# Transport Across Membranes

One of the primary functions of the membrane is to separate the intracellular environment from its extracellular environment. This separation is crucial for the maintenance of the proper conditions for cell function. To perform this important function, the membrane must regulate what enters and leaves the cell. Processes that move substances across cell membranes can be grouped into two categories based on energy requirements: **passive transport** and **active transport** . These processes rely on the principles of energy and motion, particularly **kinetic energy** , which is the energy of particles in motion.

## Passive Transport

Passive transport does not require additional energy input from the cell. Instead, it utilizes the natural kinetic energy of particles, which drives their movement across membranes. Particles move from areas of **higher concentration** to areas of **lower concentration**, a process referred to as moving "down a concentration gradient." Examples of passive transport include **simple diffusion**, **facilitated diffusion**, and **osmosis**. You can observe diffusion by placing a drop of food coloring into a glass of water. Over time, the dye disperses throughout the liquid until it is evenly mixed. Similarly, in the body, small hydrophobic solutes like oxygen (O2) and carbon dioxide (CO2) cross the cell membrane by simple diffusion. In these processes, the particles' kinetic energy is sufficient to power their diffusion through the membrane.

#### Simple Diffusion

Simple Diffusion is the passive movement of molecules form an area of high concentration to low concentration. Simple diffusion occurs when a drop of food coloring is put in a container of water. The color molecules begin immediately to disperse to areas that are low in color concentration until the color is evenly distributed throughout the cup. In the human body, simple diffusion can also help move molecules in and out of cells. However, simple diffusion across membranes is only possible if the molecules are small and hydrophobic. This is because only hydrophobic molecules can pass easily through the lipid components of a phospholipid membrane. When molecules are large or polar, they need the assistance of proteins channels or carriers to get across the membrane.

Image by Hannah Crowder 2013

#### Factors That Affect the Rate of Diffusion

The rate at which the solute diffuses is affected by several factors.

* **Concentration gradient:** The greater the difference between the concentrations on the two sides of the membrane, the faster the rate of diffusion.
* **Temperature:** The higher the temperature, the faster molecules move. Therefore, as the temperature increases, the rate of diffusion increases.
* **Size of molecules:** Smaller molecules tend to travel further before colliding with other molecules, so diffusion rates are faster for smaller molecules.
* **Viscosity of the medium:** Viscosity is a measure of the "thickness" of the solvent (a liquid that has the ability to dissolve other substances). An increase in viscosity decreases the rate of diffusion.
* **Membrane permeability:** Since we are talking about the movement of solutes into and out of the cell, the permeability of the membrane to the solute will affect how fast solutes diffuse across the cell membrane. For example, ions and other charged molecules that are hydrophilic do not readily cross the membrane due to the hydrophobic core of the bilayer. However, by opening protein channels we can increase their permeability. Conversely, oxygen and carbon dioxide, both nonpolar molecules, can readily diffuse through the membrane.
* **Surface area:** The greater the surface area of the membrane, the faster the rate of diffusion across it. Areas in our bodies where diffusion is especially important often employ structural modifications to increase the available surface area. For example, in the lungs, the hundreds of millions of small alveoli provide a total surface area of nearly 70 square meters for gas exchange—roughly the size of a typical two-bedroom apartment in Rexburg. Similarly, in the small intestine, tiny hair-like projections called villi, along with even smaller microvilli on the epithelial cells, greatly increase the surface area for nutrient absorption. Additionally, the presence of cilia (microscopic, hair-like structures) in certain regions of the intestines can help move mucus and other substances, indirectly supporting efficient nutrient absorption. These specialized structures enable rapid diffusion by maximizing the membrane’s surface area for exchange processes.
* **Distance:** Diffusion is quite rapid over short distances but gets slower the further it goes. The time it takes for something to diffuse is proportional to the square of the distance. Therefore, if it takes one second to diffuse one centimeter, it will take 100 seconds to diffuse 10 cm and 10,000 seconds to diffuse 100 cm. So, to go 100 times further takes 10,000 times longer. In the body, diffusion is quite sufficient to cross the thin cell membrane, but to travel long distances by diffusion would be very slow. This is why we have other mechanisms, like blood circulation and motor proteins along microtubule networks for moving substances long distances.

## Facilitated Diffusion

Facilitated Diffusion is influenced by all the factors that affect the rate of diffusion for simple diffusion. However, facilitated diffusion also requires the help of a membrane protein to get molecules across. Molecules that are large, polar, or that have an electrical charge, generally are prevented from moving through the membrane (hydrophobic). However, many of these solutes need to be able to enter or leave the cell. So, how does the cell solve this dilemma? Embedded in the cell membrane are several types of proteins that pass completely through the membrane (integral membrane proteins). There are several specialized integral proteins that assist in the diffusion of solutes across the membrane. This type of diffusion is referred to as **facilitated diffusion**. Facilitated diffusion can occur in two different ways, through **channel proteins** or **carrier proteins**.

#### Channel proteins

Channel proteins resemble fluid filled tubes through which the solutes can move down their concentration gradients across the membrane. These channels are often responsible for helping ions, such as Na+, K+, Ca2+, and Cl-, cross the membranes. Even though they are open tubes, they often only allow very specific ions to pass through them. For instance, a K+ channel may allow K+ to pass through but not Na+ or Cl-. **Leak channels** are the most simple of the channels. They are not gated and tend to remain open all the time. Other channels are gated and their gates become important control points as the body regulates what can enter or leave a cell. Depending on the channel, gates will open under the influence of many different stimuli. For example, gates on channels may open or close in response to voltage differences across the membrane (**voltage-gated channels**), specific signal molecules (**ligand-gated channels**), or even stretching or compressing of the membrane (**mechanically-gated channels**).

**Leak Channels**

Image by Hannah C 2013

Perhaps the most well-known leak channel is the K+ leak channel which we will learn contributes significantly to the voltage across membranes of nerves and muscles as well as other cells. Sometimes, leak channels may be referred to as "pores" in a membrane.

**Voltage Gated Channels**

Images by JS W25

While we will ultimately introduce you to voltage gated sodium, calcium, potassium and chloride channels in the body, we will use the example of a voltage gated sodium channel above. These channels open when the membrane voltage changes, which refers to the separation of charges across the membrane. How charges get separated across a membrane will be a topic we discuss later in detail. For now, try to visualize that these charges can exert electrical forces on protein components to open or close gates.

For example, this image shows black and yellow circles extending out from the positive charges. This represents the repulsive force that one "+" charge would have on another "+" charge. Notice that in the voltage gated sodium channels we have an S4 or voltage sensing subunit that has a lot of "+" charge on it. The "+" charge on the S4 subunit is generated by the specific type of amino acids in this segment (they are positively charged). The repulsive forces on the outside of the membrane push against this S4 subunit and displace it towards the intracellular surface. This position keeps the activation gate closed.

If the amount of charge separation decreases across a membrane, we say that the "voltage" has decreased and the repulsive forces of the "+" charges are not strong enough to keep the voltage sensing subunit displaced towards the intracellular surface. The S4 subunit will move up towards the extracellular surface and this causes the activation gate to open. There is a lot more sodium on the outside of the cell than the inside, so we say that there is a "**chemical gradient**" causing sodium to diffuse into the cell. Also, the remaining repulsive forces on the outside as well as the attractive forces on the inside (negative charge) helps move sodium in. The electrical forces contributing to the movement of sodium through the channel is called the "**electrical gradient**". If more charge separation occurs again and we get more positive charge building up on the outside of the cell, the S4 subunit will displace towards the intracellular surface again and the activation gate will close. We will take a closer look at this later and we will also will discuss the role of the inactivation gate.

**Ligand-Gated Channels**

Image by HC and JS W25

Ligand-gated channels open when a ligand binds to them which causes a conformational change that opens a gate and allows a solute to enter the cell. For example, during muscle stimulation, a chemical binds to ligand-gated receptors on the muscle cell membrane. This binding causes the channel to open, allowing sodium (Na⁺) ions to enter the muscle cell, which initiates muscle contraction. Interestingly, in this example, it is the influx of sodium ions through the ligand gated channel that decreases the local voltage across the membrane. This decrease in voltage (or quantity of separated charges) will change the number of positive charges on the outside of the cell and influence the opening of nearby voltage-gated sodium channel activation gates.

Another example is the GABA (gamma-aminobutyric acid) receptor, a ligand-gated chloride (Cl⁻) channel in the brain. When GABA binds to its receptor, Cl⁻ flows into the neuron, creating more negative charges in the cell separated from an increased number of positive charges outside the cell. This situation, tends to keep voltage gated sodium channels closed which has an overall inhibitory effect on neural activity.

**Mechanically-Gated Channels**

Image by HC and JS W25

Mechanically-gated channels respond to physical changes in their environment. These channels have connections that bind to fibers of the extracellular matrix. As the extracellular matrix moves or experiences changes in pressure, the fibers connected to the channel gate help pull it open. An example is the mechanosensitive ion channels in sensory neurons responsible for the sense of touch. When you touch things of different textures, you press against your skin in a way that mechanosensory channels open in response to the mechanical deformation of the cell membrane. When mechanosensory channels like this open, ions such as Na⁺ or Ca²⁺ are allowed to enter the cell. similar to previous examples, this changes the membrane voltage in a way that voltage gated channels may also open. Another example involves cells for hearing. As sound waves enter the ear, they vibrate fluid which results in the bending of tiny cellular structures. This bending opens mechanically-gated channels, allowing ions to enter the cells and create signals that the brain perceives as sound.

#### Carrier Proteins

Image by HC and JS W25

Another type of facilitated diffusion utilizes **carrier proteins** in the membrane and is known as carrier-mediated transport. Unlike the channel proteins, carriers bind to a specific solute on one side of the membrane which causes the carrier to change shape, allowing solute access to the other side of the membrane (think of a revolving door). Like the channel proteins, these carriers can be very specific for the solute they transport since the solute must bind to a receptor site within the carrier protein before it changes shape.

#### Saturation and Competition

Important ideas to conceptualize for transport mechanisms are **saturation** and **competition**. Solutes that cross cell membranes via simple diffusion, depend on the concentration gradient to determine how fast the rate of transport is. However, solutes that use facilitated diffusion depend on the concentration gradient and the number of available channels or carrier proteins. Think of these channels or carrier proteins as doors by which solutes must cross through. Once the number of doors are all "busy" transporting molecules, the rate of transport will have reached a maximum. The rate of transport for simple diffusion is linear as increasing concentration of solutes can cross anywhere. The rate of transport for facilitated diffusion has a limit or ceiling which is determined by the number of possible passage points.

Image by JS W25

**Competition** refers to the idea that two similar but distinct substances can sometimes use the same transporter. If we are calculating the rate of transport for substance "X" and substance "Y" can fit through the same protein transporter as "X". This would be a situation of having competition. The competitor for "X" will sometimes take a "spot" in the channel or carrier protein and there will be a pause before another "X" can move across.

Can you tell which letter in the graph above is associated with simple diffusion, facilitated diffusion of a single substance and facilitated diffusion of a substance with competition? [CLICK ON THIS BOX TO SEE THE ANSWER]

A = simple diffusion B = facilitated diffusion (notice that the rate plateaus as the concentration of the transported solute increases) C = facilitated diffusion with competition (notice that the rate plateaus at a smaller rate as the speed of transport is influenced by a competitor molecule)

## Active Transport

To this point, the transport processes we have discussed have all been passive processes in which the solute movement has been down a concentration gradient. However, there are times when it is important for the cell to be able to move solutes against their concentration gradient (i.e. moving a solute across the membrane where it is higher in concentration). Just like moving water from the spillway of a dam back to the reservoir, these processes require an energy source and are called active transport processes.

#### Primary Active Transport

Primary active transport requires a carrier protein that is much like the proteins involved in carrier-mediated diffusion mentioned above. However, in this case, the carrier has an ATP binding site, which upon hydrolysis into ADP and inorganic phosphate (Pi) provides the energy to move solute against its concentration gradient. These transport systems can move one or multiple ions across the membrane. One of the most important primary active transport proteins is the **Na+, K+ - ATPase** (also called the **sodium potassium pump**).

Image by JS W25

The Sodium Potassium pump as illustrated above, attaches to an ATP and takes in 3 sodium ions. The ATP yields a phosphate to the protein and leaves as ADP. The phosphate attached to the protein causes a protein conformational change that opens to the extracellular fluid to let 3 Na+ ions out. Also, 2 K+ ions can enter from the outside. The Phosphate that caused this conformational change leaves and the protein changes again to be back to an open position towards the intracellular side. 2 K+ ions leave and we are back to the beginning to accept another complement of 3 Na+ ions which will be "pumped" to the outside if another ATP is available. This pump is the reason that Na+ concentration is high on the outside of the cell and K+ concentration is high on the inside of the cell.

Image by JS W25

It becomes easier sometimes to show the Na+ / K+ pump without all the steps. A quicker way to illustrate this is shown just above.

#### Secondary Active Transport

Image by JS W25

Like primary active transport, secondary active transport also moves solutes against their concentration gradients. However, with secondary active transport, ATP is not directly involved in the pumping of the solute. Instead, this process uses the energy stored in concentration gradients to move the solute.

The example in the image above shows Glucose (GLU) as the solute being moved by secondary active transport. Since sodium is always in higher concentration outside of the cell (due to primary active transport), the sodium gradient is often used to power secondary active transport. In this process, the carrier protein has a binding site for the glucose to be transported against its concentration gradient and a binding site for sodium to come in the cell as well. Once both solutes have been bound, sodium moves down its concentration gradient into the cell and in the process provides the energy required for glucose to be transported in the same direction (**symport**...shown above) or in the opposite direction (**antiport**...not shown above). The symport and antiport processes always have one solute going with a gradient and the other paired solute going against its concentration gradient. Several organic molecules are transported across membranes by this process, such as glucose and amino acids. ATP energy is required to generate the initial sodium concentration gradient but ATP is not directly involved in moving the desired solute across the membrane. It is the dissipation of the sodium gradient that provides the energy required for secondary active transport. Although the sodium gradient is most commonly used in secondary active transport, it should be remembered that under certain circumstances, other ions could also be used to drive the process.

[[CLICK HERE]](https://video.byui.edu/media/t/1_wesu67ep) to watch an animation showing active transport

#### Bulk Transport

So far, we have been talking about the movement of relatively small solutes across the cell membranes (i.e. ions and small organic molecules). There are instances, however, when it is necessary to move much larger materials across the membrane, like when a macrophage engulfs a bacterium or when larger amounts of a given material are released from a cell, such as the release of a hormone. These processes also require ATP and are, therefore, examples of active transport, but they move materials in a very different way.

#### Bulk Transport (Endocytosis)

This is the bulk transport of materials into the cell. There are several types of endocytosis, and we will briefly explore each one.

Images by HC 2013

**Phagocytosis**

First, let's discuss phagocytosis, which means cell eating. Only a limited number of cells are capable of phagocytosis, specifically cells of the immune system. In this process, the cell sends extensions of its plasma membrane out and around the particle to be phagocytized. As these extensions surround the particle, they eventually fuse, creating a vesicle containing the particle.

**Pinocytosis**

Pinocytosis is another type of endocytosis, which means "cell drinking". In this process, rather than send out pseudopodia, the cell membrane simply invaginates (forms a pocket) and engulfs anything in the fluid that is taken into the cell. Unlike phagocytosis, pinocytosis occurs in most cells of the body. The cells are not interested in the water in the vesicles but any solutes that might be brought in. As you can imagine, this is not a very efficient way of bringing materials into the cell because it is nonspecific and brings whatever is in the fluid into the cell. It provides cells with a nonselective mechanism for sampling the extracellular environment. It is prominent in cells involved in moving large amounts of material across the membrane, like cells of the intestines and the kidneys.

**Receptor-mediated endocytosis.**

Receptor-mediated endocytosis A much more efficient mechanism for bringing specific solutes into the cell is receptor‐mediated endocytosis. As the name implies, this mechanism employs specific receptors that bind to specific compounds (ligands) within the extracellular space. Once the specific ligand binds with its receptor, the resulting complex migrates to a specific area of the membrane called a clathrin‐coated pit. The clathrin protein is activated by the bound receptor which initiates endocytosis in a process similar to pinocytosis. The advantage of receptor‐mediated endocytosis is that it can engulf large amounts of a specific solute.

#### Bulk Transport (Exocytosis)

Image by HC 2013

There is also a need to export material from the cell into the extracellular fluid. This process is called exocytosis. Exocytosis is the process by which the beta cells of the pancreatic islets secrete the protein hormone insulin into the extracellular fluids. The mechanism is essentially the reverse of endocytosis. Secretory vesicles filled with the material to be released migrate to the plasma membrane where the membrane of the vesicle fuses with and actually becomes a part of the plasma membrane. The material that was in the vesicle suddenly finds itself outside of the cell, and any integral protein within the vesicle membrane now becomes a protein expressed on the cell membrane. The usual signal that initiates exocytosis is the entry of calcium ions into the cell which bind to specific proteins (e.g. SNARE proteins...not shown in the image) that initiate this process. Since calcium concentration is higher outside the cell, it is common that activation of gated calcium channels in the membrane precedes exocytosis.

Another important example of exocytosis involves the delivery of membrane proteins to the surface of the cello. In skeletal muscle, GLUT4 proteins (glucose transporters) are found in intracellular vesicular membranes. When insulin binds to its cell surface receptor, exocytosis is initiated to allow GLUT4 expression on the plasma membrane and subsequent glucose transport into the muscle cell.

Image by JS W25

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