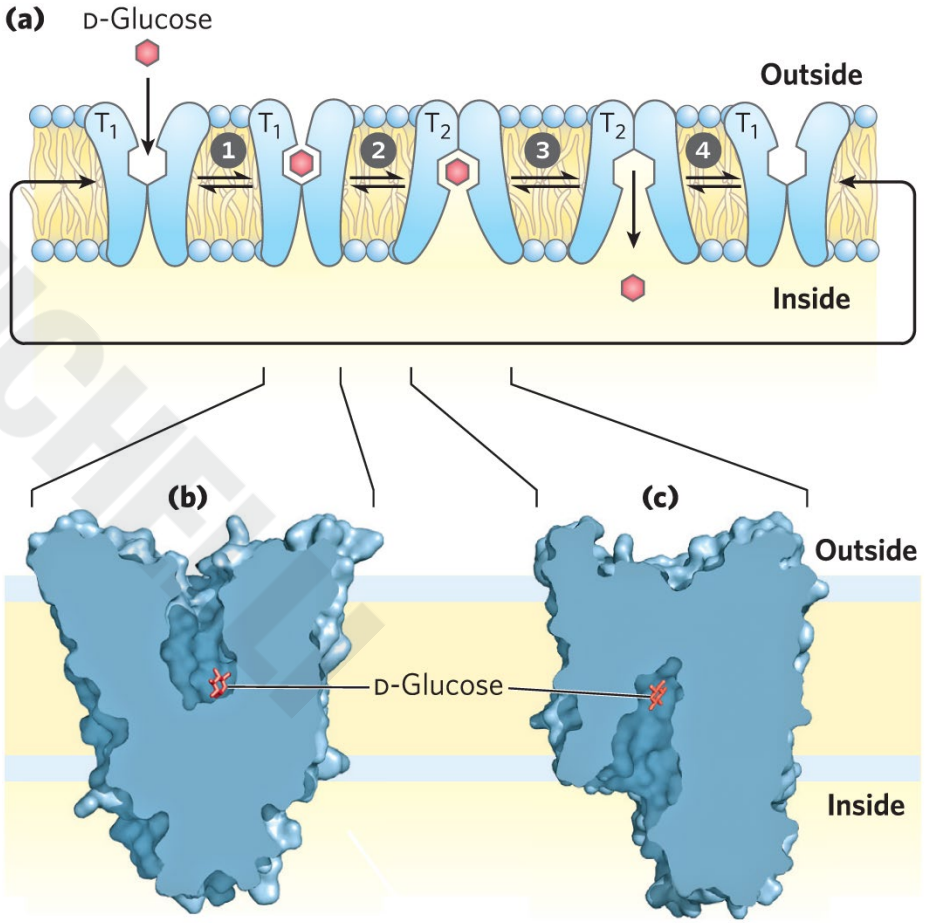
Model of Glucose Transport into Erythrocytes

- cycles between two extreme conformations:
  - T_1 form: glucose-binding site exposed on the outer membrane surface
  - T_2 form: glucose-binding site exposed on the inner surface



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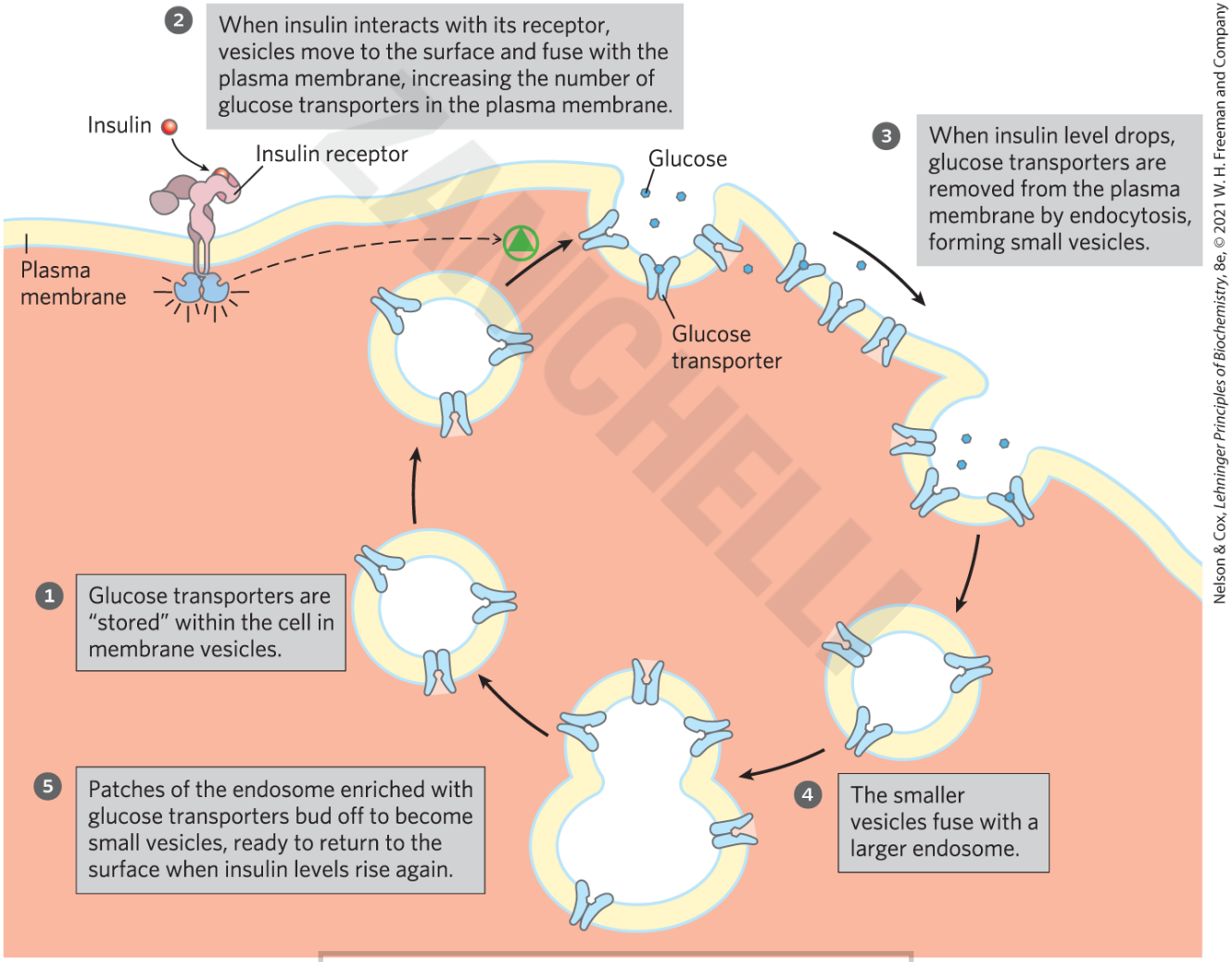
Glucose Transporters in Humans

Table 11-1 Glucose Transporters in Humans

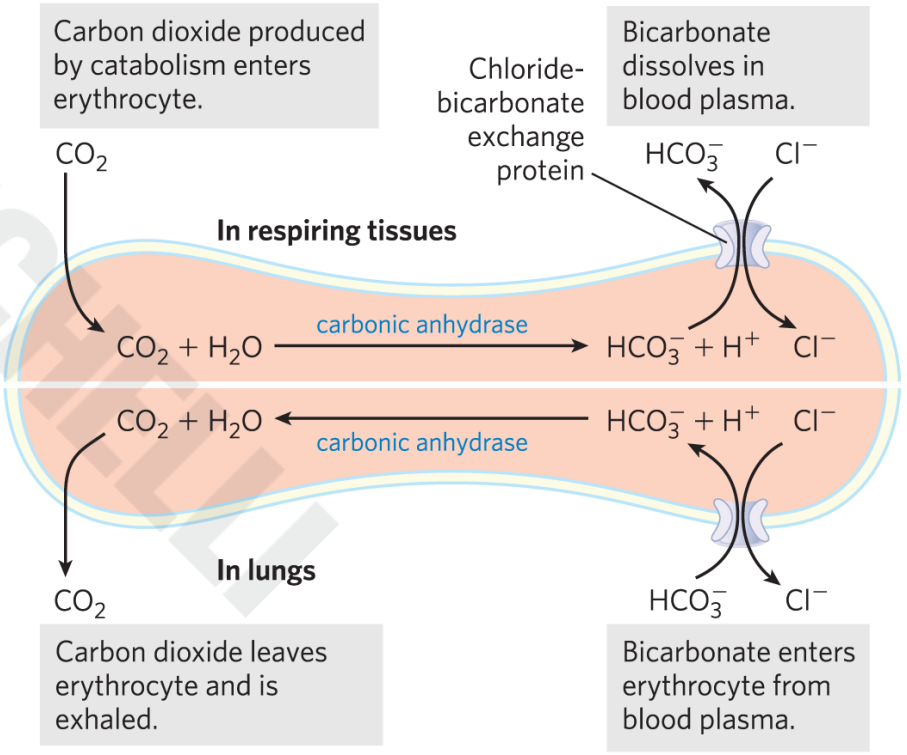
Transporter	Tissue(s) where expressed	K_t (mM)	Role/characteristics
GLUT1	Erythrocytes, blood-brain barrier, placenta, most tissues at a low level	3	Basal glucose uptake; defective in De Vivo disease
GLUT2	Liver, pancreatic islets, intestine, kidney	17	In liver and kidney, removal of excess glucose from blood; in pancreas, regulation of insulin release
GLUT3	Brain (neuron), tests (sperm)	1.4	Badal glucose uptake; high turnover number
GLUT4	Muscle, fat, heart	5	Activity increased by insulin
GLUT5	Intestine (primarily), testis, kidney	6	Primarily fructose transport
GLUT6	Spleen, leukocytes, brain	>5	Possibly no transporter function
GLUT7	Small intestine, colon, testis, kidney	0.3	—
GLUT8	Testis, sperm acrosome	−2	—
GLUT9	Liver, kidney, intestine, lung, placenta	0.6	Urate and glucose transporter in liver, kidney
GLUT10	Heart, lung, brain, liver, muscle, pancreas, placenta, kidney	0.3	Glucose and galactose transporter
GLUT11	Heart, skeletal muscle	0.16	Glucose and fructose transporter
GLUT12	Skeletal muscle, heart, prostate, placenta	—	—

Transport of Glucose Into a Myocyte by GLUT4 Is Regulated by Insulin



The Chloride-Bicarbonate Exchanger Catalyzes Electroneutral Cotransport of Anions across the Plasma Membrane

- chloride-bicarbonate exchanger = anion exchanger essential in CO_2 transport to the lungs from tissues
  - passive transport system
  - **electroneutral** exchange = no net transfer of charge



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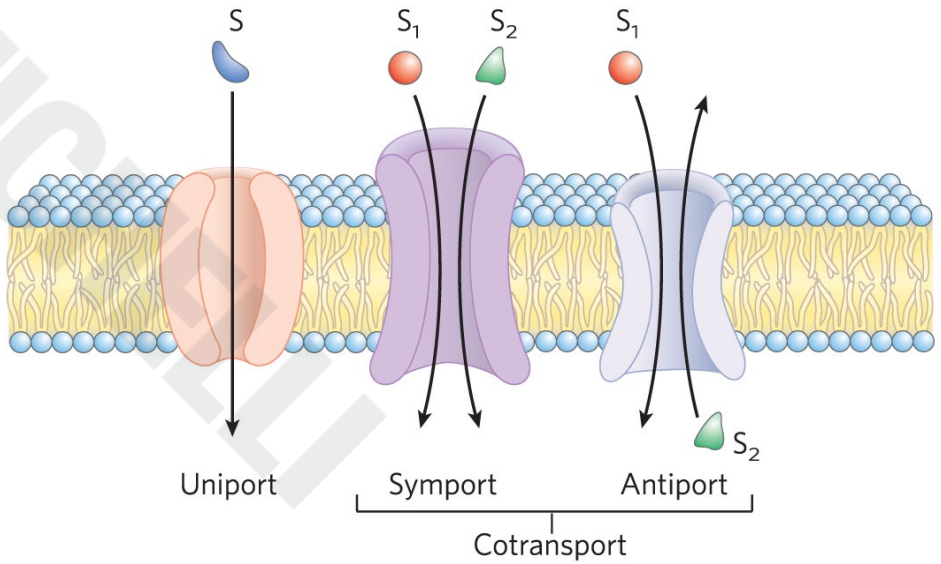
Three General Classes of Transport Systems

- **cotransport** systems = simultaneously transport two solutes across a membrane
  - **antiport** = moves in opposite directions
  - **symport** = moves in the same direction
- **uniport** systems = carry only one substrate



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P3 Principle 3 (8 of 11)

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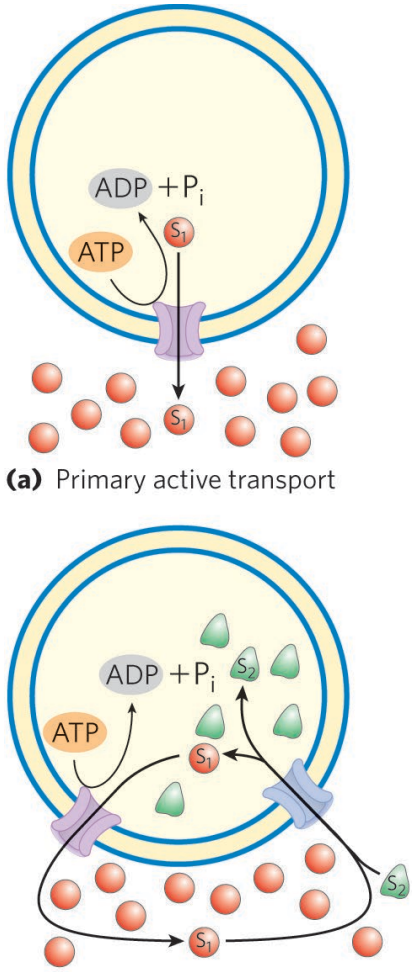
Active Transport Results in Solute Movement against a Concentration or Electrochemical Gradient

- results in the accumulation of a solute above the equilibrium point
- thermodynamically unfavorable (endergonic)
  - must be directly or indirectly coupled to an exergonic process

Two Types of Active Transport

- **primary active transport** = solute accumulation is coupled directly to an exergonic chemical reaction

- **secondary active transport** = endergonic transport of one solute is coupled to the exergonic flow of a different solute that was originally pumped uphill by primary active transport



(a) Primary active transport

(b) Secondary active transport

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Free-Energy Change for the Conversion of a Substrate to a Product

- general equation for the free-energy change:

$$\Delta G = \Delta G'^{\circ} + RT \ln ([P]/[S]) \qquad (11\text{-}2)$$

where $\Delta G'^{\circ}$ is the standard free-energy change, R is the gas constant, and T is the absolute temperature

Free-Energy Change for Transport of an Uncharged Solute

- no bonds are broken and $\Delta G'^{\circ}$ *is* zero

- free-energy change for transport, ΔG_t, of a solute from a region where its concentration is C_1 to a region where its concentration is C_2 is:

$$\Delta G_t = RT \ln(C_2/C_1) \qquad (11\text{-}3)$$

Free-Energy Change for Transport of an Ion

- without movement of an accompanying counterion, the process is **electrogenic** (produces an electrical potential)

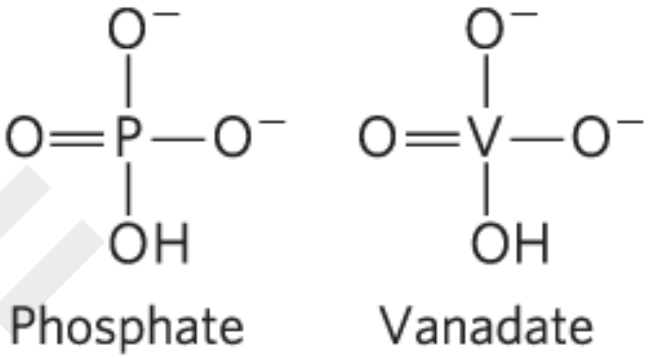
- free-energy change for transport, ΔG_t, of an ion is the sum of the chemical and electrical gradients:

$$\Delta G_t = RT \ln(C_2/C_1) + ZF\,\Delta\psi \qquad (11\text{-}4)$$

where Z is the charge on the ion, F is the Faraday constant, and $\Delta\psi$ is the transmembrane electrical potential (in volts)

P-Type ATPases Undergo Phosphorylation during Their Catalytic Cycles

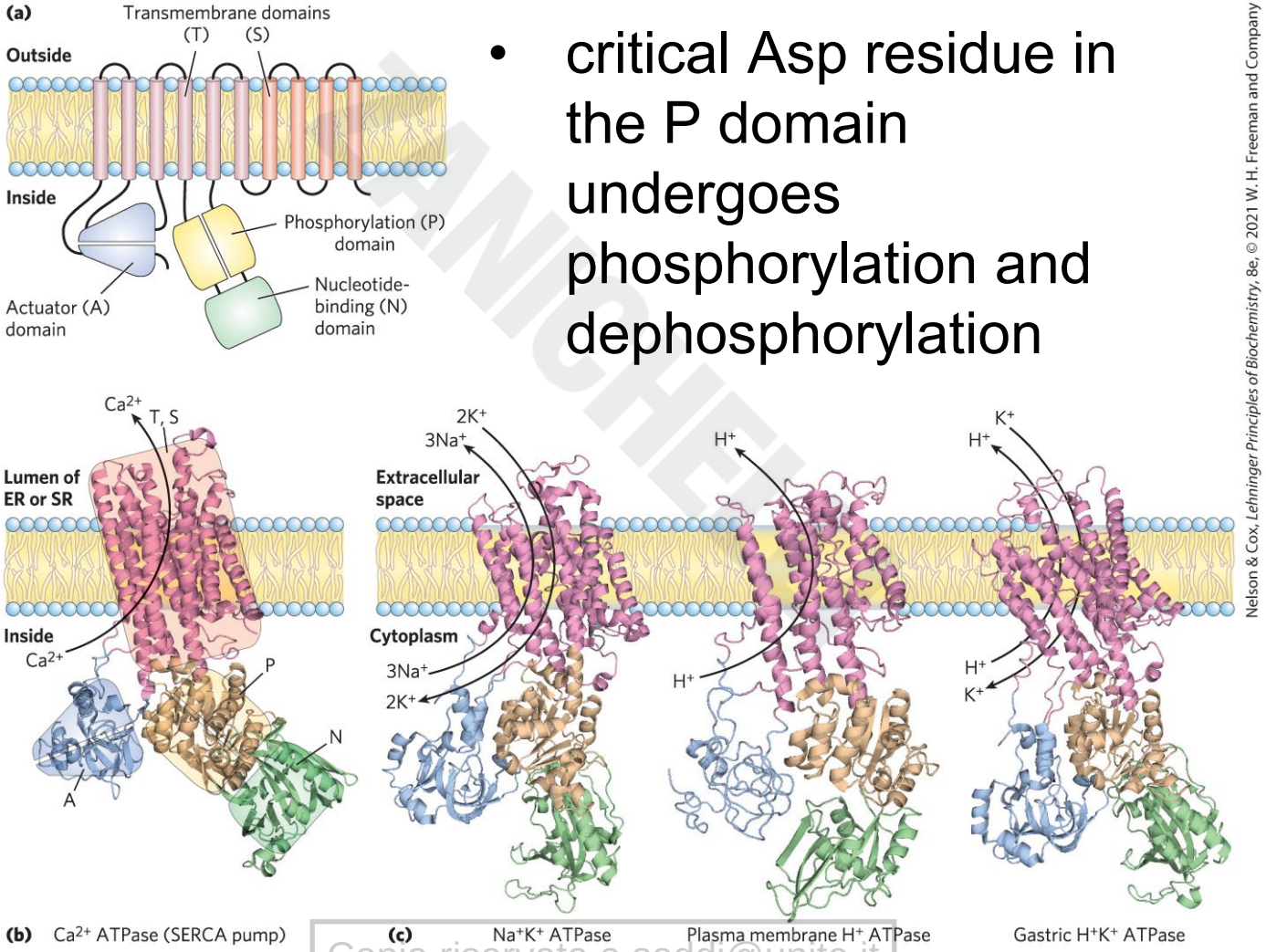
- **P-type ATPases** = family of cation transporters that are reversibly phosphorylated by ATP as part of the transport cycle
  - integral proteins with 8 or 10 predicted membrane-spanning regions
  - sensitive to inhibition by the transition-state analog **vanadate**



Examples of P-Type ATPases

- Na^+ K^+ ATPase = animal cell antiporter for Na^+ and K^+
- H^+ ATPase = plant and fungi transporter
- ***s*arcoplasmic/*e*ndoplasmic *r*eticulum *C*a^{2+} *A*TPase (SERCA) pump** and the plasma membrane Ca^{2+} ATPase pump = uniporters for Ca^{2+} ions

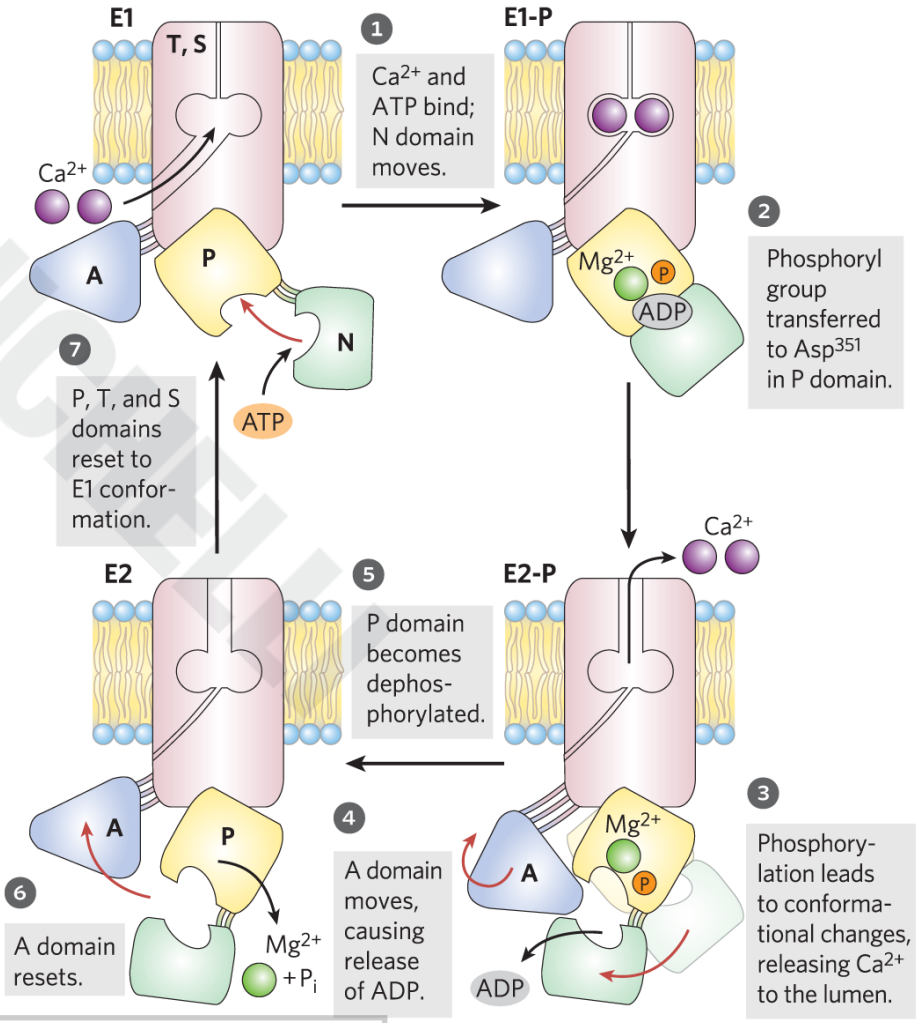
General Structure of the P-Type ATPases



- critical Asp residue in the P domain undergoes phosphorylation and dephosphorylation

Postulated Mechanism of the SERCA Pump

- each catalytic cycle moves two Ca^{2+} ions across the membrane and converts an ATP to ADP and P_i
- two conformations of the transporter, E1 and E2, interconvert



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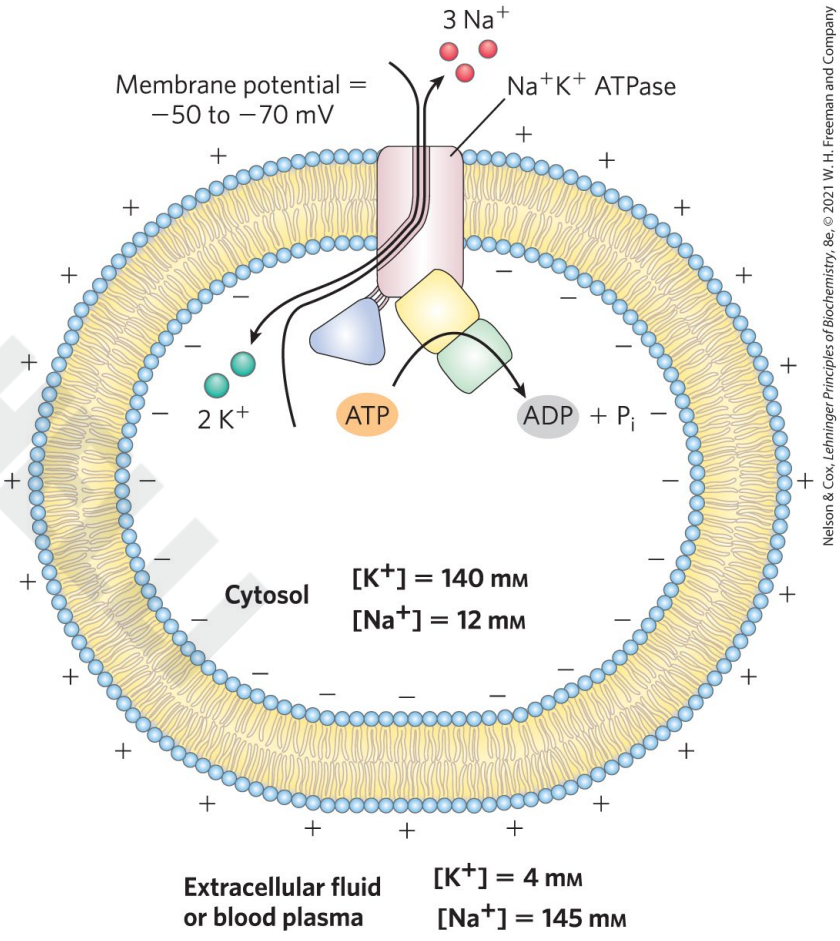
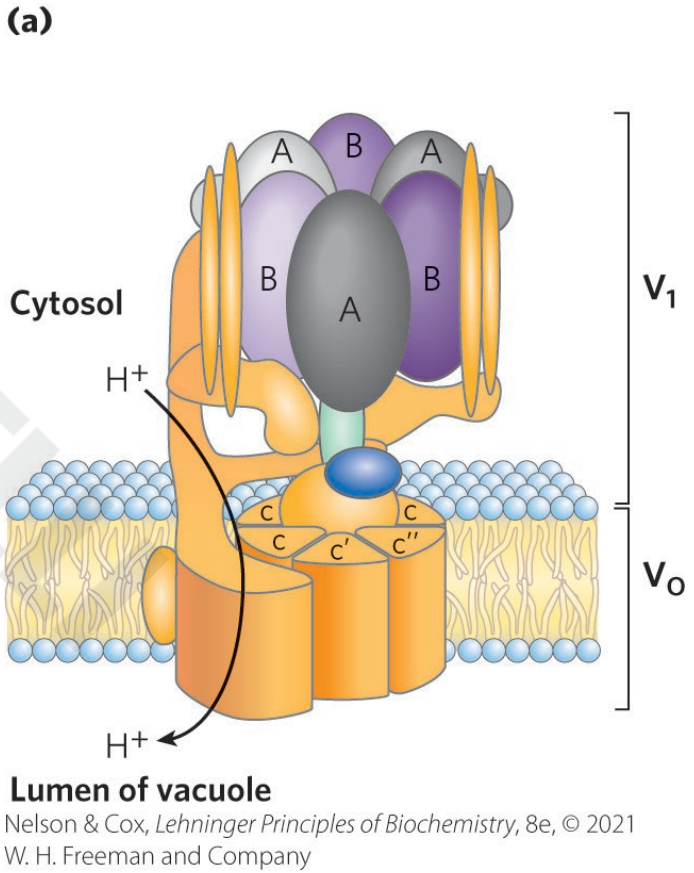
Role of the Na^+ K^+ ATPase in Animal Cells

- **Na^+ K^+ ATPase** = couples phosphorylation-dephosphorylation of the critical Asp residue to the movement of Na^+ and K^+ against their electrochemical gradients
  - maintains low [Na^+] and high [K^+] in the cell
  - essential to the conduction of action potentials in neurons



V-Type and F-Type ATPases Are ATP-Driven Proton Pumps

- **V-type ATPases** = class of proton-transporting ATPases responsible for acidifying intracellular compartments
  - V_o domain serves as a proton channel
  - V_1 domain contains the ATP-binding site and the ATPase activity



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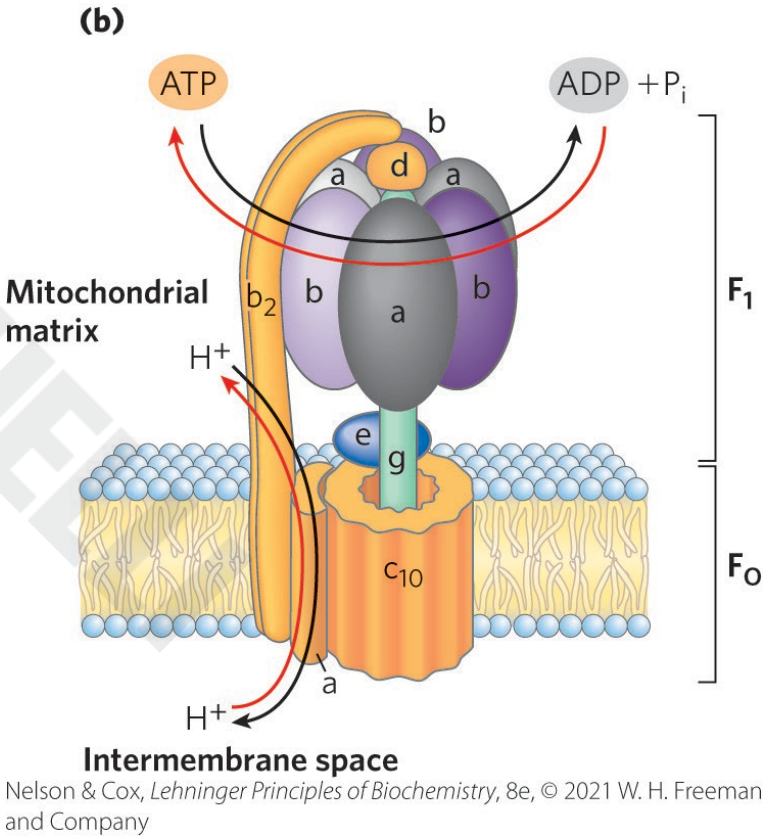
F-Type ATPases

- **F-type ATPases** = catalyze the uphill transmembrane passage of protons, driven by ATP hydrolysis
  - F_o integral membrane protein complex provides a pathway for protons
  - F_1 protein uses energy of ATP to drive proteins uphill



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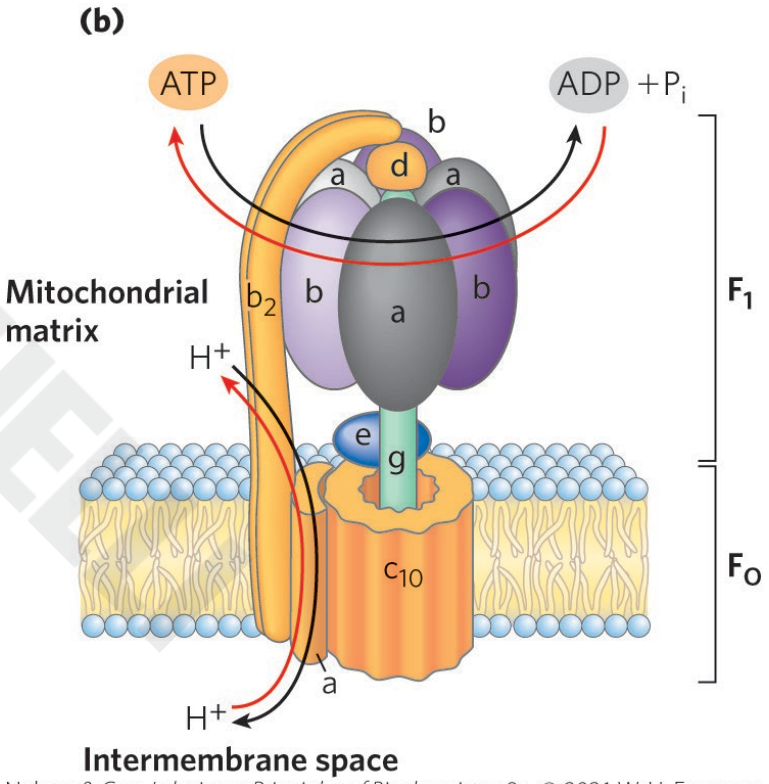
P3 Principle 3 (9 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

F-Type ATPases Catalyze Reactions in Both Directions

- a large proton gradient can supply the energy to drive ATP synthesis
- when functioning in this direction, F-type ATPases are named **ATP synthases**



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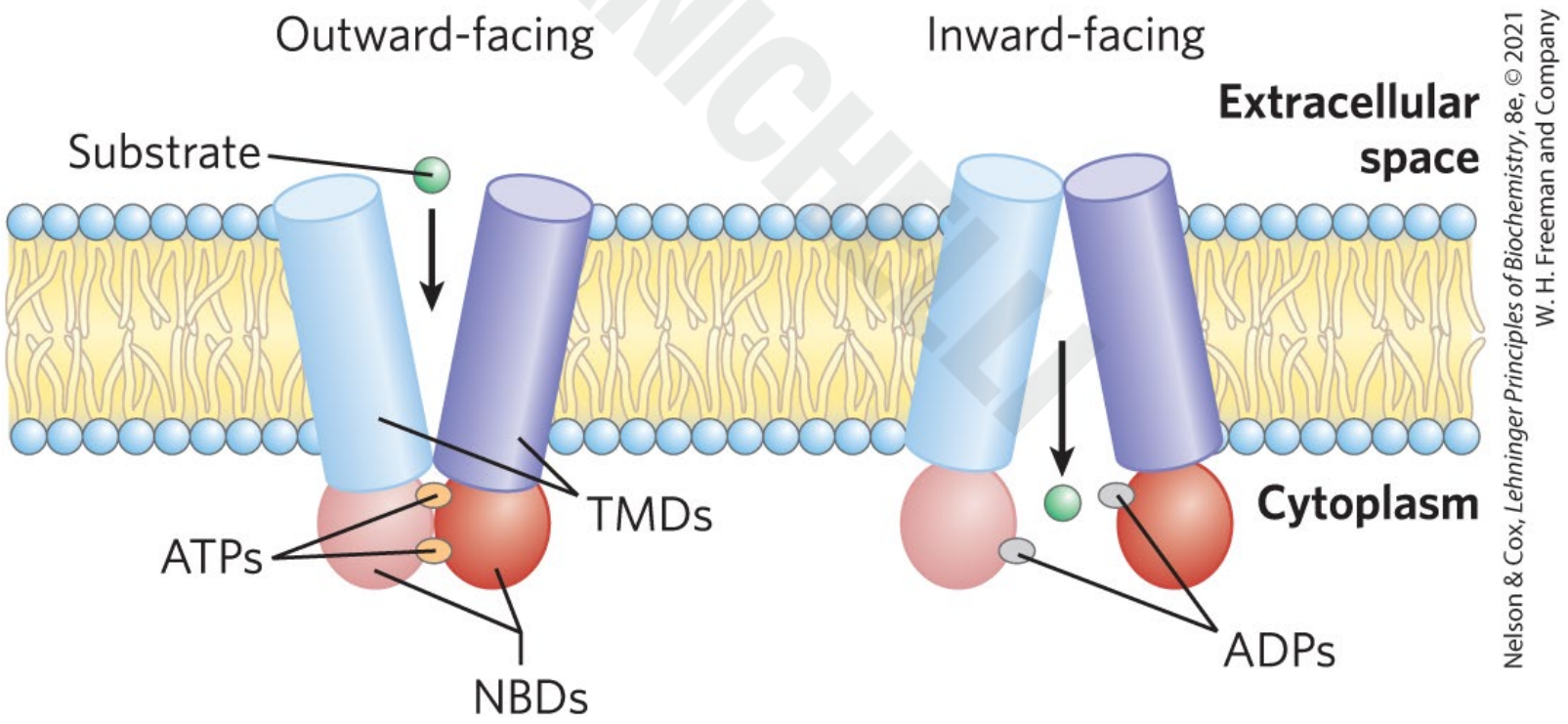
ABC Transporters Use ATP to Drive the Active Transport of a Wide Variety of Substrates

- **ABC transporters** = family of ATP-driven transporters that pump substrates across a membrane against a concentration gradient
  - have two ATP-binding domains (“cassettes”) and two transmembrane domains
  - example substrates: amino acids, peptides, proteins, metal ions, various lipids, bile salts, and hydrophobic compounds, including drugs

Mechanism of ABC Transporters

- substrates move across the membrane when two forms of the transporter interconvert
  - driven by ATP hydrolysis



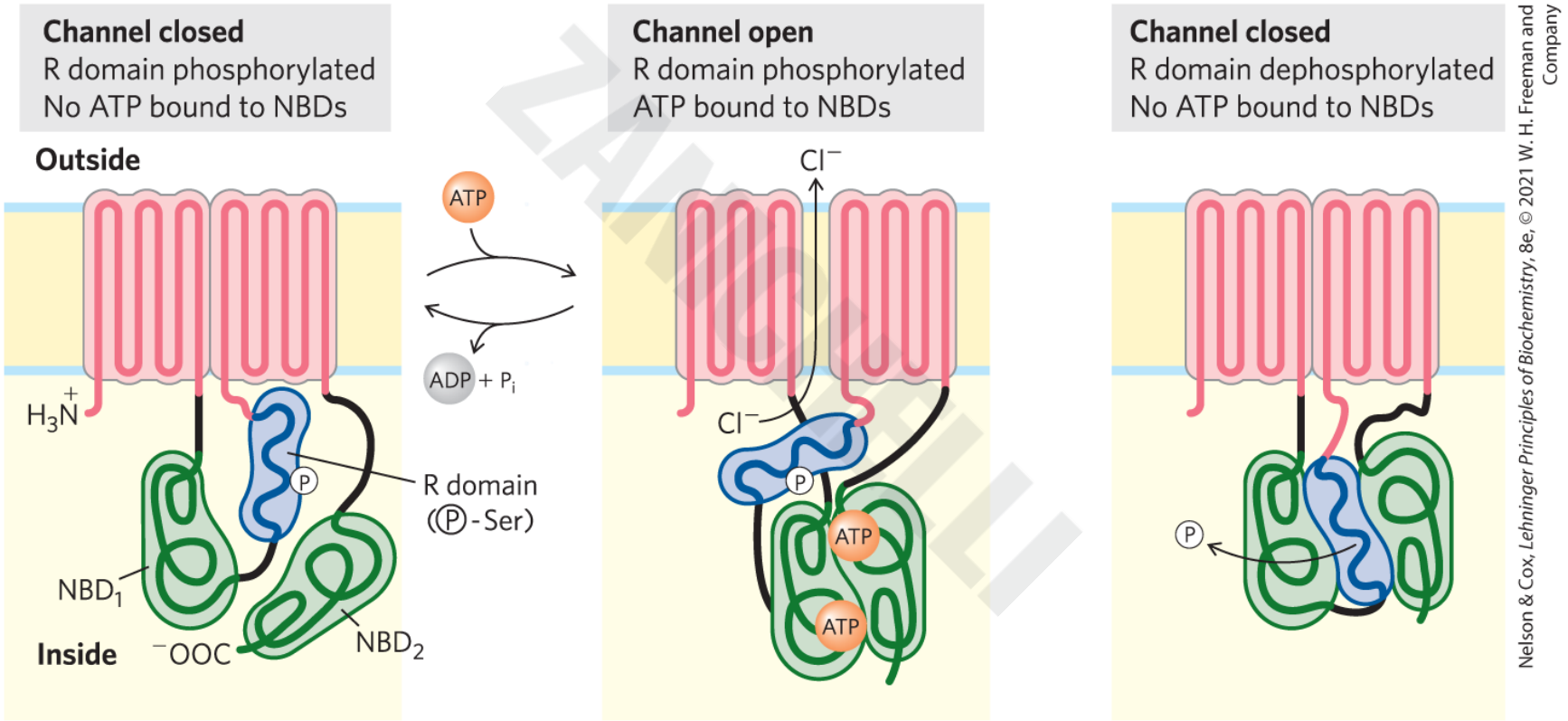
Some ABC Transporters in Humans

Table 11-2 Some ABC Transporters in Humans

Gene(s)	Role/characteristics	Text reference
ABCA1	Reverse cholesterol transport; defect causes Tangier disease	Fig. 21-47
ABCA4	Only in visual receptors, recycling of all-*trans*-retinal	Fig. 12-19
ABCB1	Multidrug resistance P-glycoprotein 1; transport across blood-brain barrier	—
ABCB4	Multidrug resistance; transport of phosphatidylcholine	—
ABCB11	Transports bile salts out of hepatocytes	Fig. 17-1
ABCC6	Sulfonylurea receptor; targeted by the drug glipizide in type 2 diabetes	Fig. 23-27
ABCG2	Breast cancer resistance protein (BCRP); major exporter of anticancer drugs	p. 396
ABCC7	CFTR (Cl^- channel); defect causes cystic fibrosis	Box 11-2

- **multidrug transporter (MDR1)** = human ABC transporter with very broad substrate specificity
  - encoded by the *ABCB1* gene
  - removes toxic compounds
  - responsible for resistance of tumors to drugs

A Defective Ion Channel in Cystic Fibrosis



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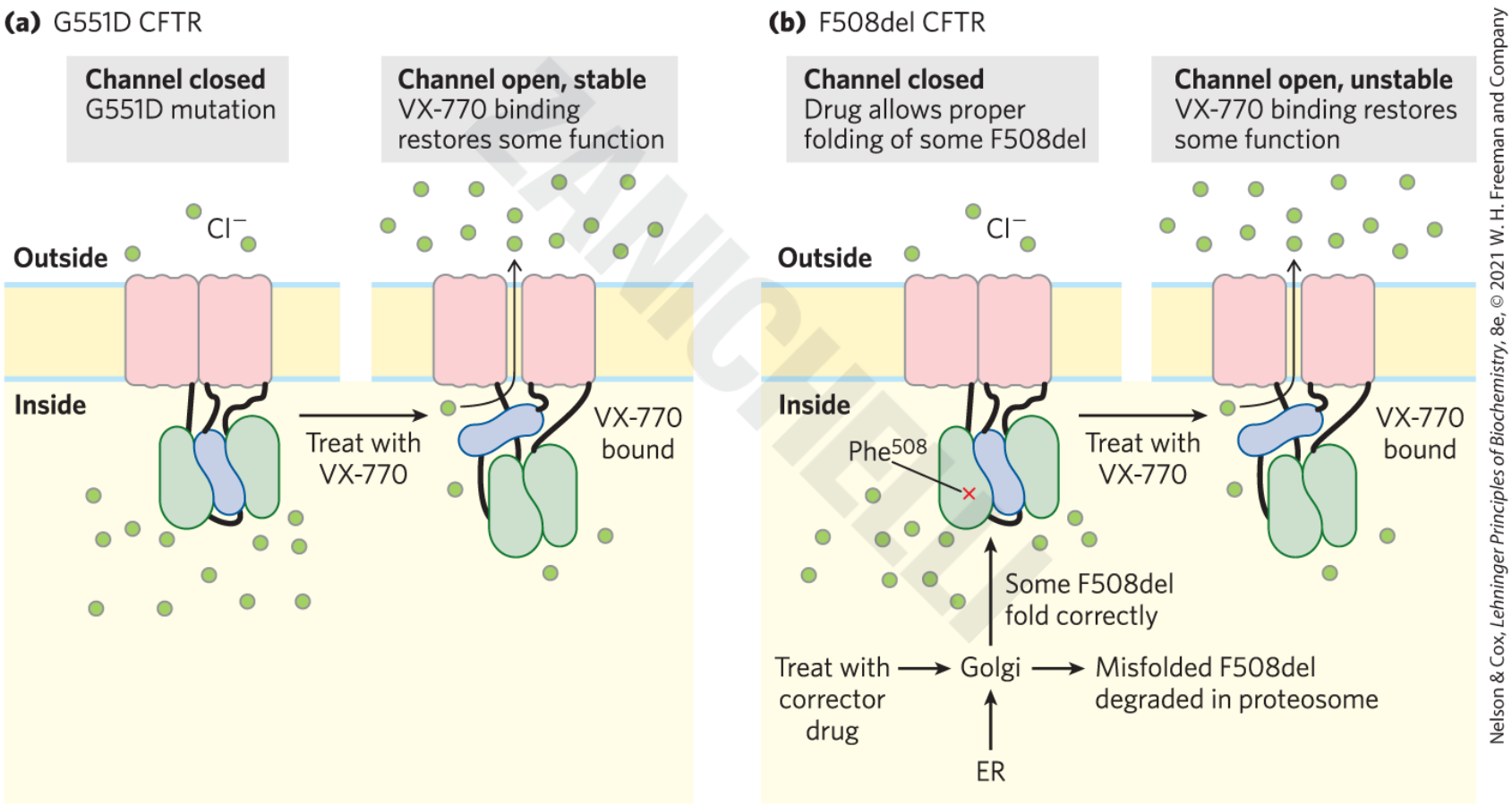
Cystic Fibrosis Therapies



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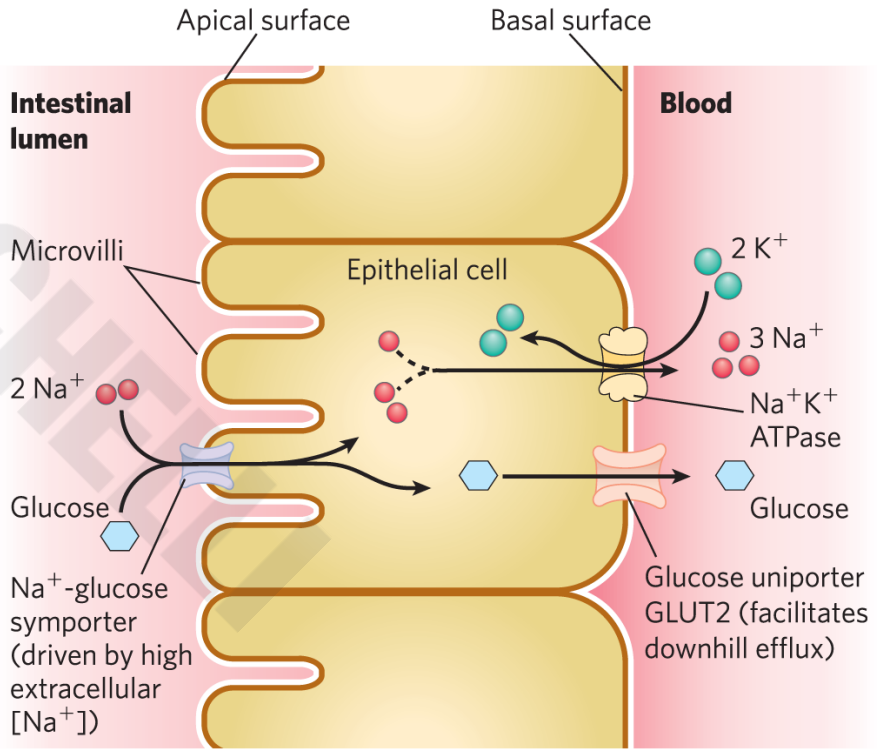
P3 Principle 3 (10 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

Ion Gradients Provide the Energy for Secondary Active Transport

- **Na^+-glucose symporter** = takes up glucose from the intestine in a process driven by the downhill flow of Na^+

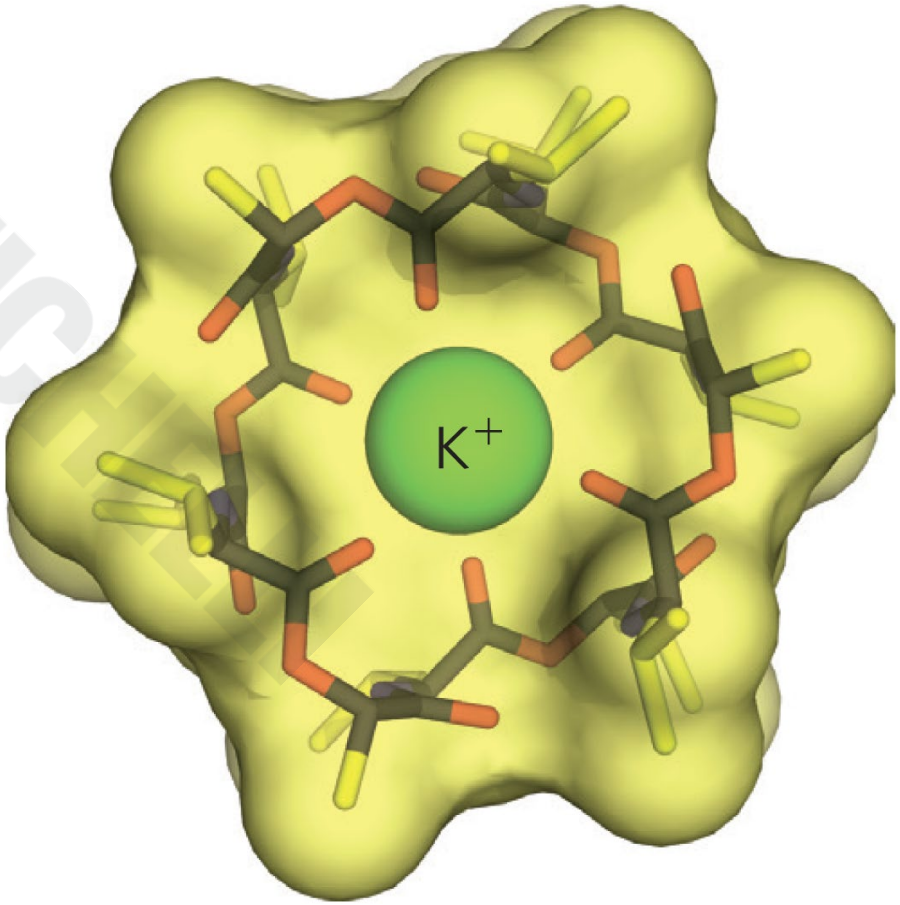
- strong thermodynamic tendency for Na^+ to move into the cell provides the energy needed for the transport of glucose into the cell



The Peptide Ionophore Valinomycin Is An Antibiotic

- acts as a shuttle, carrying K^+ across the membrane down its concentration gradient and deflating that gradient

- **ionophores** ("ion bearers") = compounds that shuttle ions across membranes in this way



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P3 Principle 3 (11 of 11)

Although the lipid bilayer is impermeable to charged or polar solutes, cells of all kinds have many membrane transporters and ion channels that catalyze transmembrane movement of specific solutes. Some transporters merely speed the movement of solutes in the direction that simple diffusion takes them, whereas others use an energy source to move solutes against a concentration gradient.

Aquaporins Form Hydrophilic Transmembrane Channels for the Passage of Water

- **aquaporins (AQPs)** = provide channels for movement of water molecules across plasma membranes
  - each protein has a specific location and role
  - low activation energy suggests that water moves in a continuous stream
  - do not allow passage of protons (hydronium ions, H_3O^+)

The 11 Known Aquaporins in Mammals

Table 11-3 Permeability Characteristics and Predominant Distribution of Known Mammalian Aquaporins

Aquaporin	Permeant (permeability)	Tissue distribution	Primary subcellular distribution
AQP0	Water (low)	Lens	Plasma membrane
AQP1	Water (high)	Erythrocyte, kidney, lung, vascular endothelium, brain, eye	Plasma membrane
AQP2	Water (high)	Kidney, vas deferens	Apical plasma membrane, intracellular vesicles
AQP3	Water (high), glycerol (high), urea (moderate)	Kidney, skin, lung, eye, colon	Basolateral plasma membrane
AQP4	Water (high)	Brain, muscle, kidney, lung, stomach, small intestine	Basolateral plasma membrane
AQP5	Water (high)	Salivary gland, lacrimal gland, sweat gland, lung, cornea	Apical plasma membrane
AQP6	Water (low), anions ($NO^-_3 > Cl^-$)	Kidney	Intracellular vesicles
AQP7	Water (high), glycerol (high), urea (high)	Adipose tissue, kidney, testis	Plasma membrane
AQP8	Water (high)	Testis, kidney, liver, pancreas, small intestine, colon	Plasma membrane, intracellular vesicles
AQP9	Water (low), glycerol (high), urea (high)	Liver, leukocyte, brain, testis	Plasma membrane
AQP10	Water (low), glycerol (high), urea (high)	Small intestine	Intracellular vesicles

Ion-Selective Channels Allow Rapid Movement of Ions across Membranes

- **ion-selective channels** = move inorganic ions across membranes
  - the rate of flux can be orders of magnitude greater than the turnover number for a transporter
  - not saturable
  - gated in response to cellular event

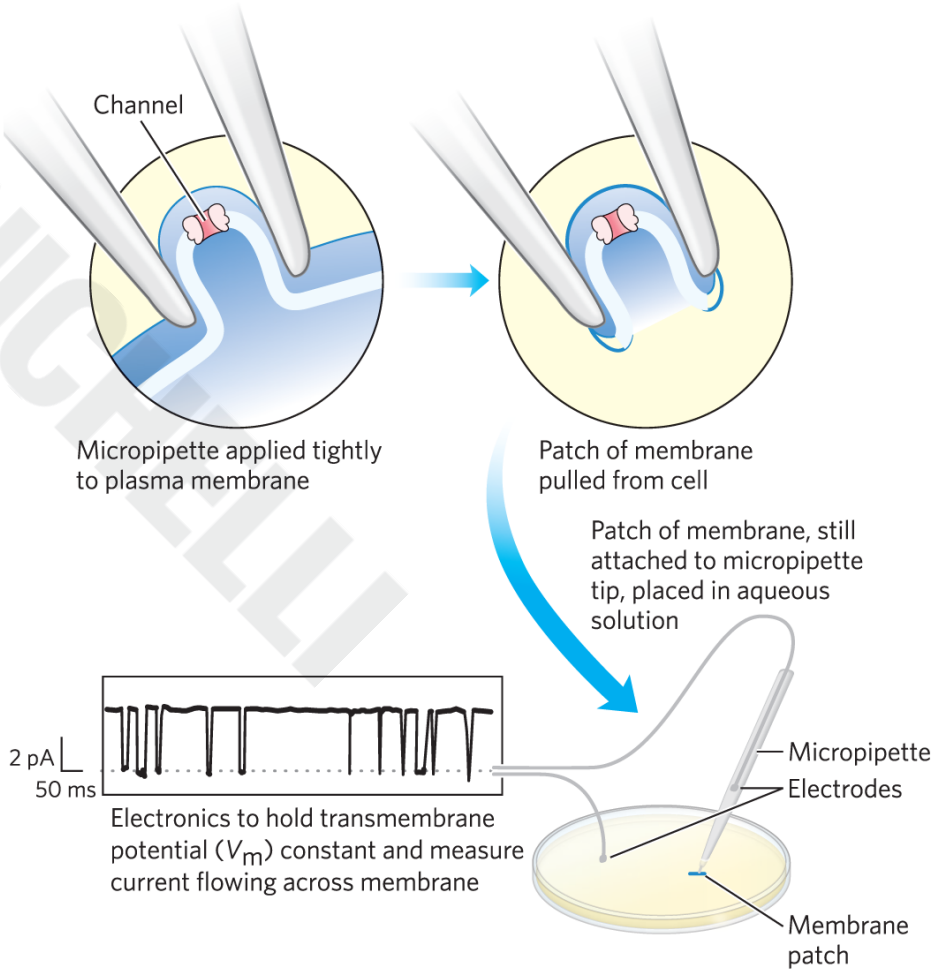
Ligand-Gated Channels and Voltage-Gated Ion Channels

- **ligand-gated channels** = binding of an extracellular or intracellular small molecule forces an allosteric transition in the protein, which opens or closes the channel
  - generally oligomeric

- **voltage-gated ion channels** = a change in transmembrane electrical potential (V_m) causes a charged protein domain to move relative to the membrane, opening or closing the channel

Electrical Measurements of Ion-Channel Function

- **patch-clamping** = currents are measured through a region of the membrane surface containing only one or a few ion-channel molecules



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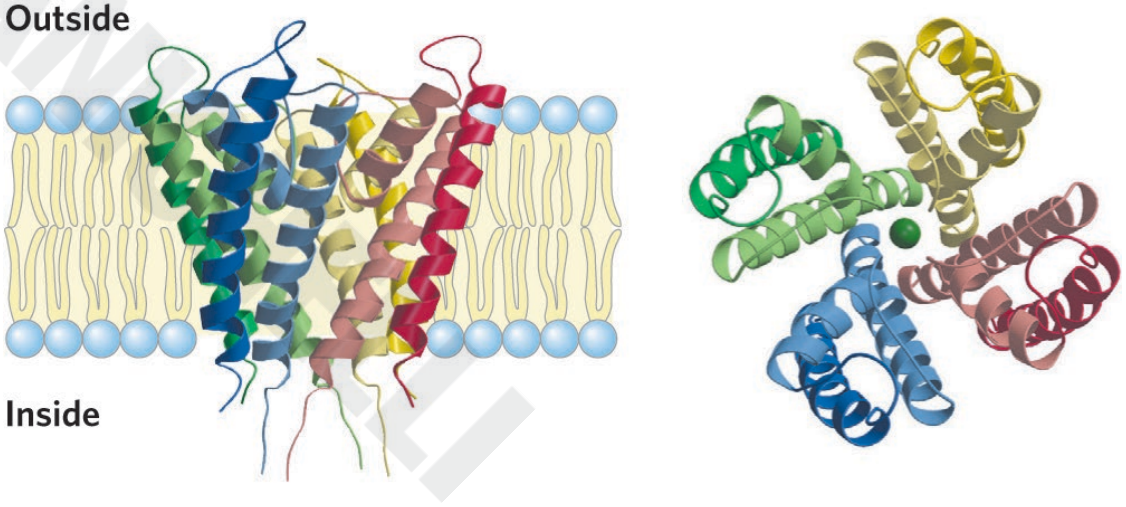
The Structure of a K^+ Channel Reveals the Basis for Its Specificity

- channel is just wide enough to accommodate an unhydrated metal ion such as potassium

- K^+ (radius 1.33 Å) passes 10^4 times more readily than Na^+ (radius 0.95 Å)



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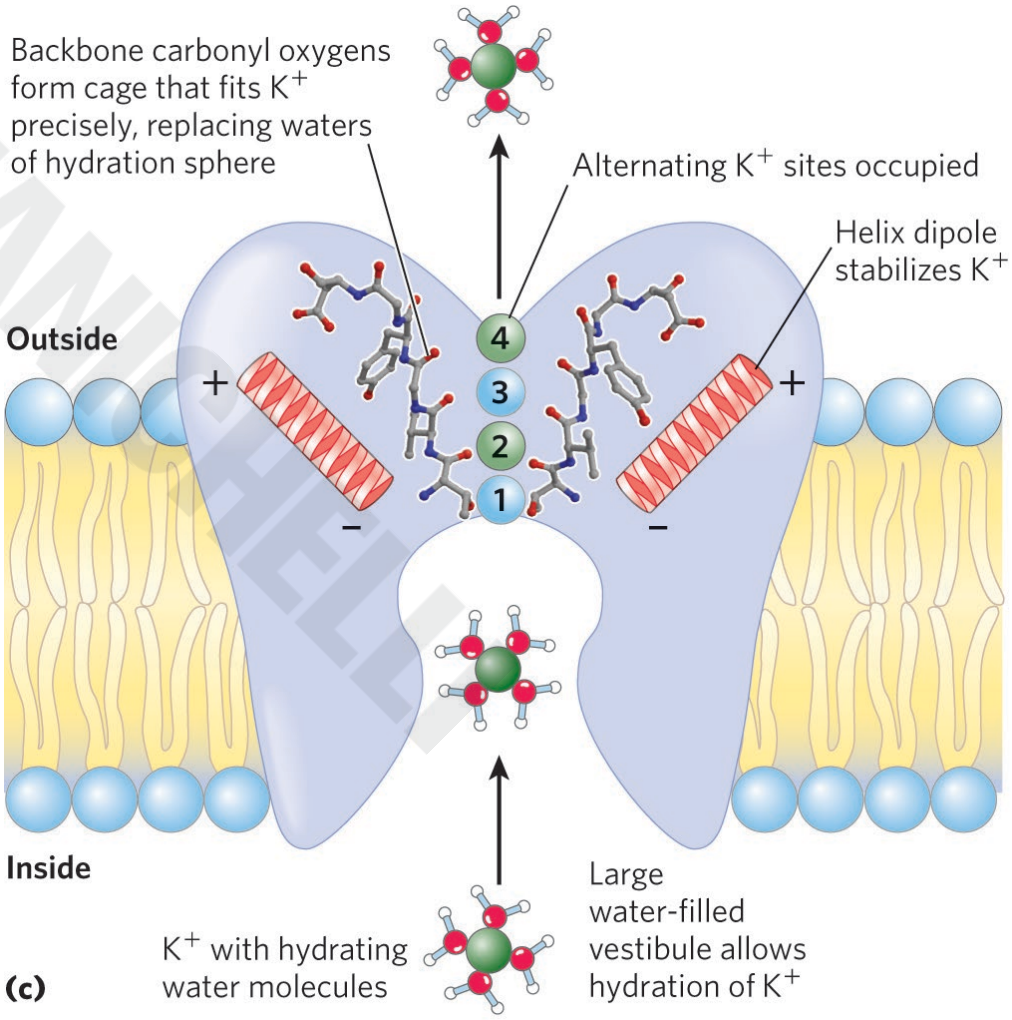
The Mechanism of the K^+ Channel

- the polar transmembrane passage precisely fits the K^+ ion



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