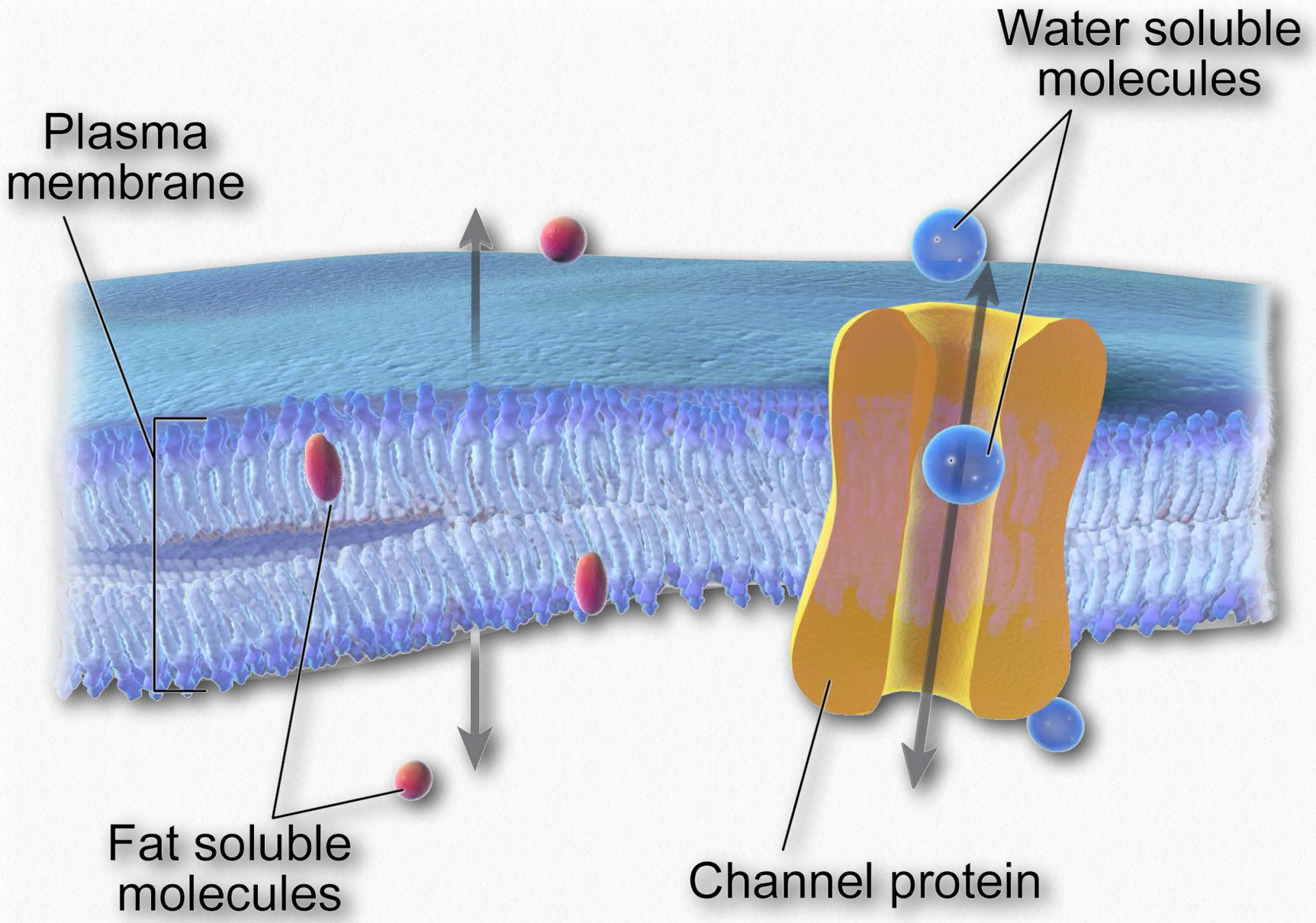
Membranes: Transport



Wikipedia

Movement of materials across membranes

As noted earlier, it is essential for cells to be able to uptake nutrients. This function along with movement of ions and other substances is provided by proteins/protein complexes that are highly specific for the compounds they move.

Selective movement of ions by membrane proteins and the ions' extremely low permeability across the lipid bilayer are important for helping to maintain the osmotic balance of the cell and also for providing for the most important mechanism for it to make ATP - the process of oxidative phosphorylation.

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Terminology

A protein involved in moving only one molecule across a membrane is called a uniport (Figure 3.25). Proteins that move two molecules in the same direction across the membrane are called symports (also called syn-

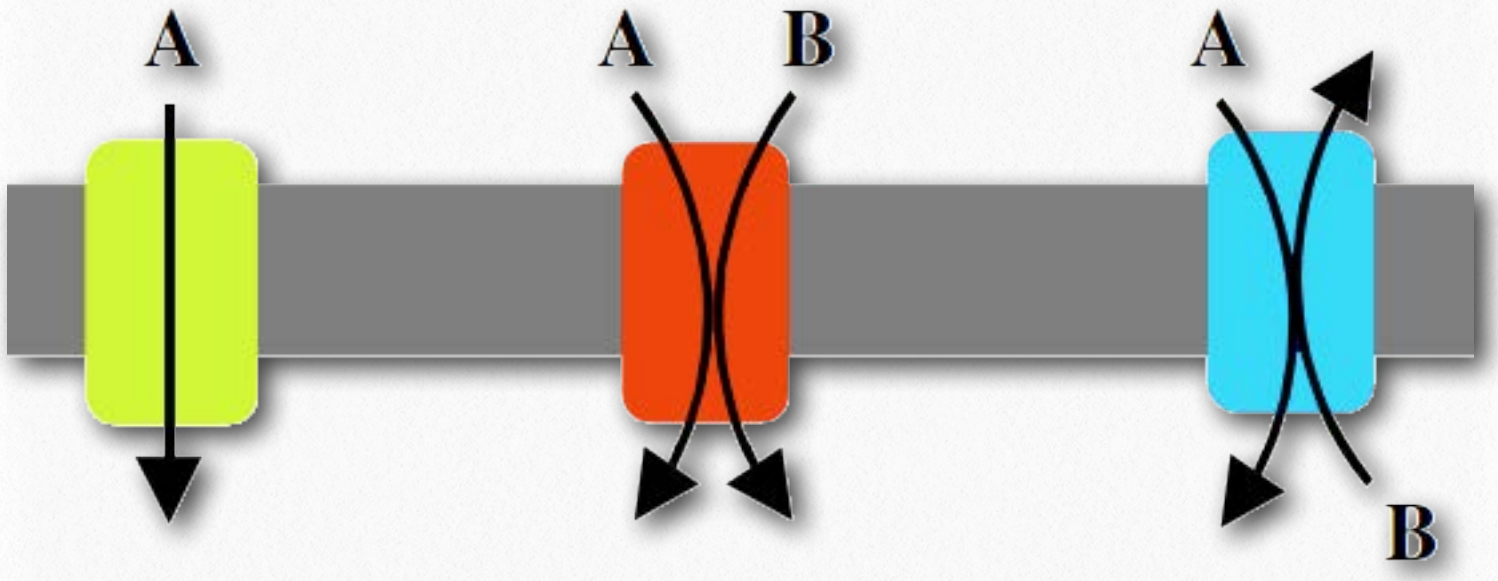

Figure 3.25 - A uniport, a symport, and an antiport

porters, synports, or symporters). If two molecules are moved in opposite directions across the bilayer, the protein is called an antiport. Proteins involved in moving ions are called ionophores.

If the action of a protein in moving ions across a membrane results in a net change in charge, the protein is described as electrogenic and if there is no change in charge the protein is described as electroneutral (Figure 3.26). When the driving force for movement through the membrane protein is simply diffusion, the process is called facilitated diffusion or passive transport and when the process requires other energy input, the process is called active transport.

Channels and transporters

With respect to movement of materials through membrane proteins, there is a difference between channels (sometimes called

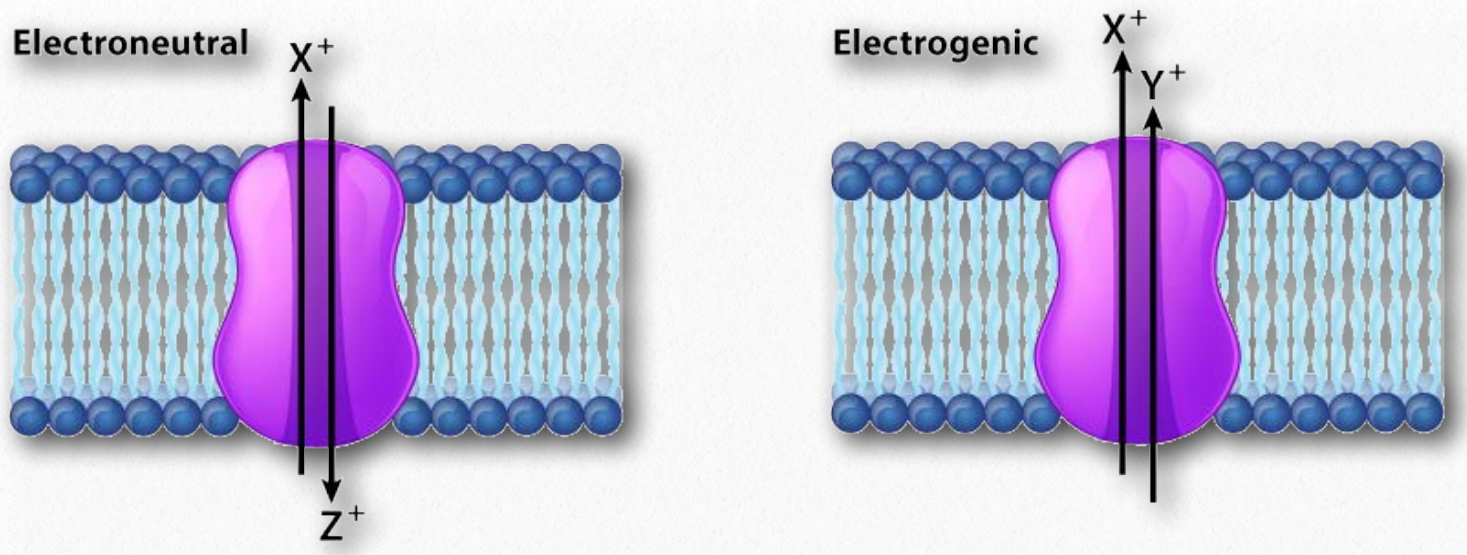

Figure 3.26 - Electroneutral and electrogenic transporters

Image by Aleia Kim

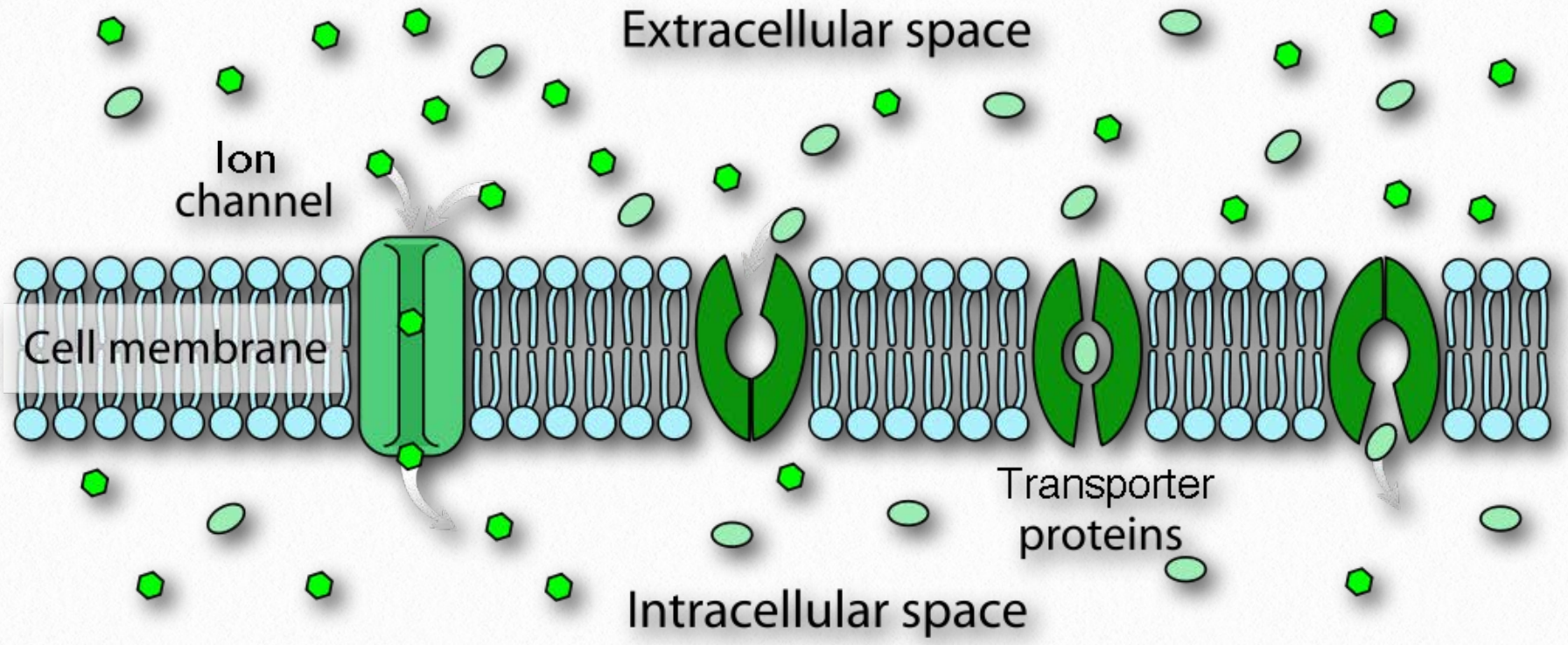

Figure 3.27 - Ion channel and transporter proteins

pores) and transporters. Channels largely provide openings with some specificity and molecules pass through them at close to the rate of diffusion. They usually involve movement of water or ions. Examples would be the sodium or potassium channels of nerve cells. Transporters have high specificity and transfer rates that are orders of magnitude slower. Transport proteins include the sodium-potassium pump, the sodium-calcium exchanger, and lactose permease, amongst many others).

Facilitated diffusion

As noted, the driving force for facilitated diffusion is concentration, meaning that in facilitated diffusion, materials will only move from a higher concentration to a lower concentration and that at the end of the process, the concentration of materials on each side of a bilayer will be equal (Figure 3.28). This may work well in many cases.

For example, the blood concentration of glucose is sufficiently high that red blood cells can use facilitated diffusion as a means of

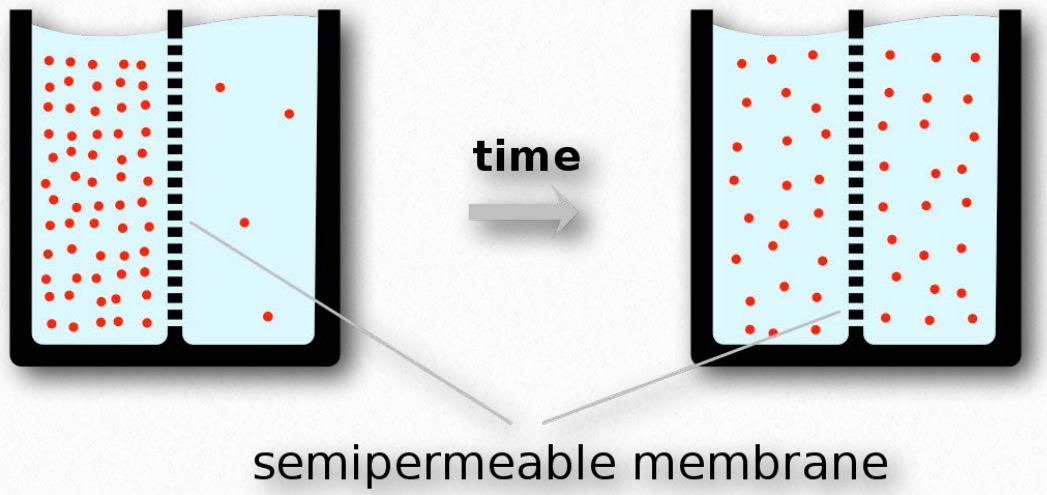

Figure 3.28 - In diffusion, solutes move from high concentration to lower concentration and eventually equalize

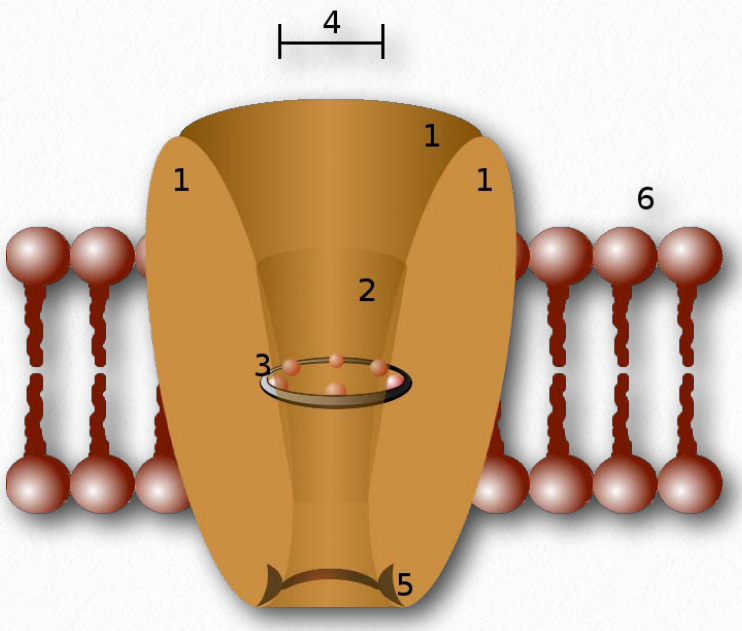

Figure 3.29 - Schematic structure of an ion channel protein - 1 = General structure / 2 = Entrance / 3 = Selectivity filter / 4 = Effective diameter / 5 = Controllable opening

acquiring glucose. Other cells, further removed from the blood supply where the glucose concentration is lower, must use active transport mechanisms because there is not a sufficient concentration of glucose to provide cells with the glucose they need.

Ion channels

Ion channels are pore-forming membrane proteins in the membranes of all cells that regulate movement of selected ions across a membrane (Figures 3.29 & 3.30). They help to establish the resting membrane potential and to affect action potentials and other electrical signals. They are very important in the process of nerve transmission. Ion channels control the flow of ions across secretory and epithelial cells, and consequently help to regulate cell volume by affecting osmotic pressure.

Ion channels are essential features of almost all cells, functioning as selective "tunnels" that restrict movement through them to ions with specific characteristics (typically size). The size of the opening is very narrow (usually one or two atoms wide) and is able to select even against ions that are too small.

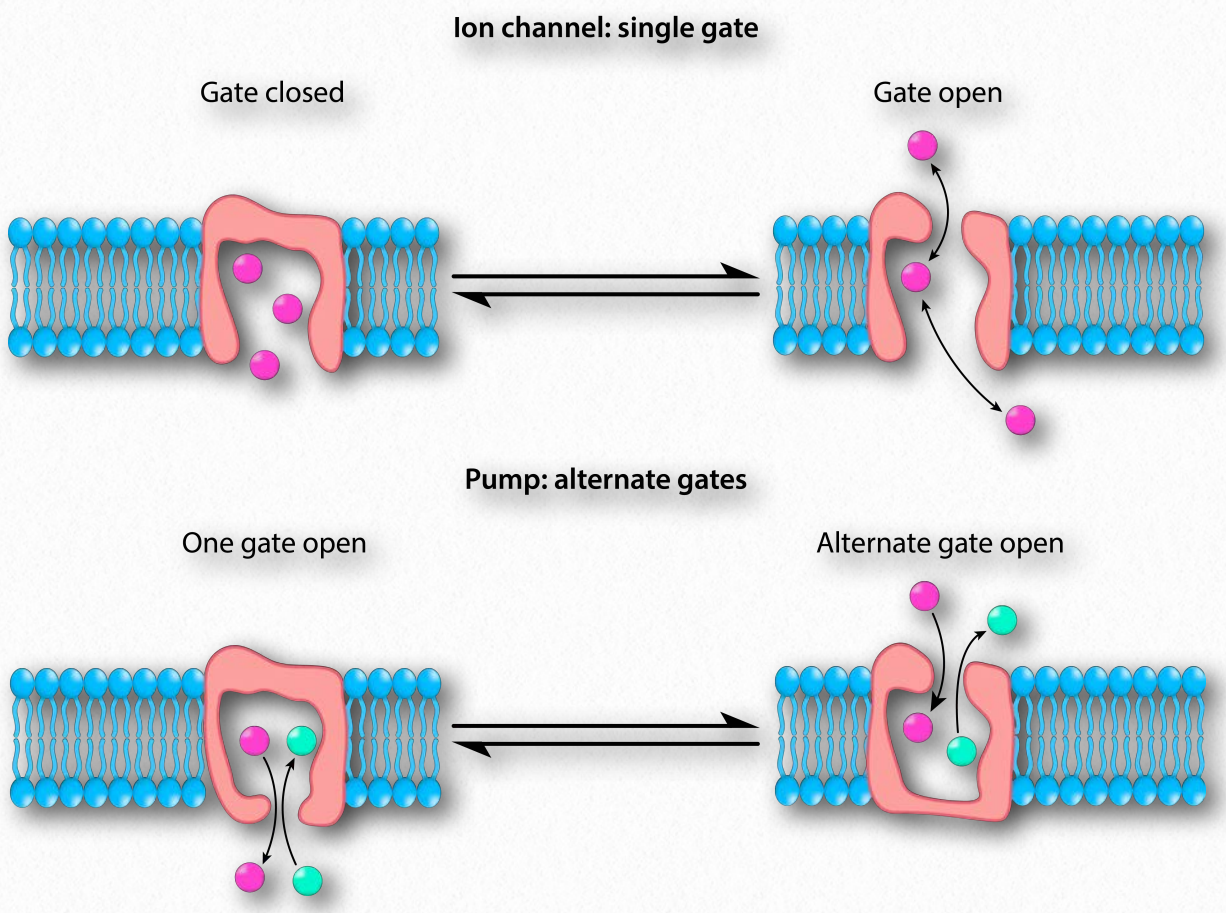

Figure 3.30 - Two types of ion channel - single and double gates

Image by Pehr Jacobson

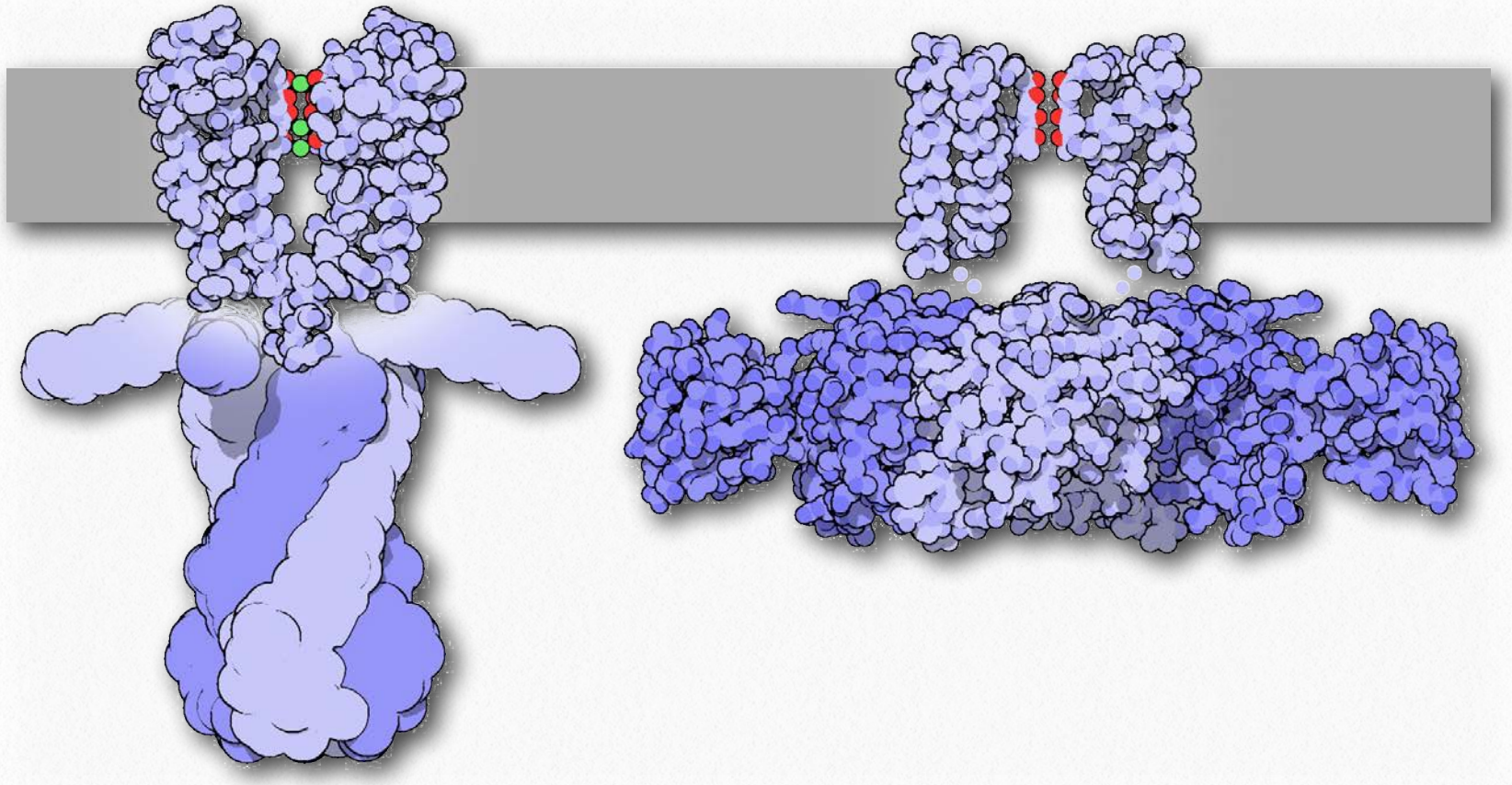

Figure 3.31 - **A potassium channel closed (left) and open (right)**

Wikipedia

Control mechanisms

Ion channels are controlled by mechanisms that include voltage, ligands, light, temperature, and mechanical deformation (stretch activated). Ligand-gated ion channels (LGICs) are transmembrane proteins which open to selectively allow ions such as Na^+, K^+, Ca^{++}, or Cl^- to pass through the membrane in response to the binding of a ligand messenger.

Sound waves cause mechanical deformation of hair cells in the ear. This results in the opening of ion channels and initiation of a nerve signal to the brain.

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Sodium ion channels in the tongue for sugar receptors open in response to binding of sucrose, allowing sodium concentration in the nerve cell to increase and initiate a nerve signal to the brain. In this case, the default for the gate is to be closed and it opens in response to binding of a ligand (sucrose).

In light sensing cells of the eye, calcium gates are open by default, but stimulation by light causes them to close, triggering a series of events that result in a signal being sent the brain about the perception of light. Thus, in this case, the stimulus (light) causes an open channel to close.

Moving the other direction, nerve signals originating in the brain travel to muscle tissue and through a complicated set of exchanges, result in the opening of calcium gates of muscle cells, increasing the concentration of calcium and stimulating muscular contraction (see HERE).

Voltage gated channels are essential for transmission of nerve signals, a process discussed in more depth HERE.

Ion movement through channels

The ability of ion channels to select against ions too large is intuitive - the size of the opening in the ion channel simply isn't big enough for a larger ion to fit through the opening. Potassium, for example, passes through sodium channels rarely because the opening is too small.

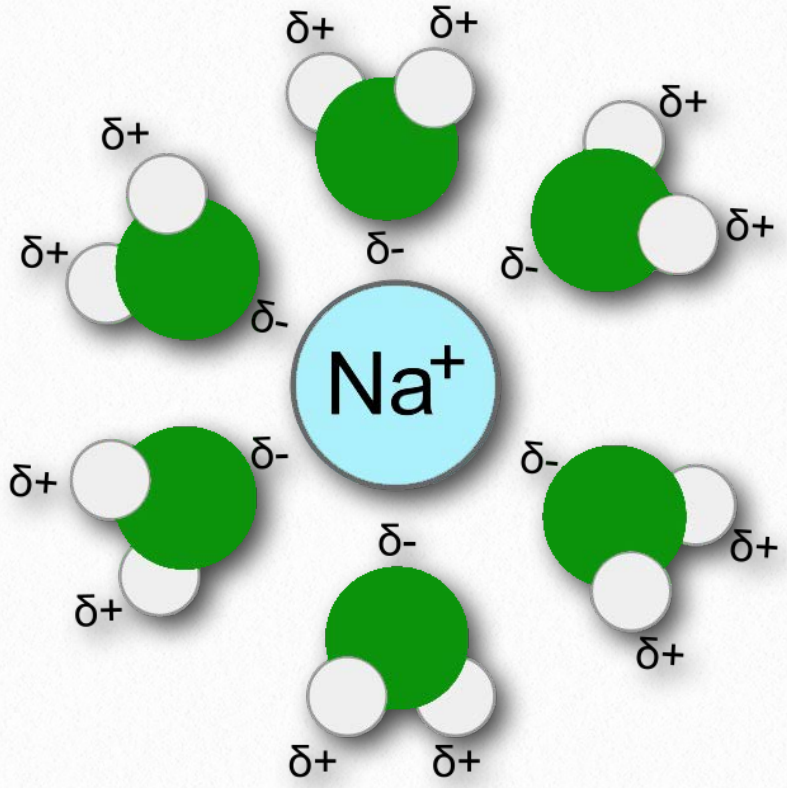

Figure 3.32 - Sodium surrounded by water molecules in a hydration shell

Potassium channels that are selective for potassium ions must be big enough to allow potassium to enter, but if size were the only selection means, then sodium ions would also readily pass through potassium channels, since sodium ions (0.95 Å) are smaller than potassium ions (1.33 Å). In order for potassium channels to select against sodium ions and favor potassium ions, other considerations come into play.

Hydration shell

To understand this unique selectivity, it is important to understand how ions move through channels. Before an ion can pass through a channel, it must first be dissociated from (stripped of) the water molecules in its hydration shell - water molecules surrounding ions in aqueous solutions (Figure 3.32). This process requires an input of energy. The initial energy required to strip the water molecules from the hydration shell has been compared to the activation energy of an enzymatic reaction.

Comparable to enzymes

Just as enzymes lower the activation energy of enzymatic reactions and thus allow them to more readily occur, so too do channel proteins

lower the energy requirements for a molecule to traverse a lipid bilayer. In the absence of the channel protein, the dehydration energy is mostly prohibitive for most polar molecules to occur, so very few make it across the lipid bilayer without the channel protein. This is why ion channel/transport proteins are so important to the cell.

After the water has been stripped, the ion can pass through the channel and when it arrives at the other side of the channel, the diffusing ion becomes rehydrated, thus regaining the energy that was required initially to strip away the water molecules from the ion.

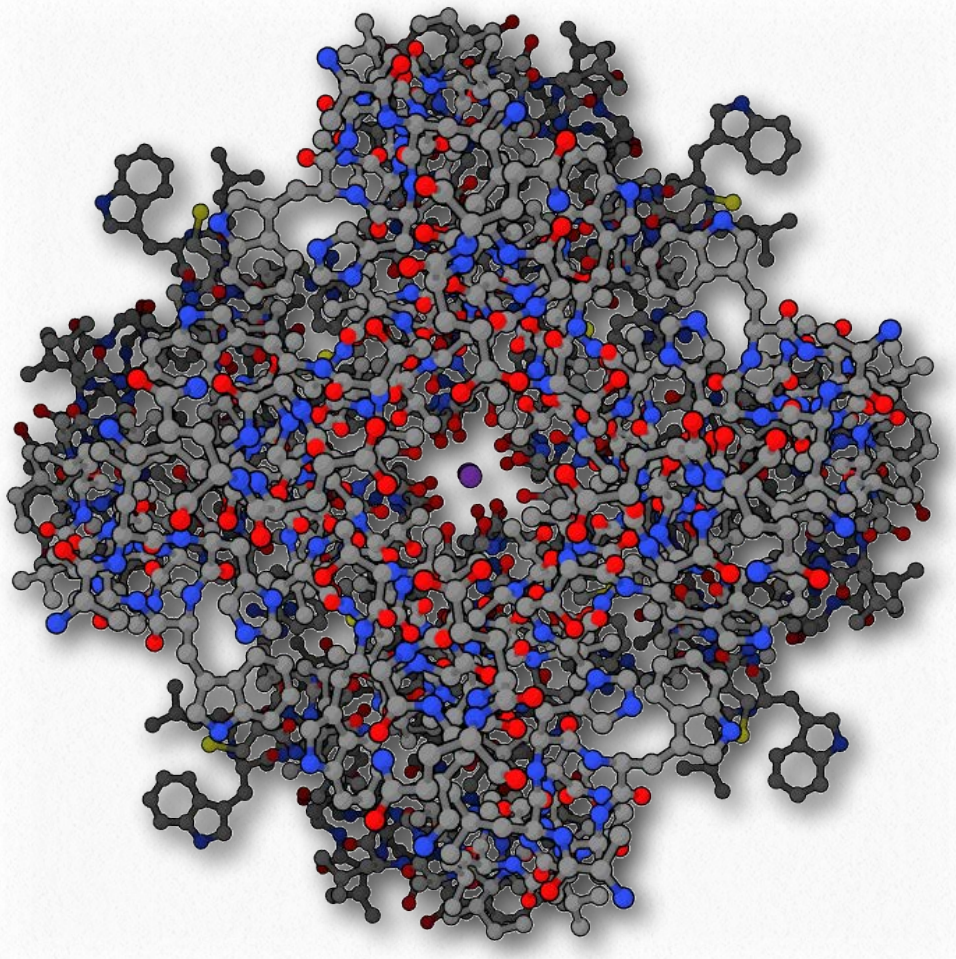

Figure 3.33 - A potassium ion (center) transiting the potassium channel

Selectivity of the potassium channel

The potassium channel (Figure 3.33) uses the dimensions of the potassium ion precisely to shepherd it through the channel. The sodium ion, which has different dimensions has a more difficult time making it through the channel despite its smaller size. The reason this is rooted in the energy required for dehydration.

For potassium ions, after the water has been stripped off, precisely positioned carbonyl groups along the channel help to stabilize the ion as it moves. The sodium ion, on the other hand is too small and does not make efficient connections with carbonyl groups and thus has a more difficult path. Because of this, the energy difference between dehydration and rehydration of a sodium ion in a potassium channel is energetically unfavorable (requires net input of energy) but the same process for a potassium ion is energetically favorable (results in a net gain of energy).

Energy factor

Thus the selection in favor of potassium and against sodium ions in a potassium channel is based on energy, not physical size, whereas in

Movie 3.1 - Gramicidin A

Wikipedia

Gramicidin

Gramicidins (Movie 3.1) are antibiotic polypeptides synthesized by the soil bacterium known as *Bacillus brevis.* These small pentadecapeptides (15 amino acids) are synthesized by the bacterium to kill other bacteria.

When released by the *Bacillus brevis*, the gramicidins insert themselves in the membranes of Gram positive bacteria and allow the movement of sodium ions into the target cells, ultimately killing them. Gramicidins can also cause hemolysis in humans so they cannot be used internally, but instead are used topically.

the selection of sodium ions over potassium ions in a sodium channel, size is the primary consideration.

Ion balance

The movement of ions across a lipid bilayer is tightly regulated, and with good reason. Maintaining a proper balance of ions inside and outside of cells is important for maintaining osmotic balance. It is also important inside and outside of organelles like the mitochondria and chloroplasts for energy generation. If the ionic balance of a cell is sufficiently disturbed by an uncontrolled ionophore, a cell may die.

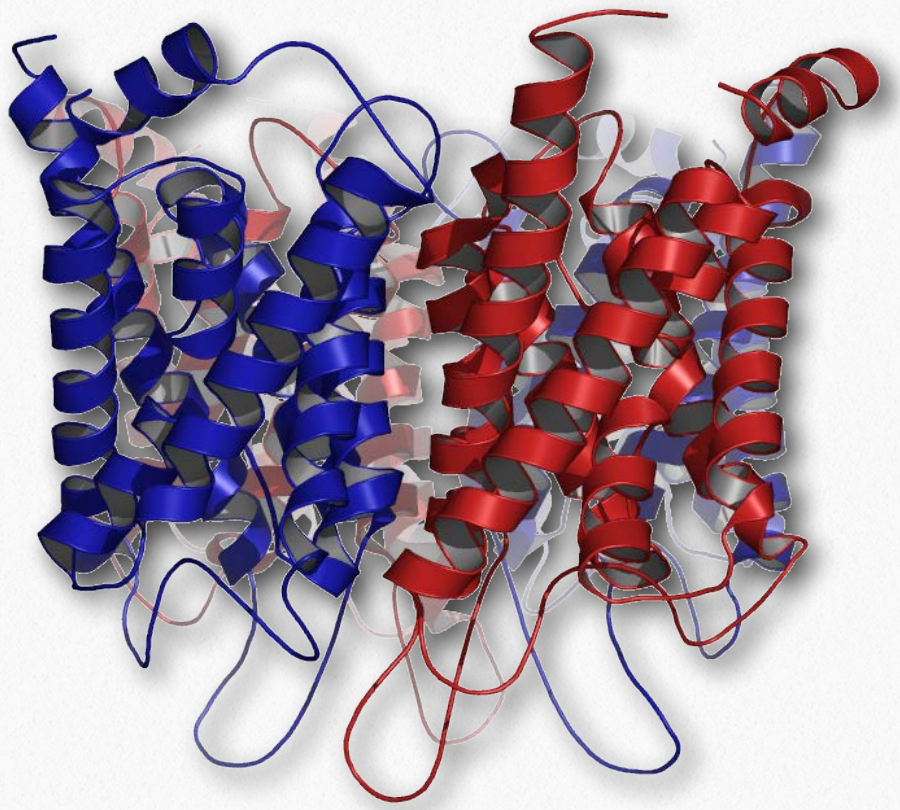

Figure 3.34 - View of aquaporin from the side

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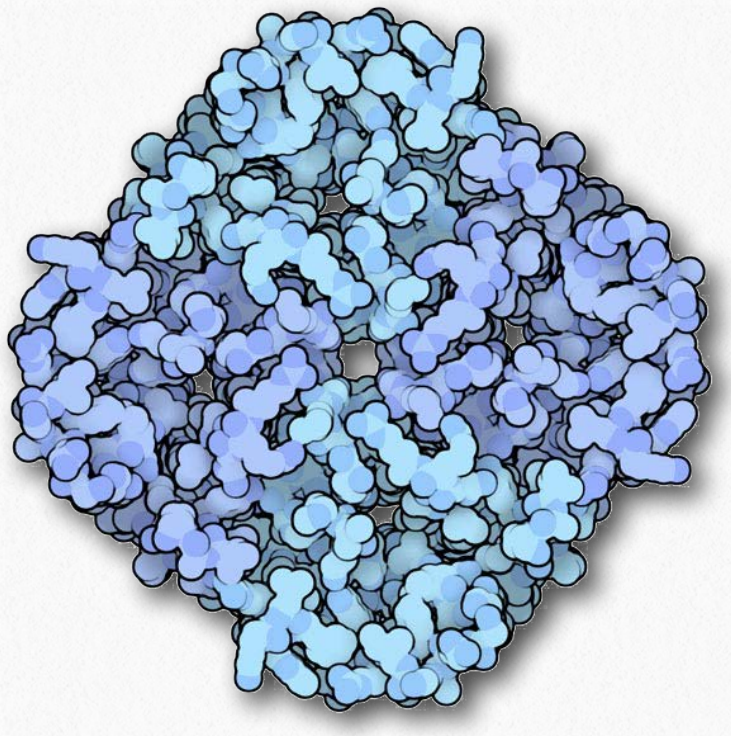

Figure 3.35 - View of aquaporin from the top

Wikipedia

Aquaporins

Aquaporins are pore-containing integral membrane proteins that selectively permit passage of water molecules in and out of the cell, while preventing ions and other solutes from moving (Figures 3.34 & 3.35). Some aquaporins called aquaglyceroporins, also transport other small uncharged entities, such as glycerol, ammonia, urea, and CO_2, across the membrane,. The water pores are completely impermeable to charged molecules, such as protons, which is important for the preserving the membrane's electrochemical potential difference.

Porins

Porins are proteins containing a β-barrel structure that crosses the cell membrane/ wall and acts as a pore/channel through which specific molecules diffuse. Porins are found in the outer membrane of Gram-negative bacteria and some Gram-positive bacteria, mitochondria, and chloroplasts.

Porins typically transport only one group of molecules or, in some cases, one specific molecule. Antibiotics, such as β-lactam and fluoroquinolone pass through porins to reach the cytosol of Gram negative bacteria. Bacteria may develop resistance to these antibiotics when a mutation occurs to the porin involved that results in exclusion of the antibiotics that would otherwise pass through.

Transporter proteins

Not all facilitated transport occurs through ion channel proteins. Transporter proteins, as noted earlier (HERE and Figure 3.27) facilitate movement of materials across a lipid bilayer, but are slower than ion channels. Figure 3.36 illustrates a transporter protein in action. As can be seen, transporter proteins rely on a specific receptor site for proper recognition of the molecule to be moved.

Binding of the proper molecule causes a conformational change in the shape of the protein (an eversion) which results in a flipping of the open side of the protein to the other side of the lipid bilayer. In this way, the molecule is moved. Like ion channels, transporter proteins facilitate movement of materials in ei-

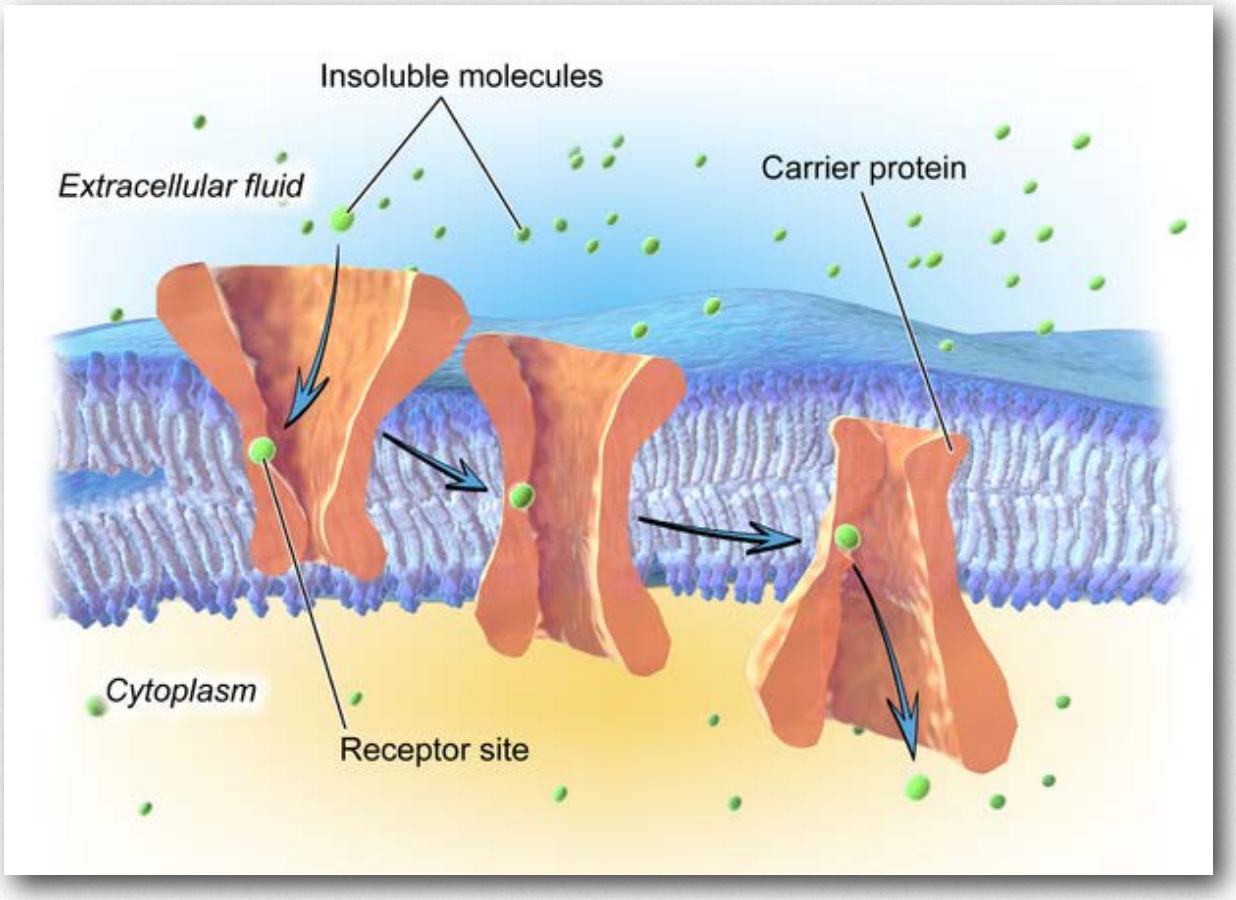

Figure 3.36 - Facilitated diffusion with a transporter protein
Wikipedia

ther direction, driven only by the concentration difference between one side and the other.

Active transport

All of the transport mechanisms described so far are driven solely by a concentration gradient - moving from higher concentrations in the direction of lower concentrations. These movements can occur in either direction and, as noted, result in equal concentrations on either side of the bilayer, if allowed to go to completion. Many times, however, cells must move materials against a concentration gradient and when this occurs, another source of energy is required. This process is known as active transport.

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A good definition of active transport is that in active transport, at least one molecule is being moved against a concentration gradient. A common, but not exclusive, energy source is ATP (see Na^+/K^+ ATPase), but other energy sources are also employed. For example, the sodium-glucose transporter uses a sodium gradient as a force for actively transporting glucose into a cell. Thus, it is important to know that not all active transport uses ATP energy.

Na^+/K^+ ATPase

An important integral membrane transport protein is the Na^+/K^+ ATPase antiport (Figures 3.37 and 3.38), which moves three sodium ions out of the cell and two potassium ions into the cell with each cycle of action. In each case, the movement of ions is against the concentration gradient. Since three positive charges are moved out for each two positive charges moved in, the system is electrogenic.

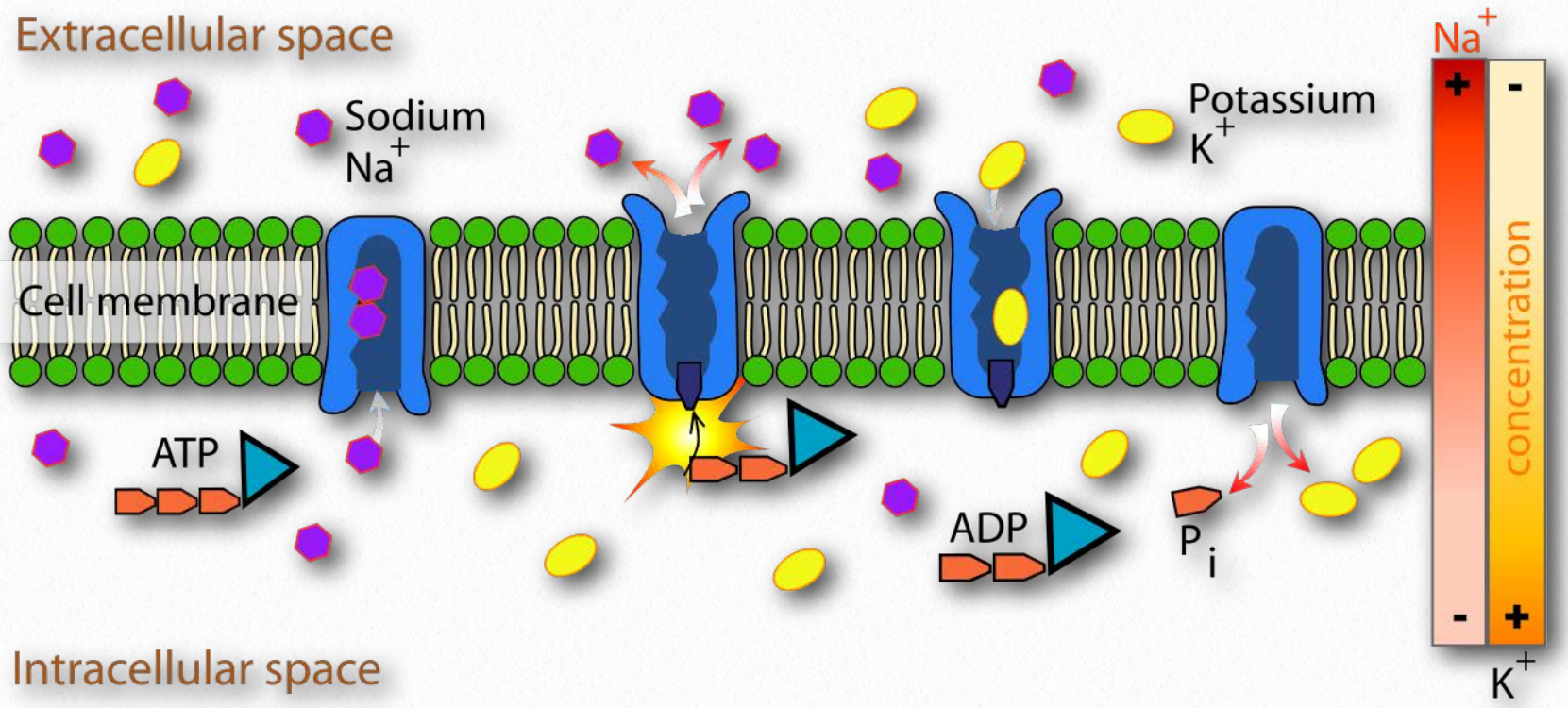

Figure 3.37 - An overview of active transport by the Na^+K^+ ATPase

The protein uses the energy of ATP to create ion gradients that are important both in maintaining cellular osmotic pressure and (in nerve cells) for creating the sodium and potassium gradients necessary for signal transmission. Failure of the system to function results in swelling of the cell due to movement of water into the cell through osmotic pressure. The transporter expends about one fifth of the ATP energy of animal cells. The cycle of action occurs as follows:

1. Pump binds ATP followed by binding of 3 Na^+ ions from cytoplasm of cell

2. ATP hydrolysis results in phosphorylation of aspartate residue of pump. ADP is released

3. Phosphorylated pump undergoes conformational change to expose Na^+ ions to exterior of cell. Na^+ ions are released.

4. Pump binds 2 extracellular K^+ ions.

5. Pump dephosphorylates causing it to expose K^+ ions to cytoplasm as pump returns to original shape.

6. Pump binds 3 Na^+ ions, binds ATP and releases 2 K^+ ions to restart process

The Na^+/K^+ ATPase is classified as a P-type ATPase. This category of pump is notable for having a phosphorylated aspartate intermediate and is present across the biological kingdoms - bacteria, archaeans, and eukaryotes.

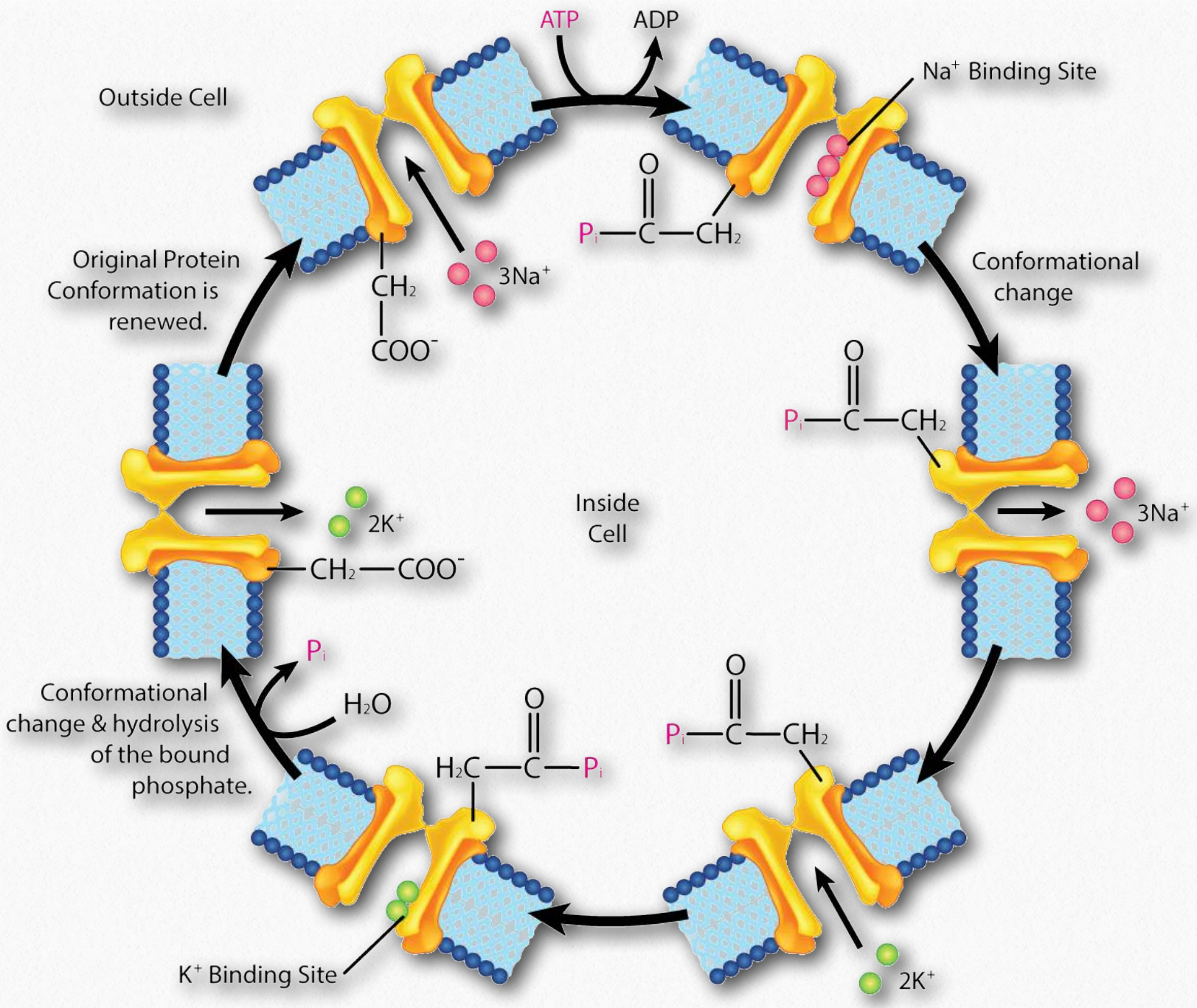

Figure 3.38 - Sequential steps in the active transport of ions by the Na^+K^+ ATPase

Wikipedia

ATPase types

ATPases have roles in either the synthesis or hydrolysis of ATP and come in several different forms.

• F-ATPases (F_1F_O-ATPases) are present in mitochondria, chloroplasts and bacterial plasma membranes and are the prime ATP synthesizers for these systems. Each uses a proton gradient as its energy source for ATP production. Complex V of the mitochondrion is an F-type ATPase.

• V-ATPases (V_1V_O-ATPases) are mostly found in vacuoles of eukaryotes. They utilize energy from ATP hydrolysis to transport solutes and protons into vacuoles and lysosomes, thus lowering their pH values.

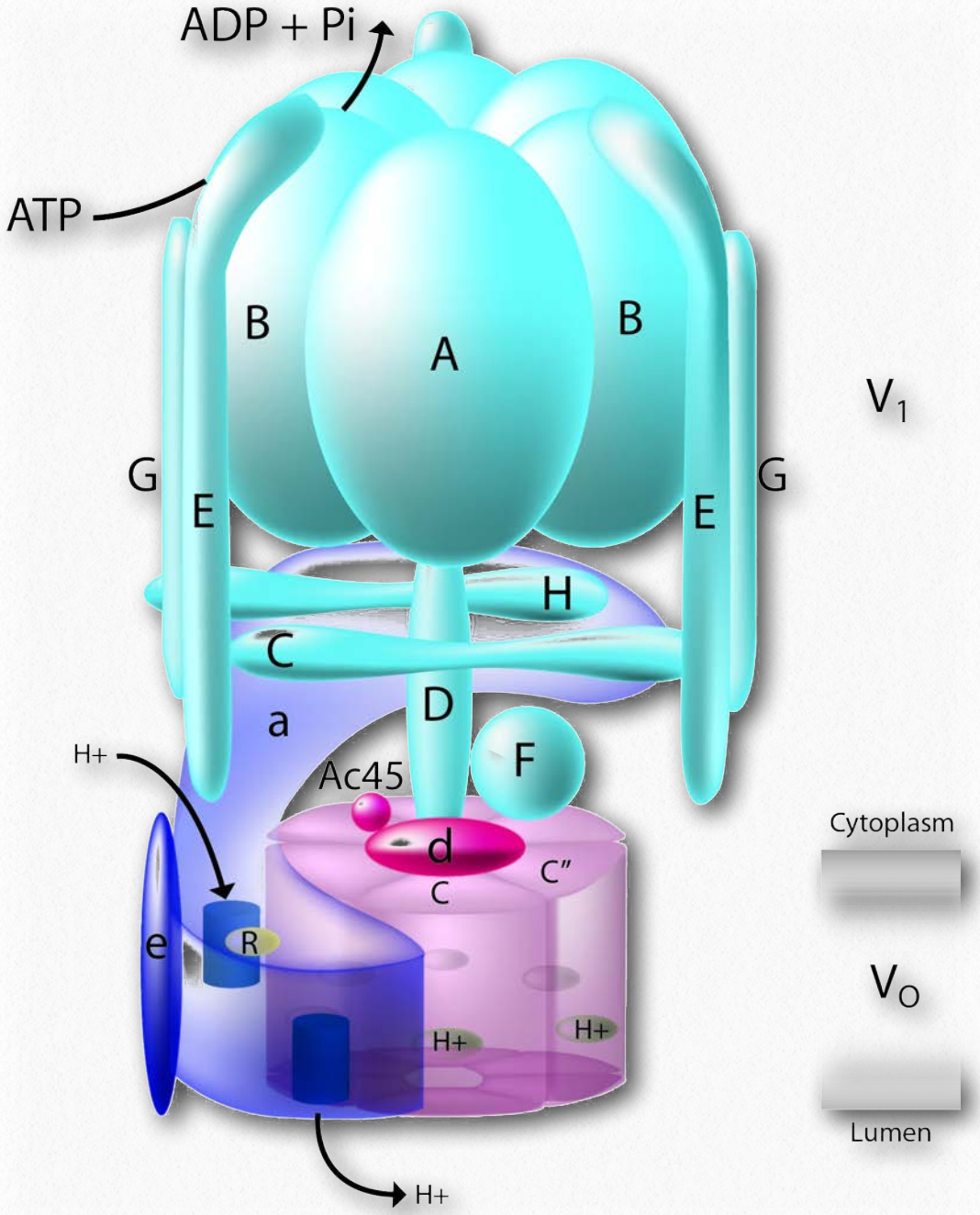

Figure 3.39 - Schematic structure of V-ATPases
Wikipedia

The V-type and F-type ATPases are very similar in structure. The V-type (Figure 3.39) uses ATP to pump protons into vacuoles and lysosomes, whereas F-types use proton gradients of the mitochondria and chloroplasts to make ATP.

• A-ATPases (A_1A_O-ATPases) are found in archaeans and are similar to F-ATPases in function.

• P-ATPases (E_1E_2-ATPases) are in bacteria, fungi and in eukaryotic plasma membranes and organelles. They transport a diversity of ions across membranes. Each has a common mechanism of action which include autophosphorylation of a conserved aspartic acid side chain within it. Examples of P-type ATPases include the Na+/K+ ATPase and the calcium pump.

• E-ATPases are enzymes found on the cell surface. They hydrolyze a range of extracellular nucleoside triphosphates, including ATP.

Nerve transmission

Now that you have seen how the Na^+/K^+ ATPase functions, it is appropriate to discuss how nerve cells use ion gradients created with it to generate and transmit nerve signals. Neurons are cells of the nervous system that use chemical and electrical signals to rapidly transmit information across the body (Figure 3.40). The sensory nerve system links receptors for vision, hearing, touch, taste, and smell to the brain for perception. Motor neurons run from the spinal cord to muscle cells. These neurons have a cell body and a very long, thin extension called an axon, that stretches from the cell body in the spinal cord all the way to the muscles they control. Nerve impulses travel down the axon to

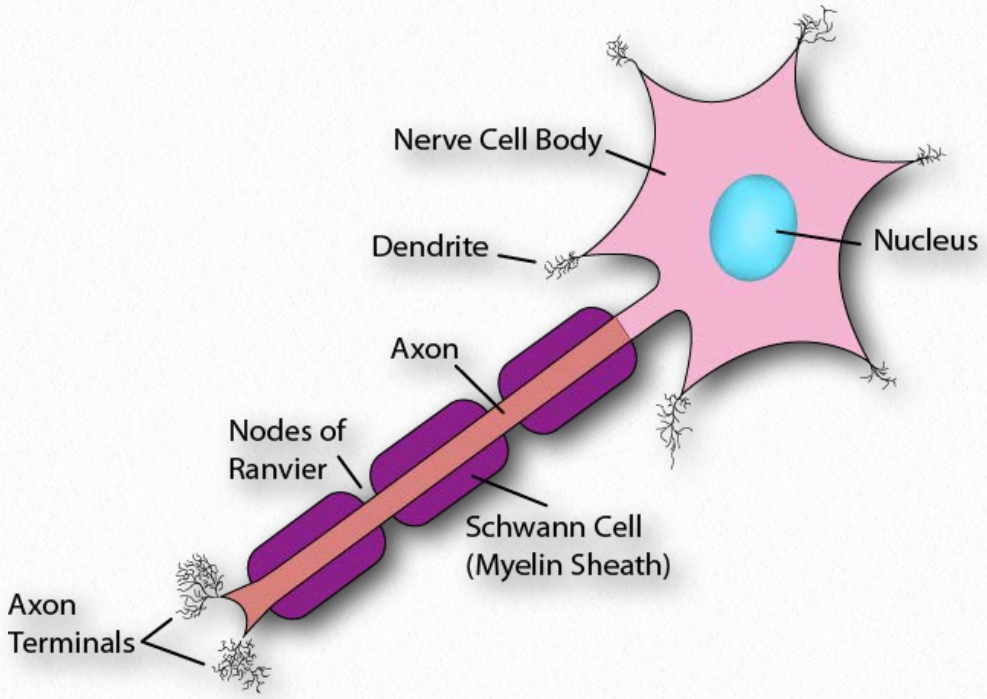

Figure 3.40 - Anatomy of a nerve cell

Image by Pehr Jacobson

the neuron releases neurotransmitters that exit the nerve cell and travel across the junction to a recipient cell where a response is generated. That response may be creating another nerve signal, if the adjacent cell is a nerve cell or it may be a muscular contraction if the recipient is a muscle cell (Figure 3.41).

stimulate muscle contraction.

Signals travel through neurons, ultimately arriving at junctions with other nerve cells or target cells such as muscle cells. Note that neurons do not make physical contact with each other or with muscle cells. The tiny space between two neurons or between a neuron and a muscle cell is called the synaptic cleft. At the synaptic cleft,

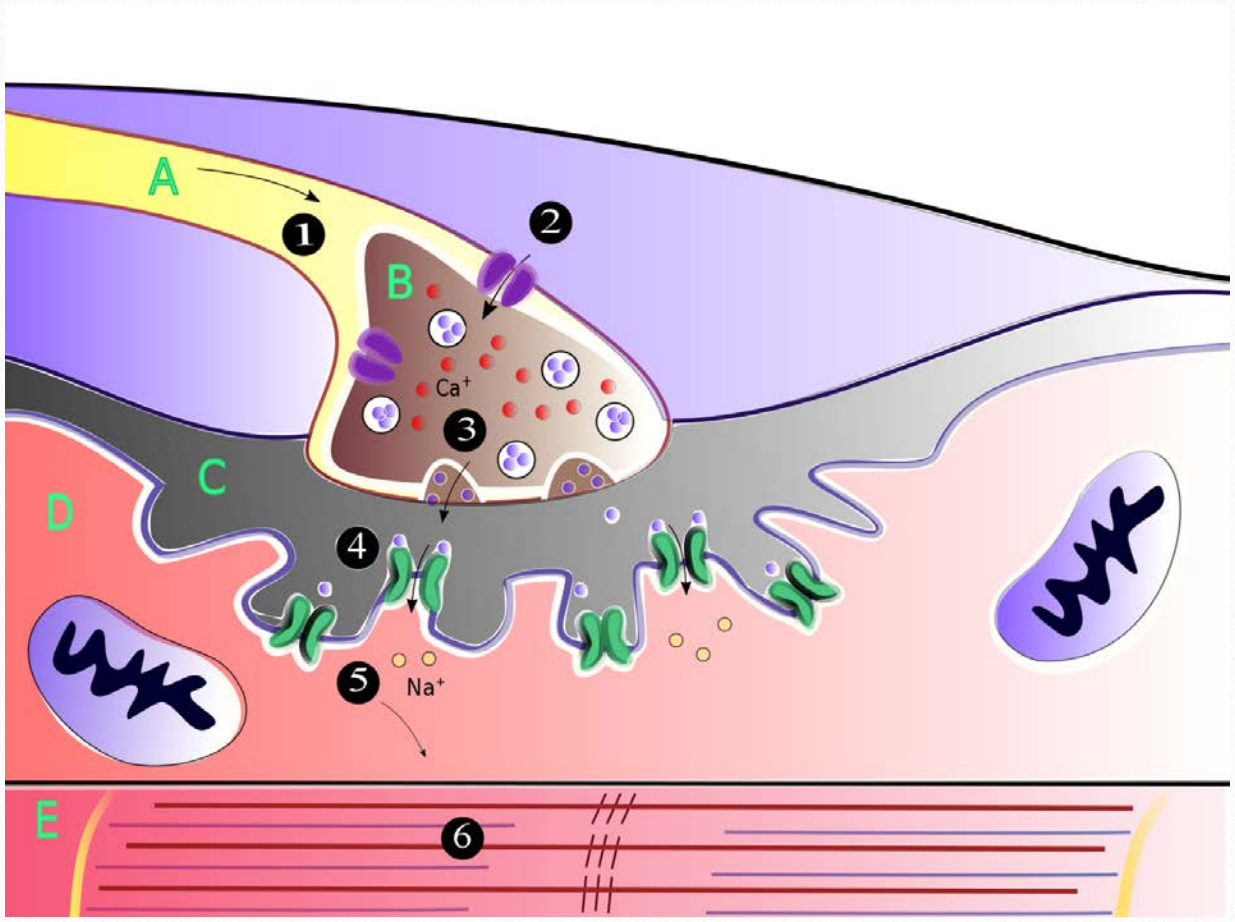

Figure 3.41 - (1) The action potential reaches the axon terminal; (2) voltage-dependent calcium gates open - calcium enters the axon terminal; (3) neurotransmitter vesicles fuse with the presynaptic membrane and release acetylcholine (ACh); (4) ACh binds to postsynaptic receptors on the sarcolemma; (5) ion channels open in response and allow sodium ions to flow into the muscle cell; (6) The flow of sodium ions into the muscle cell generates an action potential which travels to the myofibril and results in muscle contraction.

Wikipedia

In considering information movement via nerve cells, then, we will discuss two steps - 1) creation and propagation of a signal in a nerve cell and 2) action of neurotransmitters exiting a nerve cell and transiting a synaptic junction.

Signal source

Creation of a nerve signal begins with a stimulus to the nerve cell. In the case of muscle contraction, the motor cortex of the brain sends signals to the appropriate motor neurons, stimulating them to generate a nerve impulse. How is such an impulse generated?

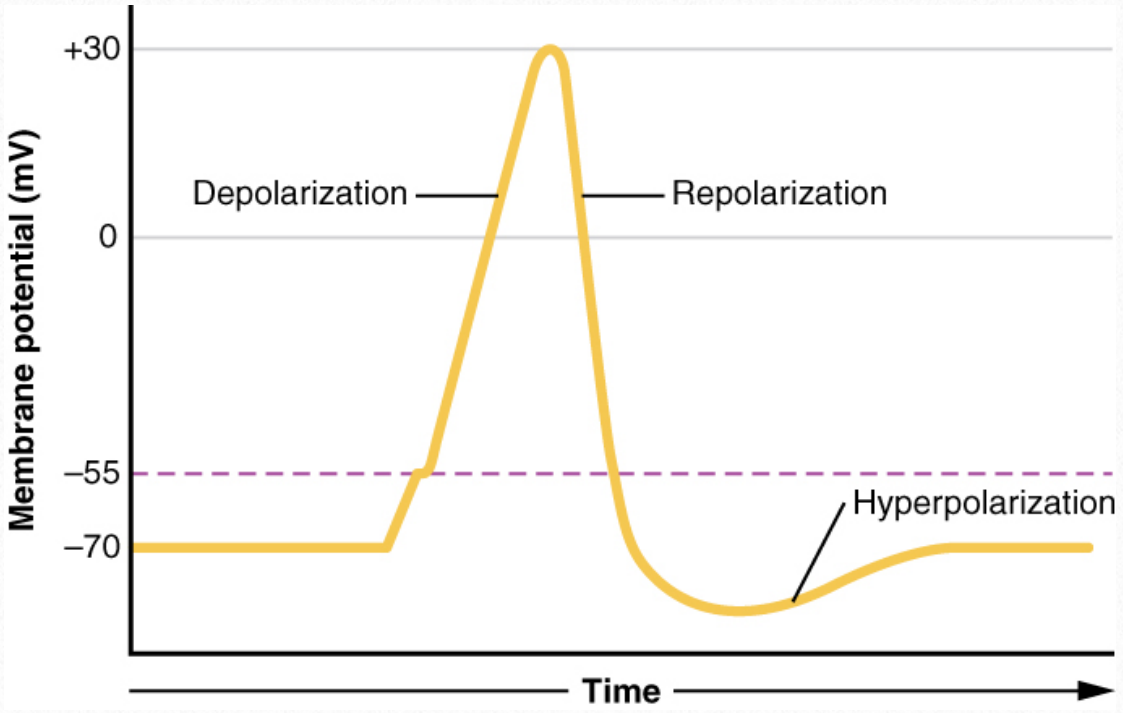

Figure 3.42 - Depolarization and repolarization of a nerve cell

Wikipedia

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Resting potential

In the unstimulated state, all cells, including nerve cells, have a small voltage difference (called the resting potential) across the plasma membrane, arising from unequal pumping of ions across the membrane. The Na^+/K^+ ATPase, for example, pumps sodium ions out of the cell and potassium ions into cells. Since three sodium ions get pumped out for every two potassium ions pumped in, a charge and chemical gradient is created. It is the charge gradient that gives rise to the resting potential.

Altering the gradients of ions across membranes provide the driving force for nerve signals. This happens as a result of opening and closing of gated ion channels. Opening of gates to allow ions to pass through the membrane swiftly changes the ionic balance across the membrane resulting in a new voltage difference called the action potential. It is the action potential that is the impetus of nerve transmission.

Initiation of signal

The signal generated by a motor neuron begins with opening of sodium channels in the membrane of the nerve cell body causing a rapid influx of sodium ions into the nerve cell. This step, called depolarization (Figure 3.42), triggers an electrochemical

signal - the action potential. Remember that the Na^+/K^+ ATPase has created a large sodium gradient, so sodium ions rush into the cell when sodium channels open. After the initial depolarization, potassium channel gates, responding to the depolarization, open, allowing potassium ions to rapidly diffuse out of the cell (remember K^+ ions are more abundant inside of the cell). This phase is called the repolarization phase and during it, the sodium gates close.

The rapid exit of potassium ions causes the voltage difference to "overshoot" the resting potential and potassium gates close. This followed by the so-called refractory period, when the Na^+/K^+ ATPase begins its work to re-establish the original conditions by pumping sodium ions out and potassium ions into the nerve cell. Eventually, the system recovers and the resting potential is re-established. The initiating end of the nerve cell is then ready for another signal.

Propagation of action potential

What we have described here is only the initiation of the nerve signal in one part of the nerve cell. For the signal to be received, the action potential must travel the entirety of the length of the nerve cell (the axon) and cause a chemical signal to be released into the synaptic cleft to get to its target. Propagating the nerve signal (action potential) in the original nerve cell is the function of all of the rest of the gated ion channels (Figure 3.43) positioned on the sides of the nerve cell. The sodium and potassium gates involved in propagation of the signal all act in response to voltage changes created by the electrochemical gradient moving down

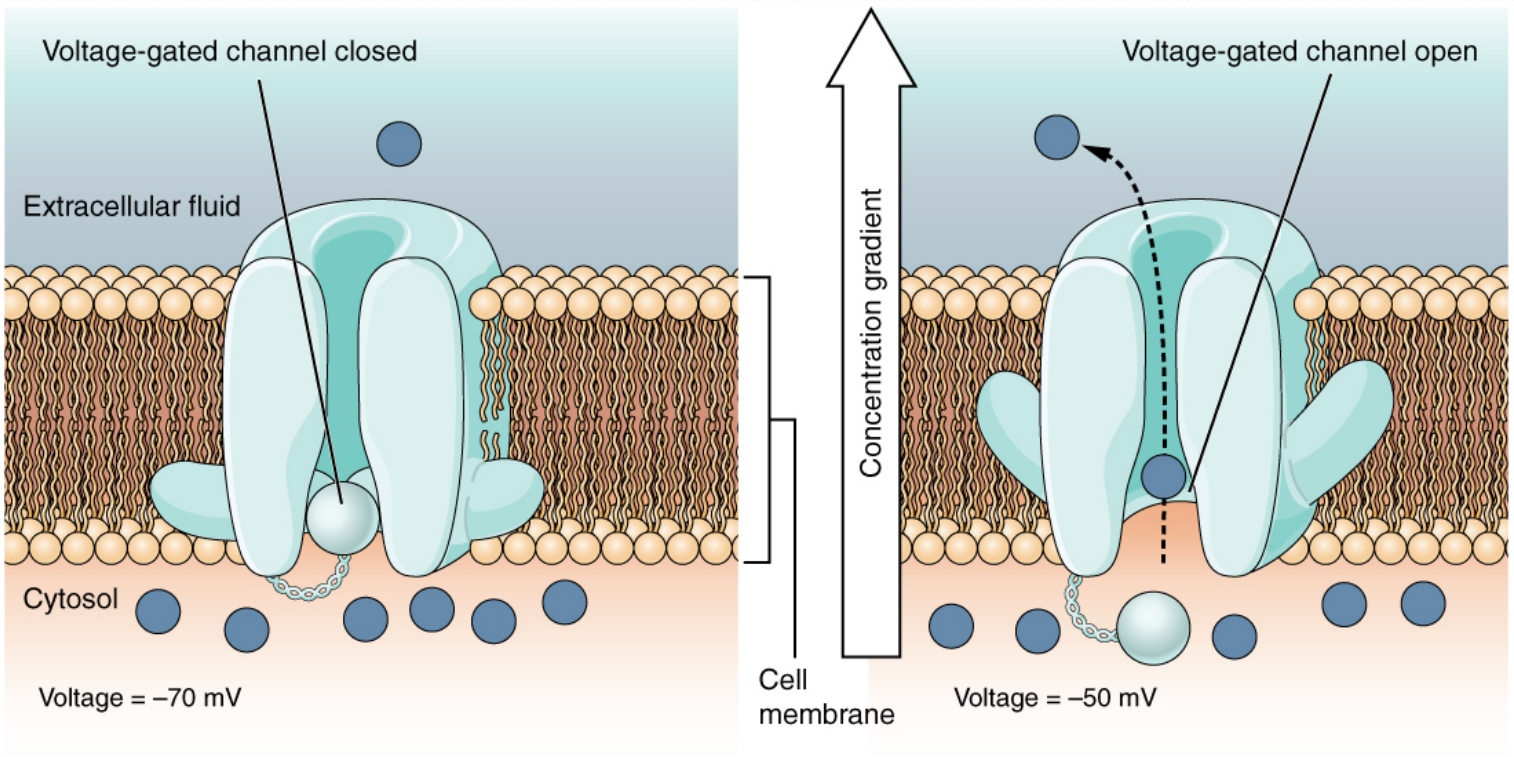


Figure 3.43 - Voltage gated ion channels

Wikipedia

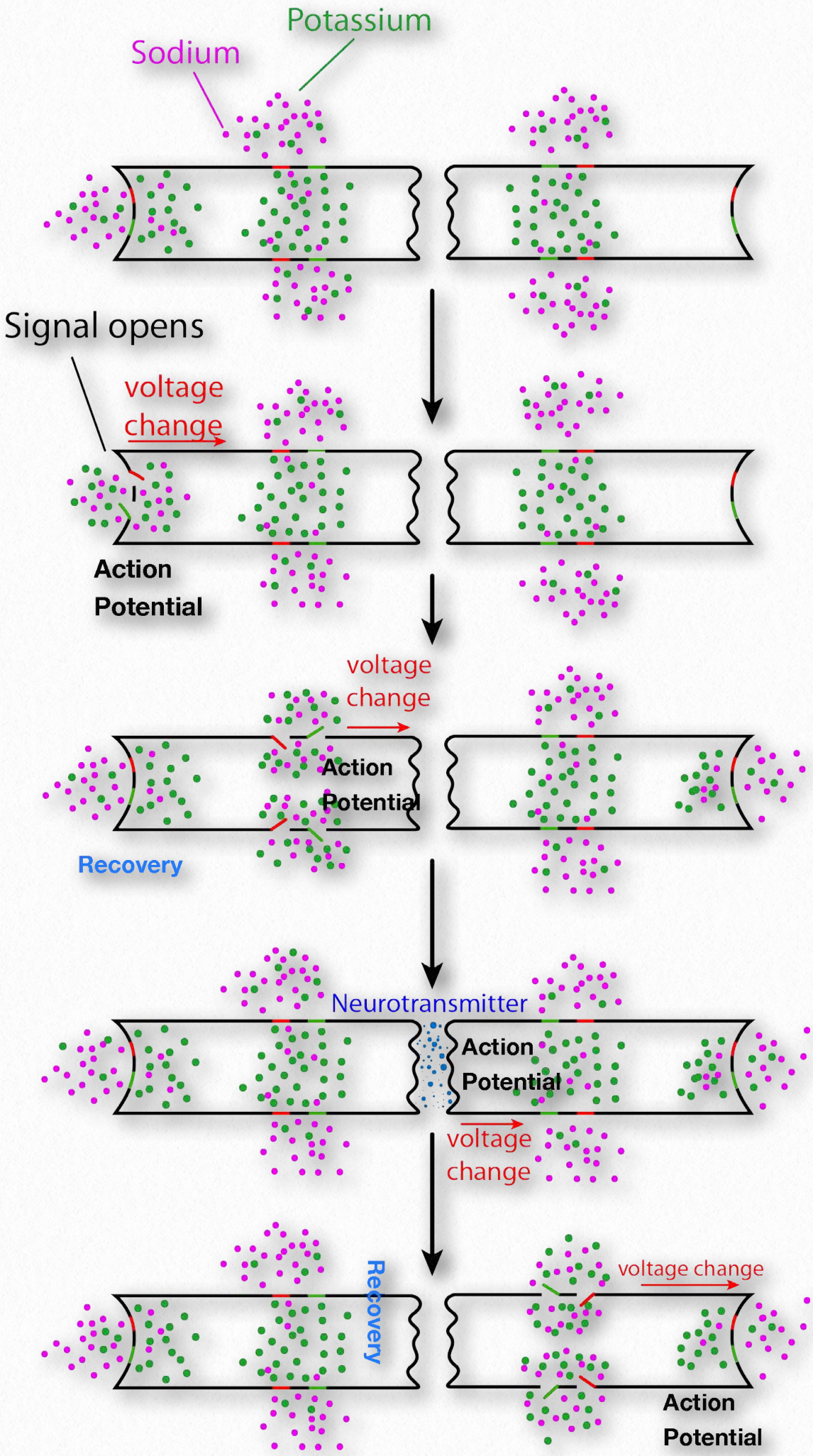


Figure 3.44 - Action potential moving across a synaptic junction of two nerve cells

Image by Pehr Jacobson

the nerve cell (Figure 3.44). Remember that opening of the initial gates at initiation of the signal created an influx of sodium ions and an efflux of potassium ions.

Moving signal

This chemical and electrical change that creates the ac-

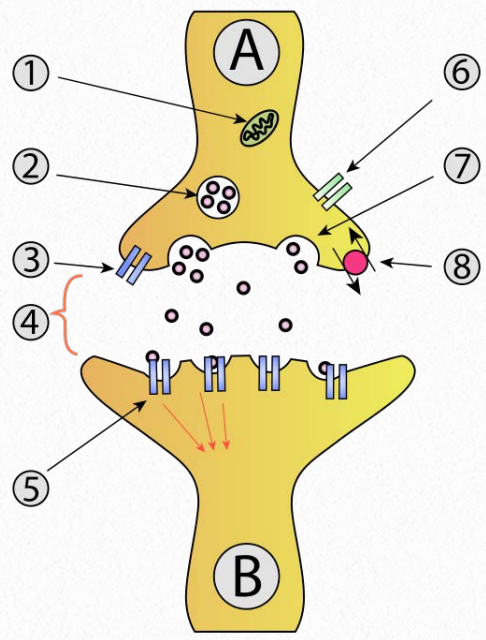


Figure 3.45 - A) Pre-synaptic neuron; B) post-synaptic neuron; 1) Mitochondria; 2) synaptic vesicle with neurotransmitters; 3) autoreceptor; 4) synapse with neurotransmitter released (serotonin); 5) postsynaptic receptors activated by neurotransmitter; 6) calcium channel; 7) exocytosis of a vesicle; 8) recaptured neurotransmitter.

Wikipedia

tion potential leaves the end of the nerve cell where it started and travels down the axon towards the other end of the nerve cell. Along the way, it encounters more sodium and potassium gated channels. In each case, these respond simply to the voltage change of the action potential and open and close, exactly in the same way the gates opened to start the signal. Thus, a rapid wave of increasing sodium ions and decreasing potassium ions moves along the nerve cell, propagated (and amplified) by gates opening and closing as the ions and charges move down the nerve cell. Eventually, the ionic tidal wave reaches the end of the nerve cell (axon terminal) facing the synaptic cleft.

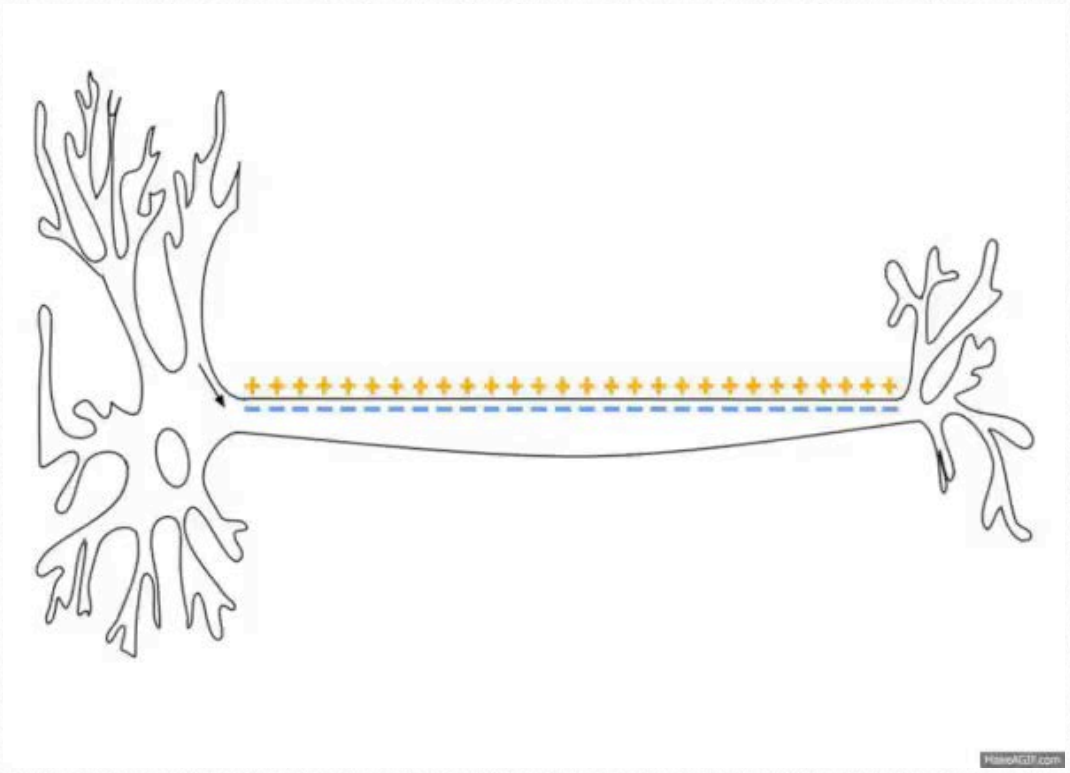
Crossing the synaptic cleft

For the signal to be received by the intended target (postsynaptic cell) from the originating neuron (presynaptic neuron), it must cross the synaptic cleft and stimulate the neighboring cell (Figure 3.45). Communicating information across a synaptic cleft is the job of neurotransmitters. These are small molecules synthesized in nerve cells that are packaged in membrane vesicles called synaptic vesicles in the nerve cell. Neurotransmitters come in all shapes and chemical forms, from small chemicals like acetylcholine to peptides like neuropeptide Y. The most abundant neurotransmitter is glutamate, which acts at over 90% of the synapses in the human brain.

Into the cleft

As the action potential in the presynaptic neuron approaches the axon terminus, synaptic vesicles begin to fuse with the membrane and their neurotransmitter contents spill into the synaptic cleft. Once in the cleft, the neurotransmitters diffuse, some of them reaching receptors on the postsynaptic cell. Binding of the neurotransmitter to the receptors on the membrane of the postsynaptic cell stimulates a response.

For motor neurons, the postsynaptic cell will be a muscle cell, and the response will be



Movie 3.2 - Movement of an action potential down a nerve cell

Wikipedia

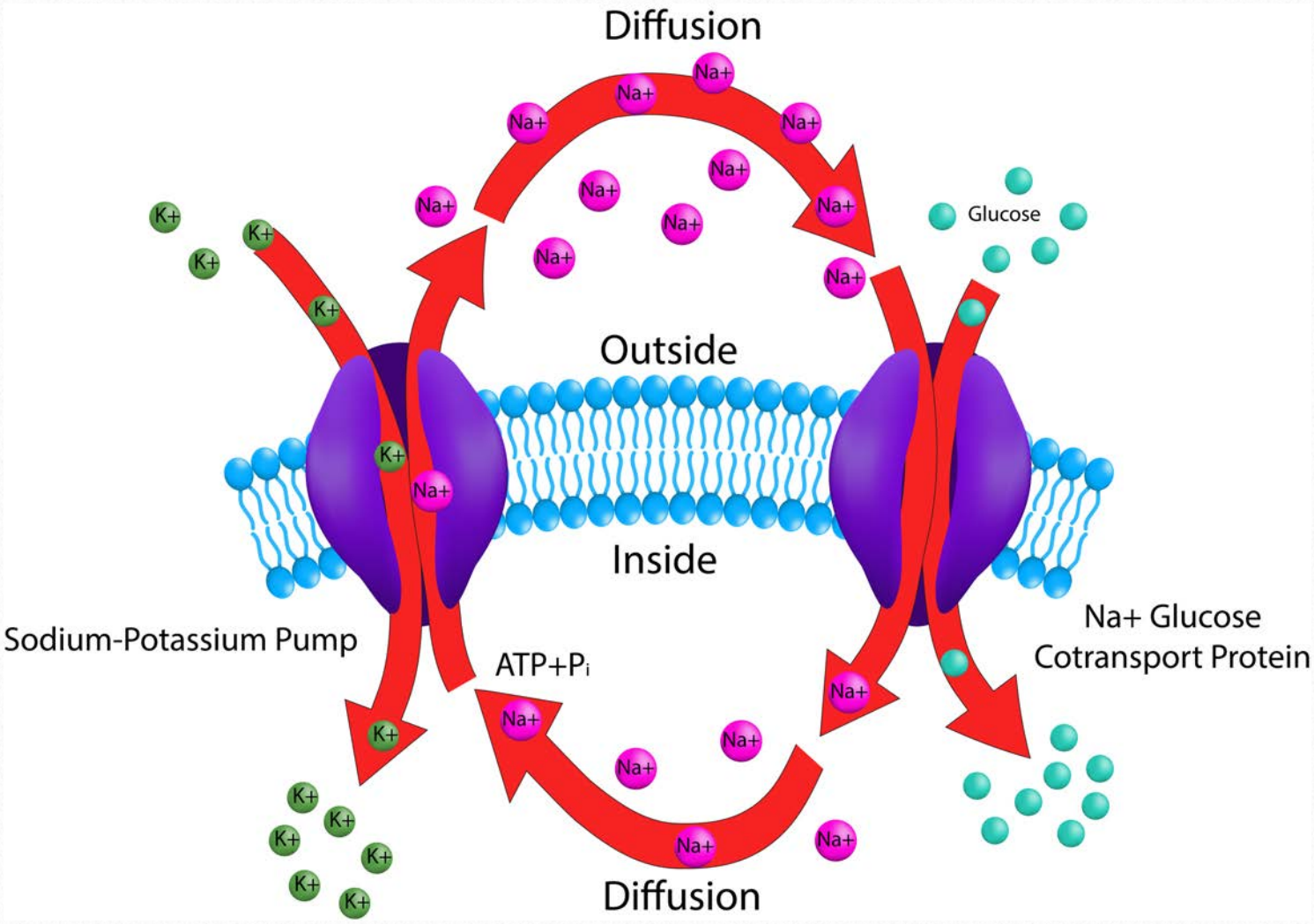


Figure 3.46 - The sodium/glucose pump (right) and the Na^+/K^+ ATPase (left). The sodium gradient generated by the Na^+/K^+ ATPase is used by the sodium/glucose pump to import glucose into the cell.

Wikipedia

muscle contraction/relaxation. At this point, the originating nerve cell has done its job and communicated its information to its immediate target. If the postsynaptic cell is a nerve cell, the process repeats in that cell until it gets to its destination.

YouTube Lectures by Kevin HERE & HERE

Na^+/glucose transporter

Absorbing nutrients from the digestive system is necessary for animal life. The sodium/glucose transport protein is an electrogenic symporter that moves glucose into intestinal cells. It is found in the intestinal mucosa and the proximal tubule of the nephron of the kidney. The sodium/glucose transport system functions in the latter to promote reabsorption of glucose. The pump works in conjunction with the Na^+/K^+ transport system. The gradient of sodium ions built up by the Na^+/K^+ pump is used as an energy source to drive movement of glucose into cells (see Figure 3.38). Use of an ion gradient established by a separate pump is known as secondary active transport. For intestinal mucosa, the pump transports glucose out of the gut and into gut cells. Later, the glucose is exported out the other side of the gut cells to the interstitial space for use in the body.

Calcium pumps

Calcium ions are necessary for muscular contraction and play important roles as signaling molecules within cells. In addition, when calcium concentrations rise too high, DNA in chromosomes can precipitate. Calcium concentration in cells is therefore managed carefully. It is kept very low in the cytoplasm as a result of action of pumps, both in the plasma membrane, which pump calcium outwards from the cytoplasm and in organelles, such as the endoplasmic reticulum (sarcoplasmic reticulum of muscle cells), which pump calcium out of the cytoplasm and into these organelles.

Opening of calcium channels, then, increases calcium concentration quickly in the cytoplasm resulting in a quick response, whether the intention is signaling or contraction of a muscle. After the response is generated, the calcium is pumped back out of the cytoplasm by the respective calcium pumps.

Some calcium pumps use ATP as an energy source to move calcium and others use ion gradients, such as sodium for the same purpose.

Na^+/Ca^{++} transporter

One calcium pump of interest uses the sodium gradient as an energy source. It is the sodium/calcium pump. This electrogenic antiport system uses sodium's movement into the cell as a driving force to move calcium out of the cell, although its direction can reverse in some circumstances. The pump is a high capacity system to move a lot of calcium quickly, moving up to 5000 calcium ions per second and is found in many tissues with many functions.

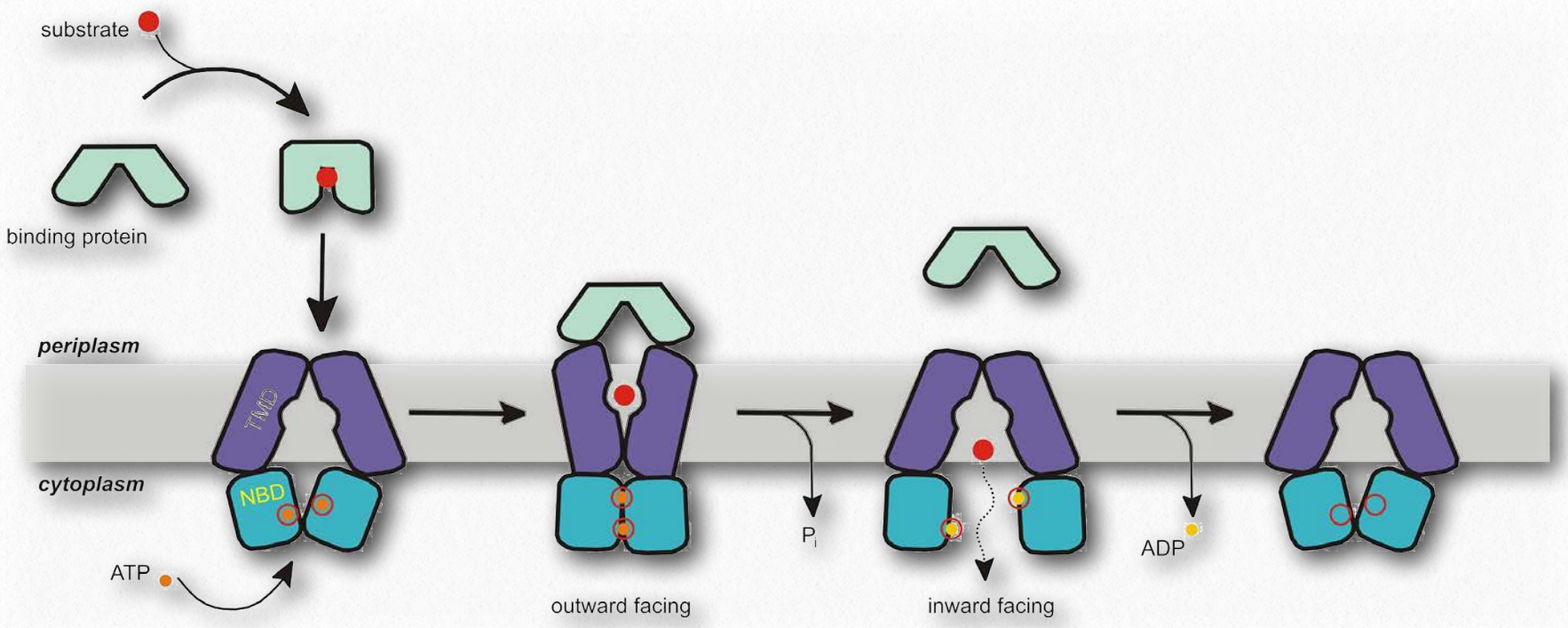


Figure 3.47 - Mechanism of an ABC importer

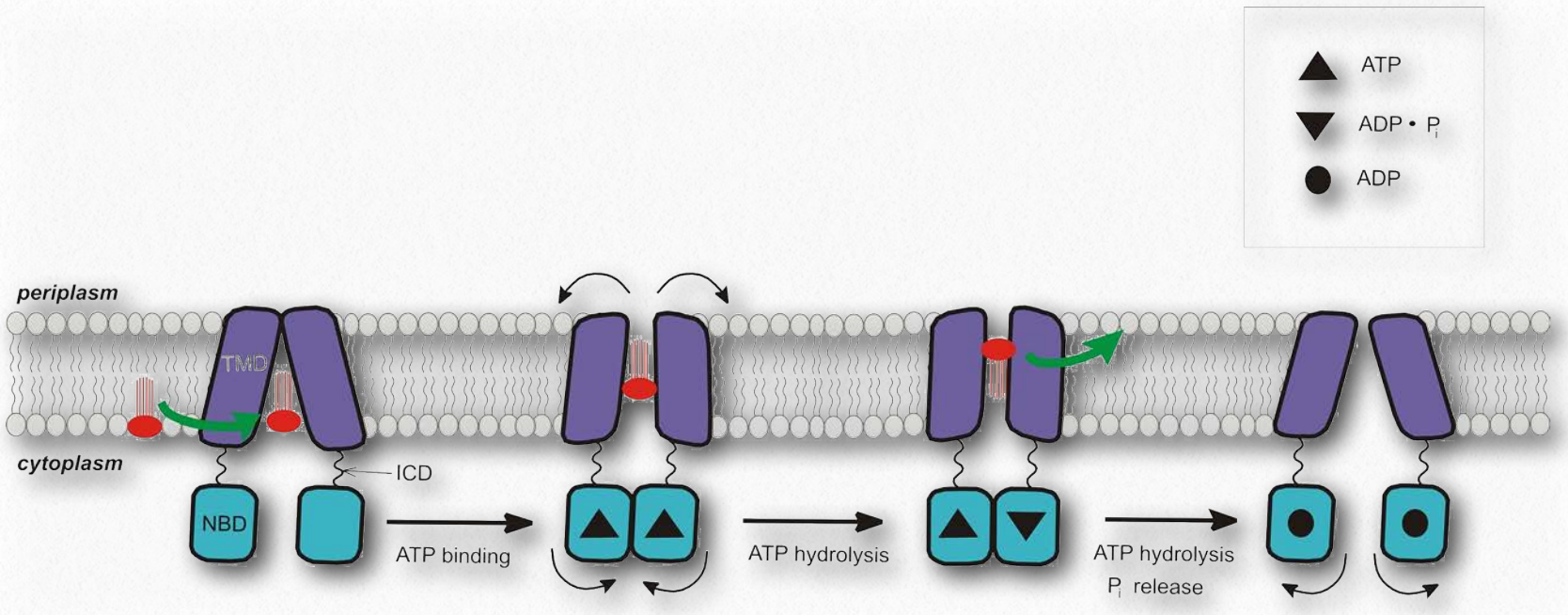


Figure 3.48 - Another view of an ABC exporter. NBD = Nucleotide Binding Domain

Digitalis

One important function of the Na^+/Ca^{++} pump occurs in heart cells. Ca^{++} is important for contraction of heart muscle. Calcium efflux from the cells is the normal operation of the pump, however, during the upstroke of the cycle, there is a large movement of sodium ions into the heart cell. When this occurs, the pump reverses and pumps Na^+ out and Ca^{++} in briefly. Since calcium helps stimulate contraction of cardiac muscle, this can help make the heart beat stronger and is the focus of the use of digitalis to treat congestive heart failure.

Digitalis blocks the sodium-potassium ATPase and interferes with the sodium ion gradient. As noted above, when the Na^+ gradient is oriented in the wrong direction, calcium is pumped in. Digitalis is therefore used to treat congestive heart failure because it increases the concentration of calcium in the heart cells, favoring more forceful beats.

ABC transporters

ABC transporters are another class of transmembrane proteins that use ATP energy to transport things against concentration gradients (Figures 3.47 & 3.48). This protein superfamily includes hundreds of proteins (48 in humans alone) and spans all extant phyla from prokaryotes to humans. These proteins function not only in membrane transport, but also in processes that include DNA repair and the process of translation.

Transport

Substances that ABC transporters move across membranes include metabolic prod-

ucts, lipids, sterols, and drugs. ABC transporters function in multi-drug resistance of many cells, and provide resistance to antibiotics in bacteria as well as resistance to chemotherapy in higher cells by exporting drugs used to treat both of these types of cells.

ABC transporters are divided into three main groups - 1) importers (prokaryotes only); 2) exporters (prokaryotes and eukaryotes), and 3) non-transporters with roles in DNA repair and translation. All ABC transport proteins have four protein domains - two that are cytoplasmic and two that are membrane bound. They are alternately open to the cytoplasmic or extracellular (or periplasmic) regions and this is controlled by hydrolysis of ATP.

Disease

ABC transporters have roles in cystic fibrosis and other inherited human diseases. They are very involved in development of resistance to multiple drugs by a diverse group of cells. ABC transporters provide multi-drug resistance by expelling drug(s) from cells. $ABCB_1$ protein, for example, pumps tumor suppression drugs out of the cell. Another ABC transporter known as

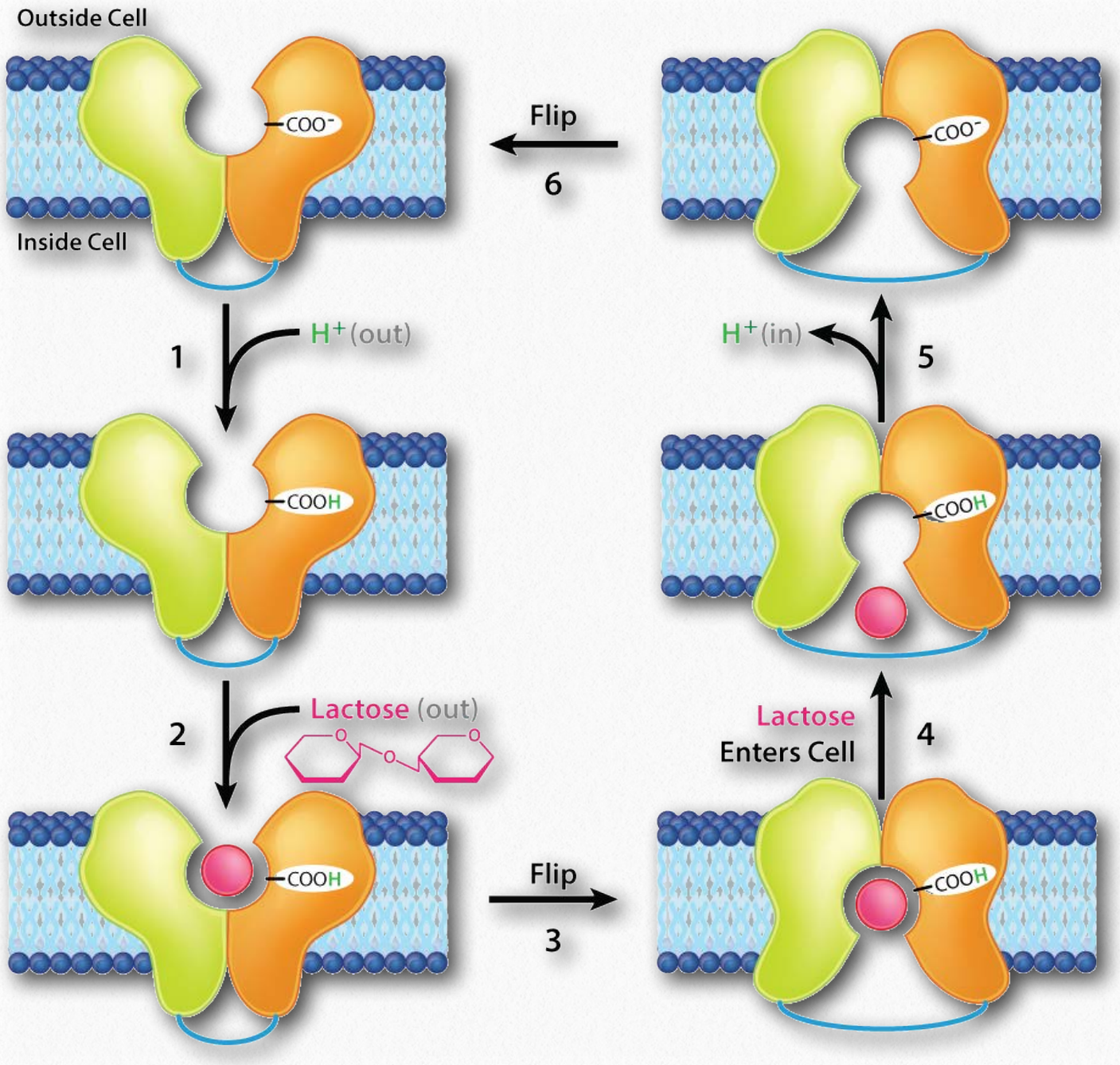


Figure 3.49 - Mechanism of action of lactose permease - Note that the proton acts by altering the charge of a carboxyl group

Image by Aleia Kim

Pgp transports organic cationic or neutral compounds.

Cystic fibrosis

Cystic fibrosis (CF) is a an autosomal recessive genetic disorder arising from mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This ABC transporter system, which moves chloride and thiocyanate ions across epithelial tissue membranes exerts its effect mostly in the lungs but the pancreas, liver, kidneys, and intestine are all also affected by it.

Function

CFTR has roles in the production of sweat, mucus, and digestive fluids. Manifestations of the disease include breathing difficulty and overproduction of mucus in the lungs. When CFTR is functional, these fluids are normally thin, but when the gene is non-functional, they become much thicker and are points of infection.

CFTR contains two ATP-hydrolyzing domains and two cell membrane-crossing domains with 6 α-helices each. It can be activated by phosphorylation by a cAMP-dependent protein kinase. The carboxyl end of CFTR is linked to the cytoskeleton by a PDZ domain.

Lactose permease

Another integral membrane protein performing active transport is lactose permease. It facilitates the movement of the sugar lactose across the lipid bilayer of the cell membrane (Figures 3.49-3.51). The transport mechanism is classified as a secondary active transport since it exploits the inwardly directed H^+ electrochemical gradient as an energy source. When lactose is transported into cells, it is broken down into its substituent monosaccharide sugars - glucose and galactose - for energy creation.

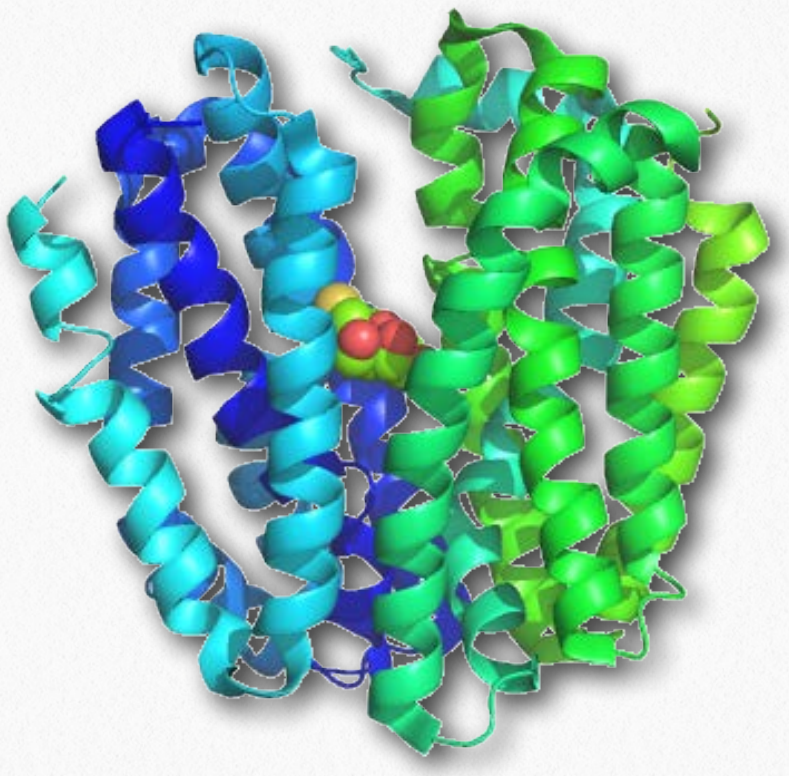


Figure 3.50 - Structure of lactose permease

Wikipedia

The enzyme catalyzing this reaction is known as lactase and deficiency of it in humans leads to lactose intolerance (see HERE).

GLUTs

GLUTs (GLUcose Transport proteins) are uniport, type III integral membrane

proteins that participate in the transport of glucose across membranes into cells. GLUTs are found in all phyla and are abundant in humans, with 12 GLUT genes. GLUT1, in erythrocytes is well-studied. Through GLUT 1, glucose enters and passes through it via facilitated diffusion at a rate that is 50,000 higher than in its absence. GLUTs of various types are found in different cells of the body. The one in red blood cells is known as GLUT 1 and has 12 membrane-spanning hydrophobic helices.

Though the structure of GLUT 1 is not known, it is speculated that the 12 helices form a chamber able to form hydrophilic bonds with glucose to facilitate its passage.

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GLUT 1 levels in erythrocytes go up as glucose levels decrease and decrease when glucose levels go down. GLUT 1 can also transport ascorbate (vitamin C) in addition to glucose in mammals (such as humans) that do not produce their own vitamin C.

Glut 4

GLUT 4 is regulated by insulin and is found primarily in adipose and striated muscle tissue. Insulin alters intracellular trafficking pathways in response to increases in blood

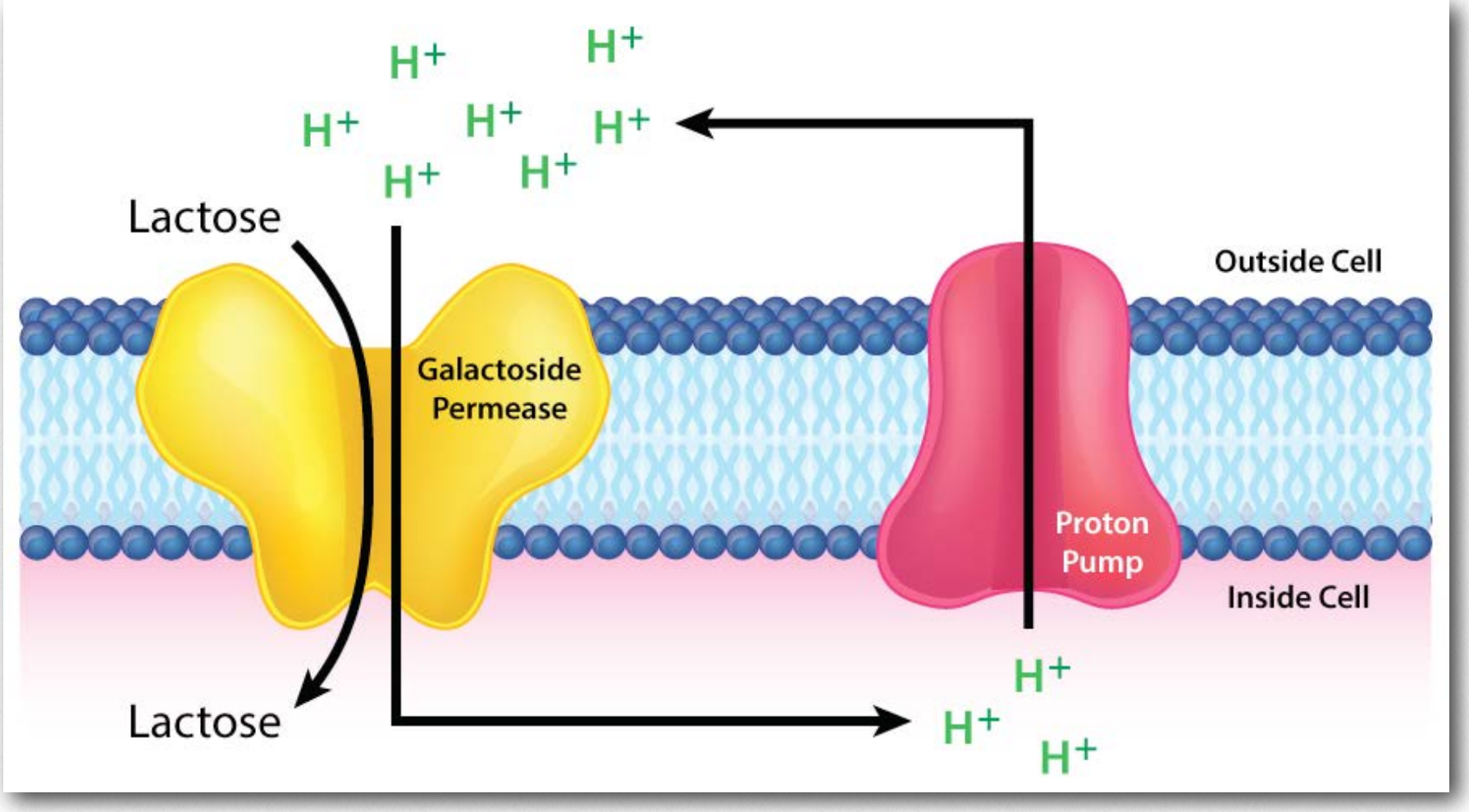

Figure 3.51 - Lactose (galactoside) permease is a secondary transporter, using a proton gradient as an energy source to pump lactose into the cell

Image by Aleia Kim

Glucose Transporters

Name	Tissue	K_M (μM)	Comments
GLUT1	All mammalian tissues	1	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15-20	Participates in insulin regulation in the pancreas; removes excess glucose from the blood in the liver
GLUT3	All mammalian tissues	1	Basal glucose uptake
GLUT4	Muscle and fat cells	5	Concentration in plasma membrane of muscles rises with endurance training
GLUT5	Small intestine	---	Fructose transport

Figure 3.52 - GLUTs found in cells

Image by Aleia Kim

sugar to favor movement of various GLUT proteins (including GLUT 4) from intracellular vesicles to the cell membrane, thus stimulating uptake of the glucose. GLUT 4 is also found in the hippocampus where, if trafficking is disrupted, the result can be depressive behavior and cognitive dysfunction.

For all of the GLUT proteins, a key to keeping the glucose in the cell is phosphorylation of it by the glycolysis enzyme, hexokinase, in the cytoplasm. Phosphorylated molecules cannot enter GLUTs and don't have an easy means of exiting the cell.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

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Distance Ed

To the tune of "*Mister Ed*"

Metabolic Melodies Website HERE

A course is a source, of course, of course
Of all of the knowledge that we endorse
A major force for better/worse is the campus Distance Ed

It's true to outsource a college course
There are a few standards to be enforced
The long and short's we reinforce the campus Distance Ed

Bridge

A classroom class meets every week the same time every day
But Distance Ed is most unique - its flexible schedule's okay

E-course is a source, of course, of course
Of online assistance for lab reports
You're not enrolled in an online course?

Then sign up for this!

"You'll love Distance Ed"

Recording by David Simmons
Lyrics by Kevin Ahern

This Song's For BB 3-5-0

To the tune of "*This Land is My Land*"

Metabolic Melodies Website HERE

It's one o'clock and
Ahern's talkin'
Henderson and
Hasselbalch and
pKa's and
Buffers I should know
This song's for BB three five oh

I hope that maybe
He'll think the way we
Wrote our answers
Wasn't crazy
I really need the
Partial credit - so
This song's for BB three five oh

It's really groovy
That it improves me
Watching lectures
In Quicktime movies
I really need to
Go and download those
Podcasts for BB three five oh

I'm feeling manic
I'm in a panic
I'd better study
My old organic
It has reactions
That I need to know
This song's for BB three five oh

I know he said it
That's why I dread it
'cause I skipped Friday's
Extra credit
'twil pro'bly haunt me
That lowly ze-ro
Grade in BB three five oh

It could be steric
Or esoteric
That carbons get so
Anomeric
I'm too hysteric
Better let it go
This song's for BB three five oh

Recording by Tim Karplus
Lyrics by Kevin Ahern