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:

$$\Delta U = U_2 - U_1 = q + w \tag{1}$$

$$w = -\int_{V_1}^{V_2} P\,dV \tag{2}$$

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

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

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

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

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

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

Deriving the Nernst equation:

$$\mu_i = \mu_i^0 + RT\ln C_i + z_i FV + \cdots$$

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

$$\mu_i^0 + RT\ln C_1 + z_i FV_1 = \mu_i^0 + RT\ln C_2 + z_i FV_2 \tag{14}$$

Note the assumption that μ_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:

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

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,

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

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

$$J_i = -u_i C_i z_i F\frac{dV}{dx} \tag{18}$$

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

$$J_i = -D\frac{dC_i}{dx} \tag{19}$$

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*.

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

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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

$$I_i = z_i Fu_i C_i\left[RT\frac{d\ln C_i}{dx} + z_i F\frac{dV}{dx}\right] \tag{21}$$

The steady-state assumption implies that flux J_i and the current density I_i are constant in the membrae, 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.

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

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

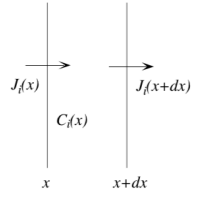$$\frac{\partial C_i}{\partial t} = -\frac{\partial J_i}{\partial x} \tag{23}$$

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

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:

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

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

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

which can be written in the form

$$I_i R_i = \Delta V - E_i \tag{26}$$

where R_i is the integral on the left hand side of Eqn. 25, ΔV 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:

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

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

so that Eqn. 21 can be rewritten as follows

$$\begin{aligned}I_i &= z_i Fu_i RT\left[\frac{dC_i}{dx} + C_i\frac{z_i F}{RT}\frac{dV}{dx}\right]\\ &= z_i Fu_i RT\frac{d}{dx}\left[C_i e^{z_i FV/RT}\right]e^{-z_i FV/RT}\end{aligned} \tag{28}$$

Integrating Eqn. 28 through the membrane gives,

$$I_i\int_0^d e^{z_i FV/RT}dx = z_i Fu_i RT\int_0^d \frac{d}{dx}\left[C_i e^{z_i FV/RT}\right]dx \tag{29}$$

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.

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

**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 $V(x)=\Delta V x/d$ for $x=[0,d]$, the integral in the denominator of Eqn. 30 can be evaluated, giving the *constant-field equation:*

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

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

Fig. 12 shows a plot of constant-field currents I_K and I_{Na} against membrane potential ΔV, 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.
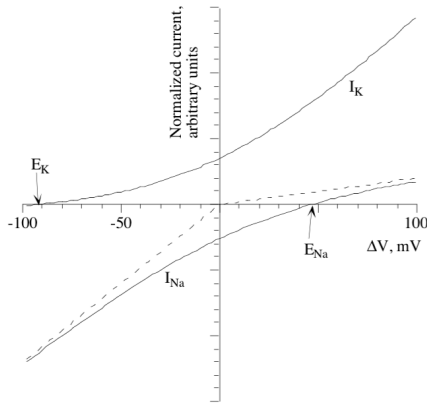
Nature of the cellular steady state

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 Läuger, 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 Läuger (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: