Transporte em Membranas

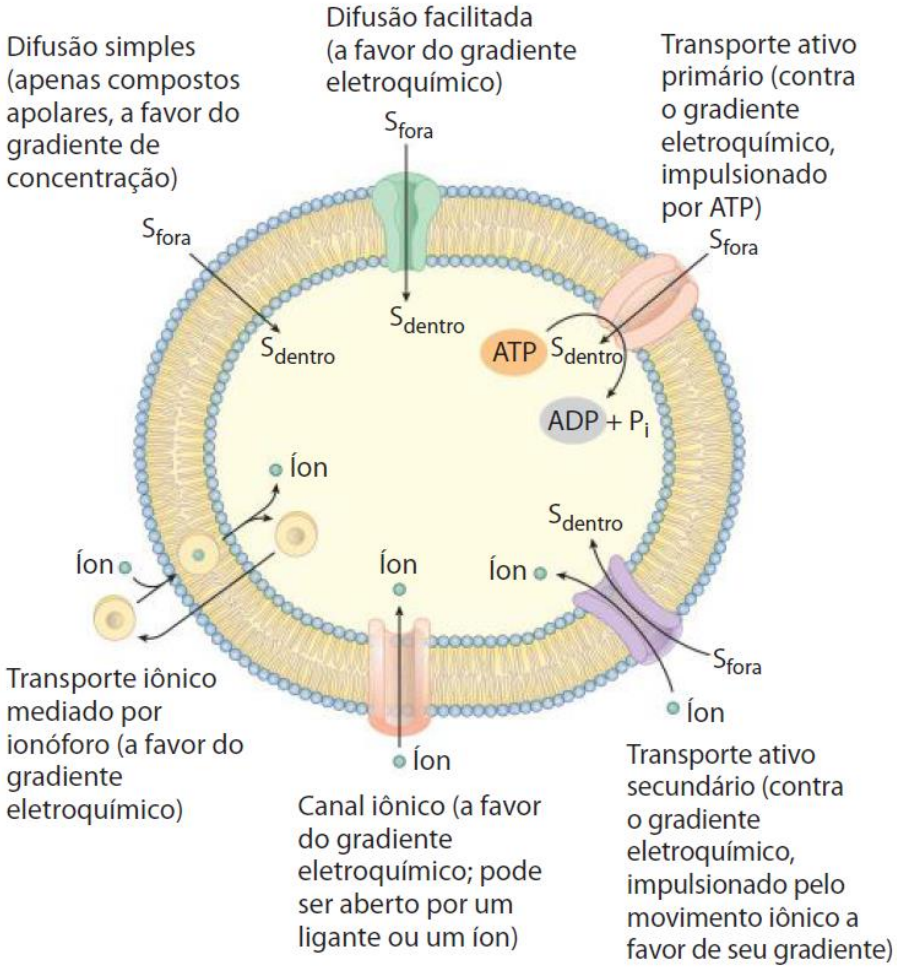

Difusão simples (apenas compostos apolares, a favor do gradiente de concentração)
Difusão facilitada (a favor do gradiente eletroquímico)
Transporte ativo primário (contra o gradiente eletroquímico, impulsionado por ATP)
S_{fora}
S_{dentro}
ATP
ADP + P_i
Íon
Transporte iônico mediado por ionóforo (a favor do gradiente eletroquímico)
Canal iônico (a favor do gradiente eletroquímico; pode ser aberto por um ligante ou um íon)
Transporte ativo secundário (contra o gradiente eletroquímico, impulsionado pelo movimento iônico a favor de seu gradiente)

TABLE 11–1 A Comparison of Inorganic Ion Concentrations Inside and Outside a Typical Mammalian Cell*

Component	Cytoplasmic concentration (mM)	Extracellular concentration (mM)
Cations		
Na^+	5–15	145
K^+	140	5
Mg^{2+}	0.5	1–2
Ca^{2+}	10^{-4}	1–2
H^+	7×10^{-5} ($10^{-7.2}$ M or pH 7.2)	4×10^{-5} ($10^{-7.4}$ M or pH 7.4)
Anions		
Cl^-	5–15	110

*The cell must contain equal quantities of positive and negative charges (that is, it must be electrically neutral). Thus, in addition to Cl^-, the cell contains many other anions not listed in this table; in fact, most cell constituents are negatively charged (HCO_3^-, PO_4^{3-}, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca^{2+} and Mg^{2+} given are for the free ions: although there is a total of about 20 mM Mg^{2+} and 1–2 mM Ca^{2+} in cells, both ions are mostly bound to other substances (such as proteins, free nucleotides, RNA, etc.) and, for Ca^{2+}, stored within various organelles.

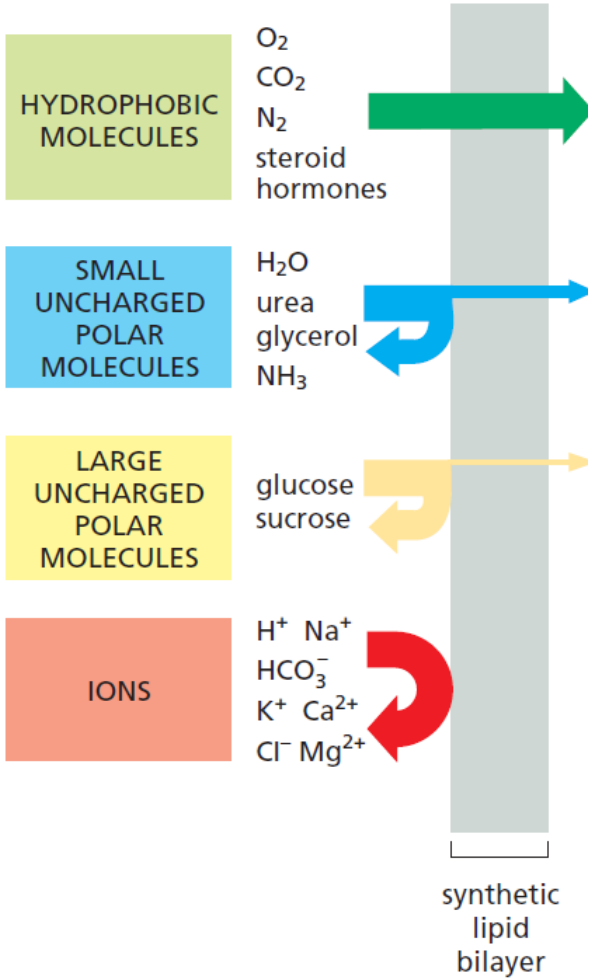
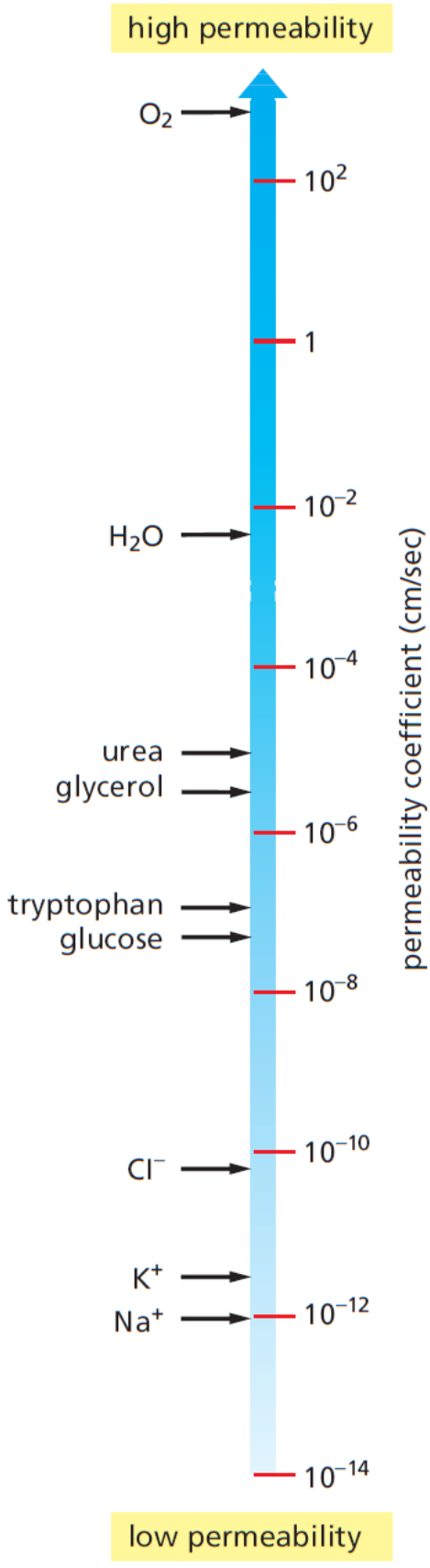
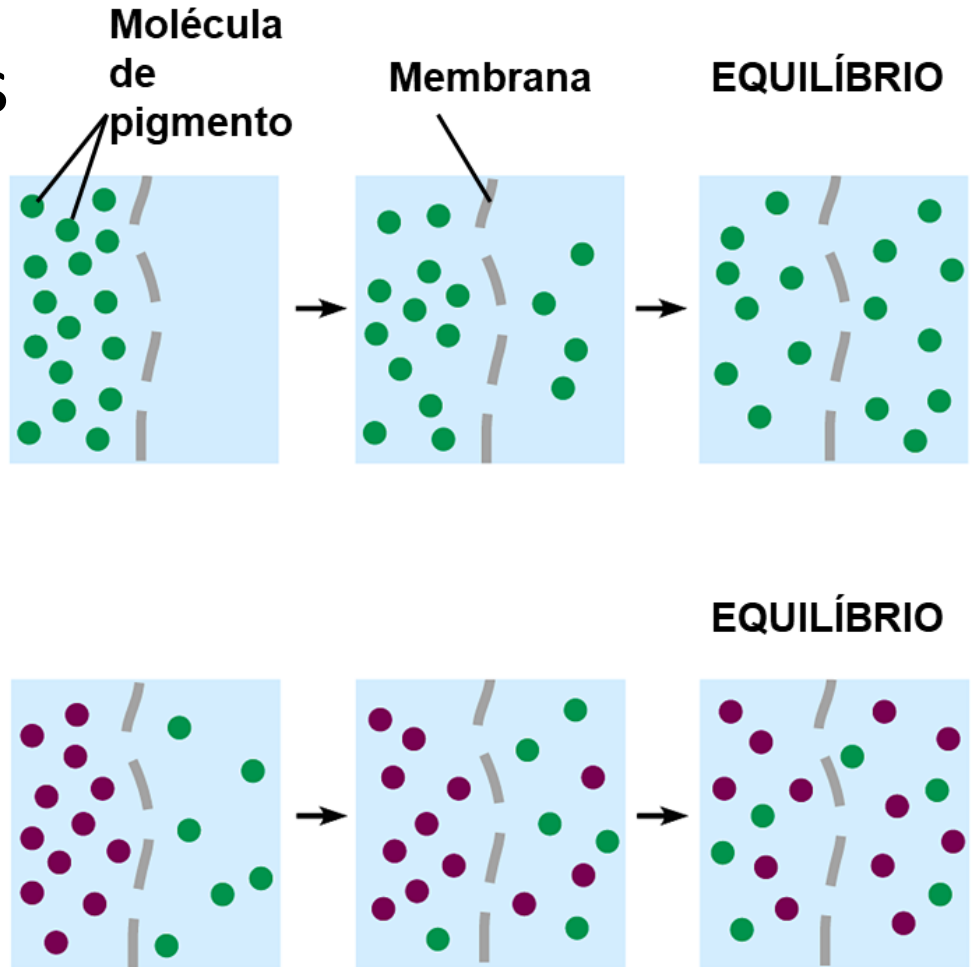


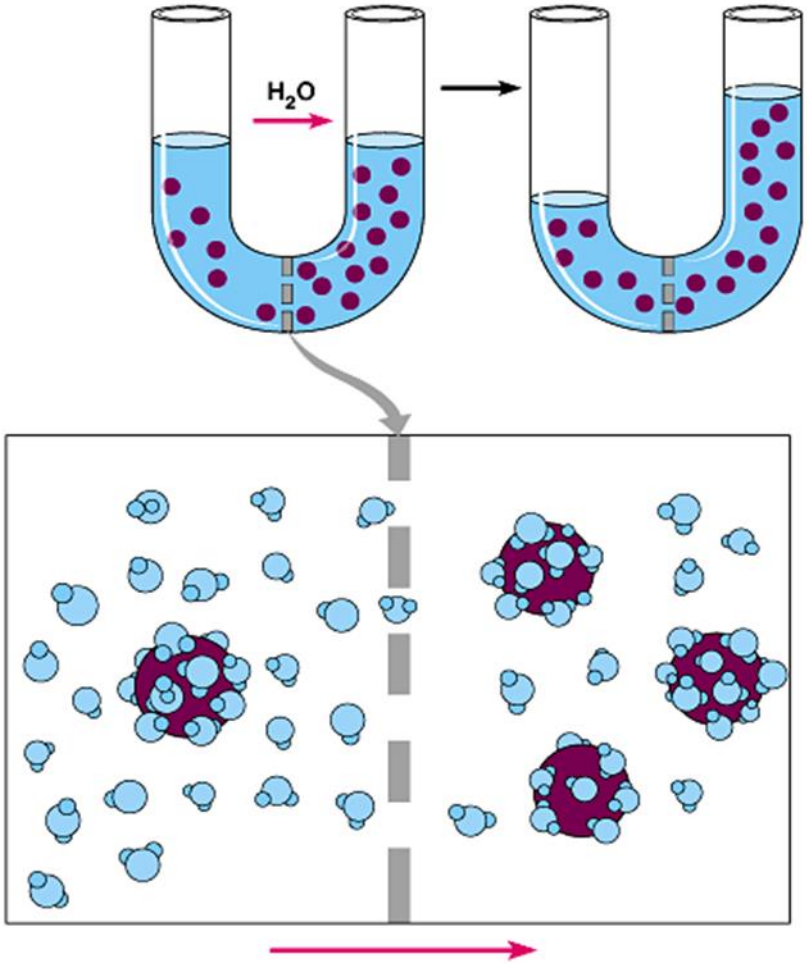
Figure 11–1 The relative permeability of a synthetic lipid bilayer to different classes of molecules. The smaller the molecule and, more importantly, the less strongly it associates with water, the more rapidly the molecule diffuses across the bilayer.


high permeability
O_2
10^2
1
10^{-2}
H_2O
10^{-4}
urea
glycerol
10^{-6}
tryptophan
glucose
10^{-8}
Cl^-
10^{-10}
K^+
Na^+
10^{-12}
10^{-14}
low permeability
permeability coefficient (cm/sec)

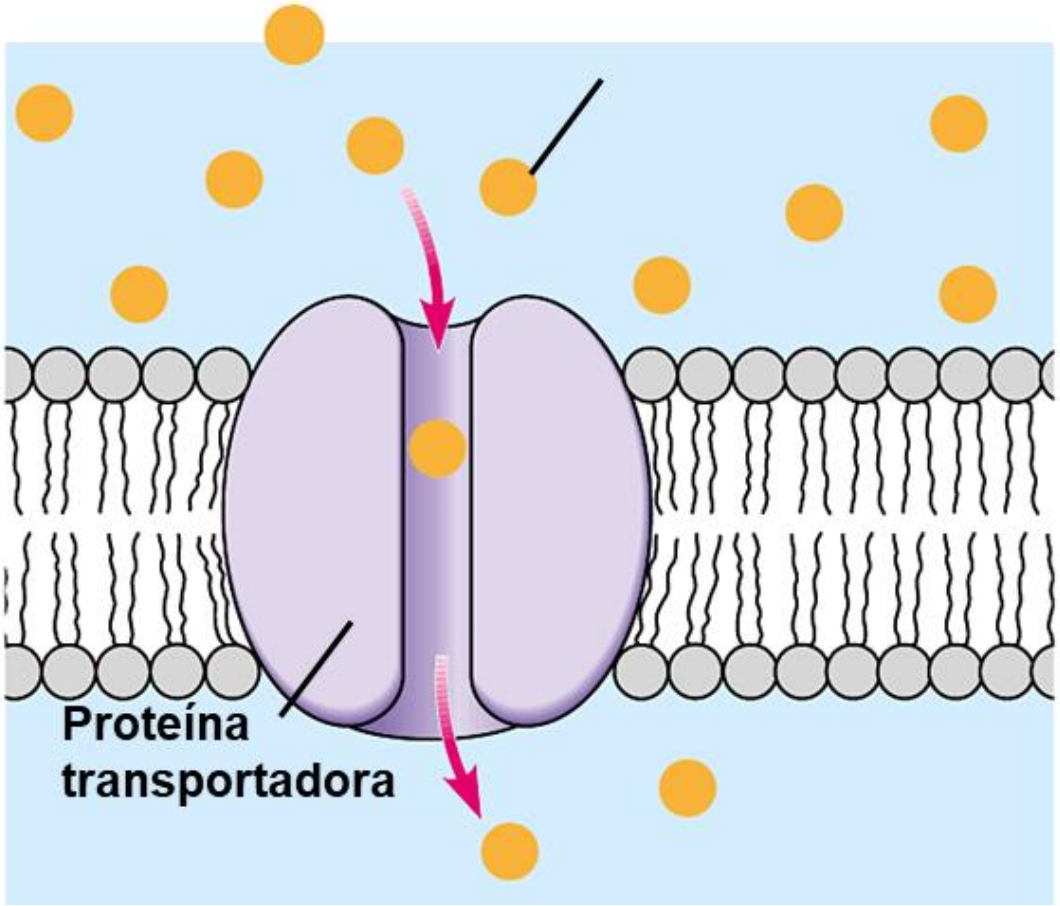
Difusão Simples



Osmose



Difusão Facilitada



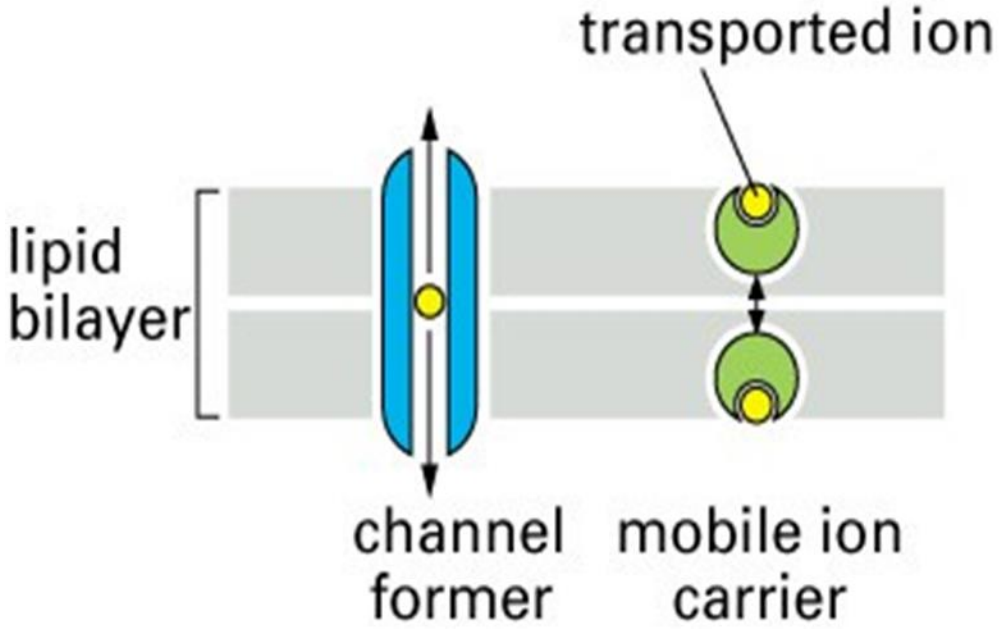
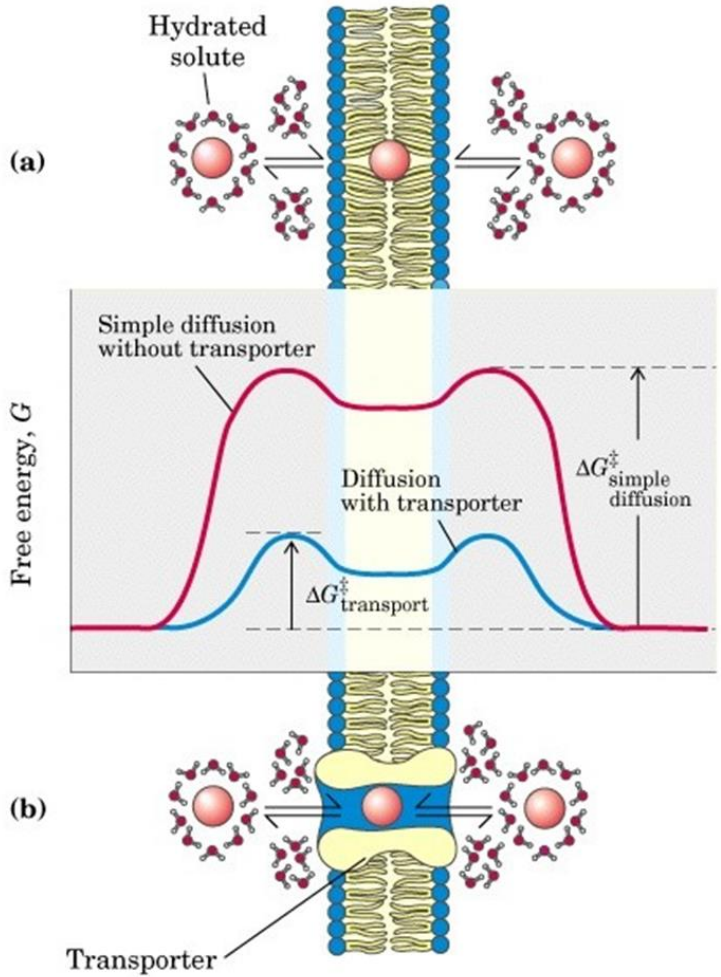
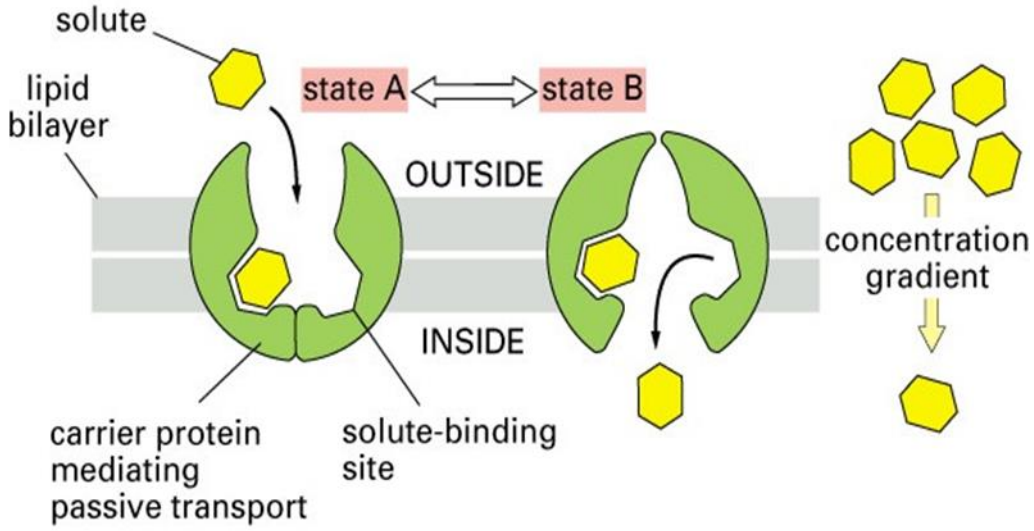


Figure 11–5. Molecular Biology of the Cell, 4th Edition.


Hydrated solute
(a)
Simple diffusion without transporter
Diffusion with transporter
$\Delta G^{\ddagger}_{\text{simple diffusion}}$
$\Delta G^{\ddagger}_{\text{transport}}$
Free energy, G
(b)
Transporter


solute
lipid bilayer
state A
state B
OUTSIDE
INSIDE
concentration gradient
carrier protein mediating passive transport
solute-binding site

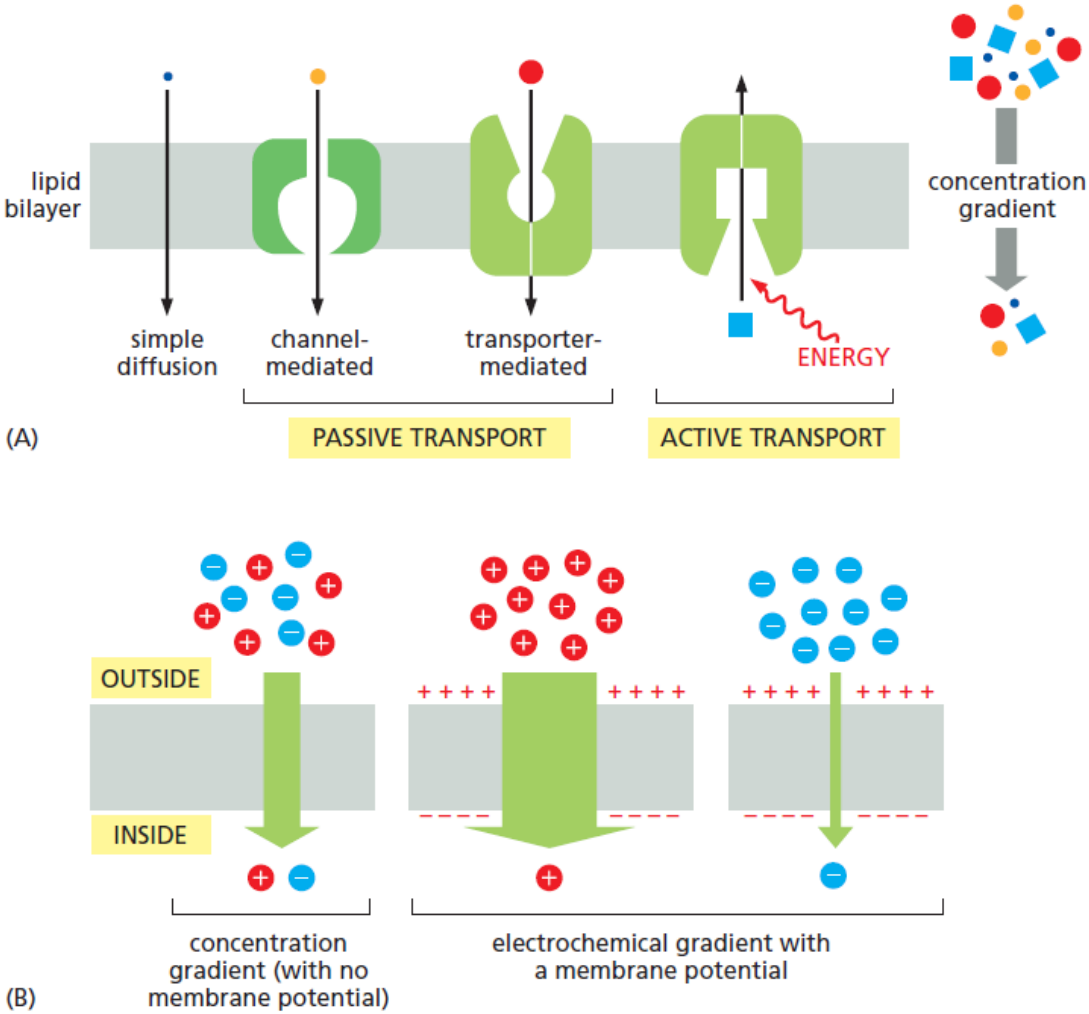


Figure 11–4 Different forms of membrane transport and the influence of the membrane. Passive transport down a concentration gradient (or an electrochemical gradient—see B below) occurs spontaneously, by diffusion, either through the lipid bilayer directly or through channels or passive transporters. By contrast, active transport requires an input of metabolic energy and is always mediated by transporters that pump the solute against its concentration or electrochemical gradient. (B) The electrochemical gradient of a charged solute (an ion) affects its transport. This gradient combines the membrane potential and the concentration gradient of the solute. The electrical and chemical gradients can work additively to increase the driving force on an ion across the membrane (*middle*) or can work against each other (*right*).

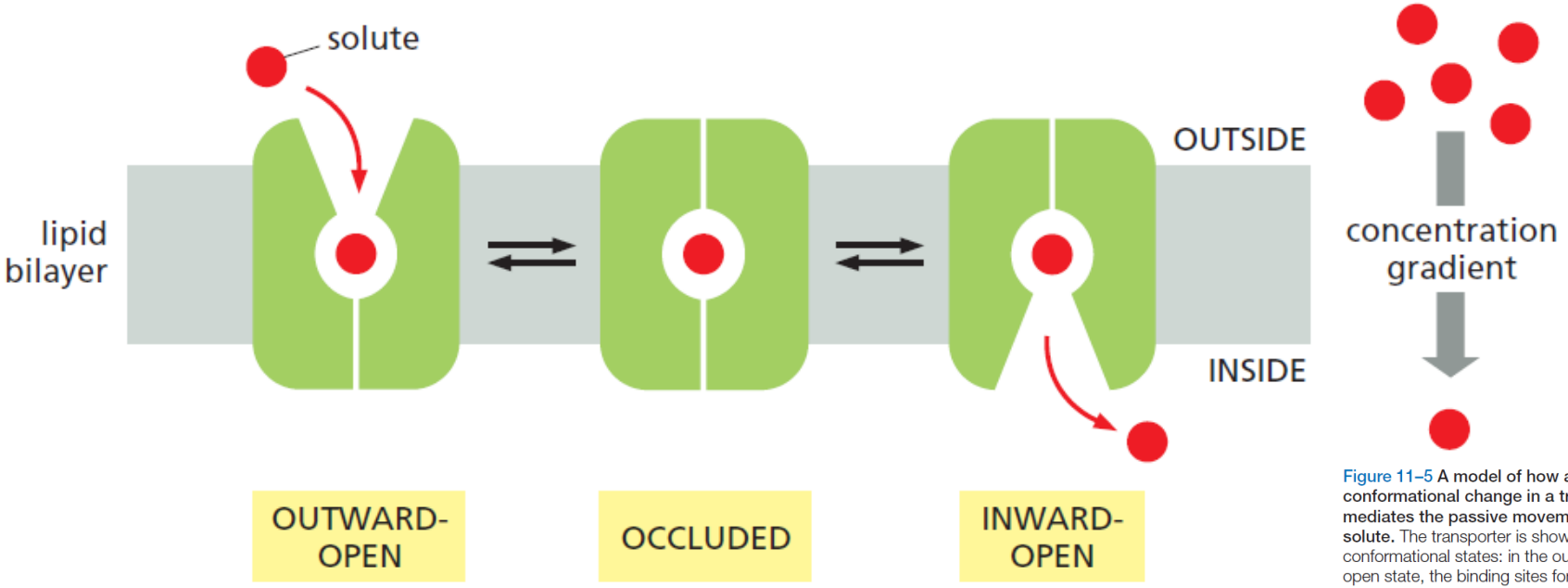


Figure 11–5 **A model of how a conformational change in a transporter mediates the passive movement of a solute.** The transporter is shown in three conformational states: in the outward-open state, the binding sites for solute are exposed on the outside; in the occluded state, the same sites are not accessible from either side; and in the inward-open state, the sites are exposed on the inside. The transitions between the states occur randomly. They are completely reversible and do not depend on whether the solute-binding site is occupied. Therefore, if the solute concentration is higher on the outside of the bilayer, more solute binds to the transporter in the outward-open conformation than in the inward-open conformation, and there is a net transport of solute down its concentration gradient (or, if the solute is an ion, down its electrochemical gradient).

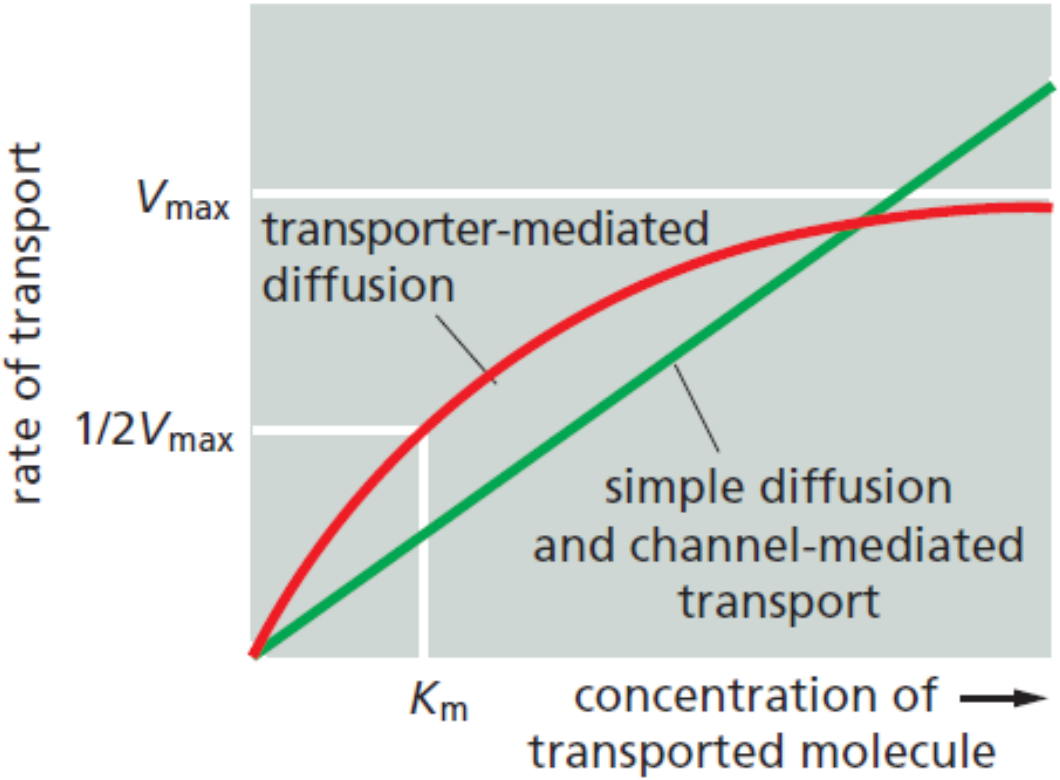


Figure 11–6 The kinetics of simple diffusion compared with transporter-mediated diffusion. Whereas the rate of diffusion and channel-mediated transport is directly proportional to the solute concentration (within the physical limits imposed by total surface area or total channels available), the rate of transporter-mediated diffusion reaches a maximum (V_{max}) when the transporter is saturated. The solute concentration when the transport rate is at half its maximal value approximates the binding constant (K_m) of the transporter for the solute and is analogous to the K_m of an enzyme for its substrate. The graph applies to a transporter moving a single solute; the kinetics of coupled transport of two or more solutes is more complex and exhibits cooperative behavior.

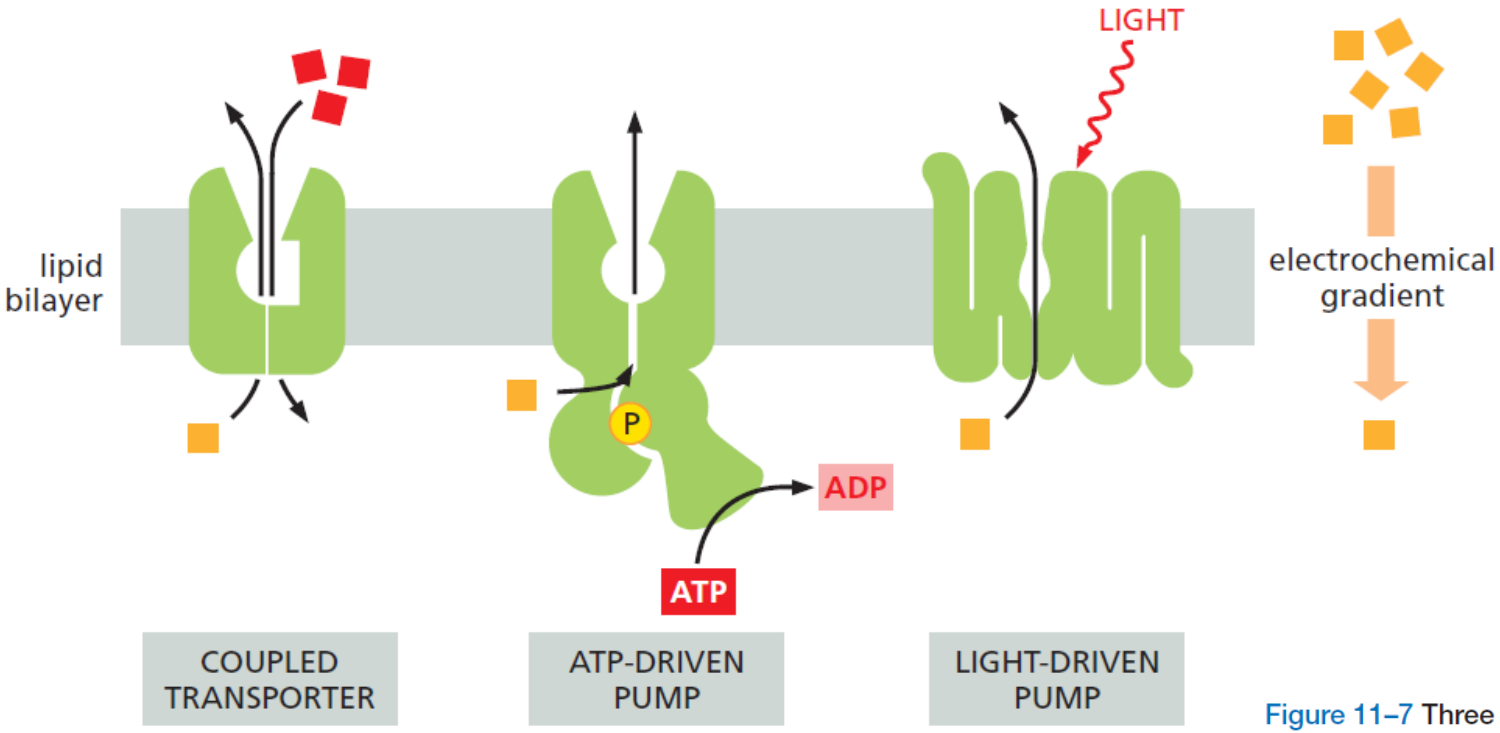


Figure 11–7 Three ways of driving active transport. The actively transported molecule is shown in *orange*, and the energy source is shown in *red*. Redox driven active transport is discussed in Chapter 14 (see Figures 14–18 and 14–19).

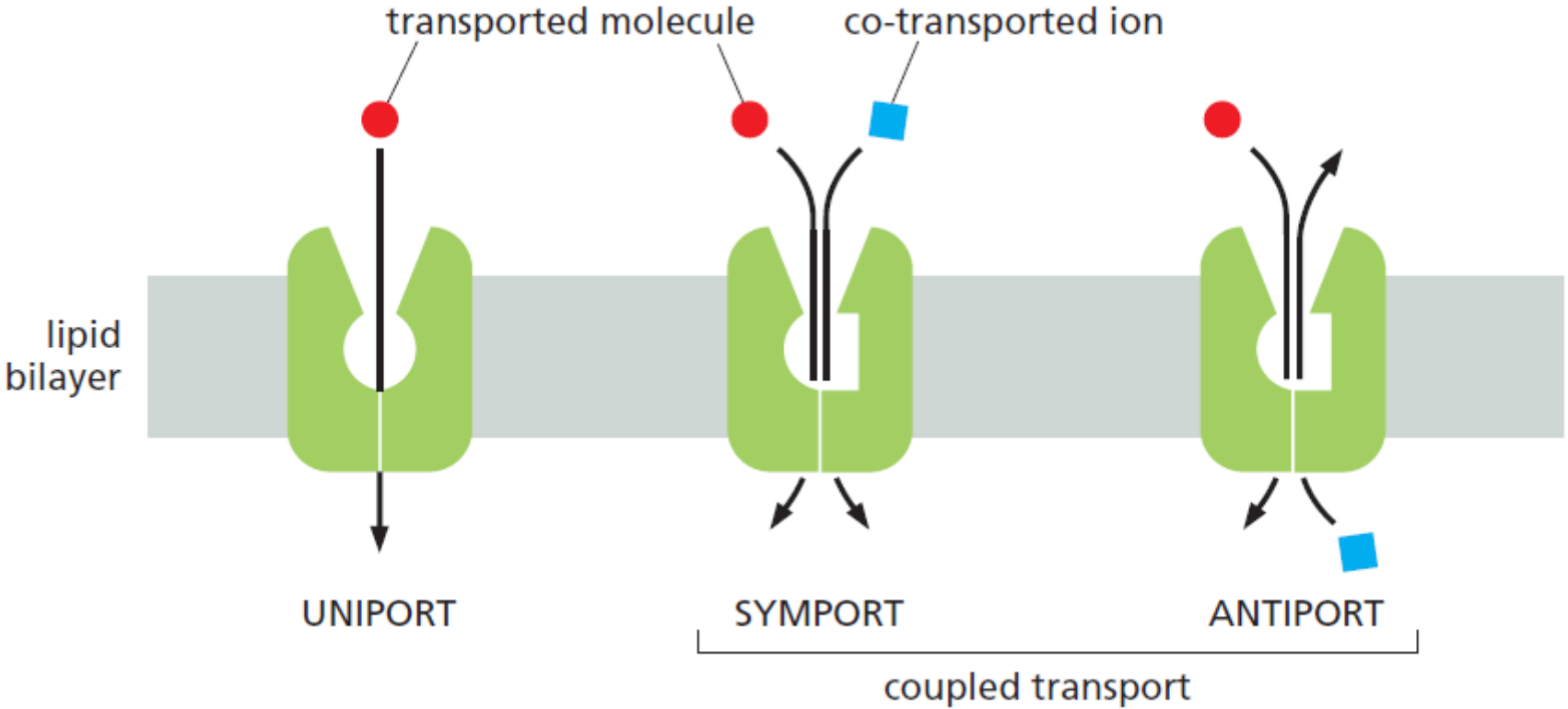
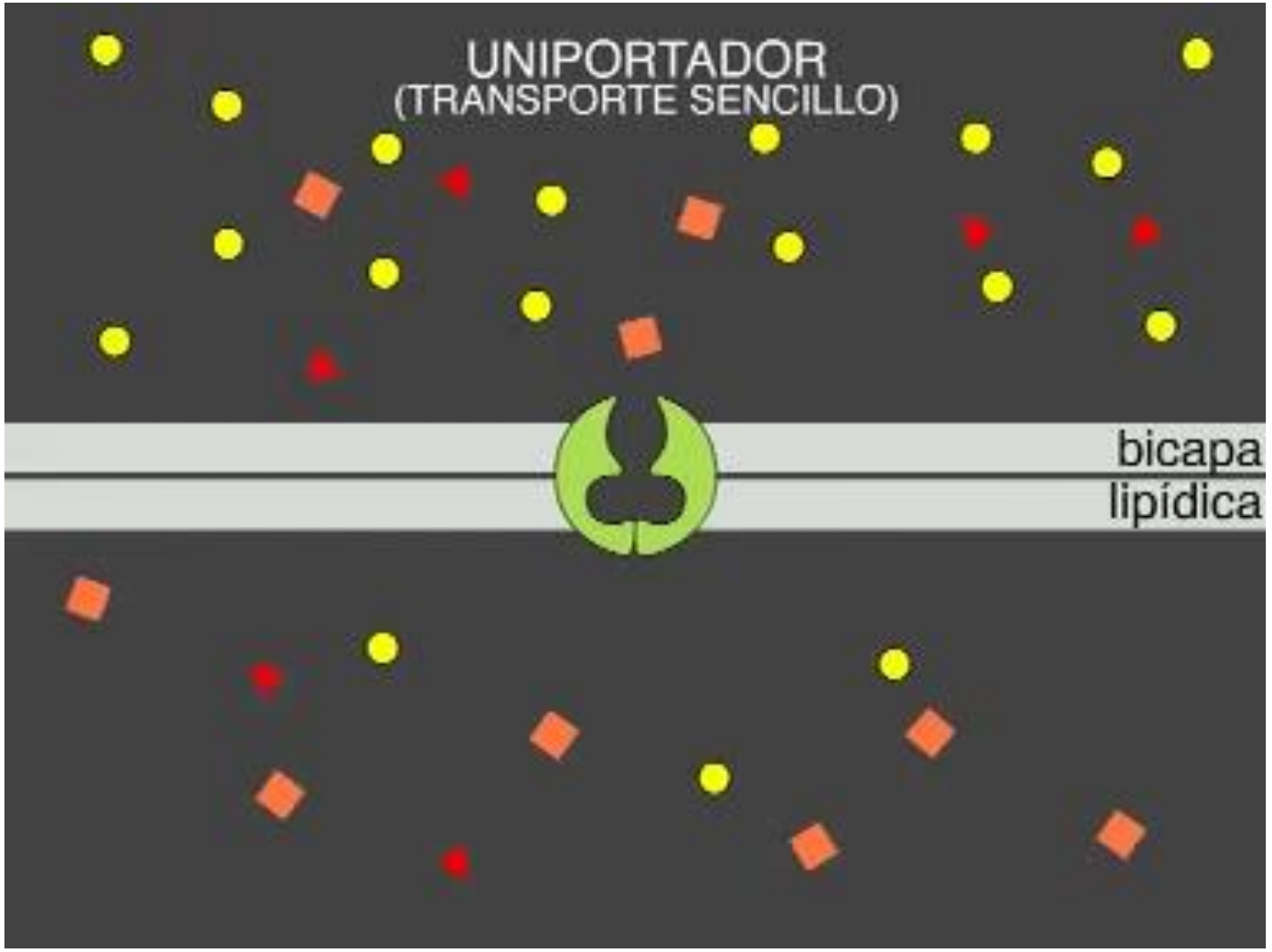


Figure 11–8 This schematic diagram shows transporters functioning as uniporters, symporters, and antiporters (Movie 11.1).


UNIPORTADOR
(TRANSPORTE SENCILLO)
bicapa
lipídica

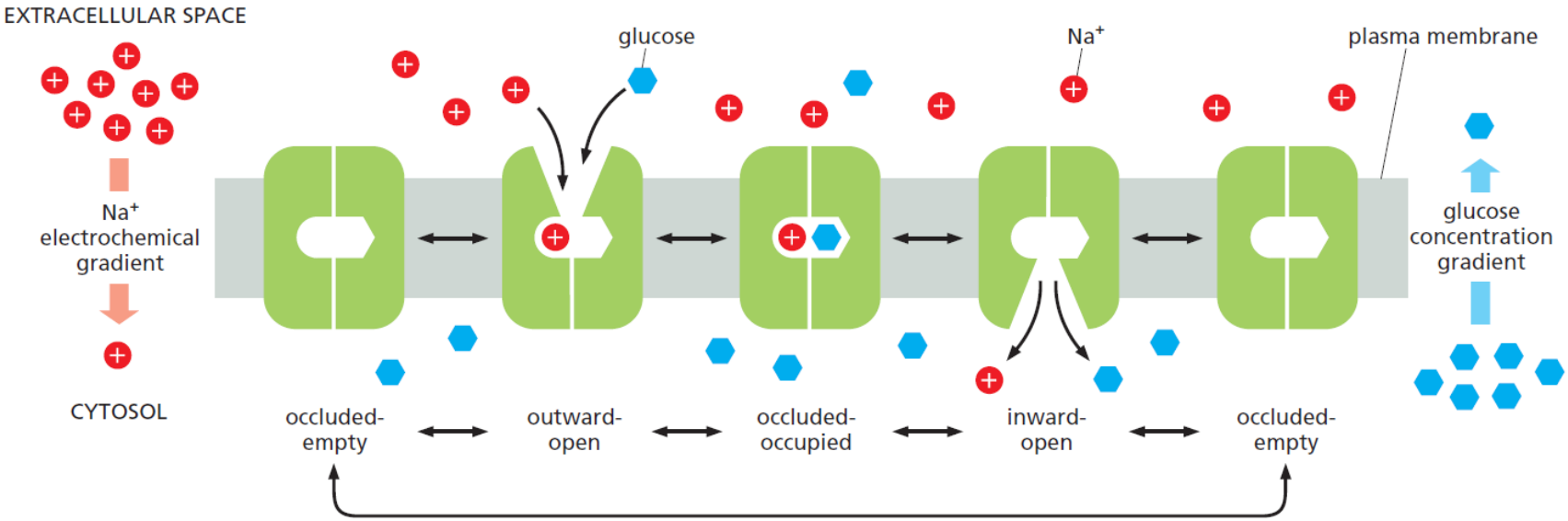


Figure 11–9 Mechanism of glucose transport fueled by a Na^+ gradient. As in the model shown in Figure 11–5, the transporter alternates between inward-open and outward-open states via an occluded intermediate state. Binding of Na^+ and glucose is cooperative—that is, the binding of either solute increases the protein's affinity for the other. Since the Na^+ concentration is much higher in the extracellular space than in the cytosol, glucose is more likely to bind to the transporter in the outward-facing state. The transition to the occluded state occurs only when both Na^+ and glucose are bound; their precise interactions in the solute-binding sites slightly stabilize the occluded state and thereby make this transition energetically favorable. Stochastic fluctuations caused by thermal energy drive the transporter randomly into the inward-open or outward-open conformation. If it opens outwardly, nothing is achieved, and the process starts all over. However, whenever it opens inwardly, Na^+ dissociates quickly in the low-Na^+-concentration environment of the cytosol. Glucose dissociation is likewise enhanced when Na^+ is lost, because of cooperativity in binding of the two solutes. The overall result is the net transport of both Na^+ and glucose into the cell. Because the occluded state is not formed when only one of the solutes is bound, the transporter switches conformation only when it is fully occupied or fully empty, thereby assuring strict coupling of the transport of Na^+ and glucose.

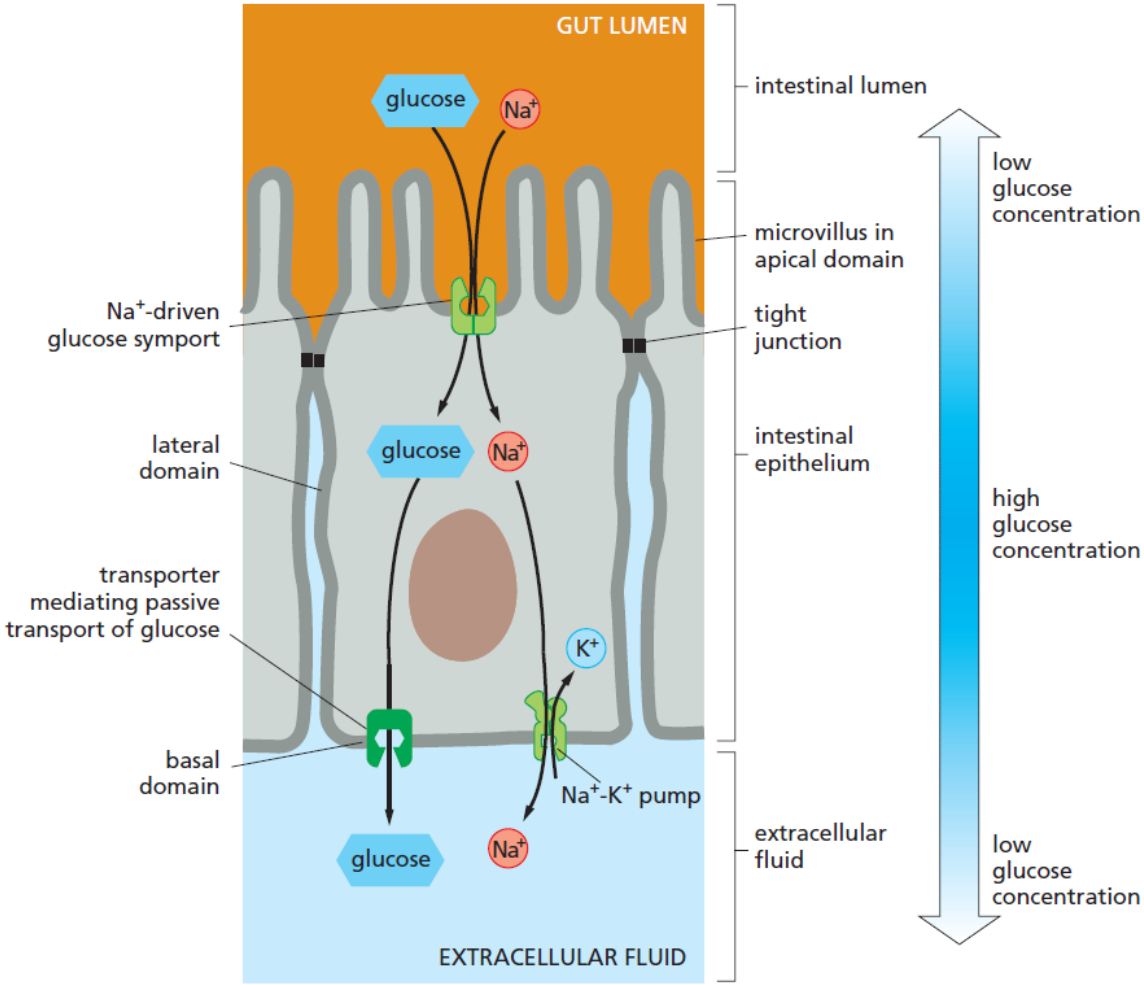
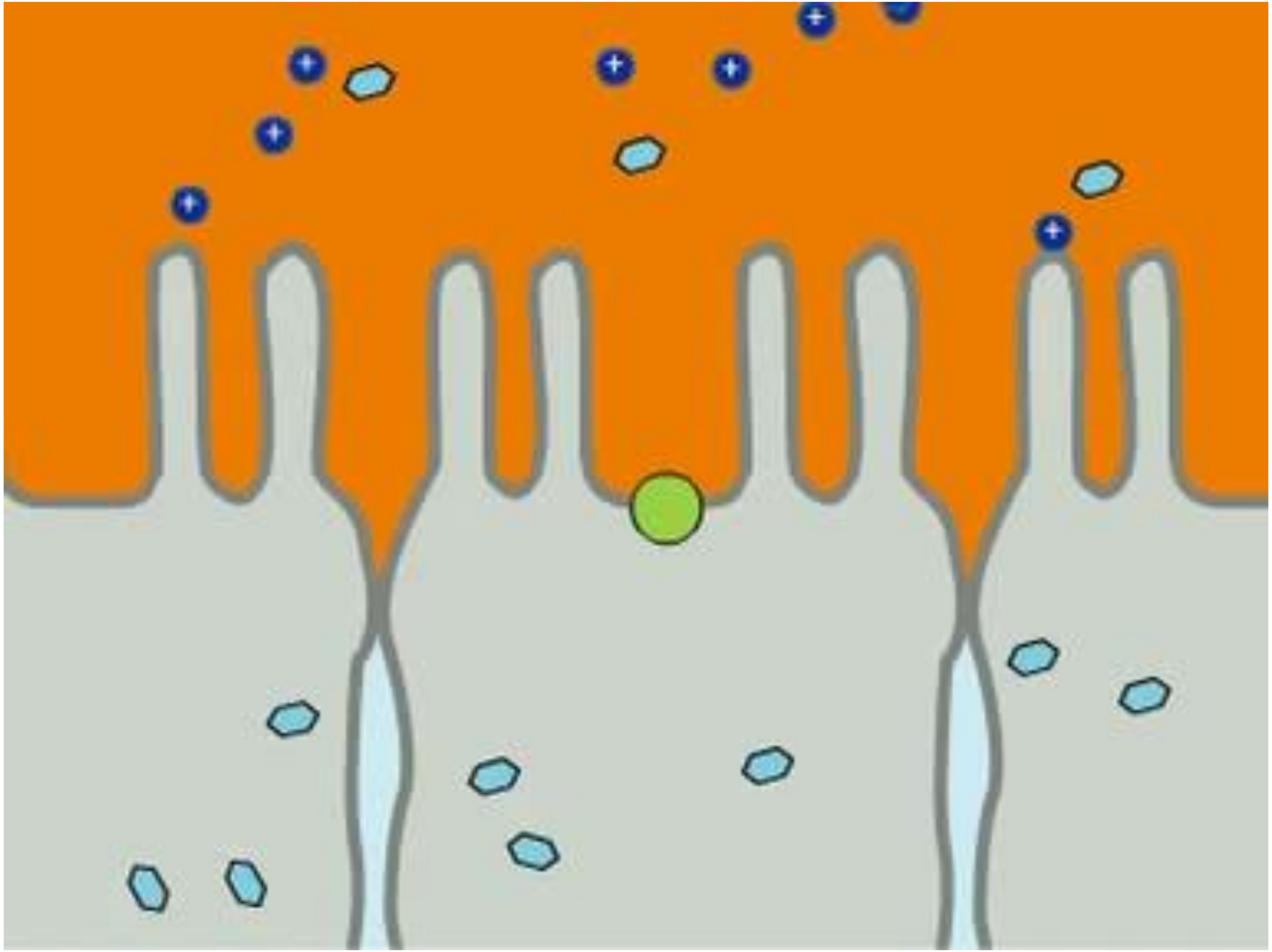


Figure 11–11 Transcellular transport. The transcellular transport of glucose across an intestinal epithelial cell depends on the nonuniform distribution of transporters in the cell's plasma membrane. The process shown here results in the transport of glucose from the intestinal lumen to the extracellular fluid (from where it passes into the blood). Glucose is pumped into the cell through the apical domain of the membrane by a Na^+-powered glucose symporter. Glucose passes out of the cell (down its concentration gradient) by passive movement through a glucose uniporter in the basal and lateral membrane domains. The Na^+ gradient driving the glucose symport is maintained by the Na^+-K^+ pump in the basal and lateral plasma membrane domains, which keeps the internal concentration of Na^+ low (Movie 11.2). Adjacent cells are connected by impermeable tight junctions, which have a dual function in the transport process illustrated: they prevent solutes from crossing the epithelium between cells, allowing a concentration gradient of glucose to be maintained across the cell sheet (see Figure 19–18). They also serve as diffusion barriers (fences) within the plasma membrane, which help confine the various transporters to their respective membrane domains (see Figure 10–34).



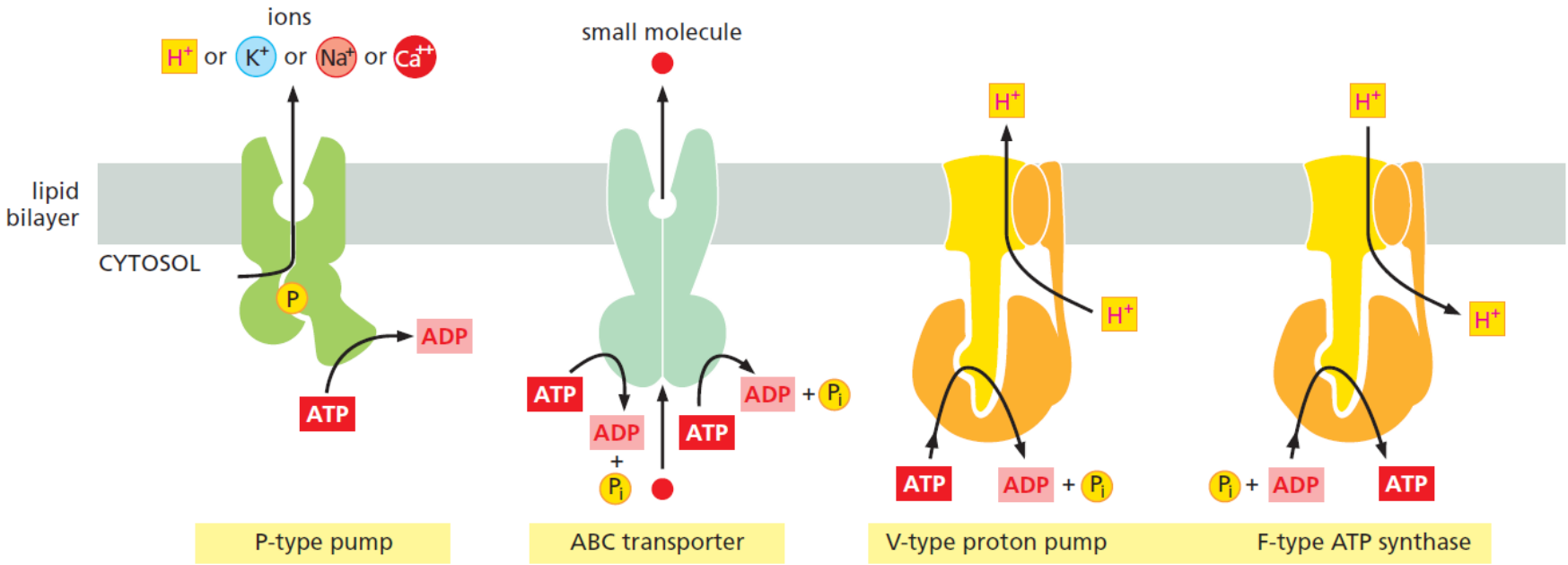


Figure 11–12 Three types of ATP-driven pumps. Like any enzyme, all ATP-driven pumps can work in either direction, depending on the electrochemical gradients of their solutes and the ATP/ADP ratio. When the ATP/ADP ratio is high, they hydrolyze ATP; when the ATP/ADP ratio is low, they can synthesize ATP. The F-type ATPase in mitochondria normally works in this "reverse" mode to make most of the cell's ATP.

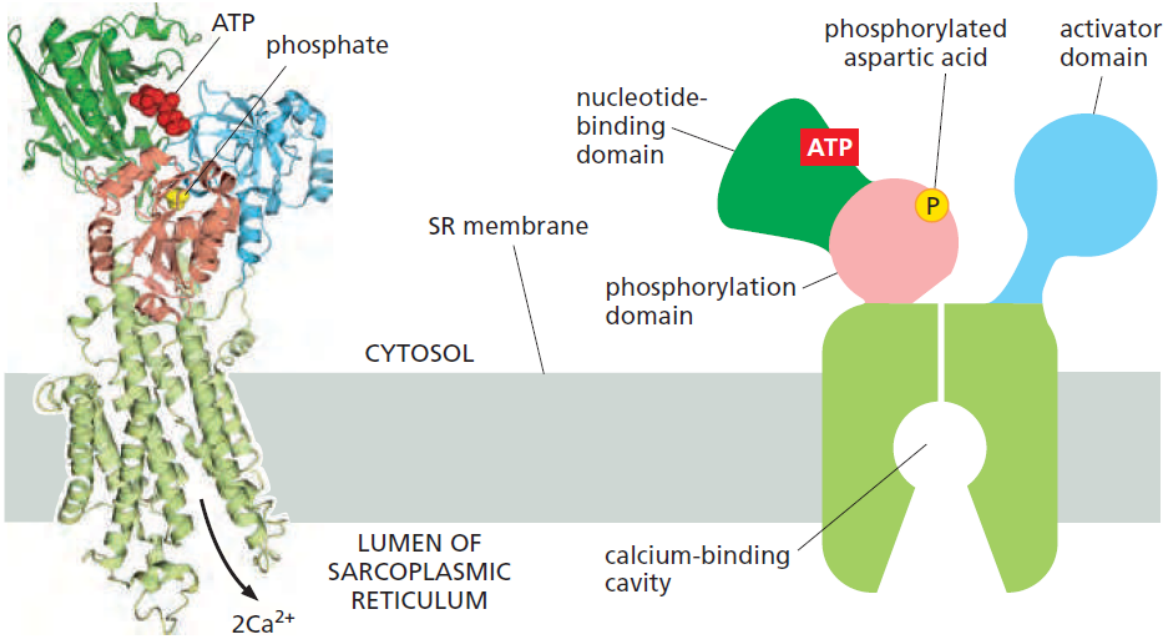


Figure 11–13 The structure of the sarcoplasmic reticulum Ca^{2+} pump. The ribbon model (*left*), derived from x-ray crystallographic analyses, shows the pump in its phosphorylated, ATP-bound state. The three globular cytosolic domains of the pump—the nucleotide-binding domain (*dark green*), the activator domain (*blue*), and the phosphorylation domain (*red*), also shown schematically on the *right*—change conformation dramatically during the pumping cycle. These changes in turn alter the arrangement of the transmembrane helices, which allows the Ca^{2+} to be released from its binding cavity into the SR lumen (Movie 11.3). (PDB code: 3B9B.)

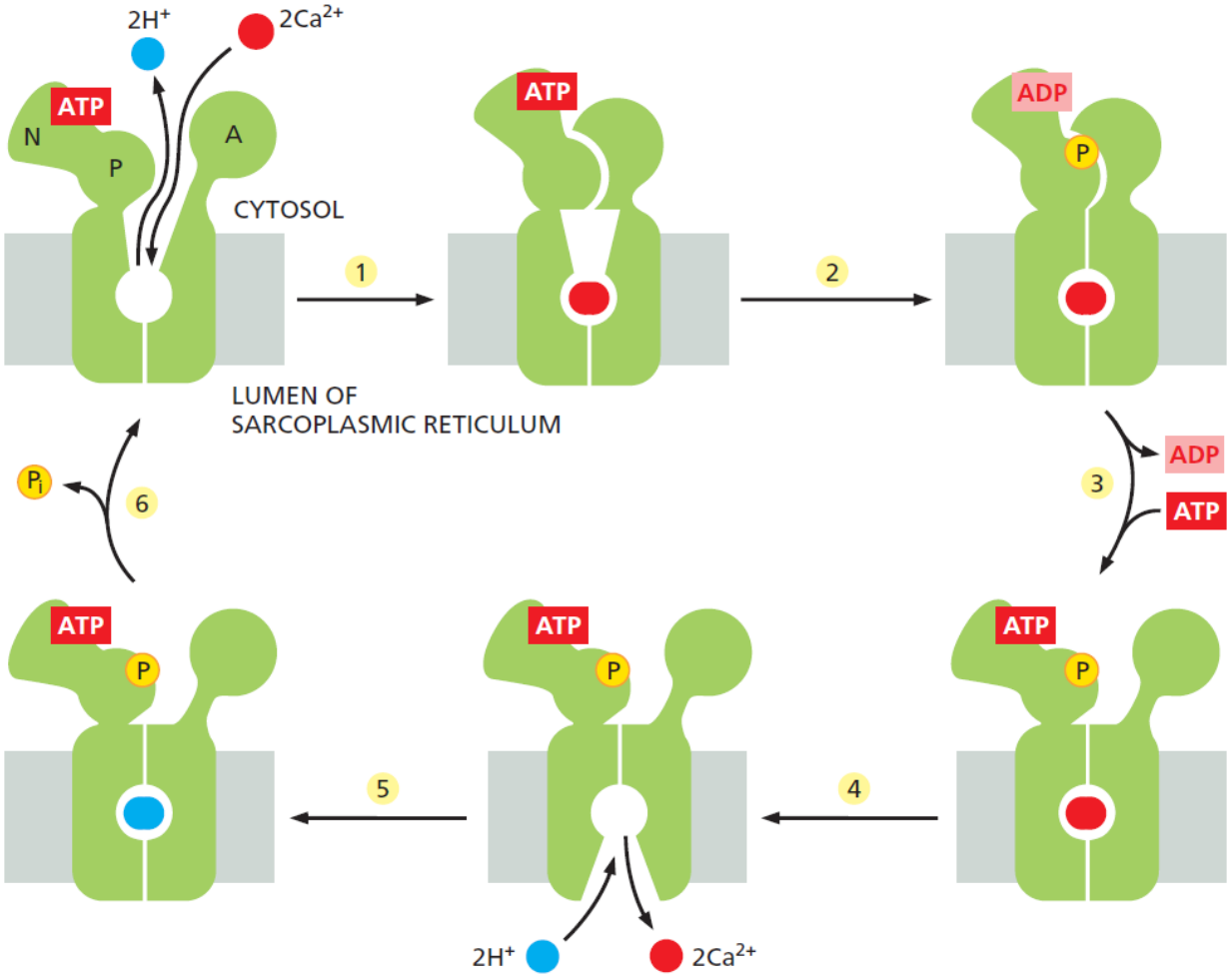
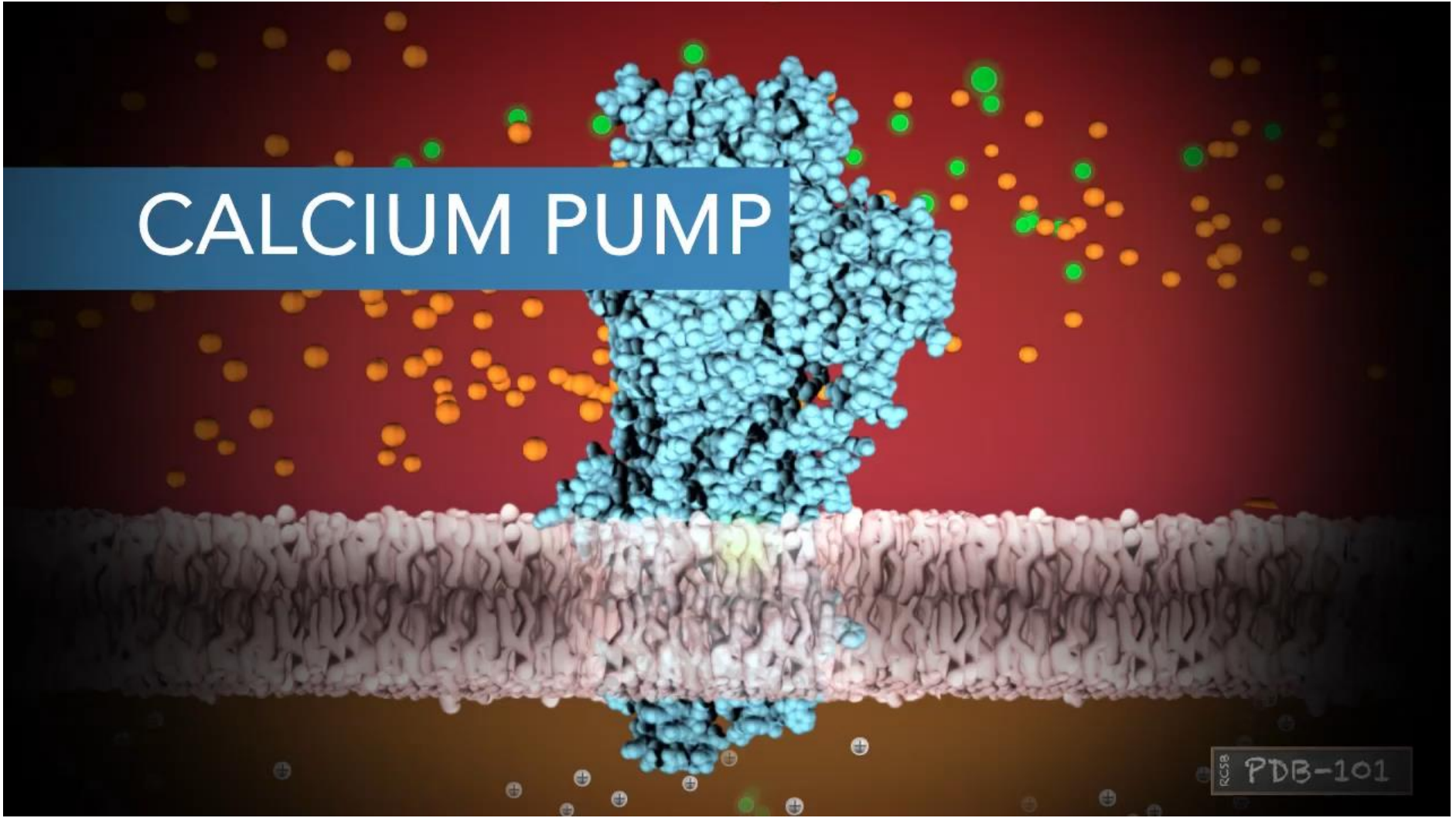


Figure 11–14 The pumping cycle of the sarcoplasmic reticulum Ca^{2+} pump. Ion pumping proceeds by a series of stepwise conformational changes in which movements of the pump's three cytosolic domains [the nucleotide-binding domain (N), the phosphorylation domain (P), and the activator domain (A)] are mechanically coupled to movements of the transmembrane α helices. Helix movement opens and closes passageways through which Ca^{2+} enters from the cytosol and binds to the two centrally located Ca^{2+} binding sites. The two Ca^{2+} then exit into the SR lumen and are replaced by two H^+, which are transported in the opposite direction. The Ca^{2+}-dependent phosphorylation and H^+-dependent dephosphorylation of aspartic acid are universally conserved steps in the reaction cycle of all P-type pumps: they cause the conformational transitions to occur in an orderly manner, enabling the proteins to do useful work. (Adapted from C. Toyoshima et al., *Nature* 432:361–368, 2004 and J.V. Møller et al., *Q. Rev. Biophys.* 43:501–566, 2010.)


CALCIUM PUMP
RCSB PDB-101

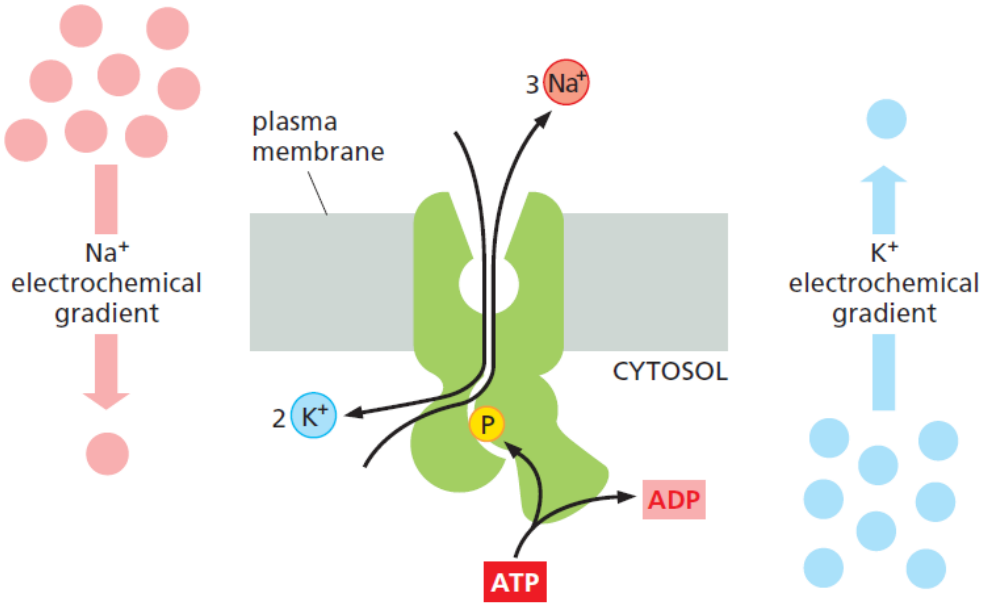
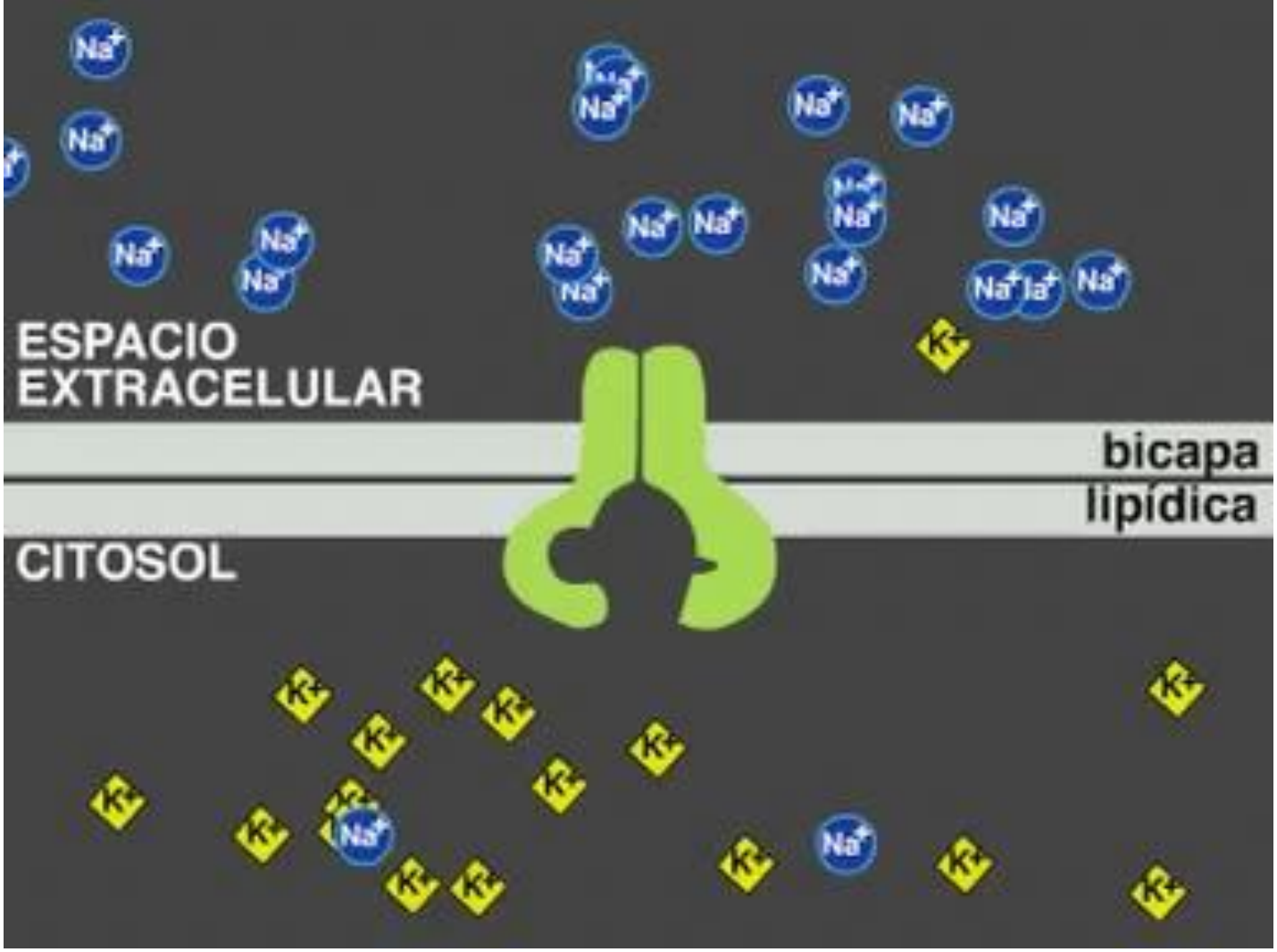


Figure 11–15 The function of the Na^+-K^+ pump. This P-type ATPase actively pumps Na^+ out of and K^+ into a cell against their electrochemical gradients. It is structurally closely related to the Ca^{2+} ATPase but differs in its selectivity for ions: for every molecule of ATP hydrolyzed by the pump, three Na^+ are pumped out and two K^+ are pumped in. As in the Ca^{2+} pump, an aspartate is phosphorylated and dephosphorylated during the pumping cycle (Movie 11.4).


ESPACIO
EXTRACELULAR
bicapa
lipídica
CITOSOL

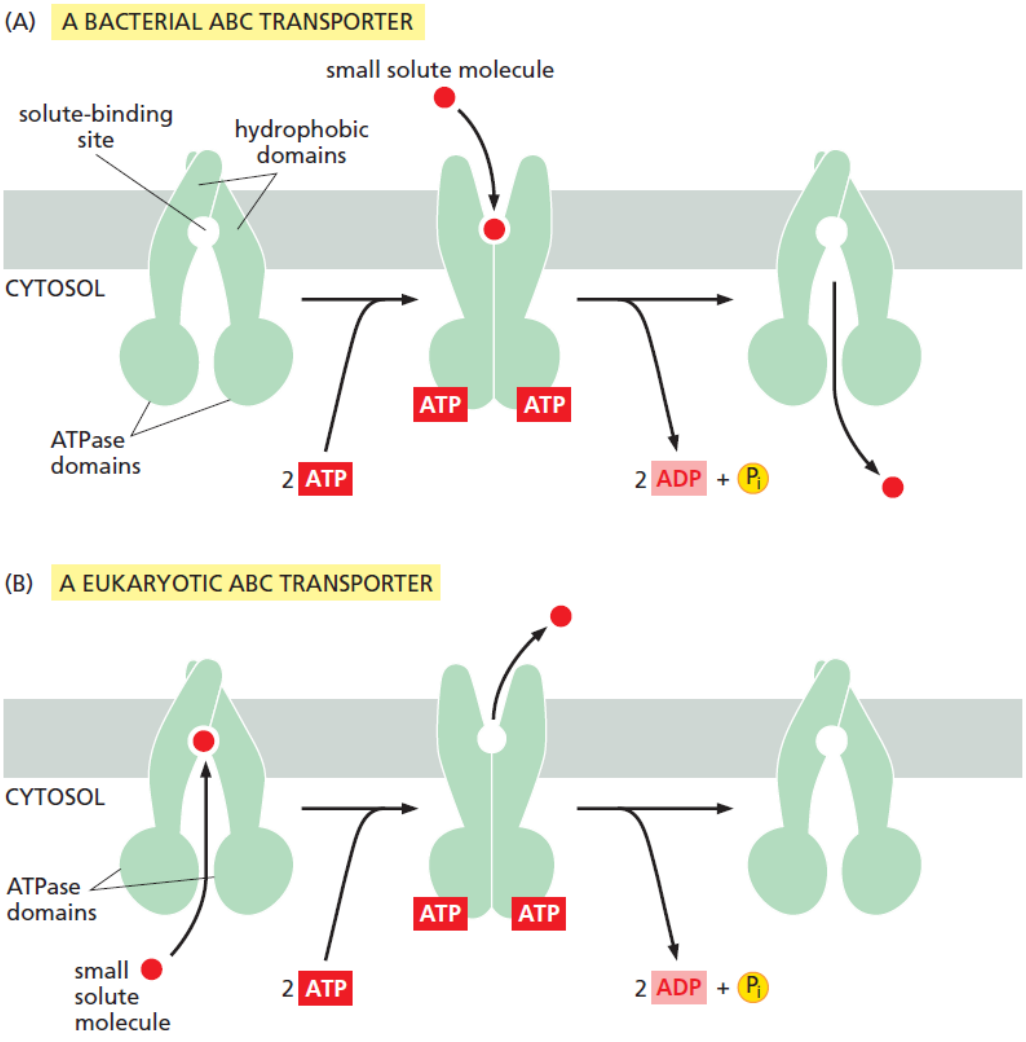


Figure 11–16 Small-molecule transport by typical ABC transporters. ABC transporters consist of multiple domains. Typically, two hydrophobic domains, each built of six membrane-spanning α helices, together form the translocation pathway and provide substrate specificity. Two ATPase domains protrude into the cytosol. In some cases, the two halves of the transporter are formed by a single polypeptide, whereas in other cases they are formed by two or more separate polypeptides that assemble into a similar structure. Without ATP bound, the transporter exposes a substrate-binding site on one side of the membrane. ATP binding induces a conformational change that exposes the substrate-binding site on the opposite side; ATP hydrolysis followed by ADP dissociation returns the transporter to its original conformation. Most individual ABC transporters are unidirectional. (A) Both importing and exporting ABC transporters are found in bacteria; an ABC importer is shown in this cartoon. The crystal structure of a bacterial ABC transporter is shown in Figure 3–76. (B) In eukaryotes, most ABC transporters export substances—either from the cytosol to the extracellular space or from the cytosol to a membrane-bound intracellular compartment such as the endoplasmic reticulum—or from the mitochondrial matrix to the cytosol.

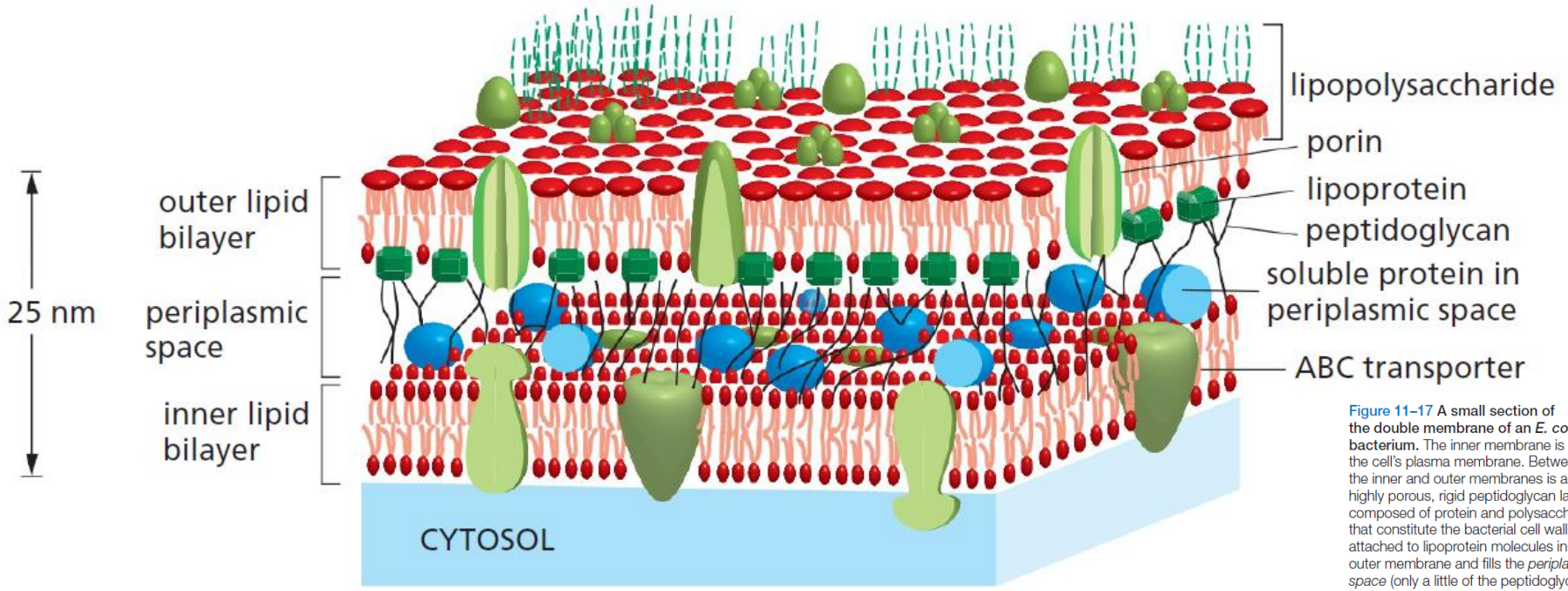


Figure 11–17 **A small section of the double membrane of an *E. coli* bacterium.** The inner membrane is the cell's plasma membrane. Between the inner and outer membranes is a highly porous, rigid peptidoglycan layer, composed of protein and polysaccharide that constitute the bacterial cell wall. It is attached to lipoprotein molecules in the outer membrane and fills the *periplasmic space* (only a little of the peptidoglycan layer is shown). This space also contains a variety of soluble protein molecules. The dashed threads (shown in *green*) at the top represent the polysaccharide chains of the special lipopolysaccharide molecules that form the external monolayer of the outer membrane; for clarity, only a few of these chains are shown. Bacteria with double membranes are called *Gram-negative* because they do not retain the dark blue dye used in Gram staining. Bacteria with single membranes (but thicker peptidoglycan cell walls), such as staphylococci and streptococci, retain the blue dye and are therefore called *Gram-positive*; their single membrane is analogous to the inner (plasma) membrane of Gram-negative bacteria.

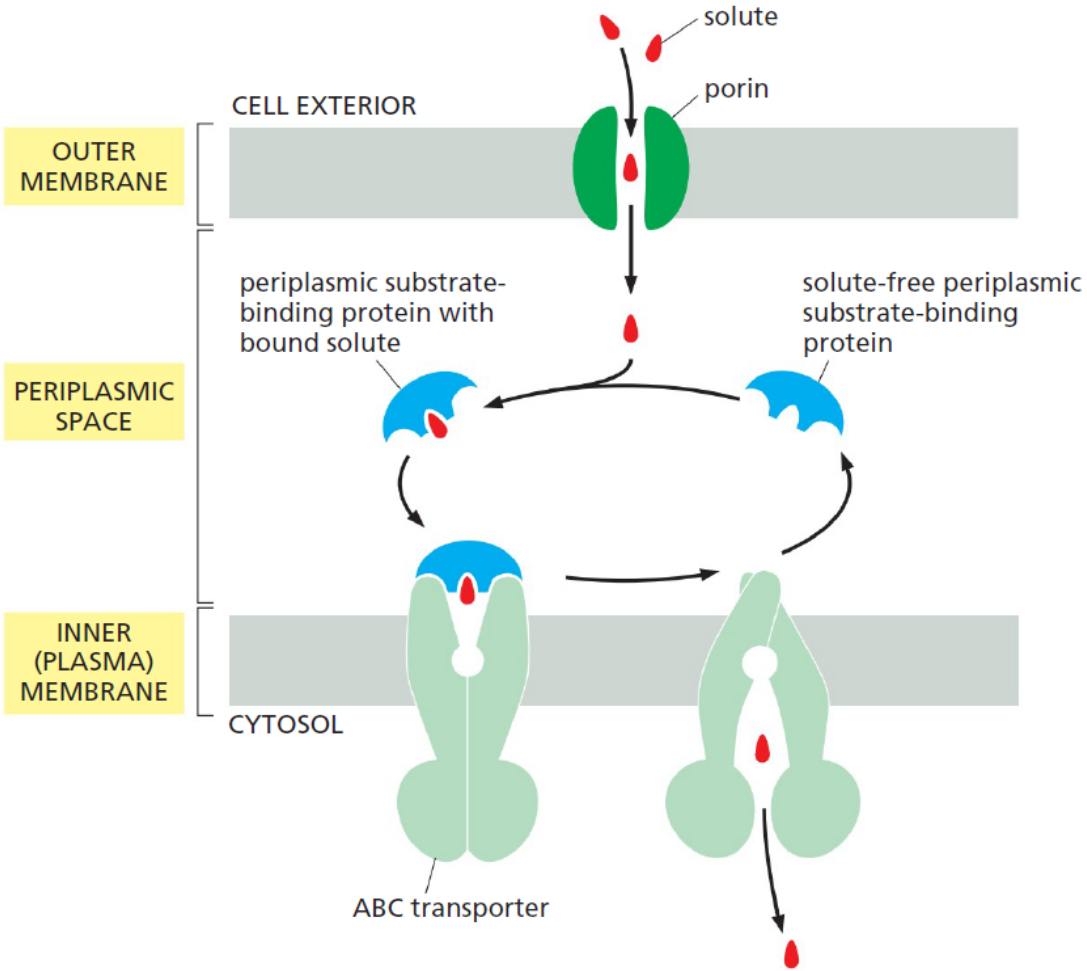
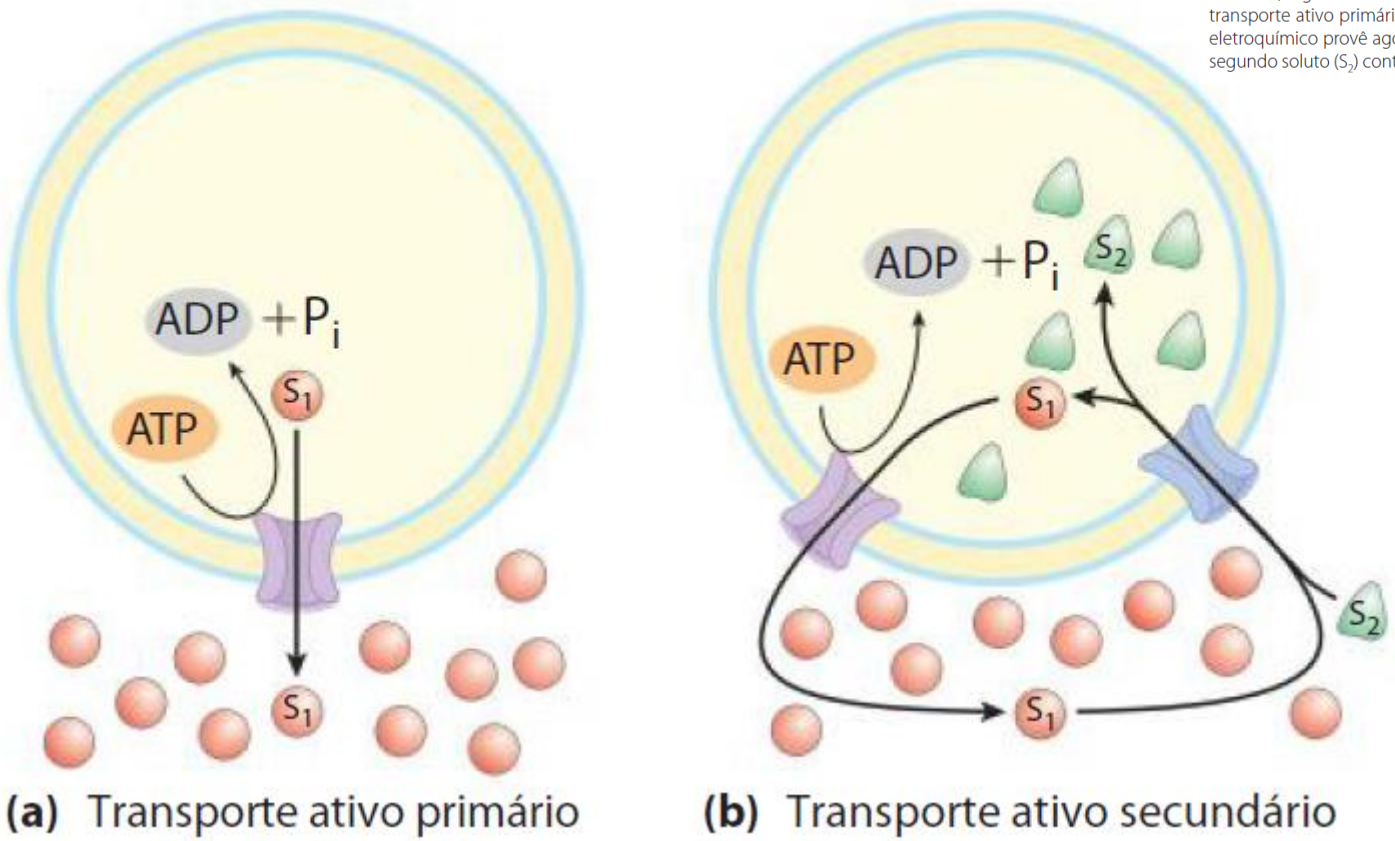


Figure 11–18 **The auxiliary transport system associated with transport ATPases in bacteria with double membranes.** The solute diffuses through channel proteins (porins) in the outer membrane and binds to a *periplasmic substrate-binding protein* that delivers it to the ABC transporter, which pumps it across the plasma membrane. The peptidoglycan is omitted for simplicity; its porous structure allows the substrate-binding proteins and water-soluble solutes to move through it by diffusion.

FIGURA 11-35 **Dois tipos de transporte ativo.** **(a)** No transporte ativo primário, a energia liberada pela hidrólise de ATP impulsiona o movimento de soluto (S_1) contra o gradiente eletroquímico. **(b)** No transporte ativo secundário, o gradiente de um íon X (S_1) (geralmente Na^+) se estabelece por transporte ativo primário. O movimento de X (S_1) a favor de seu gradiente eletroquímico provê agora energia para impulsionar o cotransporte de um segundo soluto (S_2) contra seu gradiente eletroquímico.



(a) Transporte ativo primário

(b) Transporte ativo secundário

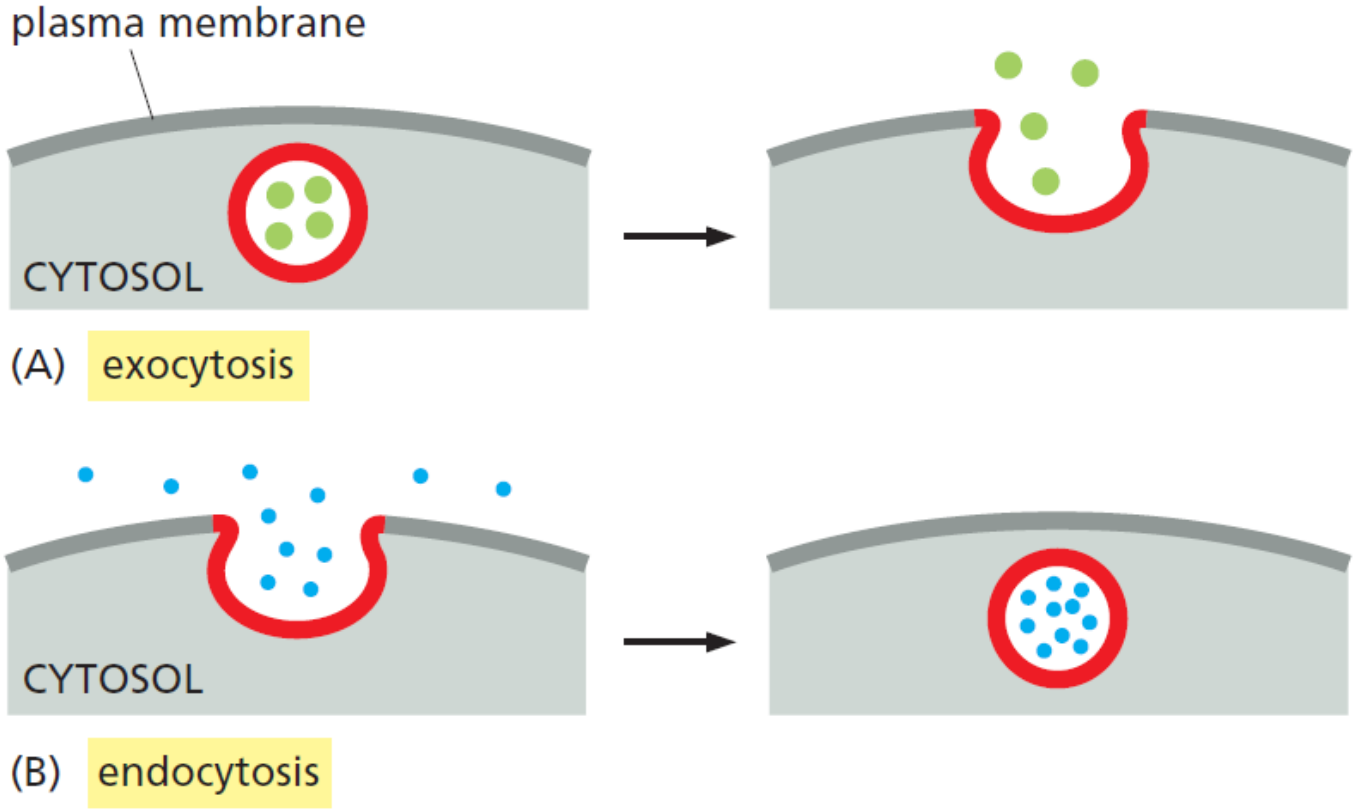
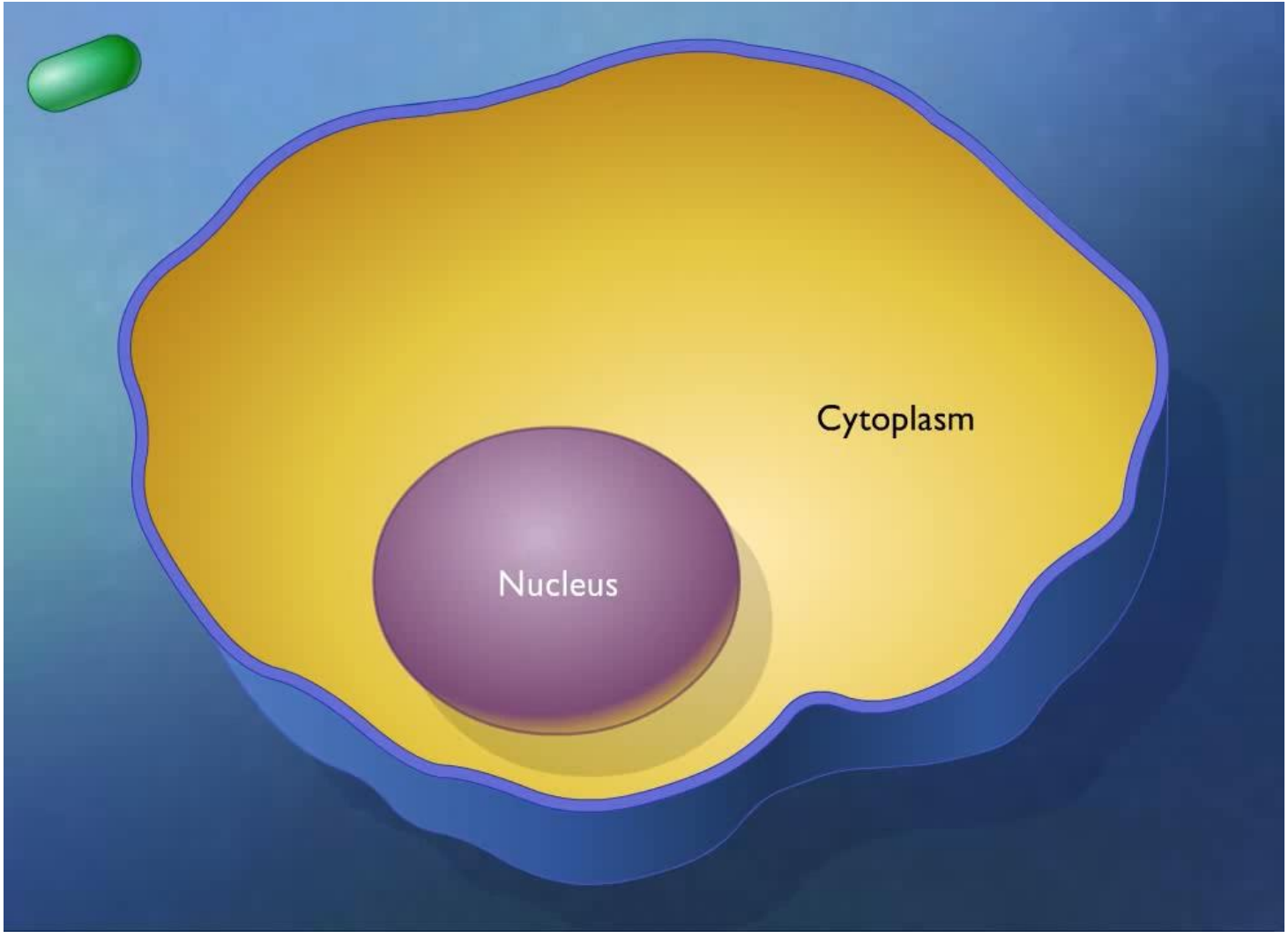


Figure 13–1 **Exocytosis and endocytosis.** (A) In exocytosis, a transport vesicle fuses with the plasma membrane. Its content is released into the extracellular space, while the vesicle membrane *(red)* becomes continuous with the plasma membrane. (B) In endocytosis, a plasma membrane patch *(red)* is internalized, forming a transport vesicle. Its content derives from the extracellular space.


Cytoplasm
Nucleus

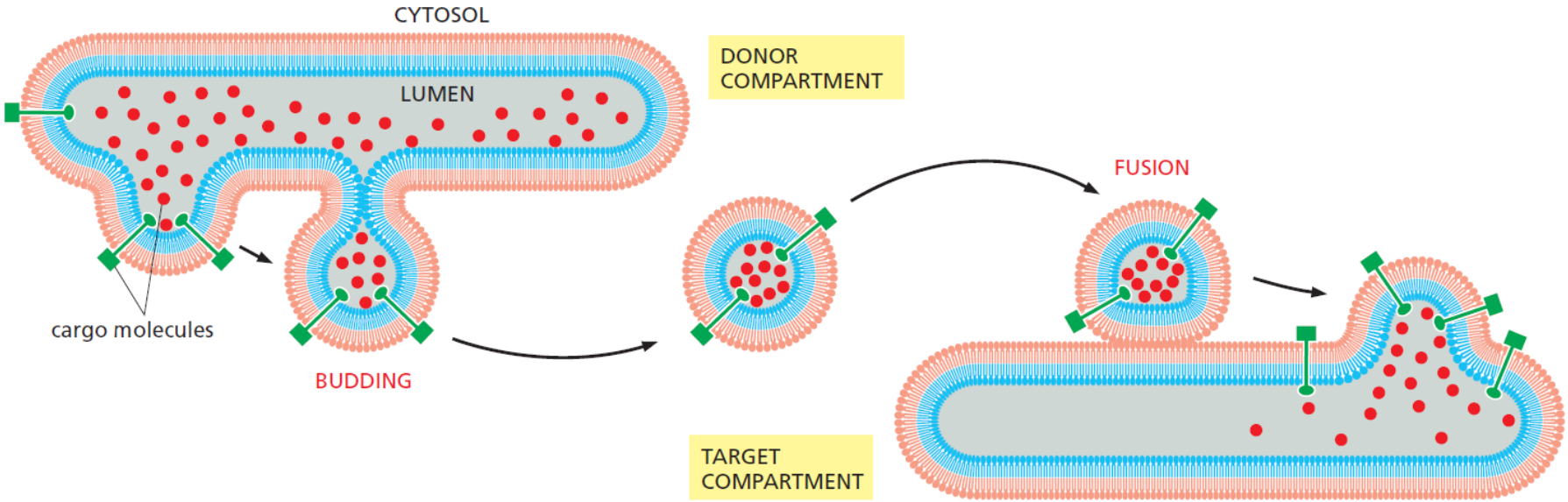


Figure 13–2 **Vesicle transport.** Transport vesicles bud off from one compartment and fuse with another. As they do so, they carry material as cargo from the *lumen* (the space within a membrane-enclosed compartment) and membrane of the donor compartment to the lumen and membrane of the target compartment, as shown.

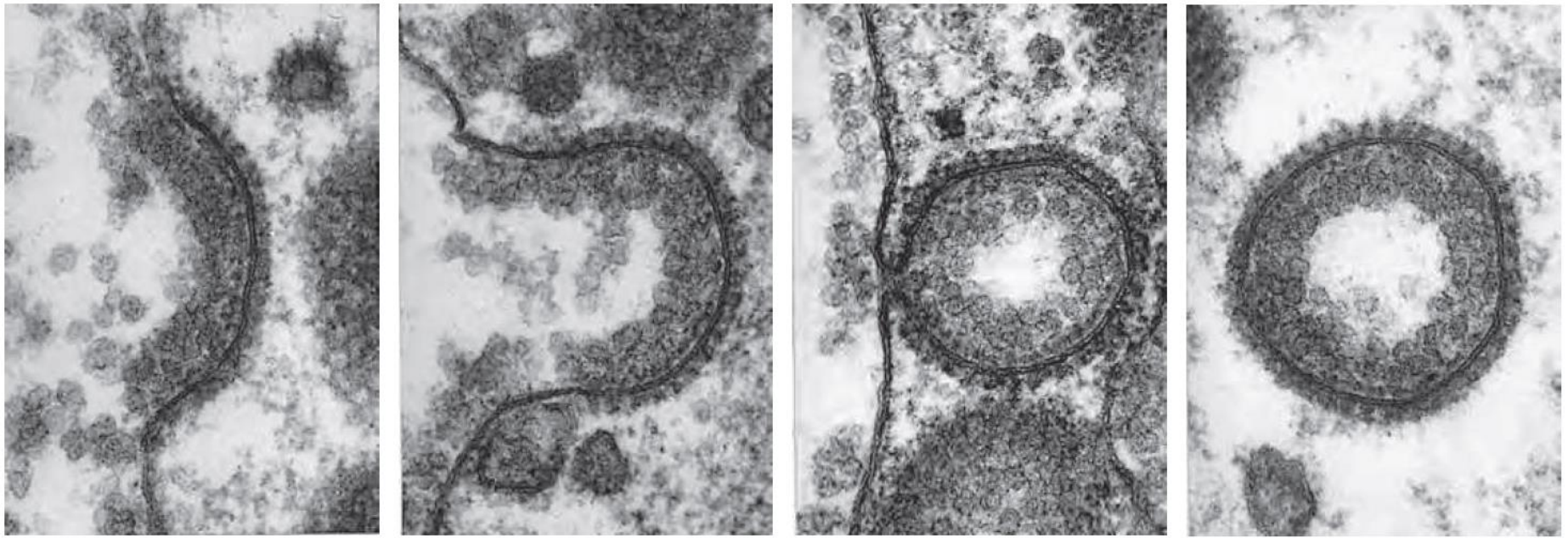


Figure 13–48 **The formation of clathrin-coated vesicles from the plasma membrane.** These electron micrographs illustrate the probable sequence of events in the formation of a clathrin-coated vesicle from a clathrin-coated pit. The clathrin-coated pits and vesicles shown are larger than those seen in normal-sized cells; they are from a very large hen oocyte and they take up lipoprotein particles to form yolk. The lipoprotein particles bound to their membrane-bound receptors appear as a dense, fuzzy layer on the extracellular surface of the plasma membrane—which is the inside surface of the coated pit and vesicle. (Courtesy of M.M. Perry and A.B. Gilbert, *J. Cell Sci.* 39:257–272, 1979. With permission from The Company of Biologists.)

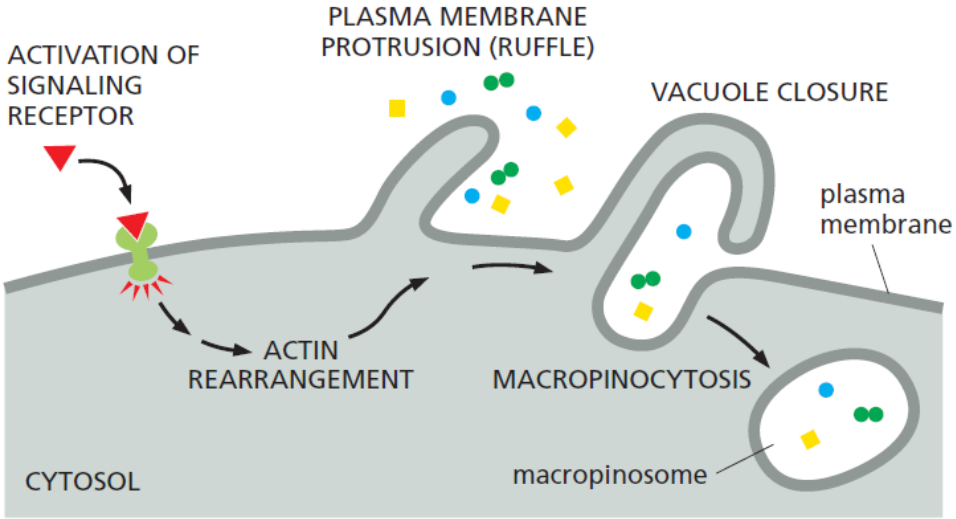


Figure 13–50 Schematic representation of macropinocytosis. Cell signaling events lead to a reprogramming of actin dynamics, which in turn triggers the formation of cell-surface ruffles. As the ruffles collapse back onto the cell surface, they nonspecifically trap extracellular fluid and macromolecules and particles contained in it, forming large vacuoles, or macropinosomes, as shown.

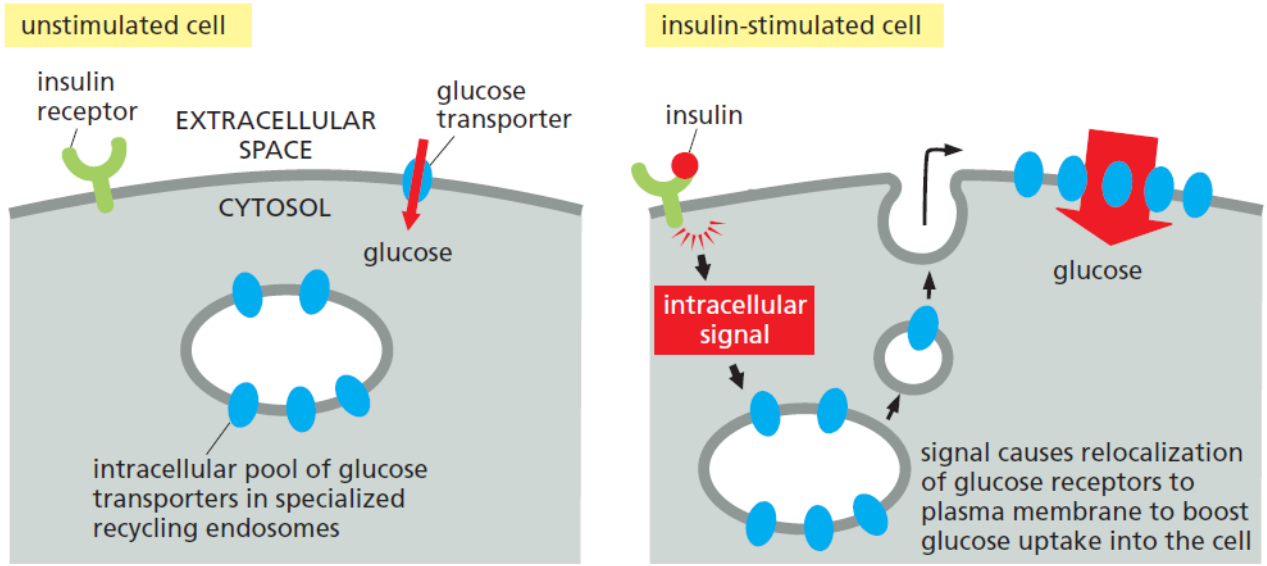


Figure 13–59 Storage of plasma membrane proteins in recycling endosomes. Recycling endosomes can serve as an intracellular storage site for specialized plasma membrane proteins that can be mobilized when needed. In the example shown, insulin binding to the insulin receptor triggers an intracellular signaling pathway that causes the rapid insertion of glucose transporters into the plasma membrane of a fat or muscle cell, greatly increasing its glucose intake.

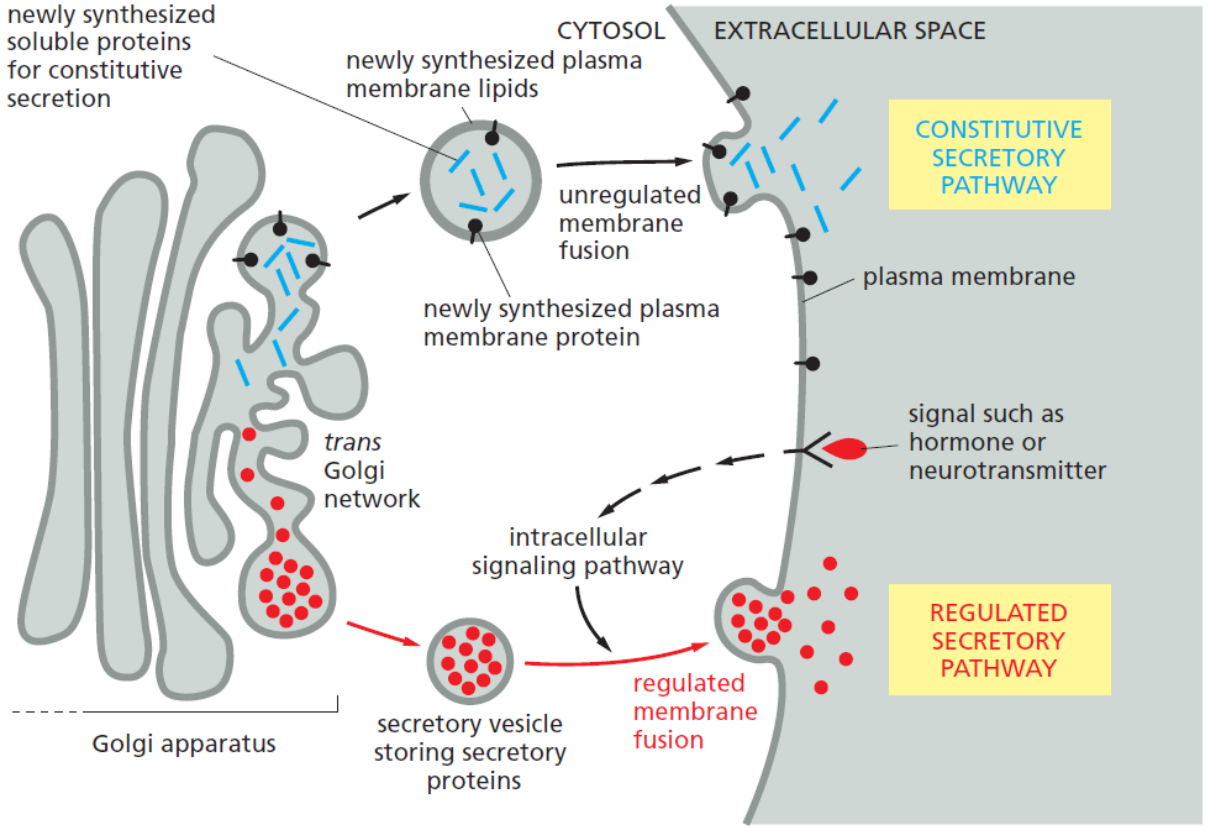


Figure 13–62 The constitutive and regulated secretory pathways. The two pathways diverge in the TGN. The constitutive secretory pathway operates in all cells. Many soluble proteins are continually secreted from the cell by this pathway, which also supplies the plasma membrane with newly synthesized membrane lipids and proteins. Specialized secretory cells also have a regulated secretory pathway, by which selected proteins in the TGN are diverted into secretory vesicles, where the proteins are concentrated and stored until an extracellular signal stimulates their secretion. The regulated secretion of small molecules, such as histamine and neurotransmitters, occurs by a similar pathway; these molecules are actively transported from the cytosol into preformed secretory vesicles. There they are often bound to specific macromolecules (proteoglycans, for histamine) so that they can be stored at high concentration without generating an excessively high osmotic pressure.

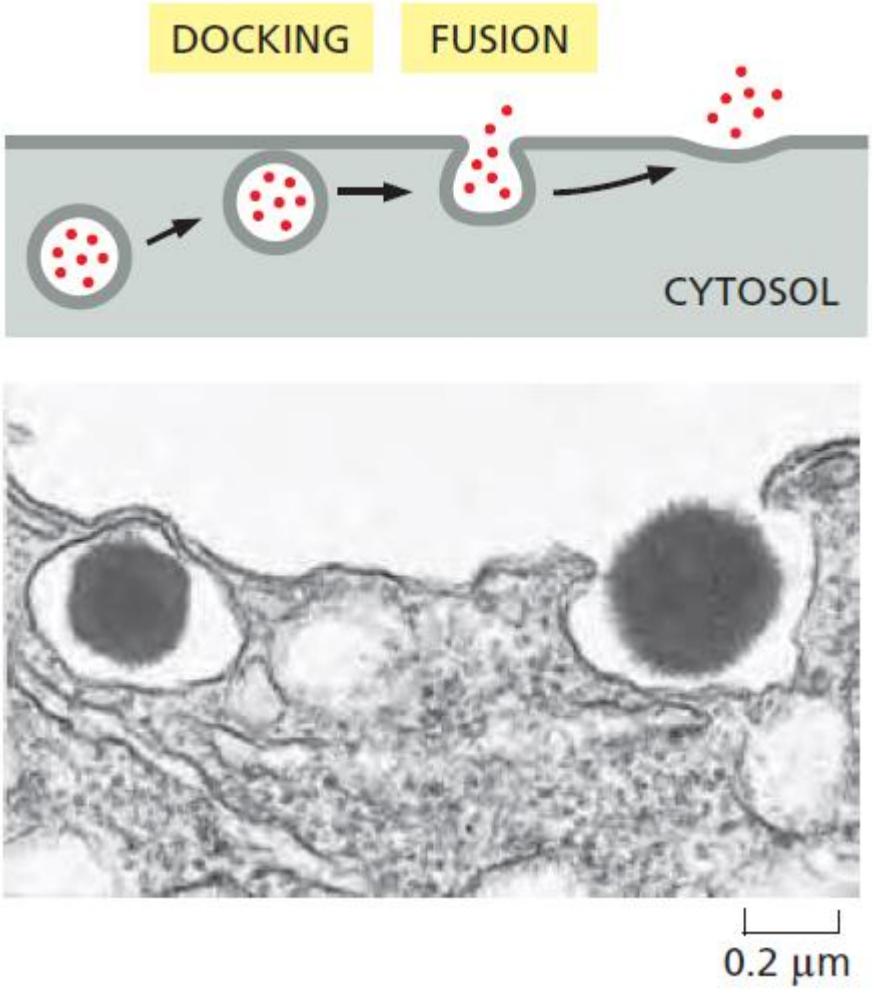


Figure 13–65 **Exocytosis of secretory vesicles.** The process is illustrated schematically (top) and in an electron micrograph that shows the release of insulin from a secretory vesicle of a pancreatic β cell. (Courtesy of Lelio Orci, from L. Orci, J.-D. Vassalli and A. Perrelet, *Sci. Am.* 259:85–94, 1988.)

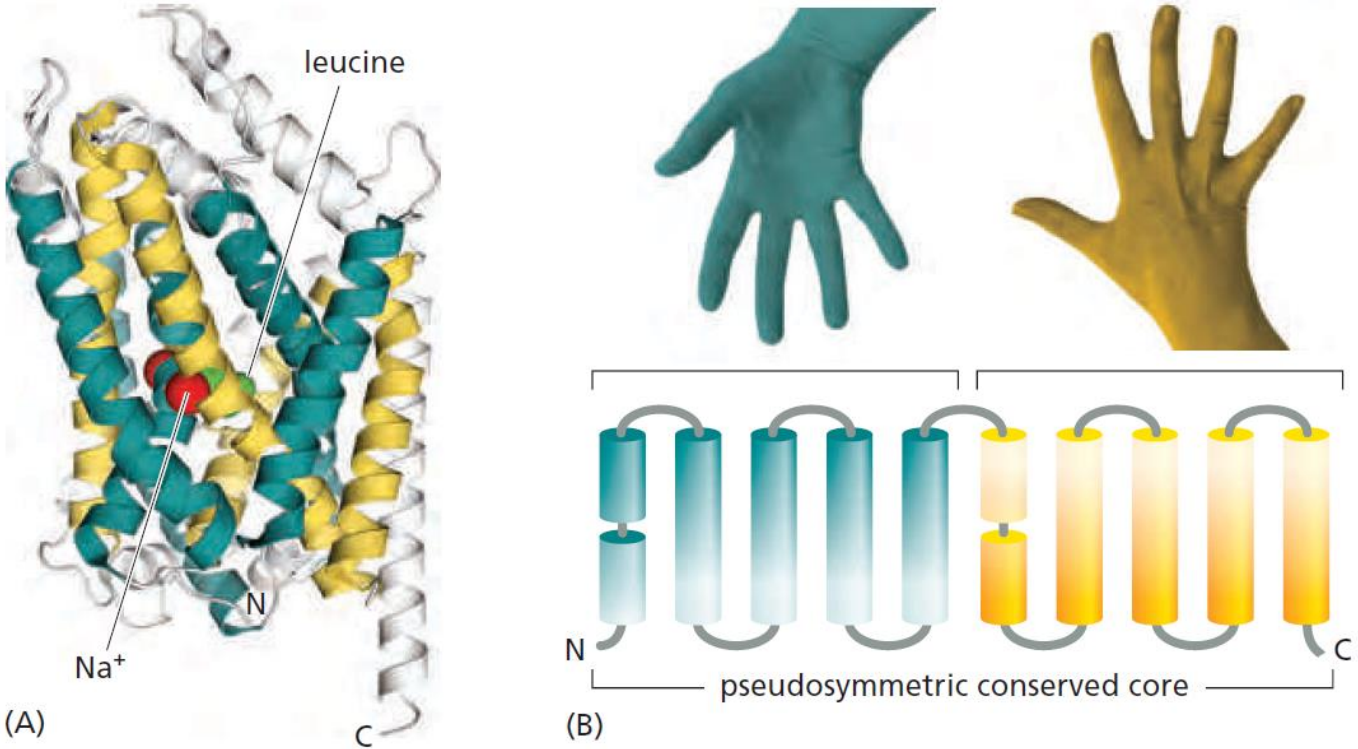


Figure 11–10 Transporters are built from inverted repeats. (A) LeuT, a bacterial leucine/Na^+ symporter related to human neurotransmitter transporters, such as the serotonin transporter, is shown. The core of the transporter is built from two bundles, each composed of five α helices (*blue* and *yellow*). The helices shown in *gray* differ among members of this transporter family and are thought to play regulatory roles, which are specific to a particular transporter. (B) Both core helix bundles are packed in a similar arrangement (shown as a hand, with the broken helix as the thumb), but the second bundle is inverted with respect to the first. The transporter's structural pseudosymmetry reflects its functional symmetry: the transporter can work in either direction, depending on the direction of the ion gradient. (Adapted from K.R. Vinothkumar and R. Henderson, *Q. Rev. Biophys*. 43:65–158, 2010. With permission from Cambridge University Press. PDB code: 3F3E.)