Scientific Foundations Primer

Water

In humans, approximately 50% to 60% of our bodies are composed by weight of water. All of our living cells are filled with and surrounded by water. Understanding the basic properties of water and how molecules interact with and move in water is essential for understanding how cells, tissues and organs function to support life.

Properties

The chemical structure of water is simple: a single oxygen atom with single covalent bonds to two hydrogen atoms. But that simple structure and the chemical features of oxygen and hydrogen create complicated and unique properties of water that are critical for sustaining life.

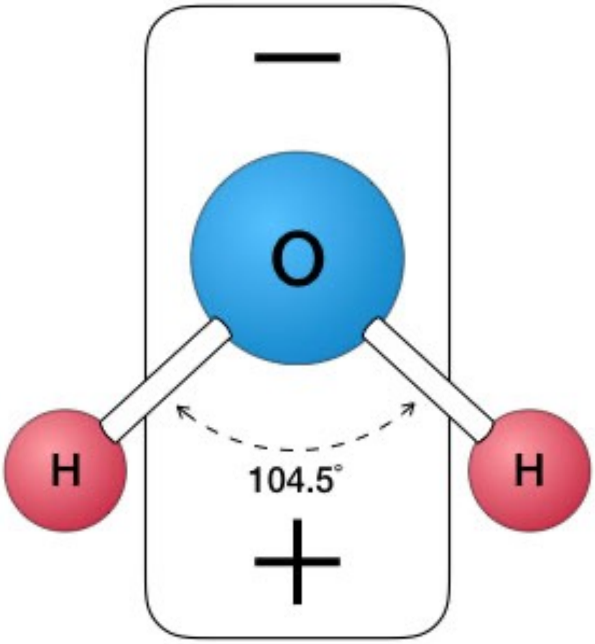
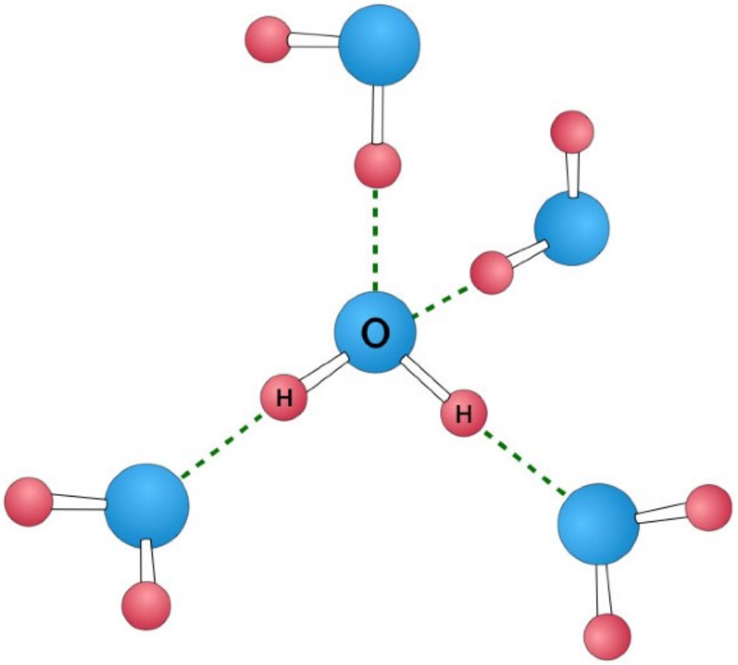


Diagram of a water molecule showing its charge distribution

The most important property of a water molecule is its charge polarity. Even though a water molecule does not contain an overall net charge, there is a slight polarity in the distribution of charge across a water molecule. The polarity arises from the nature of the covalent bonds between oxygen and hydrogen. Although the electrons in each covalent bond are shared by the oxygen and hydrogen, the larger and more strongly positive nucleus of the oxygen atom pulls the electrons in each bond closer to the oxygen atom. Consequently, a water molecule will have a slightly negative charge near its oxygen atom and slight positive charge toward its hydrogen atoms. In addition, water is a bent molecule with covalent bonds forming an angle of approximately 104˚. If water were a linear molecule (bond angle of 180˚), then the charge distributions along the bonds would cancel out. This is known as a dipole moment and underlies many of the macroscopic properties of water that are familiar to us in our daily lives and essential for supporting life.

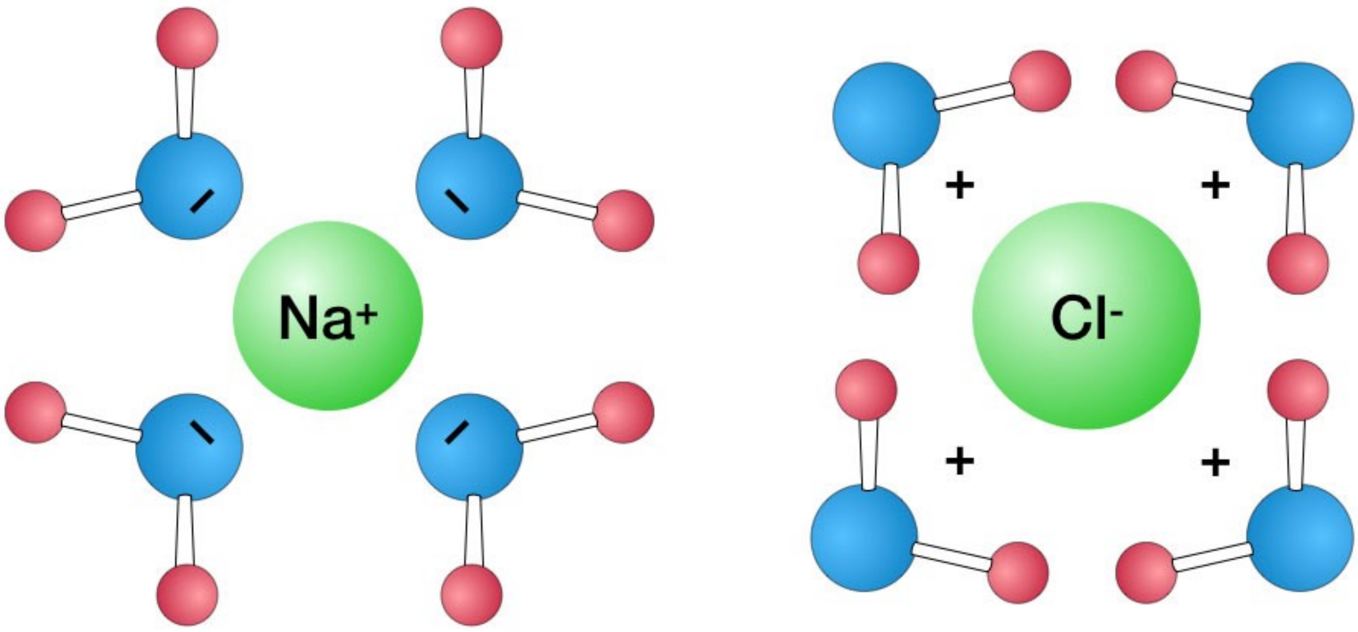
One critical property of water is that it remains in liquid form at relatively high temperatures (100˚ C/212˚ F). The ability of water to remain as a liquid is due to the interaction between individual water molecules. The dipole moment in water allows the positive end of one water molecule (hydrogen) to interact with the negative end of another (oxygen). This type of bond is called a hydrogen bond is fundamental to the interactions between biological molecules. Because each water contains two hydrogen atoms, large chains of interacting water molecules can form. The network of interactions between water molecules means more energy (heat or higher temperature) is required to convert water from a liquid to gas. Compare that to a molecule with a similar structure, H_2S (hydrogen sulfide). Like water, H_2S is a molecule with single covalent bonds between hydrogen and sulfur, but the larger size of the sulfur atom shields the positive charge of its nucleus, reducing the strength of the diplole moment in H_2S. The weaker interaction between molecules of hydrogen sulfide result in a boiling point of - 60˚ C (-75˚ F).



Hydrogen bonds link water molecules into a network.

Behavior of Biological Materials in Water

The polarity of water is also critical for its properties as a solvent. Water's polarity allows it to interact with and dissolve chemicals with electrical charges. Importantly, most salts readily dissolve in water (e.g. NaCl, KCl). The polarity of water allows it to break the ionic bond between say sodium and chloride to generate a positively charged sodium ion and negatively charged chloride ion. The water in our bodies and in our cells have specific amounts of certain ions, and maintaining the concentration of those ions is critical for the survival and function of every cell.



The charge distribution of water allows it to dissolve ions and molecules with a surface charge.

Many other important biological molecules readily dissolve in water due to the charge polarity on their surface and ability to form hydrogen bonds with water. These types of molecules are called hydrophilic.

In contrast, there are molecules or portions of molecules that lack polarity and do not interact with water. These molecules are termed hydrophobic. Because they do not interact with water, hydrophobic molecules tend to interact with each other, in effect, hide from water. For example, fats are long chains of hydrocarbons (covalently bonded carbon atoms each covalently bonded to one or more hydrogen atoms). The bonds between carbons and between carbon and hydrogen lack polarity so there is no or very small dipole moment (charge distribution), meaning that these molecules react poorly with water.

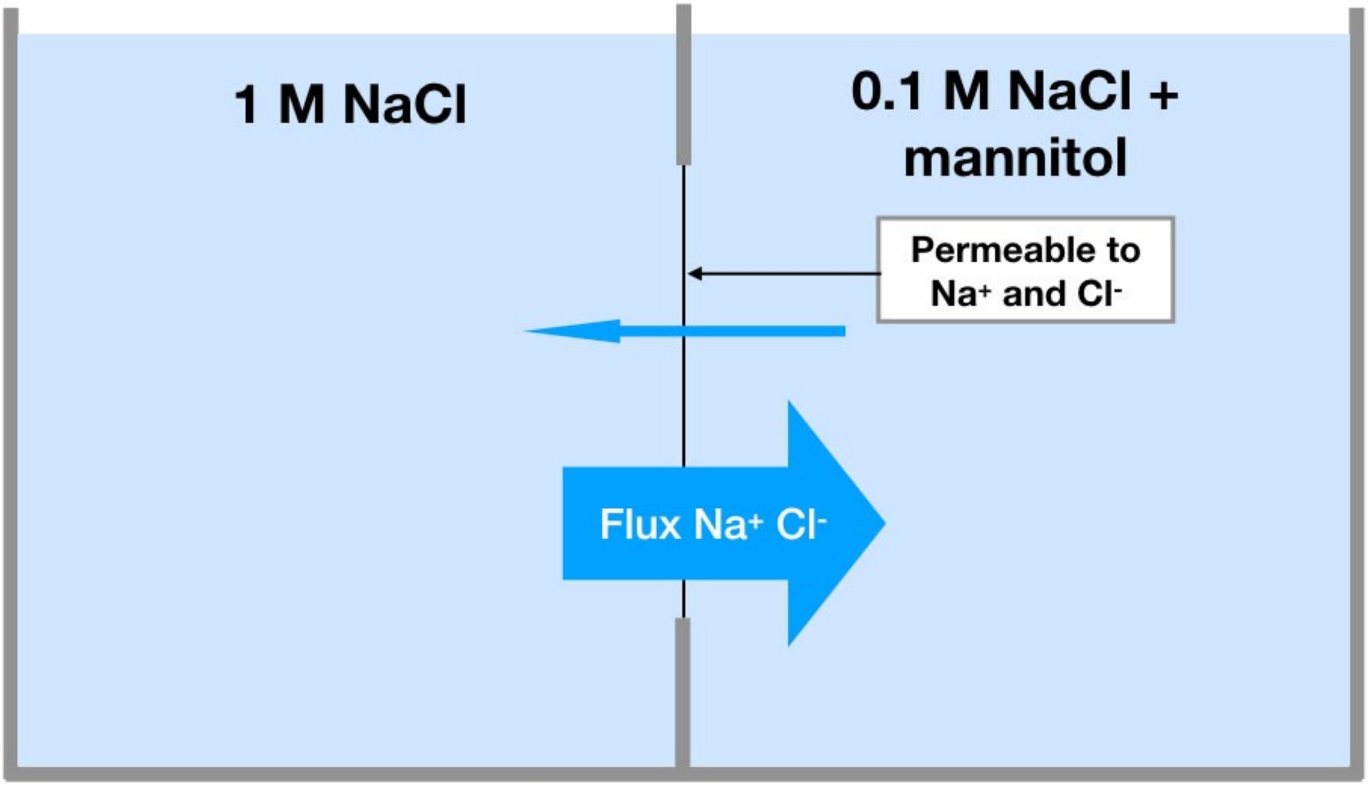
Some large molecules, such as proteins, contain hydrophobic and hydrophilic regions. In proteins, the hydrophobic regions often cluster in the interior of the molecule and help the protein to fold into a three-dimensional structure. The hydrophilic regions usually reside on the surface of the molecule where they interact with water.

Diffusion

Recall that one of the properties of water is that it remains in liquid form over a large range of temperatures and at relatively high temperatures. The high temperature of water in our bodies is a result of the thermal motion of the water molecules. The random movement of water molecules imparts movement to the solutes in water. Because the movement of water molecules is random, solutes in water move randomly, too.

One consequence of the random motion of molecules and ions in water is that a specific molecule or ion will eventually randomly distribute throughout the volume of water. So if we add a drop of a concentrated solution of an ion or molecule to a large volume of water, eventually that ion or molecule will become evenly distributed throughout the water. Thus, we say the all ions and molecules show a net movement from regions of high concentration to regions of low concentration. This movement or diffusion is driven entirely by the thermal energy in the water.

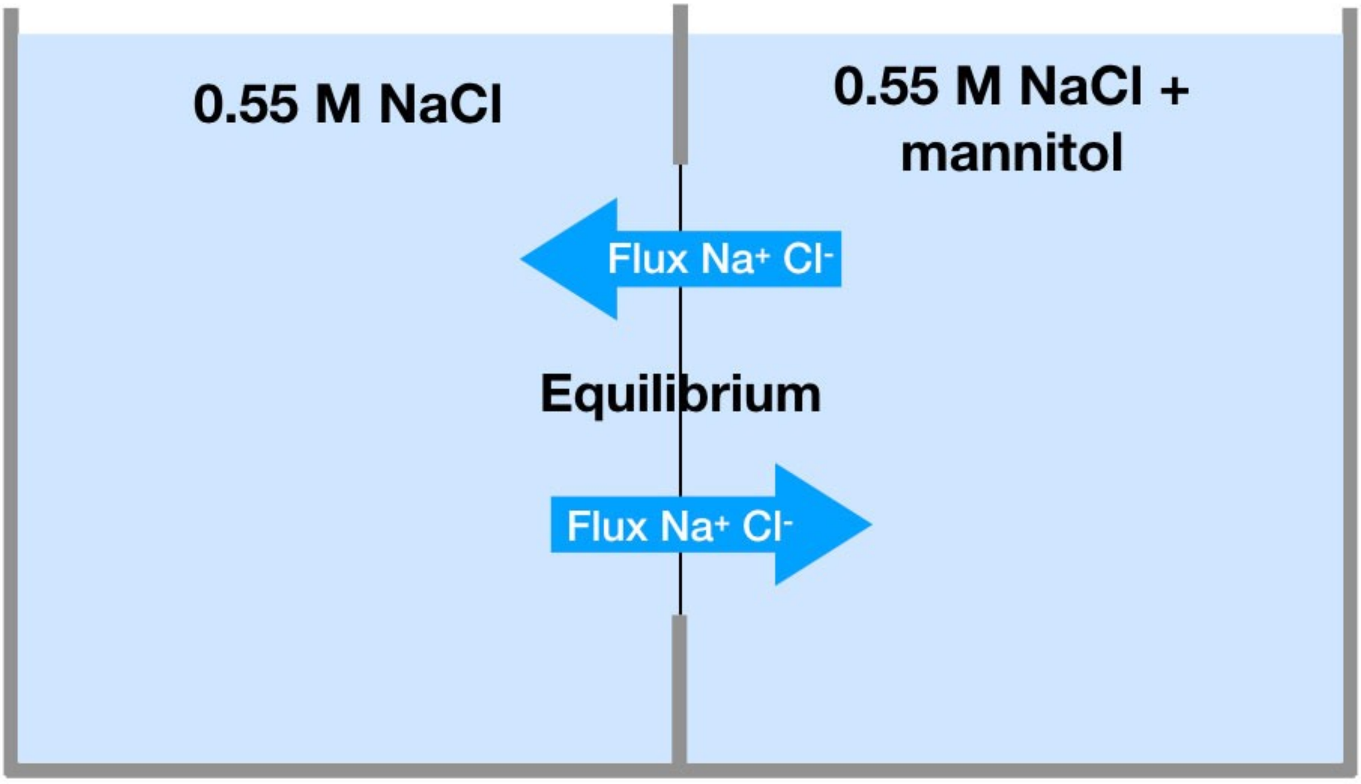
For example, let's place equal volumes of two solutions of sodium chloride in separate chambers. The solution in the left chamber contains 1 M NaCl and the one in the right chamber contains 0.1 M NaCl. The chambers are separated by a membrane that is permeable to sodium and chloride ions. Thus, sodium and chloride ions can freely diffuse from one chamber to the other across the membrane. To counter the effects of osmotic pressure created by the different amounts of solute in each chamber (see below for an explanation of osmotic pressure), we will add a solute, mannitol, to the right chamber that cannot diffuse across the membrane What will happen to the concentration of sodium and chloride in each chamber over time?



Diffusion of sodium and chloride down their concentration gradient.

To answer this question, we must recall that the sodium and chloride ions in both chambers are in constant motion due to thermal energy (the water molecules are also moving but they cannot cross the membrane). The movement of both ions means that at some point an ion will encounter a pore and pass from one chamber to another. These collisions between ions and pores happen randomly. Because the left chamber has more sodium and chloride ions than the right chamber, there is a higher probability that a sodium or chloride ion will encounter a pore in the right chamber. Consequently, more sodium and chloride ions will move from 1 M to 0.1 M chamber than move in the opposite direction. This will cause the concentration of sodium and chloride ions in the left chamber to decrease and the concentration in the right chamber to increase.

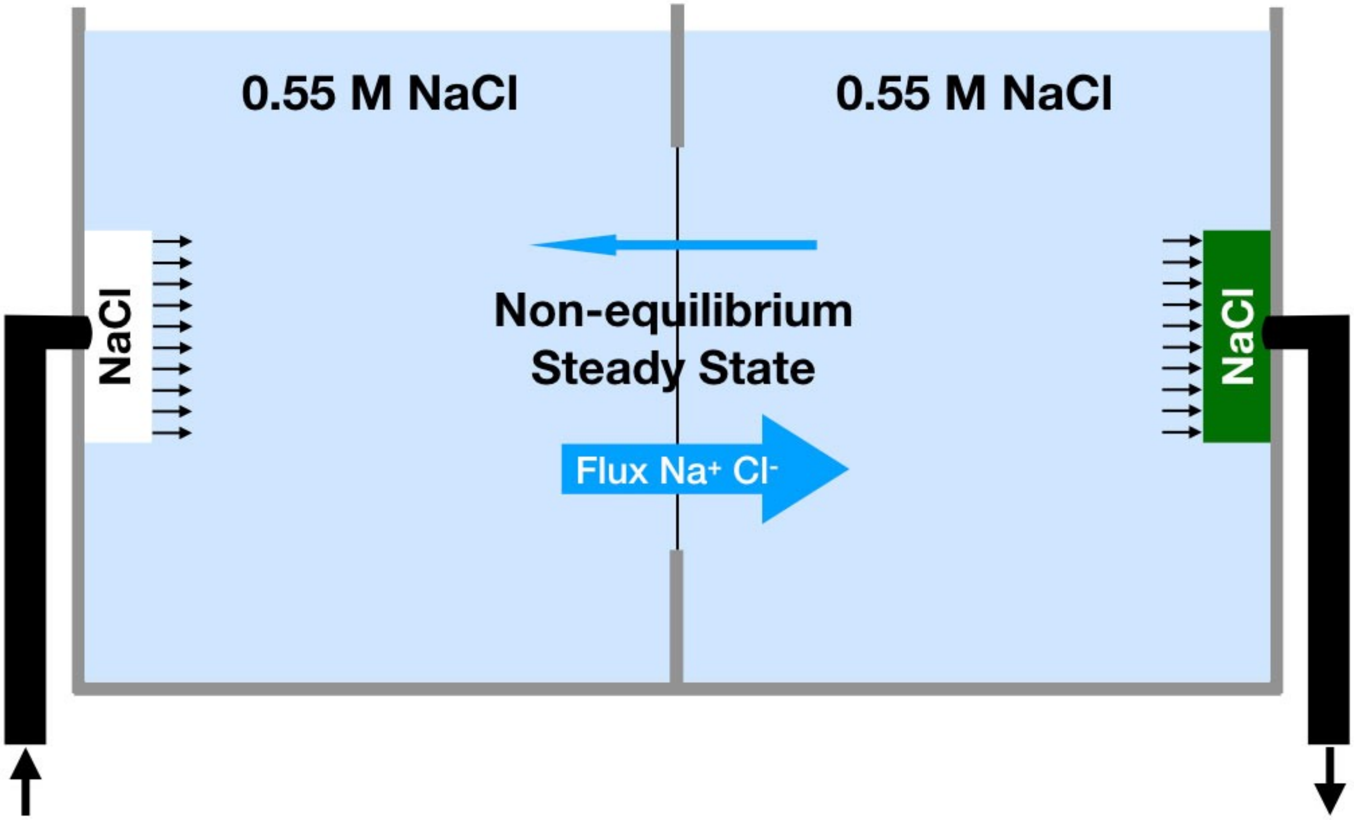
When will the movement of sodium and chloride ions between the two chambers end? As long as there is thermal energy in the solutions, the ions will constantly move through the pores from one chamber to the other. However, as the sodium chloride concentrations decreases in the left chamber while increasing in the right, the system will reach a point at which there will be an equal number of sodium and chloride ions in each chamber. The concentrations of sodium and chloride in each chamber will stop changing because there is an equal probability of ions moving in both directions across the membrane. At this point, we say that the two chambers are in equilibrium with regard to sodium and chloride ions. Even though both ions are still moving between chambers, the number of ions moving from the left chamber to the right is approximately equal to the number of ions moving from the right chamber to the left. Thus, the ions can move between chambers without causing a net change in their concentration in each chamber.



At equilibrium sodium and chloride move equally between the two chambers.

Equilibrium

Equilibrium is an example of a range of conditions called steady state. Steady state occurs when the variables of a system do not change over time. In our example, the system consists of the two chambers of NaCl in water and the variables are the concentrations of sodium and chloride in each chamber. It's clear that equilibrium satisfies this definition of steady state as the concentration of sodium and chloride do not change over time even though ions are moving across the membrane. Is there a steady state condition where the chambers are not in equilibrium. Suppose we attach to the right chamber a small filter that can selectively absorb sodium and chloride ions from a solution. Any ion that collides with the filter would be removed from solution. Thus, the filter would cause the concentration of sodium and chloride in the right chamber to decrease. At the same time that we attach the filter to the right chamber, we also attach a different type of filter to the left chamber that releases sodium and chloride ions into solution. The filters are designed so that they release or absorb ions at the same rate. Thus, ions enter the left chamber at the same rate as they leave the right chamber.



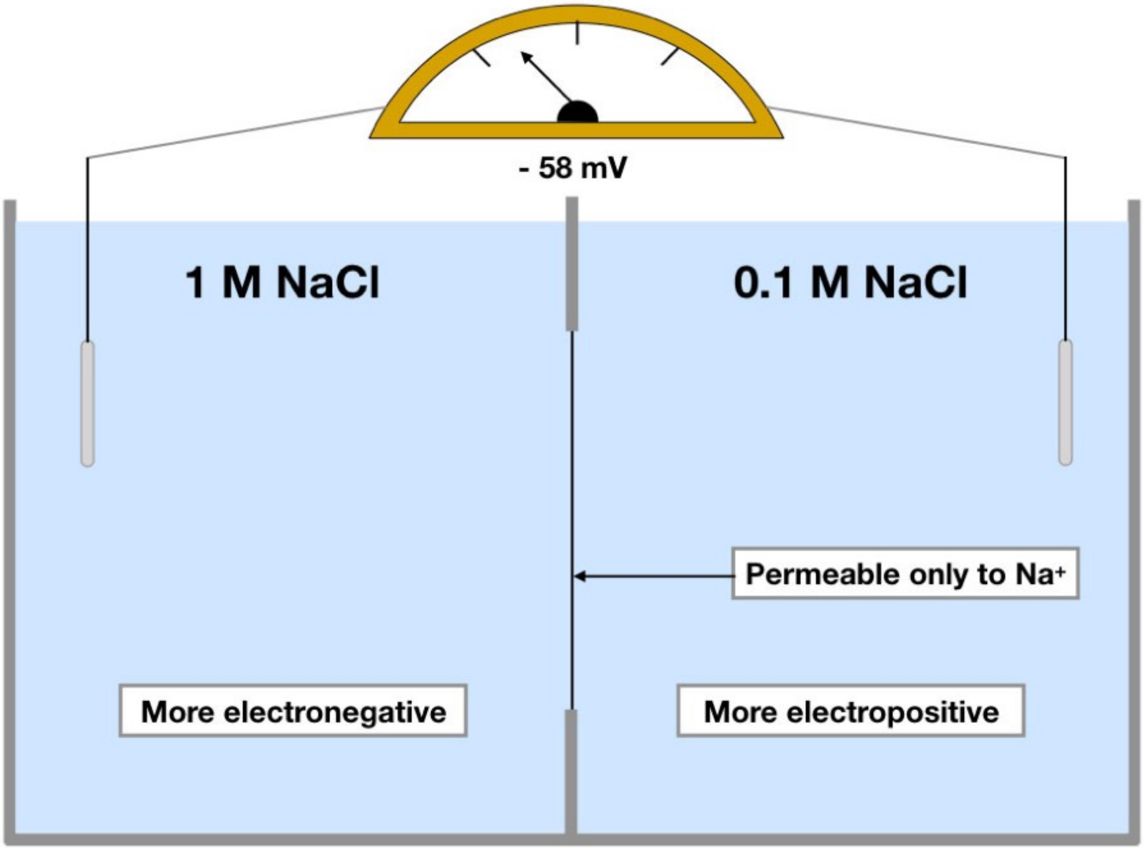
At steady state the concentration of sodium and chloride in the two chambers remains constant but are not necessarily in equilibrium.

This system will create a steady state condition that is not in equilibrium. Because ions are added to the left chamber and removed from the right chamber, there is a greater probability that ions in the left chamber will collide with the membrane to enter the right chamber. This net flow of ions from left to right will keep the concentration of ions in both chambers roughly equal but the system is not in equilibrium because the flow of ions between chambers is not equal; more ions flow from the left chamber into the right chamber than flow in the reverse direction. This concept of non-equilibrium steady state is important to remember as many biochemical reactions in cells are not in equilibrium but are at steady state.

The Roles of Size and Charge in Diffusion

The rate of diffusion of a molecule is affected by its size. Larger molecules diffuse more slowly than smaller molecules. The second factor that can affect the diffusion of a molecule or ion is its net charge. Recall that when many chemicals (e.g. salts) dissolve in water, they generate an ion or molecule with a net positive or negative charge. The diffusion of ions and molecules with a net charge are affected by electrical fields. Positively charged ions and molecules move toward the negative end of an electric field and away from the positive end, whereas negatively charged ions move toward the positive end of the field and away from the negative end. Electric fields impart a force on charged ions and molecules.

To illustrate the effect of an electric field on the diffusion of ions, let's set up our two chambers as before with one containing 1.0 M NaCl and the other containing 0.1 M NaCl and mannitol, but this time will use a membrane that is only permeable to sodium ion. Thus, sodium ions can freely diffuse across the membrane but chloride ions cannot.



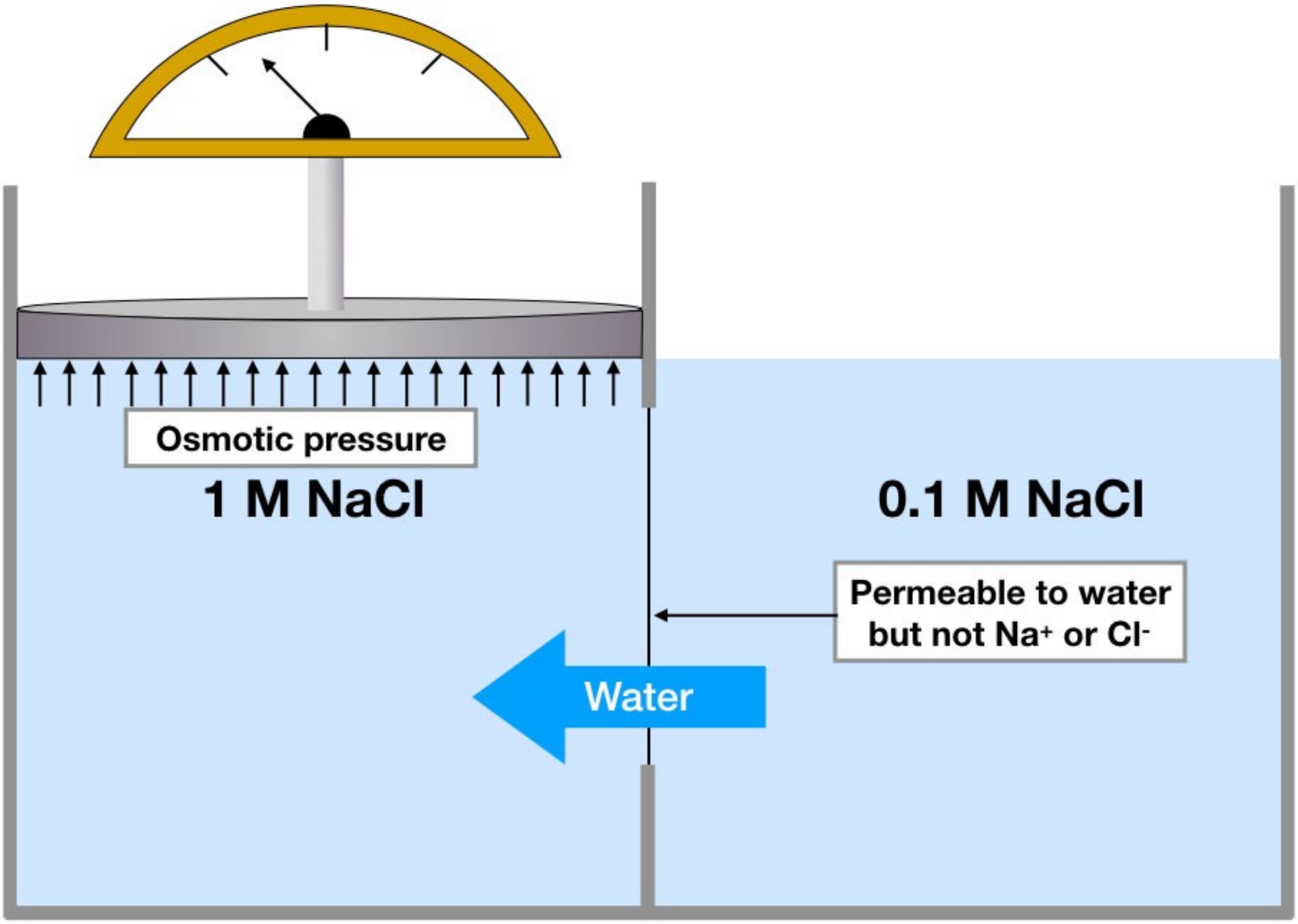
Potential across a membrane is generated when only one type of ion can pass through the membrane.

At the start of the experiment, it’s clear that sodium ions will diffuse down their concentration gradient and more sodium ions will move from the left chamber to the right than move in the opposite direction. However, note that as sodium ions accumulate in the right chamber and the ratio of sodium ion to chloride ion begins to change. The right chamber will have more sodium ions than chloride ions while the left will have fewer sodium ions than chloride ions. This makes the left chamber electronegative compared to the right chamber. As sodium ion diffuses from the left chamber to the right, the electronegativity in the left chamber increases. The electronegativity in the left chamber opposes the diffusion of sodium ions from the left chamber to the right because positively-charged sodium ions move toward the negative end of an electric field. Eventually, the electronegativity becomes strong enough to prevent net movement of sodium ions from the left chamber to the right even though the concentration gradient still favors the movement of sodium ions from the left chamber to the right. At this point the sodium is in equilibrium between the two chambers.

We can measure the potential across the membrane with a voltmeter. The amount of voltage at equilibrium is sufficient to prevent changes in the overall concentration of sodium ion between the two chambers. That is the voltage keeps the sodium ions in equilibrium between the two chambers even though the left chamber has a higher concentration of sodium ion than the right chamber. The larger the concentration difference in sodium ions between the two chambers, the larger the potential difference across the membrane must be to achieve equilibrium. You will learn in the Physiology thread how to precisely calculate the effect of a voltage gradient across a membrane on the distribution of ions in the compartments defined by the membrane.

Osmosis

Osmosis describes the net movement of water between two compartments due to an unequal number of dissolved particles in each compartment. If two compartment are separated by a membrane that is permeable to water but not the dissolved particles, water will move from the compartment with fewer dissolved particles to the one with more dissolved particles (in our example from the right chamber to the left). Consequently, the volume of fluid in left chamber will increase. We can measure the osmotic pressure generated by placing a piston on top of the left chamber. The flow of water from the right to left compartment will cause the piston to rise. By applying pressure to the piston, we can prevent the volume of the left chamber from increasing. The amount of pressure we have to apply to keep the volumes of both chambers equivalent is called the osmotic pressure of the system.



Osmotic pressure is generated by unequal concentrations of sodium chloride in the two chambers.

The osmolality of a solution reflects the number of dissolve particles or osmotically active particles in a solution. Osmolality reflects the number of moles of osmotically active particles per kg of solvent which in our case is water. Hence, 1 osmole is 1 mole of osmotically active particles in a solution that contains 1 kg of water. Because it is easier to measure the volume of a solution rather than the weight of its solvent, some solutions are expressed in osmolarity which is moles of osmotically active particles per liter of solution. Which one should you use? For most fluids found in human body their osmolality will be roughly equally to their osmolarity so either measurement is acceptable. However, certain tests return results in either osmolality or osmolarity so it's important to be familiar with both.

Osmosis and Cell Volume

Osmosis impacts a cell's volume and potentially leads to damage and cell death. The cytoplasm of cells contains many proteins, carbohydrates, amino acids, sugars and other small molecules. Each of these counts as an osmole. Thus, if placed in pure water, the osmotic pressure would be higher inside the cell and draw water into cell from the surrounding fluid. The influx of water would cause cells to rapidly swell and potentially burst.

Cells employ different mechanisms to prevent bursting. Many single cell organisms, such as bacteria and yeast, have an external cytoskeleton called a cell wall that is composed of protein and carbohydrates. The cell wall physically prevents the cell from swelling if it is placed in a hypoosmotic solution such as pure water. The cells in multicellular organisms don't have cell walls so need a mechanism to maintain an osmotic balance with their surrounding solution.

A critical feature of multicellular organisms is that the fluid surrounding their cells has large number of osmoles in the form of ions such as sodium, chloride, potassium and calcium. The presence of these ions helps cells maintain an osmotic balance between their cytoplasm and surrounding fluid. As you will learn, our bodies have several mechanisms and spend a lot of energy to maintain a proper concentration of ions in the extracellular fluid.

Because cells also need ions in their cytoplasm to perform essential biochemical reactions, cells have proteins in their membranes that allow passage of specific ions between their cytoplasm and extracellular fluid. These channels are critical for maintaining an osmotic balance between cytoplasm and extracellular fluid and for generating a membrane potential across the cell membrane.

Acids and Bases

Of particular biological and medical importance is the concentration of hydrogen ion (H+) in the body fluids. The concentration of H+ in a fluid is called its pH and is measured using a log scale:

$$pH = -log_{10}[H^+]$$

A higher concentration of H+ generates a lower pH value.

Pure water contains a small concentration H^+ and OH^- because a small fraction of H_2O dissociates.. At 25° C, pure water has 1×10^{-7} M H^+ and 1×10^{-7} M OH^-. Because the the concentration of H^+ equals the concentration of OH^-, pure water is considered neutral. Compounds that increase the concentration of H^+ when added to water are called acids, whereas those that decrease the H^+ concentration are called bases.

The strength of an acid or base depends on its ability to lose (acid) or gain (base) a hydrogen ion. When dissolved in water, a strong acid will almost completely ionize so that almost all of the acid has released a hydrogen ion. In contrast, in weak acids only a small fraction of the acid ionizes. For example, let's consider an acid HA that dissociates into H^+ and A^- in water. The strength of the acid can be described by this formula:

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

The larger the Ka, the more likely the acid will release a hydrogen ion and therefore lower the pH of a solution.

The A^- in our solution is called the conjugate base. If the acid has a large Ka (readily dislocates), the conjugate base (A^-) is considered a weak base. If the acid has a small Ka, it is considered a weak acid and its conjugate base is a strong base.

The same concept applies to bases. A strong base is one that completely ionizes in solution and its conjugate acid is weak.

In medicine, we are often concerned with the extent to which a molecule ionizes given the pH of the surrounding fluid. Although most fluids in the body range from pH 7 - 7.4, some fluids, such as the fluid in the lumen of the stomach can be very acidic. To determine the fraction of molecule that is ionized we can use the Henderson-Hasselbach equation which for acids is

$$pH = pK_a + log_{10}\frac{[A^-]}{[HA]}$$

where HA is the concentration of unionized molecule and A^- is the concentration of ionized molecule. As an example, let's look at a molecule that is a weak acid with a pK_a of 6. If the plasma pH is 7.4, then the ratio of ionized to unionized molecule is

$$7.4 = 6.0 + log_{10}\frac{[A^-]}{[HA]}$$

$$1.4 = log_{10}\frac{[A^-]}{[HA]}$$

$$25 = \frac{[A^-]}{[HA]}$$

So, the concentration of ionized molecule is 25-fold more than the concentration of nonionized. What if the molecule were ingested and reached the stomach? In this case with the pH of the stomach about 2.0, the ratio of ionized to unionized molecule changes dramatically:

$$2.0 = 6.0 + log_{10}\frac{[A^-]}{[HA]}$$

$$-4.0 = log_{10}\frac{[A^-]}{[HA]}$$

$$0.0001 = \frac{[A^-]}{[HA]}$$

In the stomach, the concentration of unionized molecule is 10000-fold higher than the amount of ionized.

Knowing whether a molecules is ionized or unionized has important biological and medical consequences. Because an ionized molecule has a charge, it reduces its ability to diffuse across cell membranes, whereas unionized molecules that lack an overall charge can more easily diffuse across cell membranes. This will be important when we consider to what extent drugs are absorbed into the body.

Electrons

You may have thought you saw the last of these tiny, charged particles in your final chemistry or physics class, but the transfer of electrons from one molecule to another plays a critical role in biology and in particular, in many metabolic reactions. Perhaps, the most well-known metabolic reaction is the complete breakdown of glucose into carbon dioxide and water:

$$Glucose + 6\ O_2 \text{->} 6\ H_20 + 6\ CO_2$$

Cells use the the energy released by the breakdown of glucose to generate ATP from ADP.

$$Glucose + 6\ O_2 + 36\ ADP \text{->} 6\ H_2O + 6\ CO_2 + 36\ ATP$$

Hidden beneath this reaction of molecules is the transfer of electrons from glucose to oxygen which is responsible for generating 34 of the 36 molecules of ATP. Breaking down the reaction into two half reactions reveals the movement of electrons:

$$Glucose + 6\ H_2O \text{->} 6\ CO_2 + 24\ e^- + 24\ H^+$$

$$6\ O2 + 24\ e^- + 24\ H^+ \rightarrow 12\ H_2O$$

These two reactions are an example of an oxidation-reduction pair. The top reaction is the oxidation of glucose which results in the loss of 24 e- from the 6 carbons in glucose. In the reduction reaction, those 24 e- are accepted by oxygen to form water.

How do the electrons get from glucose to oxygen? The transfer of electrons is indirect and proceeds through intermediaries and some these intermediaries will help the cell convert ADP to ATP. Most important for the breakdown of glucose are two sets of metabolites: NAD+/NADH and FAD/FADH2

$$NAD^+ + 2\ e^- + 2\ H^+ \rightarrow NADH$$

$$FAD + 2\ e^- + 2\ H^+ \rightarrow FADH_2$$

Cells will transfer the electrons in NADH and $FADH_2$ to proteins that compose the electron transport chain. These proteins will use energy of electron transfer to generate a proton gradient that will power the generation of ATP from ADP.

Because the transfer of electrons between molecules happens often in biological reactions (and inorganic reactions), the reactions have specific names. A reaction in which a molecule (or atom) loses an electron is called oxidation, and a reaction in which a molecule (or atom) gains an electron is called reduction.

$$\text{Oxidation: } A \rightarrow 1\ e^- + A^+$$

$$\text{Reduction: } B^+ + 1\ e^- \rightarrow B$$

Keep in mind that although the reaction in which an electron is lost is called oxidation, the reaction does not always involve oxygen (though in many biological reactions oxygen is involved).

Oxidation and reduction reactions are usually coupled so that the electron lost in the oxidation reaction is consumed by the reduction reaction. The pairing of reactions leads to some confusing nomenclature. A molecule that is oxidized (A in the above reactions) is said to be a reducing agent because it facilitates the reduction of another molecule (B in the above reactions). Likewise, B is termed an oxidizing reagent because it facilitates the oxidation of A.

As you'll learn, many metabolic reactions involve the transfer of electrons to or from a biological molecule (e.g. glucose, lipid) using metabolite pairs such as NAD^+/NADH, FAD/$FADH_2$, $NADP^+$/NADPH. In each of these pairs, the first molecule is the oxidizing reagent because it accepts electrons which helps oxidize another molecule. The second molecule in each pair is the reducing agent. Cells maintain specific ratios of oxidizing to reducing agents to help drive biological reactions.