Ion Transport, Resting Potential, and Cellular Homeostasis

Introduction

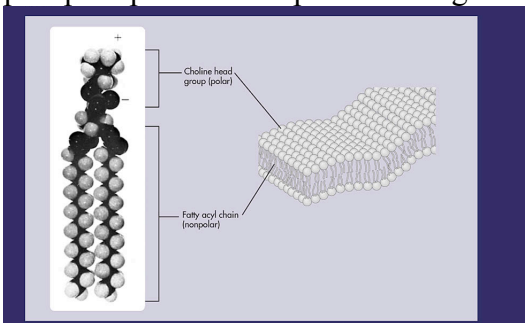
These notes cover the basics of membrane composition, transport, resting potential, and cellular homeostasis. After a brief introduction to the first two topics, we will spend most of our time on the 3rd and 4th. We will discuss ions that are subject both to diffusion and to an electric field. Current flux in this case is described by a nonlinear partial differential equation (PDE), the *Nernst-Planck equation*. Under equilibrium conditions (i.e., with no flux) the Nernst-Planck equation can be simplified to give the *Nernst equation*, a simple algebraic formula that we can use to calculate the value of membrane potential at which a given ion undergoes no net flux. We will derive a circuit-theory-based model of steady-state, non-equilibrium conditions in multi-ion systems. We will also discuss how ionic pumps can be accounted for mathematically.

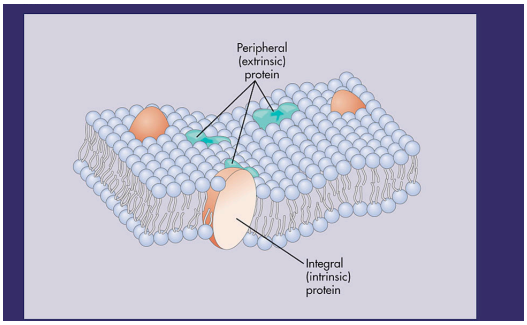
Because of limitations in time, we will not examine several important and interesting questions related to this material. We will skip several classic and important derivations (e.g., derivations of conductance in semi-permeable membranes, and the time- and length-scales over which the condition of electroneutrality applies).

Hille is a terrific book, but it does not cover this material that well. The best detailed derivation of these results I have seen is in Weiss, *Cellular Biophysics*, Vol. 1, MIT Press.

Composition of cell membranes

1. *The lipid bilayer*, composed of phospholipids (polar heads, hydrophobic tails). Bilayer is the most stable structure in a charged aqueous environment. Lipids are mostly choline-containing (phosphatidylcholine, sphingomyelin), with significant contributions from aminophospholipids (phosphatidylethanolaimine, phosphatidylserine). Other components, small in number but structurally important, include inositol phospholipids. Tails of all phospholipids are composed of long trains of hydrocarbons.





Other important components of the lipid bilayer are not phospholipids. These include cholesterol, which regulates the fluidity of the membrane, and glycolipids (lipids with attached carbohydrate chains), the carbohydrates of which typically protrude from the external surface of the cell, acting as receptors or antigens. Many elements of the lipid bilayer (especially glycolipids) are preferentially distributed on the outer or inner face of the membrane.

2. *Membrane proteins*, including enzymes, transport proteins, ion channels, receptors. Proteins can be *integral* (inserted in the membrane) or *peripheral* (on surface, bound by charge interactions with integral proteins).

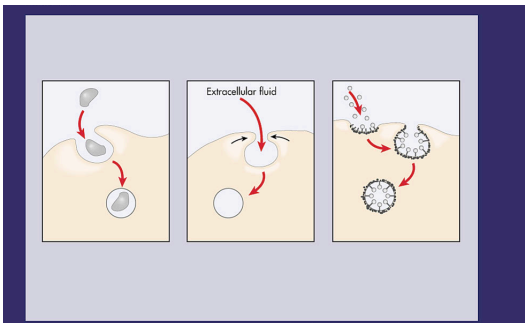
The distribution of membrane elements can often be well-described by a 2-dimensional diffusion model, with a reasonably fast time scale of diffusion and a slower time-scale of "flip-flopping" (i.e., changing from one face of the bilayer to another). Many membrane elements, however, do not diffuse in the membrane because they are tethered by intracellular elements.

For more on membrane composition, see Alberts, Bray, Lewis, Raff, Roberts, and Watson, *Molecular Biology of the Cell*, 3rd edition, Garland Publishing, New York, 1994.

Membrane transport

Lipid-rich membranes serve as permeability barriers. Material can cross cell membranes in one of several ways:

1. *Endocytosis.* In this process, the cell membrane envelopes a particle (phagocytosis) or volume of extracellular fluid (pinocytosis). The enclosed particle or fluid is brought in within a membrane-bound vesicle. Endocytosis requires energy, in the form of ATP hydrolysis. Endocytosis often occurs at specialized sites with receptors for a given protein. Vesicles associated with receptor-mediated endocytosis are often coated with "bristles" made of clathrin.



2. *Exocytosis.* A molecular entity is ejected from a vesicle that fuses with the cell membrane. Endocytosis in reverse. This is the way that neurotransmitters are released.

3. *Diffusion through the lipid bilayer*. Driven by random thermal motion, described by Fick's First Law:

$$\text{In general: } \vec{\varphi}_n = -D_n \nabla c_n,\ \nabla c_n = \text{gradient of } c_n = \frac{\partial c_n}{\partial x}\mathbf{i} + \frac{\partial c_n}{\partial y}\mathbf{j} + \frac{\partial c_n}{\partial z}\mathbf{k}$$

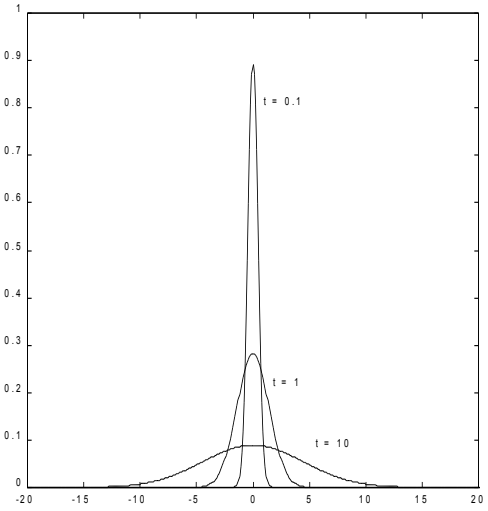
$$\text{In 1D steady-state: } \varphi_n = -D_n \frac{dc_n}{dx}$$

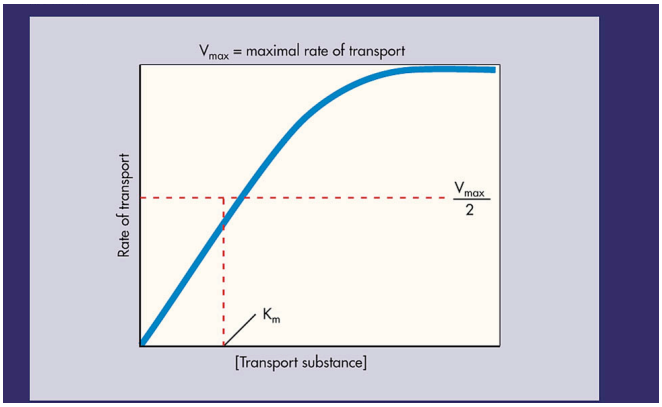
c_n [=] mol/ L = M $\qquad$ φ_n [=] mol/(s m^2) $\qquad$ D_n [=] m^2/s

The diffusion coefficient D_n for a molecule depends on its *lipid solubility* (the more lipid-soluble, the faster the diffusion) and its size (the smaller the molecule, the faster the diffusion). Some very small water soluble molecules (MW < 200) can diffuse very quickly

through the membrane. The most important example of this phenomenon is water itself, which equilibrates across the cell membrane reasonably rapidly. In some cells (notably in the kidney), the diffusion of water is aided by water-selective channels called *aquaporins*.

Fick's First Law and the principle of conservation of matter lead to the diffusion equation: $D_n \frac{\partial^2 c_n}{\partial x^2} = \frac{\partial c_n(x,t)}{\partial t}$. Green's function {the response to a space-time impulse, δ(x,t)} for this equation, assuming an infinitely long path of diffusion, is $c(x,t) = \frac{u(t)}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$ (see figure below). The fact that the width of this function grows proportionally $t^{-0.5}$ justifies the statement by B&L that diffusion works well over short distances, but poorly over long distances.

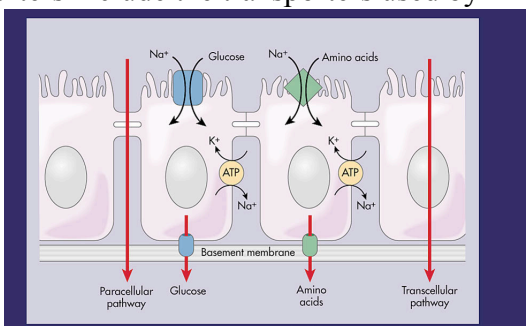




4. *Protein-mediated transport*. Many water-soluble substances are transported by intrinsic proteins called *carriers* or *channels*. Mediated transport exhibits several hallmark traits, including *saturation* (see the figure), *chemical specificity*, *competitive inhibition*, and the potential for *inhibition* by compounds that affect the transport protein. There are two broad classes of protein-mediated transport:

   a. *Active transport*. Requires the expenditure of energy derived from the hydrolysis of ATP. This expenditure can be direct (primary active transport, in which ATP is hydrolyzed by the transport molecule) or indirect (secondary active transport, in which an electrochemical gradient previously established by primary active transport is used to drive an additional transport process). *A crucial property of active transport is that it can drive the net flux of a molecule against an electrochemical gradient.*

Primary active transporters include the Na^+-K^+-ATPase, which will come up many times in this course, and the Ca^{2+}-ATPase which cells use to accumulate Ca^{2+} in the endoplasmic reticulum. Secondary active transporters include the transporters used by cells to take up neutral amino acids and sugars (figure). These transport processes are powered by a gradient in Na^+ concentration, established by the Na^+-K^+-ATPase.



b. *Facilitated transport*. In facilitated transport, a protein speeds the diffusion process. No energy is required, and the net movement of substances is only *down* an electrochemical gradient. Sugars and neutral amino acids are transported from intestinal and renal epithelia into the bloodstream via facilitated transport (figure).

For many examples of active and passive transport, read Chapter 1 of Berne and Levy.

Diffusion with an external force in a frictional system

From Fick's first law, we know that the (1D, s-s) molar flux due to pure diffusion of particle *n* is $\varphi_{n(D)} = -D_n \frac{dc_n}{dx}$. Now, let's add an external force that acts to induce an additional flux term:

$\varphi_{n(F)} = c_n v_n$, where v_n [=] m/s is the *drift velocity* of species *n*

If *f* is the force per mole, and we assume that collisions between particles make the system frictional, the system acts like a dashpot, with velocity proportional to force:

$v = u_n f$, where u_n [=] (m mol)/(N s) is the *molar mechanical mobility of n.*

The total steady-state flux is the sum of the fluxes due to diffusion and the force:

$$\varphi_n = \varphi_{n(D)} + \varphi_{n(F)} = -D_n \frac{dc_n}{dx} + u_n f c_n(x,t)$$

Let's specify that the force *f* is induced by an electrical field $\varepsilon = -\frac{d\psi}{dx}$, where ψ [=] V is potential. Remember from freshman physics that 1 V = 1 J/C (energy/charge), implying that ε is a measure of force per charge (N/C). We convert from force per charge to force per mole by multiplying by $z_n F$, where z_n is the valence of the particle and $F = 9.65\times10^4$ C/mol.

$$f = \varepsilon z_n F = -z_n F \frac{d\psi}{dx}$$

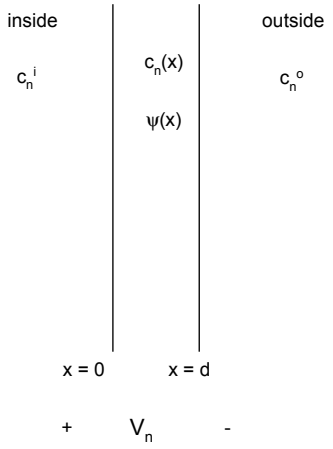
Thus, for a charged species *n* in a 1-dimensional electric field and with a 1-dimensional concentration gradient, we get a net steady-state flux:

$$\varphi_n = -D_n \frac{dc_n}{dx} - u_n z_n F c_n(x,t) \frac{d\psi(x)}{dx}$$

Note: This is a steady-state version of a very famous partial differential equation called the *Nernst-Planck equation*. Solving the Nernst-Planck equation is very difficult in general, but easy for specific cases (like the steady-state equilibrium case we will treat below). .

Steady-state equilibrium for a single ion

We will look at this problem for a membrane of width *d* under steady-state equilibrium, with 1-dimensional effects only (in the direction of *x*). This condition implies that the net flux = 0.



$$\varphi_n(x) = 0 \Rightarrow u_n z_n F c_n(x) \frac{d\psi(x)}{dx} = -D_n \frac{dc_n(x)}{dx}$$

Because $D_n = u_n RT$ (this is the *Einstein relationship,* which relates the diffusion coefficient to molar molecular mobility), we can write:

$$RT \frac{dc_n(x)}{dx} = -z_n F c_n(x) \frac{d\psi(x)}{dx}$$

$$\Rightarrow RT \frac{1}{c_n(x)} \frac{dc_n(x)}{dx} = -z_n F \frac{d\psi(x)}{dx}$$

Because the term $\frac{1}{c_n(x)} \frac{dc_n(x)}{dx} = \frac{d[\ln c_n(x)]}{dx}$, we can write:

$$\frac{RT}{z_n F} \frac{d[\ln c_n(x)]}{dx} = -\frac{d\psi}{dx}$$

Integrate both sides of this equation over the interval [0,*d*]:

$$\frac{RT}{z_n F} \left[\ln c_n(d) - \ln c_n(0)\right] = \frac{RT}{z_n F} \ln \frac{c_n(d)}{c_n(0)} = \psi(0) - \psi(d)$$

Assuming that both $c_n(x)$ and $\psi(x)$ are continuous at the boundaries, we get:

$$V_n = \frac{RT}{z_n F} \ln \frac{c_n^{\,o}}{c_n^{\,i}}$$

This is the *Nernst equation*. It gives the value of membrane potential V_n at which the ion n is in steady-state equilibrium. In other words, at this value of V_n, the electrostatic energy per mole (inside - outside):

$$z_n F V_n \text{ [=] J/mol}$$

is exactly counterbalanced by the chemical energy per mole (inside - outside):

$$RT \ln \frac{c_n^{\,o}}{c_n^{\,i}} \text{ [=] J/mol}$$

Because the energies counterbalance, the fluxes caused by these energies counterbalance as well, giving a net flux $J_n = 0$. The value of V_n is *independent* of the concentration or voltage profile within the membrane!

We often find it convenient to write the Nernst equation in terms of $\log_{10}$:

$$V_n = \frac{RT}{z_n F} \frac{1}{\log e} \log \frac{c_n^{\,o}}{c_n^{\,i}}$$

The term $\frac{RT}{z_n F} \frac{1}{\log e}$ has units of voltage and depends only on T and z_n; all other factors are constants. For $T = 24°C$, $\frac{RT}{F} \frac{1}{\log e} \approx 59$ mV. At this temperature, for a monovalent cation ($z_n = 1$) or anion ($z_n = -1$), V_n changes approximately 59 mV for every 10-fold change in internal or external concentration. The sign of the change depends on z_n. For $T = 37°C$, $\frac{RT}{F} \frac{1}{\log e} \approx 61$ mV.

Modeling resting potential: the Bernstein and Gibbs-Donnan models

Almost all cells have voltage gradients across their plasma membranes. Membrane potential has been known for many years to depend on concentrations of ions, particularly K^+. One of the first mathematical models proposed to explain the resting membrane potential of cells was the *Bernstein model*, which argued that cells at rest are permeable to K^+ *only*. Thus, the cell's resting potential is simply the K^+ *Nernst potential*, V_K (also known as the K^+ *equilibrium potential*). This model predicts that a resting cell should follow the V_K as we manipulate $c_K^{\,o}$ or $c_K^{\,i}$. This turns out not to be true. Real cells often act like "K^+ electrodes" only for high concentrations of external K^+.

Another model that has been considered is a model in which several ions are in equilibrium simultaneously. This condition, known as Gibbs-Donnan equilibrium, requires a very specific relationship among ratios of internal and external concentrations and is not seen in practice:

$$V_{Na} = V_K = V_{Cl} \Rightarrow \frac{RT}{F}\ln\frac{c_{Na}{}^{o}}{c_{Na}{}^{i}} = \frac{RT}{F}\ln\frac{c_K{}^{o}}{c_K{}^{i}} = \frac{RT}{F}\ln\frac{c_{Cl}{}^{i}}{c_{Cl}{}^{o}} \Rightarrow \frac{c_{Na}{}^{o}}{c_{Na}{}^{i}} = \frac{c_K{}^{o}}{c_K{}^{i}} = \frac{c_{Cl}{}^{i}}{c_{Cl}{}^{o}}$$

NOT LIKELY!

The Gibbs-Donnan equilibrium is also problematic in that it leads to osmotic imbalances. See Berne and Levy, Chapter 2.

Steady-state, non-equilibrium

Real cells exist in a multi-ion steady-state, non-equilibrium condition, implying that while all partial derivatives with respect to time = 0, each molar flux φ_n or current flux $J_n = z_n F \varphi_n$ need not be zero. Instead, we will impose the condition that the sum of all fluxes is zero (e.g., for a system with Na^+, K^+, and Cl^-, $J_{Na} + J_K + J_{Cl} = 0$). The total current flux across the membrane (we'll call it $J_m = \sum_{n=1}^{N} J_n$) must equal zero to keep V_m constant.

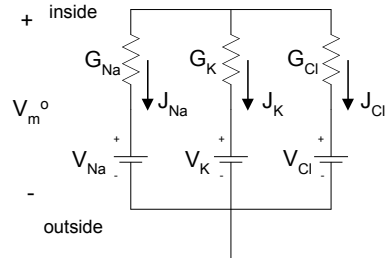
This condition was first handled by Goldman, Hodgkin, and Katz (GHK). They derived the steady-state, non-equilibrium value of membrane potential V_m under two assumptions: (1) the assumption of a semi-permeable membrane (as we have assumed so far); and (2) a constant electrical field (implying a linear change in V_m) across the membrane. The GHK equation, also called the constant-field equation, looks like this for a system including Na^+, K^+, and Cl^- (see Weiss, *Cellular Biophysics, Vol. 1*, MIT Press, for a derivation):

$$V_m = \frac{RT}{F}\ln\left\{\frac{P_{Na}c_{Na}{}^{o} + P_K c_K{}^{o} + P_{Cl}c_{Cl}{}^{i}}{P_{Na}c_{Na}{}^{i} + P_K c_K{}^{i} + P_{Cl}c_{Cl}{}^{o}}\right\}$$

In this equation, the terms P_{Na}, P_K, and P_{Cl} refer to the *permeabilities* of the membrane to each of these ions. For each ion n, $P_n = D_n/d$. (This definition of P_n assumes that concentrations of ion n are continuous at the boundaries.)

In the GHK formulation, we think of ions as diffusing through a continuous, semi-permeable membrane. We now know that the lipid bilayer is essentially impermeable to ions, and that ions travel through specific *ion channels*. To a first approximation, most ion channels are permeable only to one biologically relevant ion. Populations of ion channels are well modeled as conductances in series with batteries, where the conductances represent the summed conductances of a population of open channels in parallel, and the battery is the Nernst (equilibrium) potential for the ions in question:

This formulation is very useful for both steady-state and non-steady-state conditions. For example, it allows us to look at the steady-state current fluxes in membranes using simple electrical circuit theory. A system with three permeant ions (Na^+, K^+, and Cl^-), would look like this in the steady-state:



The conventions we impose here ($V_m = V_{in} - V_{out}$, outward currents positive) will are standards and will hold for the entire

course; remember them! Under resting (steady-state) conditions, we can impose the condition that $J_m = J_{Na} + J_K + J_{Cl} = 0$. This is Kirchoff's current law for membranes!

It is easy to solve a circuit like this for *resting potential* V_m^0:

$$J_m = \sum_n G_n \left[V_m^{\,0} - V_n \right] = 0$$

$$\Rightarrow V_m^{\,0} = \frac{\sum_n G_n V_n}{\sum_n G_n} = \frac{\sum_n G_n V_n}{G_m}, \text{ where } G_m \equiv \sum_n G_n$$

G_m is the *resting conductance* of the cell.

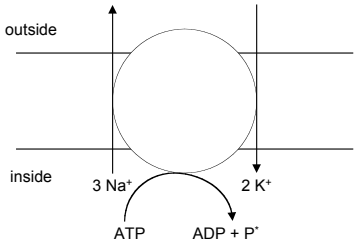
Away from resting potential, we have a *Thevenin equivalent* relationship:

$$J_m = G_m V_m - \sum_n G_n V_n = G_m \left[V_m - V_m^{\,0} \right]$$

Modifications of the steady-state membrane model

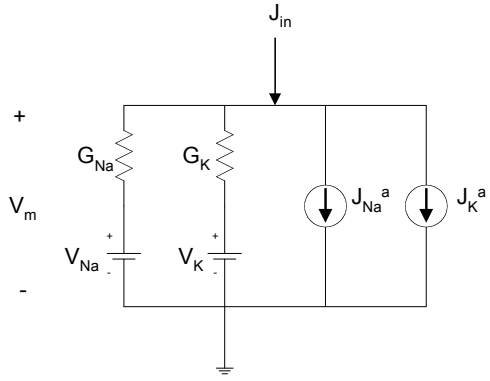
In our steady-state membrane model, the total membrane flux $J_m = 0$, but, because the membrane does not sit at the equilibrium potential of any ion (in general), each flux is non-zero. These ongoing fluxes slowly erode the electrochemical gradients underlying the Nernst potentials.

Real cells overcome this problem of run-down by expending energy to maintain their concentration gradients. Ions are moved up their electrochemical gradients, in a process called *active transport*. The most famous example of active transport is the sodium-potassium pump (Na^+-K^+ ATPase):



The Na^+-K^+-ATPase is an example of an *electrogenic* pump, because it causes a net electrical current. (In this case, the net flow of positive charge is outward; it is a net positive current in our sign convention.)

Pump currents can be modeled reasonably well as *ideal current sources* (i.e, current sources with a very large parallel resistance), as long as they have reasonable amounts of their preferred ions to work with. For a system including Na^+ and K^+ ions, the new circuit would look like this:



where $J_{Na}^{\,a}$ and $J_K^{\,a}$ are pump current fluxes and J_{in} represents current from an external source (e.g., an electrode that one has inserted into the cell). If we know that $J_{Na}^{\,q}$ and $J_K^{\,a}$ are due to the Na^+-K^+-ATPase only, we can apply the constraint $3\,J_{Na}^{\,a} = -2\,J_K^{\,a}$. Pumps have been studied quantitatively and have been found in general to obey the following phenomenological equations:

$$J_{Na}^{a}(t) = z_{Na} F \nu_{Na} \alpha_{ATP}(t) = 3F \alpha_{ATP}(t)$$

$$J_{K}^{a}(t) = z_{K} F \nu_{K} \alpha_{ATP}(t) = -2F \alpha_{ATP}(t)$$

$$\alpha_{ATP}(t) = \alpha_{\max}\left[\frac{c_{ATP}{}^{i}(t)}{c_{ATP}{}^{i}(t) + K_{ATP}{}^{i}}\right]\left[\frac{c_{Na}{}^{i}(t)}{c_{Na}{}^{i}(t) + K_{Na}{}^{i}}\right]^{\nu_{Na}}\left[\frac{c_{K}{}^{o}(t)}{c_{K}{}^{o}(t) + K_{K}{}^{o}}\right]^{\nu_{K}}$$

$$= \alpha_{\max}\left[\frac{c_{ATP}{}^{i}(t)}{c_{ATP}{}^{i}(t) + K_{ATP}{}^{i}}\right]\left[\frac{c_{Na}{}^{i}(t)}{c_{Na}{}^{i}(t) + K_{Na}{}^{i}}\right]^{3}\left[\frac{c_{K}{}^{o}(t)}{c_{K}{}^{o}(t) + K_{K}{}^{o}}\right]^{2}$$

In these equations, ν_{Na} and ν_K are number of molecules of Na^+ and K^+ pumped per molecule of ATP hydrolyzed; $\alpha_{ATP}(t)$ is the time-varying pump rate; $\alpha_{\max}$ is the maximal value of the pump rate; and $K_{ATP}{}^{i}$, $K_{Na}{}^{i}$, and $K_K{}^{o}$ are dissociation constants. In this model, the internal concentration of ATP, the internal concentration of Na^+, and the *external* concentration of K^+ control the pump rate. For large concentrations ($c >> K$), the square-bracketed terms act like constants; for small concentrations ($c << K$), the square-bracketed terms have linear dependence on concentration.

Cellular homeostasis

Pumps serve the crucial function of keeping the concentration gradients of vital ions from "running down." Thus, over time, the passive fluxes through conductances should be exactly canceled by opposing active fluxes. This is a form of *cellular homeostasis*, which we define here as the study of the mechanisms by which cells maintain a constant intracellular environment.

Think of the world as a very tough neighborhood. A given excitable cell has to maintain energetically unfavorable electrochemical gradients for signaling purposes. It can be subjected to large changes in the osmolarity of its environment, particularly in animals like sea slugs that allow the osmolarity of their internal environment to change with that of the external environment (*osmoconformers*), but also in *osmoregulators* such as ourselves.

The mathematical equations of homeostasis fall into two general categories. *First*, some equations describe the ion channels, pumps, chemical buffering systems, and other properties that pertain to a specific population of cells. The equations we have discussed for pumps and channels fall into this category. *Second*, some equations describe rules of conservation. These equations apply to all conditions.

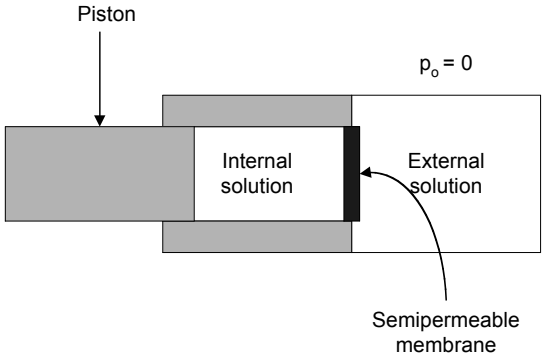
Conservation of solute

Consider a cell with time-varying membrane surface area $A(t)$. The law of conservation of solute is a continuity equation stating that any ionic fluxes into or out of the cell must affect the concentrations within the cell. It amounts to conservation of matter:

$$\frac{dn_n{}^{i}}{dt} = -A(t)\sum_j \varphi_n{}^{j}(t)$$

In this equation, $n_n^i(t)$ is the number of molecules of ionic species n inside the cell; $\varphi_n^j(t)$ is the flux of ionic species n due to membrane mechanism j. Different membrane mechanisms would include flow through ion channels pumps. If the species n is bound by intracellular buffers, the influence of the buffers would be added to the right side of the equation (see Weiss, Vol. 1, p. 577). The negative sign comes from our sign convention, in which a positive flux is defined as an outward flow of the ion.

Conservation of volume



If a cell is subjected to different external and internal pressures, its volume will change to compensate. More importantly in practice, as the osmolarity of internal and external solutions changes, these osmotic changes change cellular volume through the effects of *osmotic pressure*. Differences in osmotic pressure across a membrane can be described very simply by van't Hoff's Law:

$$\pi_i - \pi_o = RT\left[\sum_n \Phi_n c_n{}^i - \sum_n \Phi_n c_n{}^o\right]$$

where R is the molar gas constant; T is absolute temperature; Φ_n is the *osmotic coefficient*, which is a measure of how well the particles of n act independently at a given concentration and temperature ($\Phi_n = 1$ for very small concentrations; it is near 1 for most physiological solutes under physiological conditions); and $c_n{}^i$ and $c_n{}^o$ are the internal and external concentrations of species n. In the sums, all solute species must be accounted for, including impermeant ones.

Please note: in comparing the equation above with equation 1-2 from B&L, there is a tricky ambiguity in notation. My terms $c_n{}^i$ and $c_n{}^o$ refer to the concentration of the dissolved ionic species, while B&L use c to stand for the concentration of the solute before it is dissolved, and use the factor i to account for the fact that the ion may dissolve into multiple particles. For example, consider a solution of 1 M $CaCl_2$. In my notation, $c_{Ca} = 1$M, $c_{Cl} = 2$ M. In the notation of B&L, $c_{CaCl_2} = 1$ M and i=3.

Flux of water caused by pressure-driven fluxes of water are described by the equation:

$$\dot{V}_w = L_V \left[\left[p_o - p_i \right] + \sigma_n \left[\pi_i - \pi_o \right] \right]$$

$$= L_V \left[\left[p_o - p_i \right] + \sigma_n RT \left[\sum_n \Phi_n c_n^{\,i} - \sum_n \Phi_n c_n^{\,o} \right] \right]$$

In this equation, L_V [=] m/(Pa s) is the *hydraulic conductivity* of the membrane. The *reflection coefficient* σ_n represents the ability of the membrane to filter out the solute dissolved in the water. A perfectly impermeant solute has σ_n=1; conversely, a solute that passes through the membrane as easily as water has σ_n=0 and generates no net osmotic flow. In practice, we often assume σ_n=1. Usually, the hydraulic pressure gradient p_o - p_i = 0, implying that the internal and external osmotic pressures must remain equal to meet the condition of conservation of volume.

Notes on notation and other issues. In general, I've used the notation from another, much more thorough text on this subject (Weiss, *Cellular Biophysics, Vol. 1*, MIT Press, 1996). Here, I use the notation of Berne and Levy for the osmotic coefficient. The osmotic coefficient of solute *n* (Φ_n) should not be confused with the molar flux of solute *n* (φ_n). Sorry for the notational ambiguities, but it makes no sense to develop an entirely new set of notation to work around the poorly-developed notation of Berne and Levy. In comparing my version of van't Hoff's Law with that of Berne and Levy, there is the important difference that my notation tracks the concentration of an individual ion, whereas theirs does not. This is only a notational issue.

Important summary points about osmosis:

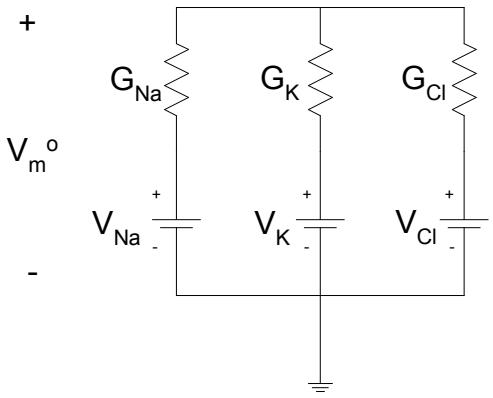
1. The steady-state volume of the cell is determined the concentrations of impermeant ions.

2. Permeant solutes redistribute according to the rules of electrodiffusion, and hence only transiently affect the volume of the cell. The more permeant the solute, the more transient its effects on volume, because more permeant ions will redistribute more quickly. This behavior can be understood in terms of the reflection coefficient σ_n. For $\sigma_n < 1$, some solute passes through the membrane along with the water, implying a molar flux that is proportional to the flux of water with constant of proportionality $(1-\sigma_n)$. Thus, the solute will redistribute itself until the system reaches a new equilibrium.

Cellular homeostasis: an example

The condition of cellular homeostasis implies that, while each flux $\varphi_n^j(t)$ may be non-zero, the sum of fluxes (and buffering reactions, if they are present) of a given ion should be zero to make $\frac{dn_n^{\,i}}{dt} = 0$. Also, under homeostasis, the volume is unchanging, implying that $\sum_n c_n^{\,i} = \sum_n c_n^{\,o}$ if $p_o = p_i$, as is usually the case and we assume that the osmotic coefficient $\Phi_n = 1$ for each solute. The cell is said to be in *osmotic equilibrium* if the internal and external osmotic pressures are equal. Finally, the condition of electroneutrality must be met, implying that for both the inside and outside of the cell, positive and negative ions must be present in equal numbers.

Consider the implications of cellular homeostasis for a simple 3-ion model:



We'll take outer concentrations $c_{Na}^{\,o} = 120$ mM, $c_K^{\,o} = 5$ mM, and $c_{Cl}^{\,o} = 125$ mM; internal impermeant anions present at a concentration $c_A^{\,i} = 121$mM; and conductance values $G_{Na} = 0.01$ mS/cm^2, $G_K = 0.05$ mS/cm^2, and $G_{Cl} = 0.01$ mS/cm^2. Let's see under what conditions we can get a homeostatic solution.

In this case, with only one flux per ion, our quasi-equilibrium solution, if it exists, is a true equilibrium solution: $J_{Na}^{\,p} = J_K^{\,p} = J_{Cl}^{\,p} = 0 \Rightarrow V_m^{\,0} = V_{Na} = V_K = V_{Cl}$. This is the Donnan equilibrium condition, which implies that concentration ratios are equal for the three ions: $\frac{c_{Na}^{\,o}}{c_{Na}^{\,i}} = \frac{c_K^{\,o}}{c_K^{\,i}} = \frac{c_{Cl}^{\,i}}{c_{Cl}^{\,o}}$. Electroneutrality $\Rightarrow c_{Na}^{\,i} + c_K^{\,i} = c_{Cl}^{\,i} + c_A^{\,i}$, $c_{Na}^{\,o} + c_K^{\,o} = c_{Cl}^{\,o}$. We can combine and rearrange these equations to give a quadratic equation in $c_{Na}^{\,i}$ with no other unknowns:

$$\left[1 + \frac{c_K^{\,o}}{c_{Na}^{\,o}}\right]\left(c_{Na}^{\,i}\right)^2 - c_A^{\,i} c_{Na}^{\,i} - c_{Cl}^{\,o} c_{Na}^{\,o} = 0$$

This equation has the solution:

$$c_{Na}^{\,i} = \frac{c_A^{\,i} \pm \sqrt{\left(c_A^{\,i}\right)^2 + 4c_{Cl}^{\,o}\left[c_{Na}^{\,o} + c_K^{\,o}\right]}}{2\left[1 + \frac{c_K^{\,o}}{c_{Na}^{\,o}}\right]} = \frac{c_A^{\,i} \pm \sqrt{\left(c_A^{\,i}\right)^2 + 4\left(c_{Cl}^{\,o}\right)^2}}{2\left[1 + \frac{c_K^{\,o}}{c_{Na}^{\,o}}\right]}$$

With the values listed above, we get $c_{Na}^{\,i} = 191.4$ mM, -75.2 mM. We will neglect the negative solution, because it is physically impossible. $c_{Na}^{\,i} = 191.4$ mM $\Rightarrow V_{Na} = -12.1$ mV, $c_K^{\,i} = 7.97$ mM, and $c_{Cl}^{\,i} = 78.37$.

We have determined this putative quasi-equilibrium state without accounting for the condition of osmotic equilibrium. Have we gotten a solution that meets this last condition?

$$\sum_n c_n^{\,i} = 191.4 + 7.97 + 78.37 + 121 = 398.74 \text{ mM} \neq \sum_n c_n^{\,o} = 120 + 5 + 125 = 250 \text{ mM}$$

No. This solution does not obey the condition of osmotic equilibrium. For this system, there is no quasi-equilibrium condition! We would have to add other elements to the circuit (e.g., pumps) to make the quasi-equilibrium state possible.