

## 580.439 Course Notes: Thermodynamics and the Nernst-Planck Eqn.

**Reading:** Johnston and Wu, chaps 2, 3, 5; Hille, chaps 10, 13, 14.

In these lectures, the nature of ion flux in free solution and in diffuse membranes is discussed, using ideas from thermodynamics. This theory ignores the specific properties of ion channels, but is important as a general background for more specific theories that are considered later. Most important, the thermodynamic theories provide boundary conditions for all models of ion flux in biological membranes.

### First law of thermodynamics

The starting point for this discussion is the first and second laws of thermodynamics. These laws are concerned with *functions of state* of systems. A *system* is simply whatever collection of objects is of interest. For this course, the systems will generally consist of a membrane and the solutions bounding the two sides of the membrane, as in Fig. 1. The important constituents of the system are the membrane and the ionic solutes in the solutions.

Systems have various parameters, including pressures, temperatures, concentrations of solutes, etc. These are generally divided into *extensive parameters*, such as volume or the total quantity of a solute in the system, which depend on the size of the system and *intensive parameters*, such as concentration and pressure which do not depend on the size of the system. Functions of state are thermodynamic quantities that are uniquely defined by the extensive and intensive parameters of the system. That is, all solutions like the one in Fig. 1 will have the same thermodynamic state functions if their temperatures, volumes, solute concentrations, etc. are the same.

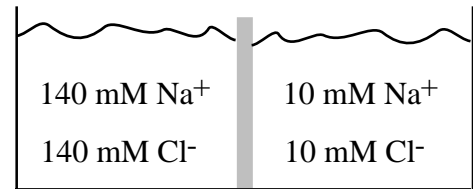


Figure 1: example of a system consisting of a membrane (fuzzy line) separating two NaCl solutions

An example of a thermodynamic function of state is the internal energy  $U$ . The first law of thermodynamics provides an indirect definition of  $U$  by stating the conditions under which  $U$  can be changed:

**First law:** the internal energy  $U$  of a system is a function of state that is changed only by heat flow or work done on the system:

$$\Delta U = U_2 - U_1 = q + w \quad (1)$$

When the system goes from state 1 to state 2 its internal energy changes by an amount equal to the heat  $q$  that flows into the system plus the work  $w$  done on the system by its surroundings. Notice that  $U$  has units of Joules, or similar units of energy.

The first law is essentially a statement of conservation of energy.

As an example, suppose that an ideal gas is compressed from volume  $V_1$  to volume  $V_2$ . In this situation the work done on the gas is given by

$$w = - \int_{V_1}^{V_2} P dV \quad (2)$$

$PdV$  is the pressure-volume work done by the gas when it expands by a volume change  $dV$  against a pressure  $P$ . The minus sign makes this the work done on the gas during such an expansion and the integral computes the total work going from one volume to another.

The change in  $U$  of the gas during the compression from  $V_1$  to  $V_2$  is the sum of the work in Eqn. 2 and whatever heat is allowed to flow. Suppose that no heat is allowed to flow into or out of the gas during the compression (a system that does not exchange heat with its environment is called *adiabatic*). In this case, the pressure and volume of an ideal monoatomic gas follow the rule  $PV^\gamma = c$ , where  $c$  is a constant and  $\gamma \approx 5/3$ . Using this rule, the work done in compressing the gas is

$$w = - \int_{V_1}^{V_2} \frac{c}{V^\gamma} dV = \frac{c}{\gamma - 1} \left( \frac{1}{V_2^{\gamma-1}} - \frac{1}{V_1^{\gamma-1}} \right) \quad (3)$$

and  $\Delta U = w$  in this case, since  $q=0$ .

As another example, suppose the gas is placed on a heat reservoir at temperature  $T$  during the compression and that heat flows between the gas and the reservoir in such a way as to maintain the temperature of the gas constant at  $T$ . Now, the internal energy of an ideal gas turns out to depend only on its temperature, so in this case  $\Delta U = 0$  since the temperature of the gas does not change. Using the first law, we can conclude that the heat flow into the gas is the negative of the compression work done on the gas,  $q = -w$  so that

$$q = -w = \int_{V_1}^{V_2} P dV = \int_{V_1}^{V_2} \frac{nRT}{V} dV = nRT \ln \frac{V_2}{V_1} \quad (4)$$

where the ideal gas law  $PV=nRT$  was used.

**Question 1:** An engine runs in a cycle; each time it goes around the cycle once, it absorbs heat  $q_1$  from one reservoir and delivers heat  $q_2$  to a second reservoir; it also delivers work  $w$  to its environment and ends up in exactly the same thermodynamic state as at the beginning of the cycle. What does the first law tell you about  $q_1$ ,  $q_2$ , and  $w$ ?

## Second law of thermodynamics

The second law provides a rule that describes the direction of change in a system in the absence of external forces. We know from experience, for example, that heat flows from warm objects to cold objects, that objects fall downward in a gravity field, that gas expands from a pressure into a vacuum, and that solutes diffuse from regions of high concentration into regions of low concentration. The second law is a rule which captures these facts in a remarkably concise way.

Flows in thermodynamic systems are driven by forces; flows and forces occur in conjugate pairs. That is, heat flow is driven by differences in temperature, volume flow by differences in pressure, charge flow by differences in electrical potential, and mass flow by differences in concentration. In complex systems, there may be cross-coupling between forces and non-conjugate flows, but this subtlety will be ignored for the time being.

Essential to the second law is the idea of a *reversible* flow. A flow is reversible when it is driven by an infinitesimal force, i.e. a force which is so close to zero that a small change in the magnitude of the force at the appropriate place can reverse the direction of the flow. In real systems, flows are almost always irreversible, for example the flow of electric current through a lamp which occurs across a substantial electrical potential difference or the flow of heat into an ice cube from a glass of warm water, which occurs between a substantial temperature difference.

The second law of thermodynamics deals with heat flow and defines a new state function, the *entropy*.

**Second law:** the entropy  $S$  of a system is a state function which changes with heat flow as

$$\Delta S = S_2 - S_1 = \int_1^2 \frac{dq}{T} \quad (5)$$

by a reversible process. For an irreversible process, the entropy change is greater than the integral above.

The limits in the integral in Eqn. 5 mean that the quantity  $dq/T$  should be summated over the path that the system takes to get from state 1 to state 2. Exactly how the limits are written will depend on the problem. The point is that entropy is the accumulation of  $dq/T$ , heat flow into the system divided by temperature, by a reversible process. Note that for adiabatic systems,  $\Delta S \geq 0$  with equality only for reversible changes. Thus in an adiabatic system any naturally occurring irreversible process must occur in the direction which increases the entropy of the system.

The fact that the entropy of an adiabatic system can only increase sets a direction for all natural processes. As an example of this, consider the case of an irreversible heat flow  $q$  between two reservoirs at temperatures  $T_1$  and  $T_2$ , as shown in Fig. 2A. In order to compute the entropy change associated with this flow, it is shown as an equivalent process in Fig. 2B consisting of two reversible flows. The entropy change associated with the heat flow can then be computed as

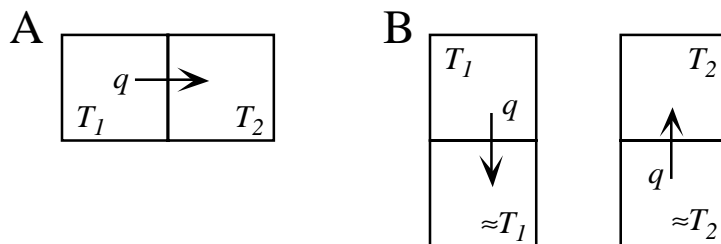


Figure 2: A. Heat  $q$  flows by an irreversible process between temperatures  $T_1$  and  $T_2$ . B. Same flow, but by two reversible processes.

$$\Delta S = -\frac{q}{T_1} + \frac{q}{T_2} \quad (6)$$

The first term is the entropy change of the  $T_1$  part of the system and the second term is the entropy change of the  $T_2$  part. Now the system in Fig. 2A is adiabatic, in that heat flows only internally, so the second law says that  $\Delta S > 0$ . Therefore, if  $q > 0$ , then

$$\Delta S = q \left( \frac{1}{T_2} - \frac{1}{T_1} \right) > 0 \quad \Rightarrow \quad T_1 > T_2 \quad (6a)$$

In other words, the second law says that heat flows from a higher temperature to a lower one in an irreversible process. Note that the assumption  $q > 0$  is not necessary; if we had assumed  $q < 0$  then the same conclusion would be reached, except now  $T_2 > T_1$ .

**Question 2:** An alternate statement of the second law is that net work cannot be done by an engine which only draws heat from a single reservoir. To see that the second law implies this statement, consider an engine which runs in a cycle. Each time around the cycle it draws heat  $q$  from a reservoir at temperature  $T$  and delivers work  $w$  to the environment. There are no other heat flows. The engine is cyclic, meaning that its state is exactly the same at the end of a cycle as at the beginning (in particular,  $S$  and  $U$  are the same at the beginning and end of each cycle). Show that this engine is consistent with the first law, but violates the second law. Does the engine of Question 1 necessarily violate the second law (Hint: suppose the heat exchanges in question 1 occur reversibly)?

### Gibbs Free Energy

The analysis of Fig. 2 shows how the second law can be applied to heat flows. For systems consisting of ionic solutions, it is difficult to make a similar analysis, because the heat flows associated with ionic movements in solution are hard to compute. This problem can be simplified by using a different state function, called the *Gibbs free energy*  $G$ , which is defined as

$$G = U + PV - TS \quad (7)$$

Here,  $P$  is pressure and  $V$  is volume. The Gibbs free energy allows an alternative statement of the second law which is more useful for our purposes. Consider a small change in  $G$  which can be defined by differentiating Eqn. 7:

$$dG = dU + PdV + VdP - TdS - SdT \quad (8)$$

Rearranging this equation and using the fact that  $dU = q + w$  (first law) and that  $dS \geq q/T$  (second law) gives

$$\begin{aligned} dG - VdP + SdT &= q + w + PdV - TdS \\ &\leq w + PdV \end{aligned} \quad (9)$$

Now in ionic solutions, the pressure and temperature are usually constant, so  $dP=dT=0$  and Eqn. 9 can be written as

$$dG_{T,P} \leq w + PdV = w' \quad (10)$$

The notation  $dG_{T,P}$  means the change in free energy in a system in which temperature and pressure are constant.  $PdV$  is the pressure-volume work done by the system on its environment, i.e. the work done by expansion or contraction of the system.  $w$  is the sum of various kinds of work, one component of which is  $-PdV$ , the pressure-volume work done by the environment on the system. Thus,  $w+PdV$  is the net work done by the environment on the system, exclusive of pressure-volume work. This is denoted  $w'$  in Eqn. 10.

Eqn. 10 is an alternate statement of the second law of thermodynamics which says that, for a system at constant temperature and pressure, the change in Gibbs free energy in any change of state is less than or equal to the non-PV work done on the system by the environment. Equality holds only for reversible changes. Typically in membrane transport problems  $w'=0$ , and the second law says that the Gibbs free energy must decrease or stay constant in any spontaneously-occurring state change.

### Electrochemical potential

$G$  is an extensive parameter of a system, i.e. it increases linearly with the size of the system. Because it is inconvenient to keep track of system size in most calculations, the *electrochemical potential*  $\mu_i$  is used instead.  $\mu_i$  is the contribution of one mole of the  $i^{\text{th}}$  constituent of the system to the system's free energy, its molar free energy. If  $n_i$  is the number of moles of the  $i^{\text{th}}$  constituent in the system, then

$$G = \sum_i n_i \mu_i \quad (11)$$

or equivalently,  $\partial G/\partial n_i = \mu_i$ .

The electrochemical potential is the drive for flux of substances across a diffusion barrier. Consider the situation diagrammed in Fig. 3. A solution is separated into two phases by a membrane. The electrochemical potentials of the solute in the two phases are  $\mu_1$  and  $\mu_2$ . Suppose that a small amount of solute  $dn$  moves from side 1 to side 2. Using Eqns. 10 and 11, it must be the case that

$$dG = -\mu_1 dn + \mu_2 dn \leq 0 \quad (12)$$

because the process occurs at fixed temperature and pressure and there is no external work. That is, the change in free energy of the whole system ( $dG$ ) is the free energy lost on side 1 ( $-\mu_1 dn$ ) plus the free energy gained on side 2 ( $\mu_2 dn$ ). If  $dn>0$  as drawn, then Eqn. 12 implies that  $\mu_2 \leq \mu_1$ . Thus transport of solutes occurs from regions of higher electrochemical potential to regions of lower

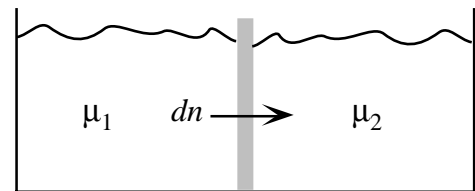


Figure 3:  $dn$  moles of solute moves through the membrane between electrochemical potentials  $\mu_1$  and  $\mu_2$ .

potential. This is an alternative statement of the second law which is convenient for membrane problems.

Note in particular that if  $\mu_2 = \mu_1$  then  $dG = 0$  for any flux through the membrane; that is, there is no way to decrease  $G$  by transport of solute through the membrane. This condition is *equilibrium*. As we will see below, there is no net flux through the membrane of a solute that is at equilibrium.

In order to use the electrochemical potential, it is necessary to discover how it varies with important system parameters; in the case of membrane transport, important parameters are the ion concentration and the electrical potential (pressure can also be included for cases where osmotic flows are important, but these are negligible in neurons). The appropriate expression is Eqn. 13.

$$\mu_i = \mu_i^0 + RT \ln C_i + z_i FV + \dots \quad (13)$$

The subscript  $i$  identifies the particular ion to which this equations refers; there is one such equation for each solute. The third term on the right hand side,  $z_i FV$  is the contribution of electrical potential.  $z_i$  is the charge on the ion (e.g. +1 for  $\text{Na}^+$ , -1 for  $\text{Cl}^-$ , +2 for  $\text{Ca}^{++}$ );  $F$  is the number of Coulombs of charge in a mole of unit charges ( $9.65 \times 10^4$  coul/mole), and  $V$  is the electrical potential (NOTE the change in notation,  $V$  is voltage, not volume, from here on). The product  $z_i FV$  is the work required to bring a mole of ions with charge  $z_i$  from 0 potential to potential  $V$ . Consistent with the definitions of  $G$  as the non-pressure-volume work done on the system (Eqns 9 and 10), this is the electrical contribution, per mole, to  $G$ .

The second term on the right hand side of Eqn. 13,  $RT \ln C_i$  is the contribution of the ion's concentration  $C_i$ .  $R$  is the gas constant (8.315 Joule/°mole) and  $T$  is the temperature. It is not possible to give a simple derivation of this term. Ultimately, it depends on the empirical behavior of solutions, as expressed by phenomena like osmotic pressures. A derivation of this type is given by Katchalsky and Curran (1965, pp. 54-56). For the present, the form of this term will be accepted as an assumption. Later, it will be shown to be consistent with the results of other, quite different, approaches. This term is expressed in terms of concentration  $C_i$ ; in many cases, especially for more concentrated solutions, this term is inaccurate, which has led to the development of an empirically corrected concentration, called *activity*. For the purposes of this course, however, concentration will be used.

The first term on the right hand side of Eqn. 13,  $\mu_i^0$  is the electrochemical potential of the ion at unity concentration and zero electrical potential. It contains the contributions of all factors other than concentration and electrical potential to the electrochemical potential of the ion. This includes effects such as interaction between the ion and the solvent, the effects of pressure, and other such effects.

**Question 3:** When there is a flux of solute across the membrane in the situation diagrammed in Fig. 3, the concentration of solute will decrease on side 1 and increase on side 2. From Eqn 13, this should produce a change in  $\mu_i$  in the solutions. Such a change was not considered in the analysis leading to Eqn. 12. That is, the full differential  $dG$  should include terms like  $n_1 d\mu_1$ . By using Eqn. 13 to compute  $d\mu_i$ , show that, even when such terms are considered, the result in Eqn. 12 is correct, as long as the flux  $dn$  is small.

## Equilibrium

The discussion of Fig. 3 and Eqn. 12 showed that transport through membranes is driven by electrochemical potential differences. *Equilibrium* occurs when there are no electrochemical potential differences. In this situation, there is no force driving transport in the system, and no flux should be observed.

Fig. 4 shows a membrane with the relevant parameters identified. An ion exists at concentrations  $C_1$  and  $C_2$  on the two sides of a membrane. There is also an electrical potential difference  $\Delta V = V_2 - V_1$  across the membrane. As a result of these differences, there could be a difference in the electrochemical potential of the ion across the membrane. However, it is also possible that the potential due to the concentration difference could be equal and opposite to the electrical potential, producing no difference in electrochemical potential, i.e. an equilibrium. The *Nernst equation* expresses the conditions under which this is true.

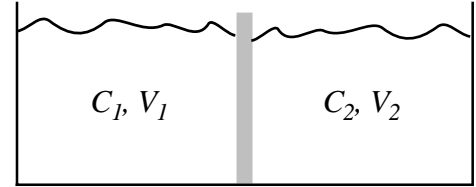


Figure 4: a membrane separating two solutions. The concentration of an ion differs in the two solutions and there is a difference in electrical potential between the solutions.

Directly writing the condition for equality of electrochemical potential across the membrane gives:

$$\mu_i^0 + RT \ln C_1 + z_i F V_1 = \mu_i^0 + RT \ln C_2 + z_i F V_2 \quad (14)$$

Note the assumption that  $\mu_i^0$  is the same in both solutions. This should be true if the solutions differ only in ion concentration and electrical potentials. Canceling common terms and rearranging Eqn. 14 gives the Nernst equation:

$$V_2 - V_1 = E_i = \frac{RT}{z_i F} \ln \frac{C_1}{C_2} \quad (15)$$

That is, when the electrical potential difference is equal to the value  $E_i$ , given by the function of concentration on the right-hand side, then the electrochemical potential of the ion is the same in the two solutions and the ion is at equilibrium. The value  $E_i$  is called the *equilibrium potential* of the ion.

Speaking loosely, the equilibrium of Eqn. 15 can be considered to describe the condition in which the electrical force pushing the ion one way through the membrane is just balanced by an equal and opposite “concentration force” pushing the other way.

**Question 4:** An important condition for many analyses of membrane systems is *charge electroneutrality*, which means that the net charge in a solution is zero. That is, the total concentration of anionic charge is equal to the total concentration of cationic charge:

$$\sum_{\text{all cations}} z_i C_i = - \sum_{\text{all anions}} z_i A_i \quad (16)$$

Of course, in order to have a membrane potential, there must be some charge separation across the membrane; thus, if the membrane potential is negative, then there must be a net negative charge inside the cell and a net positive charge outside the cell. Consider a spherical cell of radius  $10\ \mu\text{m}$  with a membrane potential of  $-70\ \text{mV}$ . The cell is filled with a  $140\ \text{mM}$  solution of  $\text{KCl}$ . How large is the charge imbalance relative to the total concentration of ion inside the cell? Do this problem by assuming a membrane capacitance of  $1\ \mu\text{fd}/\text{cm}^2$  and compute the charge on the membrane capacitance necessary to produce the  $-70\ \text{mV}$  potential. You should conclude that Eqn. 16 is a very good approximation.

**Question 5:** For a typical mammalian cell, the ion concentrations are something like those given in the table at right. Compute the equilibrium potential for each ion.

ion	inside cell	outside cell
$\text{Na}^+$	20 mM	120 mM
$\text{K}^+$	140 mM	4 mM
$\text{Cl}^-$	7 mM	140 mM
$\text{Ca}^{++}$	$10^{-4}\ \text{mM}$	1.5 mM

If the membrane potential is  $-60\ \text{mV}$ , which ions are at equilibrium? For the ions that are not at equilibrium tell which direction (into the cell or out of the cell) they will flow. That is, on which side of the membrane is their electrochemical potential lower?

**Question 6:** Argue that the equilibrium discussed in connection with Fig. 4 is stable. That is, suppose that the membrane potential  $\Delta V$  is slightly smaller or larger than the equilibrium potential  $E_i$  for ion  $i$ . The ion will not be at equilibrium and there will be a net flux of the ion through the membrane. Argue that the flux will carry charge in such a direction as to bring the ion back to equilibrium. Is this result related in any way to the rule that  $\Delta G \leq 0$ ?

**Question 7:** Usually the ionic constituents of real cells are not at equilibrium across the cell membrane. However, the *Donnan equilibrium* is an approximation for the membrane potentials of certain cells. The situation is diagrammed in Fig. 5. A membrane permeable to both potassium and chloride separates the solutions indicated. The concentrations of potassium and chloride outside the cell are fixed at  $10\ \text{mM}$ . The concentrations inside the cell are adjusted by transmembrane fluxes until both potassium and chloride are at equilibrium across the membrane.  $N_{in}$  represents the concentration of fixed negative charges inside the cell. These charges are impermeable to the membrane and their concentration cannot change. By using the Nernst equation to express the equilibrium potentials for potassium and chloride and by assuming that charge electroneutrality (Eqn. 16) holds in both solutions, compute  $K_{in}$ ,  $\text{Cl}_{in}$ , and  $\Delta V = V_{in} - V_{out}$ , the transmembrane potential, in terms of the external concentrations and  $N_{in}$ . (Note the situation analyzed here is not realistic for a membrane system; in particular there is a large osmotic pressure difference between the two solutions which would lead to substantial water flow through the membranes; see the next question.)

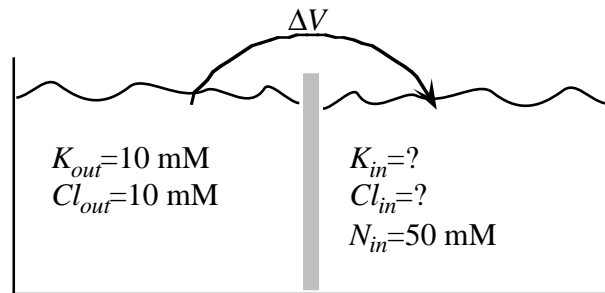


Figure 5: A membrane separates two solutions. Potassium and chloride are allowed to come to a Donnan equilibrium.



**Question 7.5:** The effects of pressure-volume effects can be added to the electrochemical potential by adding a term  $V_i P$  to the r.h.s. of Eqn. 13, where  $V_i$  is the partial molar volume of the  $i$ th constituent of the system and  $P$  is the pressure applied to the solution. The partial molar volume is a constant equal to the change in volume of the solution when a mole of the  $i$ th solute is added. Thus  $V_i P$  can be considered as the work required to add a mole of the  $i$ th solute against a pressure  $P$ . Consider a cell containing an aqueous solution of a single non-ionic solute (so that  $z_i=0$ ). The solute has concentrations  $C_{out}$  outside and  $C_{in}$  inside the cell. Show that the solute is not at equilibrium if  $C_{out} \neq C_{in}$ , unless there is a difference in pressure between the inside and outside of the cell. Write an expression for the equilibrium pressure difference in terms of the concentrations (this should remind you of the development of Eqn. 15). The osmotic pressure of a solute is usually written as  $\Pi_i = RT \ln C_i$ ; justify this terminology. Osmotic pressure differences usually lead to water flux through membranes, because if the solutes are out of equilibrium, then so is the water.

**Question 8:** Suppose that an aqueous solution of NaCl has an interface with a solvent (oil) which does not mix with water. What is the equilibrium distribution of Na and Cl between the two phases? Assume that, at equilibrium, the electrochemical potentials of Na and Cl are the same in the two phases, that charge electroneutrality (Eqn. 16) holds in both phases, and that the concentrations of Na and Cl in the aqueous phase are fixed at 100 mM. Assume also that  $\mu_{Na}^0(\text{water}) \neq \mu_{Na}^0(\text{oil})$  and that  $\mu_{Cl}^0(\text{water}) \neq \mu_{Cl}^0(\text{oil})$ , to account for different solute/solvent interactions in the two phases. Is there a potential difference between the two phases at their interface? If so, what is its value?

The potential difference that develops in this situation is called a *junction potential*. Such potentials should exist at the surfaces of the membrane models to be considered below, but they will be ignored, in order to focus on the properties of the diffusion regimes inside the membrane. Real membranes have additional potentials at their surfaces, due to fixed charges on the membrane lipids (discussed briefly by Hille, p. 427-429). These potentials will also be ignored.

**Question 9:** The ion concentration gradients in the table of Question 5 are maintained by active transport. One such transport system is Na-K-ATPase, which moves 3 Na ions out of the cell and 2 K ions into the cell, using the energy supplied by hydrolysis of an ATP molecule to ADP. Compute the work required to transport 3 moles of Na and 2 moles of K under the conditions of Question 5. You should find that substantial positive work is required, meaning that the free energy of the Na and K ions increases when such transport occurs. In order to make the free energy of the total system decrease during active transport, there must be a large decrease in free energy of the ATP molecule when it is hydrolyzed to ADP and phosphate. Compare the free energy increase of the ions with the free energy release of ATP hydrolysis ( $\approx 60$  kJ/mole under cellular conditions).

### Nernst-Planck Equation

The goal of membrane modeling is usually computing fluxes of ions in non-equilibrium situations. This requires development of models that relate flows to forces in ionic solutions. In the following, two approaches to this problem will be taken. The first depends on models of diffusion and of ion transport driven by electric fields. The second will use the electrochemical potential discussed above as the potential field driving the flux.

Consider first the situation of an ionic solution of uniform concentration with an imposed electric field given by  $dV/dx$ . The field will produce a force on a charge  $q$  equal to  $-q dV/dx$ . The

charge  $q$  carried by a mole of ions is given by  $z_i F$ , so the force on a mole of ions due to the electric field is  $-z_i F dV/dx$ .

In an aqueous solution, the interactions of solute and solvent molecules result in transport processes being limited largely by the equivalent of frictional forces; there are no elastic forces restraining an ion in a liquid solution (i.e. no little springs restricting an ion to certain positions) and the frictional forces turn out to be larger than inertial ( $f=ma$ ) forces. Thus when an ion is acted on by an electric field, it tends to move with a drift velocity that is proportional to the force provided by the field. This assumption is motivated by the usual behavior of friction, in which the force needed to overcome friction is proportional to the velocity. The *mobility*  $u_i$  of an ion is the ratio between the drift velocity and the applied force. That is,

$$\left( \begin{array}{c} \text{drift} \\ \text{velocity} \end{array} \right) = u_i \times (\text{force / mole}) = -u_i z_i F \frac{dV}{dx} \quad (17)$$

where  $u_i$  has units (m/s)/(N/mole). In some texts, mobility is defined as the electrical mobility, the ratio of drift velocity to the quantity  $z_i dV/dx$ .

The flux  $J_i$  of the ion is the number of moles of ion passing through a unit area per second and is given by  $J_i = C_i \times (\text{drift velocity})$ . Thus the ion flux driven by an electric field is

$$J_i = -u_i C_i z_i F \frac{dV}{dx} \quad (18)$$

Net flux can also be produced in solution by concentration gradients, as described by Fick's law:

$$J_i = -D \frac{dC_i}{dx} \quad (19)$$

Fick's law can be derived from a consideration of the effects of random thermal motion of particles in a concentration gradient.

The net flux in solution is then the sum of Eqns. 18 and 19. Usually the expression is simplified by noting that  $u_i RT = D$  (Einstein relationship, see Feynman, pp. 43-8 for a derivation). The result is the *Nernst-Planck equation*.

$$J_i = -u_i \left[ RT \frac{dC_i}{dx} + C_i z_i F \frac{dV}{dx} \right] = -u_i C_i \left[ RT \frac{d \ln C_i}{dx} + z_i F \frac{dV}{dx} \right] \quad (20)$$

Another way to approach the Nernst-Planck equation is to assume that the spatial gradient of the electrochemical potential is the force that drives ions in solution, that is  $force = -d\mu_i/dx$ . This assumption is justified by the general relationship between force and work (energy), where the latter is the integral of the former through distance. With the same definitions for mobility and flux, Eqn. 20 follows directly from differentiating Eqn. 13. Thus, the Nernst-Planck equation can be derived from either the electrochemical potential of equilibrium thermodynamics or from properties of diffusion and electrostatics.

In order to model ion transport through a cell membrane, a set of differential equations like Eqn. 20 has to be solved, one for each ion. Additional constraints, such as charge electroneutrality, steady state, or some model for the electrical potential are usually added. Because the term  $C_i dV/dx$  makes the equations non-linear, they cannot be solved in general in closed form. Implicit solutions have been obtained, but these are difficult to use in practice. Thus the Nernst-Planck equations are usually solved for special cases or using approximations for idealized situations.

### Electrical equivalent circuit

An important insight into ion transport across a diffusion barrier comes from integrating the Nernst-Planck equation for the situation shown in Fig. 6. The concentration  $C(x)$  of an ion is sketched along with the electrical potential profile  $V(x)$  in a membrane separating two solutions, representing the outside and inside of a cell. Of course, there are other ions present, but we consider only this one for the present. The concentration and electrical potential profiles in Fig. 6 are simplified in that no transitions are shown between solution and membrane, at the edges of the membrane. Such transitions exist in real membranes (Questions 8 and 11), but are ignored here. They do not affect the main results of the analysis below.

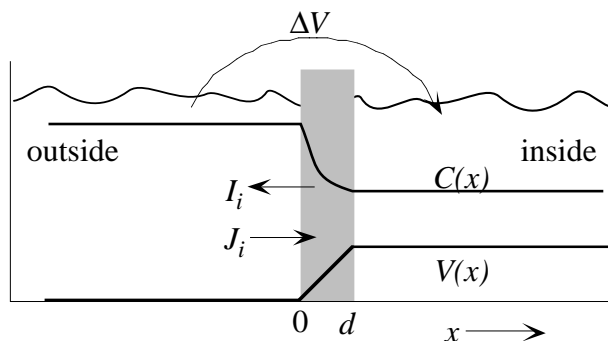


Figure 6: A membrane separates two solutions. The concentration  $C(x)$  of an ion and the electrical potential  $V(x)$  are shown.

Eqn. 20 expresses the chemical flux of the ion in moles/m<sup>2</sup>s. Because current-voltage relationships are of interest, Eqn. 20 is converted to *electrical current density* by multiplying by  $z_i F$ , the charge per mole. Flux  $J_i$  is positive for net flow in the positive  $x$  direction, as indicated by the arrow in Fig. 6. However, electrical current density  $I_i$  is defined as positive in the opposite direction, in order to be consistent with the usual convention in electrical circuit theory, in which current is positive when it flows from the positive side of the voltage arrow ( $\Delta V$  in Fig. 6). This is also the convention in membrane physiology, where the membrane potential is the potential inside the cell minus the potential outside and current is positive in the outward direction. The Nernst-Planck equation in terms of current density, with the reversed sign convention, is

$$I_i = z_i F u_i C_i \left[ RT \frac{d \ln C_i}{dx} + z_i F \frac{dV}{dx} \right] \quad (21)$$

Assume that the membrane system is in *steady state*. Steady state means that all parameters of the system are constant in time, that is  $dC/dt = dV/dt = \dots = 0$ . Of course, this is an idealization because, if there is a net flux of ion through the membrane, then the concentration must be decreasing on one side and increasing on the other. That effect will be ignored by assuming that the solutions bounding the membrane are large enough that the concentrations do not change over the period of observation, or by assuming that other mechanisms such as active transport maintain the concentrations. We also ignore the small electrochemical potential gradients in solution that are necessary to move ions to the surface of the membrane.

The steady-state assumption implies that flux  $J_i$  and the current density  $I_i$  are constant in the membrane, not functions of  $x$ . To see this, consider Fig. 7 which shows the flux at two points  $x$  and  $x+dx$  in the membrane. The total amount of ion in a unit area between  $x$  and  $x+dx$  is  $C_i(x)dx$  and the time rate of change of this amount is the difference between the flux into this region and the flux out.

$$\frac{\partial(C_i dx)}{\partial t} = J_i(x) - J_i(x+dx) \quad (22)$$

Dividing through by  $dx$  and taking the limit as  $dx$  goes to zero,

$$\frac{\partial C_i}{\partial t} = -\frac{\partial J_i}{\partial x} \quad (23)$$

Now in the steady state,  $\partial C_i/\partial t=0$  so that  $\partial J_i/\partial x=0$  also; thus in the steady state, the flux, and the current density  $I_i$  are constant, independent of  $x$ .

Now Eqn. 21 can be rearranged and integrated through the membrane as follows:

$$I_i \int_0^d \frac{dx}{z_i^2 F^2 u_i C_i} = \frac{RT}{z_i F} \int_0^d \frac{d \ln C_i}{dx} dx + \int_0^d \frac{dV}{dx} dx \quad (24)$$

Current density  $I_i$  has been taken out of the integral on the left-hand side because of the steady state assumption. The integrals on the right hand side can be evaluated, giving

$$I_i \int_0^d \frac{dx}{z_i^2 F^2 u_i C_i} = \frac{RT}{z_i F} \ln \frac{C_i(d)}{C_i(0)} + V(d) - V(0) \quad (25)$$

which can be written in the form

$$I_i R_i = \Delta V - E_i \quad (26)$$

where  $R_i$  is the integral on the left hand side of Eqn. 25,  $\Delta V$  is the transmembrane potential ( $V(d)-V(0)$ ), and  $E_i$  is the equilibrium potential for the ion (Eqn. 15).

Eqn. 26 is just a statement of Ohm's law for electrical circuits; it shows that the Nernst-Planck equation is equivalent to the following electrical model for current flow through a membrane:

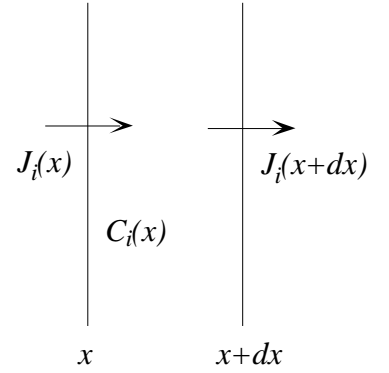


Figure 7: Relationship of fluxes and concentration at two points in the membrane.

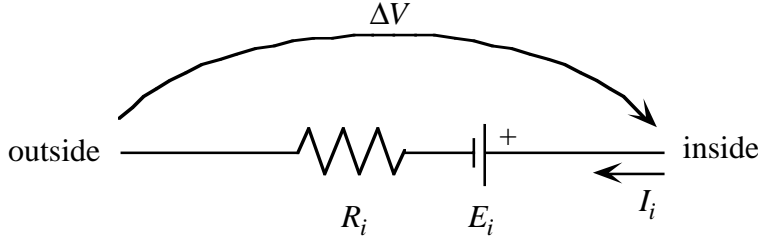


Figure 8: electrical circuit equivalent of Eqn. 26

The model of Eqn. 26 and Fig. 8 separates ion permeation into two parts: the *driving force* represented by  $\Delta V - E_i$  and the *resistance of the membrane* represented by  $R_i$ . The driving force is the difference between the electrical potential across the membrane and electrical equivalent of the concentration gradient, as represented by the equilibrium potential. Thus the driving force is zero when the ion is at equilibrium (Eqn. 15). The membrane resistance is generally a complex expression which depends on the details of the conductance mechanism in the membrane. Note that  $R_i$  is a nonlinear element, the resistance of which varies with membrane potential and concentration.

The model of Fig. 8 is the basis for most models of current flow through membranes.

### The diffusion potential

Eqn. 21 can be integrated in a different way, again for the situation in Fig. 6; this integration will yield useful information about current-voltage relationships and membrane potentials in two special cases. Note that

$$\frac{d}{dx} \left[ C_i e^{z_i F V / RT} \right] e^{-z_i F V / RT} = \frac{dC_i}{dx} + C_i \frac{z_i F}{RT} \frac{dV}{dx} \quad (27)$$

so that Eqn. 21 can be rewritten as follows

$$\begin{aligned} I_i &= z_i F u_i RT \left[ \frac{dC_i}{dx} + C_i \frac{z_i F}{RT} \frac{dV}{dx} \right] \\ &= z_i F u_i RT \frac{d}{dx} \left[ C_i e^{z_i F V / RT} \right] e^{-z_i F V / RT} \end{aligned} \quad (28)$$

Integrating Eqn. 28 through the membrane gives,

$$I_i \int_0^d e^{z_i F V / RT} dx = z_i F u_i RT \int_0^d \frac{d}{dx} \left[ C_i e^{z_i F V / RT} \right] dx \quad (29)$$

The current density has been taken out of the integral because of the steady state assumption. The right hand side can be evaluated, giving an expression for the current-voltage relationship for the ion.

$$I_i = z_i F u_i RT \frac{\left[ C_i(d) e^{z_i F \Delta V / RT} - C_i(0) \right]}{\int_0^d e^{z_i F V / RT} dx} \quad (30)$$

As in Eqn. 25, there remains one integral that cannot be evaluated, in this case involving the membrane potential.

In one special case, shown in Fig. 9, a useful result can be obtained without evaluating the integral in the denominator of Eqn. 30. Suppose that there are only two ions  $A$  and  $B$  permeable through the membrane and suppose that  $z_A = z_B$ . If the system is in steady state, then the membrane potential must be constant in time, meaning that there can be no net current flow through the membrane:

$$I_A + I_B = 0 \quad (31)$$

Substituting Eqn. 30 for  $I_A$  and  $I_B$  in Eqn. 31 gives

$$z_A F u_A RT \frac{[A(d)e^{z_A F \Delta V / RT} - A(0)]}{\int_0^d e^{z_A F V / RT} dx} + z_B F u_B RT \frac{[B(d)e^{z_B F \Delta V / RT} - B(0)]}{\int_0^d e^{z_B F V / RT} dx} = 0 \quad (32)$$

Because  $z_A = z_B$ , the integrals in the denominator are the same. Because the value of the integral is non-zero for all finite  $V$ , the integrals can be cancelled. With that and with some rearrangement, the following expression relating the transmembrane potential to the ion concentrations results:

$$\Delta V = \frac{RT}{zF} \ln \frac{u_A A(0) + u_B B(0)}{u_A A(d) + u_B B(d)} = \frac{RT}{zF} \ln \frac{u_A A_{out} + u_B B_{out}}{u_A A_{in} + u_B B_{in}} \quad (33)$$

where  $z = z_A = z_B$  and it has been assumed that the concentrations of  $A$  and  $B$  at the edges of the membrane ( $x=0$  and  $x=d$ ) are equal to the concentrations in free solution, as drawn in Fig. 9 (but see Question 11).

Eqn. 33 is commonly used to determine the relative mobility (or permeability, see Question 12) of two equal-valence ions through a membrane.

The steady-state membrane potential in Eqn. 33 is a *diffusion potential*. It arises through the action of the steady state assumption, Eqn. 31. Consider the situation in Fig. 9. The concentration gradients of the two ions through the membrane will drive fluxes  $I_A$  and  $I_B$ . If these are not equal and opposite, then there will be net charge transport through the membrane, which will produce a membrane potential. The sign of the membrane potential will depend on the directions of the currents and on which current is larger. In the situation of Fig. 9, suppose that  $A$  and  $B$  are cations.  $I_A$  will be negative (net flow to the right, using the convention of Fig. 6) and  $I_B$  will be positive. Suppose  $I_A$  is larger in magnitude than  $I_B$ . Then the potential will be positive since net charge is flowing into the cell. The positive potential will increase  $I_B$  and decrease  $I_A$ ; the potential will continue to increase until the steady state of zero charge transfer is reached. This is the characteristic of diffusion potentials, which are the potentials needed to achieve a steady state of zero net charge transfer.

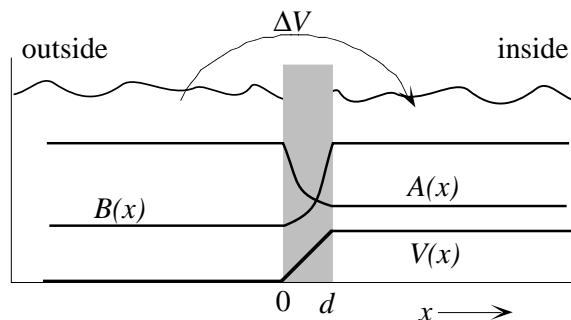


Figure 9: A membrane separates two solutions. The membrane is permeable only to ions  $A$  and  $B$ . The concentration profiles of the ions and the electrical potential are shown.

**Question 10:** Consider what happens when the relative mobility  $u_A/u_B$  increases to infinity, i.e. the membrane becomes *semi-permeable* to A only because  $u_B$  goes to 0. Show that, in this case,  $\Delta V$  approaches  $E_A$  the equilibrium potential of A. What does Eqn. 30 predict about  $I_A$  and  $I_B$  in this limit? You should conclude that the net flux of both A and B go to zero in this case, but for very different reasons. Make sure you understand the difference.

**Question 11:** Usually Eqn. 33 is expressed in terms of membrane permeabilities  $P_A$  and  $P_B$  instead of mobilities  $u_A$  and  $u_B$ . The relationship between these two is given by

$$P_i = \frac{u_i RT}{d} \beta_i \quad (34)$$

where  $\beta_i$  is the *partition coefficient*, which gives the relative solubility of the ion in the membrane vs in solution. That is,  $A(0) = \beta_A A_{out}$ , see Fig. 10. Explain why  $A(0)$  and  $A_{out}$  might be different (see Question 8). Repeat the derivation of Eqn. 33 to show how the partition coefficient enters into the problem.

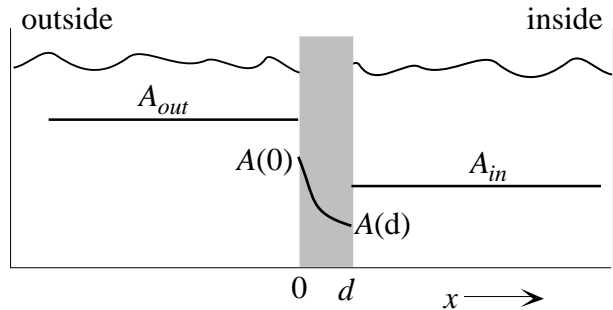


Figure 10: Showing the effect of the partition coefficient at the membrane surface on the concentration profile.

**Question 12:** Starting from Eqn. 33, as modified in question 11, derive an expression for relative permeability  $P_A/P_B$  of two equal-valence ions ( $z_A=z_B$ ) and explain how it could be determined from experimental data.

**Question 13:** Another diffusion potential situation arises in the case of a single salt solution which is placed at different concentrations on the two sides of a membrane (Fig. 11). From charge electroneutrality, the concentrations of the two ions  $A(x)$  and  $C(x)$  must be equal everywhere. Use Eqn. 20 and the steady state assumption to derive an expression for the diffusion potential that arises in this case. Assume that  $z_A=-1$  and  $z_C=1$ . The result should have a different form than Eqn. 33. Make sure you understand how these two situations are different. Explain qualitatively why a diffusion potential arises in this case, i.e. why a potential difference is needed to achieve a steady state.

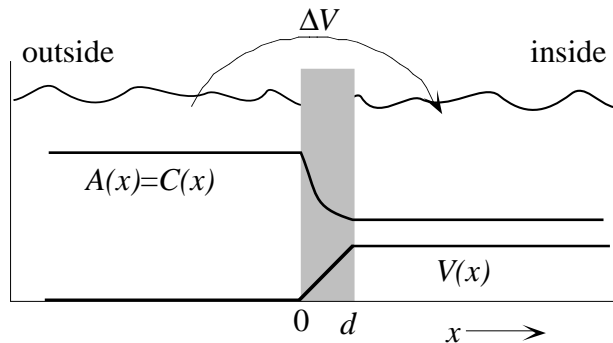


Figure 11: A membrane separates two solutions containing only one anion A and one cation C. The concentrations  $A(x)$  and  $C(x)$  are equal everywhere by charge electroneutrality.

### The constant-field equation

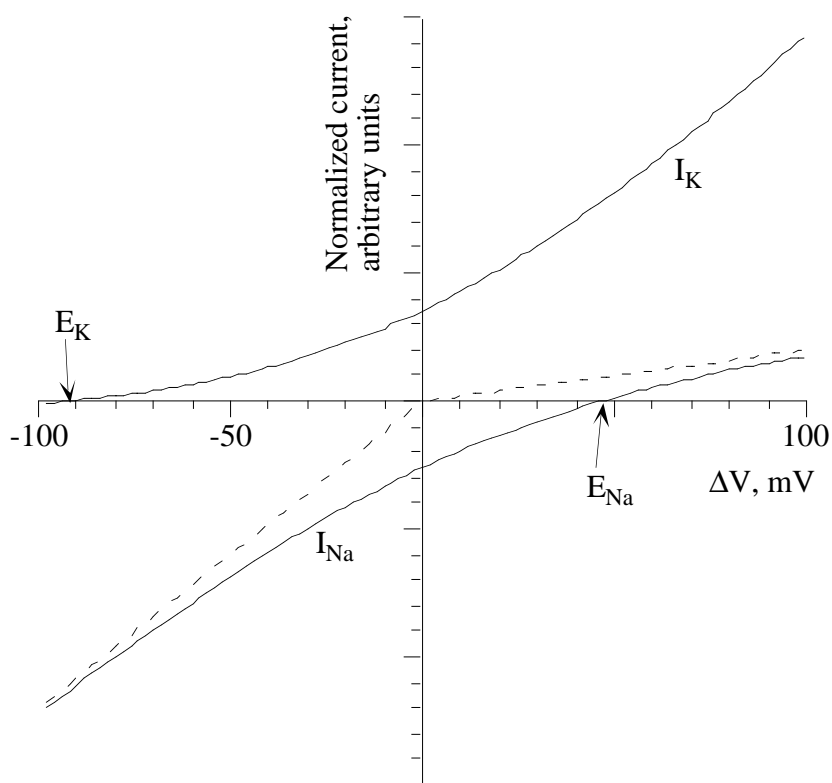
Frequently it is assumed that the membrane potential is a linear function of distance through the membrane (as drawn in Figs. 6, 9 and 11). While this can be shown to be true in one special case (see Question 14), it is at best an approximation in most cases. Nevertheless, it provides a

useful approximation for many membrane currents. With the assumption that  $V(x)=\Delta Vx/d$  for  $x=[0,d]$ , the integral in the denominator of Eqn. 30 can be evaluated, giving the *constant-field equation*:

$$I_i = \frac{(z_i F)^2 u_i}{d} \Delta V \frac{[C_i(d)e^{z_i F \Delta V / RT} - C_i(0)]}{e^{z_i F \Delta V / RT} - 1} \quad (35)$$

Figure 12. Current-voltage plots for sodium and potassium using the constant-field theory.

Fig. 12 shows a plot of constantfield currents  $I_K$  and  $I_{Na}$  against membrane potential  $\Delta V$ , for the ion concentrations listed in Question 5. Note that the currents go to zero at the equilibrium potentials, as expected. The current-voltage curves are nonlinear; this nonlinearity is called *rectification*. The sodium current is larger for inward currents (negative), called *inward rectification* and the potassium current is the opposite, *outward rectification*. The origin of the rectification in this case is the difference in intracellular and extracellular concentrations. Essentially, the outward current for  $\Delta V > E_i$  is supplied by the intracellular concentration and vice versa. Thus the current will be outward rectifying (like potassium) if the ion concentration is higher inside than outside the cell.



To further illustrate the rectification behavior of these curves, consider the behavior of Eqn. 35 in the limit as  $\Delta V$  becomes very large and positive or very large and negative. The relevant limits are

$$\Delta V \gg I_i \approx (\text{const.}) C_i(d) \Delta V \quad \text{and} \quad \Delta V \ll I_i \approx (\text{const.}) C_i(0) \Delta V \quad (36)$$

The currents are asymptotically linear, with a slope proportional to the concentration from which the current flows. These asymptotic lines are plotted as dashed lines in Fig. 11 for the sodium current.

Rectification in membrane currents comes from two sources. One is rectification due to channel conductance properties. The rectification in Fig. 12 is of this type. The second is rectification due to channel gating, which will be discussed later in the course.



The constant-field equation can be used to derive an expression for a diffusion potential which is similar to Eqn. 33. Consider the situation drawn in Fig. 13 in which there are three ions, sodium, potassium, and chloride. The concentration gradients are arranged in a fashion similar to those in a real cell, except that the chloride concentration inside real cells is much smaller because of negatively charged macromolecules in cells. Consistent with charge electroneutrality, the chloride concentration is equal to the sum of the sodium and potassium concentrations everywhere; this assumes that there are no other ions present. In steady state, to give zero net charge transfer through the membrane,

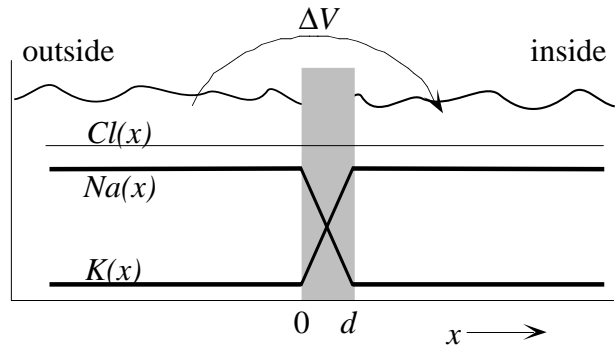


Figure 13: A membrane separates two solutions containing Na, K, and Cl at the concentrations shown. By charge electroneutrality,  $Cl(x)=Na(x)+K(x)$  (see also Question 14).

$$I_K + I_{Na} + I_{Cl} = 0 \quad (37)$$

Substituting Eqn. 35 for the three currents in Eqn. 37 and rearranging gives the *Goldman-Hodgkin-Katz equation*:

$$\Delta V = \frac{RT}{F} \ln \frac{P_K K_{out} + P_{Na} Na_{out} + P_{Cl} Cl_{in}}{P_K K_{in} + P_{Na} Na_{in} + P_{Cl} Cl_{out}} \quad (38)$$

The properties of this equation are similar to those of Eqn. 33. Unlike Eqn. 33, Eqn. 38 depends on the constant-field assumption. While this assumption can be shown to be valid for the special case of Fig. 13 (see Question 14), it is certainly not true in general. Nevertheless, Eqn. 38 turns out to predict the behavior of data in many cases and serves as a useful approximation for membrane potentials.

**Question 14:** For the special case diagrammed in Fig. 13, the potential in the membrane is linear. To see this, consider the first form of the Nernst-Planck equation in Eqn. 20. Form the sums

$$\sum_{\substack{\text{all cations} \\ \text{and anions}}} \frac{J_i}{u_i} \quad \text{and} \quad \sum_{\substack{\text{all cations} \\ \text{and anions}}} \frac{z_i J_i}{u_i} \quad (39)$$

Using these sums, the steady state assumption, and the electroneutrality condition (Eqn. 16) you should be able to show two results:

$$\text{if } N = \sum_{\text{all ions}} C_i \quad \text{then} \quad \frac{dN}{dx} = (\text{const}) \quad \text{and} \quad \frac{dV}{dx} = (\text{const}) / \sum_{\text{all ions}} z_i^2 C_i \quad (40)$$

For the special case of Fig. 13, you should be able to conclude from Eqn. 40 that  $N=(\text{const})$  in the membrane and  $dV/dx=(\text{const})$  in the membrane.

**Question 15:** For the special case of Fig. 13, show that the concentration of potassium in the membrane is given by

$$K(x) = \frac{K(0)(e^{-F\Delta Vx/RTd} - e^{-F\Delta V/RT}) + K(d)(1 - e^{-F\Delta Vx/RTd})}{1 - e^{-F\Delta V/RT}}$$

To do this, start with the NP equation for potassium and assume that  $dV/dx = \Delta V/d$ , where  $d$  is the thickness of the membrane. As part of this development, you should derive the constant-field flux equation (like Eqn. 35, except for flux  $J_K$ ). Alternatively, you can start with Eqn. 35 and the constant field equation and solve the NP equation for  $K$ . Similar equations can be derived for sodium and chloride.

### Nature of the cellular steady state

In the models considered above, the means by which concentrations gradients are set up and maintained was ignored. Of course, in a real cell, there must be active transport mechanisms to maintain the ions out of equilibrium. A variety of mechanisms have been described (see Lauger, 1991 for a complete description). The most common mechanisms in neurons include Na-K-ATPase, which transports sodium and potassium against their electrochemical potential gradients (Na out of the cell, K into the cell) using ATP hydrolysis as the energy source (Question 9); Ca-ATPase, which does the same for calcium; and the Na-Ca exchanger, which transports calcium out of the cell using the energy in the sodium electrochemical potential.

In the presence of active transport, the nature of the steady state equations used above (Eqns. 31 and 37) is different. For each ion in the system there must be both an active transport  $I_i^A$  and a passive transport  $I_i^P$ . The passive transport is described by the flux equations developed above (i.e. Eqns. 30 and 35). For similar models of active transport, see Lauger (1991). In the steady state, the ion's concentrations must be constant, so that the net flux of ion through the membrane must be 0,  $I_i^A + I_i^P = 0$ . If this equation holds for every ion in the system, then there can be no net flux of any ion through the membrane and the net charge transfer through the membrane is guaranteed to be zero. Looking at the system this way, Eqns. 31 and 37 do not capture the true nature of the steady state.

Apparently the true steady state in a cell is a more complex situation than has been considered in deriving the traditional diffusion-potential models above (Eqns. 33 and 38). A natural question is why these models apparently work for data from real cells, given the inaccuracy in the assumptions that underlie them. One special case in which active transport can be included in the membrane-potential model occurs when only sodium and potassium are permeable through the membrane by passive transport. Their concentrations are maintained by active transport through Na-K-ATPase. A characteristic of this enzyme is that 3 Na ions are transported for each 2 K ions. The steady state equations then become:

$$I_{Na}^A + I_{Na}^P = 0 \quad (41a)$$

$$I_K^A + I_K^P = 0 \quad (41b)$$

$$I_{Na}^A = -rI_K^A \quad (41c)$$

The first two equations express the steady state condition for sodium and potassium *concentration* and the third equation is the transport ratio for the ATPase ( $r=3/2$ ). No equation is needed to guarantee that  $dV/dt=0$ , because the first two equations guarantee that no net charge is transferred in this system (assuming that no other ions are permeable). The three equations together imply that  $I_{Na}^P + rI_K^P = 0$ . Using this as the steady state condition and substituting Eqn. 30 for the sodium and potassium currents gives the following equation for the diffusion potential (the *Mullins-Noda* eqn.):

$$\Delta V = \frac{RT}{F} \ln \frac{u_{Na} Na_{out} + r u_K K_{out}}{u_{Na} Na_{in} + r u_K K_{in}} \quad (42)$$

In this case, the active transport only changes the apparent relative permeability of potassium and sodium!

In a real cell, the actual steady state will involve a complex set of conditions like Eqns. 41. The steady-state will be the simultaneous solution of this set of equations. The passive currents will be represented by models like Eqn. 35 and the active currents will be represented by similar equations that capture the membrane potential dependency of the active transport.

**Question 16:** Eqn. 42 is the steady-state diffusion potential in the presence of active transport. If the active transport is completely blocked pharmacologically, then the assumptions of Eqns. 31 and 33 become accurate. That is, the concentrations will be constant (approximately, they will actually change slowly) and membrane potential will equal the diffusion potential modeled by those equations; in particular, there will be no active fluxes, so the only ion fluxes will be passive. Comparing Eqns. 33 and 42 shows that the diffusion potential in the absence of active transport is different than the potential in the presence of active transport. This change is expected from the fact that Na-K-ATPase transports net charge through the membrane (3 Na in one direction for every 2 K in the other). This is called an *electrogenic* active transport process. Write an equation for the difference  $\Delta V_A - \Delta V_P$ , where  $\Delta V_A$  is the membrane potential in the presence of active transport and  $\Delta V_P$  is the diffusion potential with the active transport blocked. The value of this difference should depend on the relative permeability of the ions,  $u_{Na}/u_K$ . What is the maximum potential difference that could result from an active transport ratio  $r=3/2$ ? Argue that no change in potential should occur (in the short-term, before concentrations change) if a non-electrogenic active transport is blocked.

**Question 17:** More insight into the effects of active transport can be gained by considering a cell in which there are several ions which are transported both actively and passively. In the steady state, an equation like Eqn. 41a or 41b holds for each transported ion in the system. Using Eqn. 30 as the model for passive current flow of the ion, show that the diffusion potential in this case can be written as

$$\Delta V = \frac{RT}{z_i F} \ln \left[ \frac{C_i(\text{outside})}{C_i(\text{inside})} - \frac{I_i^A}{\text{const} \cdot f_i(\Delta V) \cdot C_i(\text{inside})} \right] \quad (43)$$

where  $f_i(\Delta V)$  is a function of membrane potential related to the denominator of Eqn. 30. If there are  $n$  ions in the system, Eqn. 43 must be true for each of them. Explain how this can be so; that is, specify a set of equations and unknowns that could lead to a unique solution for this problem. Notice that  $\Delta V \approx E_i$  as  $I_i^A \approx 0$ , that is the membrane potential becomes equal to the ion's equilibrium potential if the ion is not actively transported. Explain what this means (Hint: what happens to the ion's concentration ratio if it is not transported?).

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