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Vignette

Applications of Physical Chemistry: A Biological Example

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Physical Chemistry Applied to Biology

Biologists try to understand how complicated structures, built by evolution, follow physical laws to produce their natural functions. The model of electrolyte solutions we studied in Section 26.5 provides much of the basis for this understanding because much of life occurs in salt solution.

Here we consider proteins called ionic channels that are embedded in the membranes constituting the "walls" of cells. Channel proteins form "holes in the wall" lined by fixed charges that control many of the properties of channels. Proteins are such important components of most biological systems that understanding the physical laws governing their behavior is essential to understanding the physical basis of life.

Channels are probably the simplest protein structures of general biological importance. Channels are responsible for signaling in the nervous system, for coordination of muscle contraction, including the pump we know as the heart muscle. Channels are intimately involved in the secretion of urine and hormones and most other transport processes in cells; they are natural targets that viruses attack and use to enter cells.

Channels conduct a definite amount of current, once they are open, and this single channel current can be easily recorded by the patch clamp method introduced by Sakmann and Neher (1995). When the solutions on either side of the channel are kept at definite concentrations, and the electrical potential between those two solutions is maintained at a fixed value, the mean ion current carried through the open channel is remarkably constant and reproducible. Once the channel is open, the instantaneous current recorded shows substantial variance, but the mean current does not drift at all, on the time scale relevant to biology, longer than say 10 μsec. The mean current is the same from opening to opening, from channel to channel, from day to day, from animal to animal, and from laboratory to laboratory, within the error of measurement, with a precision more commonly found in measurements of physical than biological systems. It is not trivial to maintain the concentration of ions fixed, or the electrical potential fixed near a channel, when a large current flows through it. The biological cell must use elaborate machines to supply matter and charge to control the environment around channels, e.g., to maintain boundary conditions of constant concentration. Indeed, in a sedentary human being—who is reading this book, for example—a substantial fraction of all metabolism is used (in the nerve cells of the brain) to maintain these boundary conditions. The "voltage clamp" or "patch clamp" was designed to mimic properties of the biological cells that sustain channels, while allowing precise experimental measurement of current flow.

Channels carrying current must be studied as the nonequilibrium systems they are, with tools described in Chapters 27–31. Steady-state flux can cross boundaries of the cell only if its boundary conditions are (spatially) nonuniform. This simple statement rules out those models of channels and biochemical systems that assume spatially uniform boundary conditions and so do not allow steady flux.

Channels can also be viewed as proteins that modify and control the flow of current, like devices of our electronic technology. Current is driven through channels by external sources; it is driven through transistors and other semiconductor devices by power supplies (Lundstrom, 1992).

Channel currents are constant in the sense that the mean current through a particular type of open channel, under a particular set of conditions, does not vary with time (on the biological time scale). The average amount of current that flows through a channel varies according to the concentration, electrical potential, and type of permeating ion, as well as the type of channel. Channels are characterized by their curves that display the dependence of their current I on electrical potential V, usually in the range of ± 150 mV. Concentrations of ions in cells or in sea water, typically in the range between 20 millimolar (mM) and 2 M, change by about 300 mM when channel currents flow. Changes of potential are typically of order $RT/\mathcal{F}$ or more.

The amplitude of the current through a channel depends on the type of channel—and hence the protein—through which the ions flow. In some channel proteins, just one type of ion, typically potassium, sodium, or calcium, carries the current. In other types of channels, any cation can carry the current; in still others, any anion will do. The selectivity of channels is of such great biological importance that many proteins carry names that identify their channels: Na-channels are proteins that conduct mostly Na^+ ions; K-channels are proteins that conduct mostly K^+ ions. Channel proteins are called by those

common names (to the confusion of students) even if they are quite different in other respects, with quite different structures and functions.

Selectivity is usually studied indirectly by measuring current flow as a function of voltage, in various solutions. The picoamperes of current associated with chemical fluxes can be measured, e.g., as carried by radioactive tracers, as they flow through one channel molecule using the patch clamp techniques that have made channology a molecular science.

Imagine then that we have a complete set of measurements of current through a potassium channel, in a wide range of solutions and as a function of a wide range of potentials. How do we interpret these results? How can we analyze and then predict these I and V curves in terms of the structure and properties of the ionic channel itself? Can we develop a theory to predict the properties of the hole in the wall, from the structure of the protein that forms the hole?

A mature theory of an open channel would start with the three-dimensional structure of the channel protein, combining that information with the concentrations of ions and the electrical potential maintained experimentally in the baths to predict the current through the channel, perhaps with only the friction (i.e., diffusion) coefficients of the permeant ions as parameters.

No such theory is available yet. The main impediments are the problems involved in solving the three-dimensional field and transport equations for given macroscopic boundary conditions. Consequently, we resort to a common tactic of science: We average away some of the three-dimensional detail, hoping that a one-dimensional theory will retain enough of the essential behavior to predict the currents observed.

A typical channel protein might be 40 Å long and perhaps even 40 Å in diameter. The protein is embedded in a lipid bilayer some 30 Å thick. The pore of the channel protein is much smaller than the protein, often not more than 7 Å in diameter. The most important part of the pore is the narrow portion (more or less a cylinder 10 Å long and 7 Å in diameter), the "selectivity filter" that controls current flow. The total electrical charge of the charged and polar residues of the protein that line the walls of the selectivity filter is of the order of 1 e. Because the system is approximately (but not exactly, as discussed later) electrically neutral, the number of mobile ions of opposite charge in the pore (averaged over a time of microseconds, for example) should be roughly 1 as well, giving a concentration of some 5 m, much higher indeed than biological electrolyte solutions surrounding the channel.

When the density of electrical charge is very large, like this, one might naively expect electrical interactions with the mean field to dominate, and theoretical work on the electrochemistry of highly charged surfaces supports this view. Thus, we will try a simple mean field theory, very much in the spirit of the Debye–Hückel theory of ionic solutions, or the Gouy–Chapman theory of interfaces, or the Poisson–Boltzmann theory of proteins, c.f. Section 26.5. But these theories must be generalized to allow current flow. Mean field theories depend on approximations that are hard to evaluate *a priori* and that cannot be true for all conditions and all systems and so it is necessary to check them with real data. The theory begins with Poisson's equation, Eq. 26.61, which describes how the average charge produces the average electrical potential $\phi(x)$ (units: volts), where x is the location along the channel axis, or more precisely, along its reaction coordinate. Here we assume that all quantities are averaged over time for the duration of the briefest current we can measure, namely a few μsec. We consider only the dominant charges, namely the ions of species j and charge z_jF (units: coulombs mole^{-1}) and the permanent fixed structural charges of the protein $P(x)$ (units: coulombs cm^{-1}) that line the wall of the channel. The mobile species j are Na^+, K^+, Cl^-, and/or Ca^{++} in most biological problems.

$$-\epsilon_{pore}\epsilon_0 \frac{d^2\varphi}{dx^2} = eP(x) + e\sum_j z_j C_j(x). \qquad (1)$$

Here $\epsilon_{pore}\,\epsilon_0$ is the product of the dielectric constant of the channel's pore and the permittivity of free space (units: farads cm^{-1} or cou volt^{-1} cm^{-1} or amp sec volt^{-1} cm^{-1}).

We assume that the Poisson equation is true on all scales—that is to say, the Poisson equation can be used on any length or time scale provided we average the potential (on the left hand side) and the charge (on the right hand side) the same way. This assumption provides a good way to start an analysis of a novel physical system, like an open ionic channel. How reasonable the assumption is theoretically can be seen by considering the alternative: What would happen if the average potential did not correspond to potential of the average charge: What would sustain the extra forces, where would the extra energy come from to do that?

Mobile ions in the channel (that contribute so importantly to the charge on the right hand side of Eq. 1) move and carry current and so we need an equation to describe how their mean flux J_j (units: concentration × cm^{-2} sec^{-1}) varies with potential and concentration. The simplest relation between mean flux and potential and concentration (units: cm^{-3}) is the diffusion equation (see Eqs. 20.15 and 20.16 and Table 28.1), which is written here in its form as the Nernst–Planck equation, using the Einstein relation (see Eq. 30.92) between mobility and diffusion coefficient D_j (units: cm^2 sec^{-1}). The Nernst–Planck equation is simply the diffusion equation, Eq. 20.7, for charged particles:

$$J_j = -D_j\left[\frac{dC_j(x)}{dx} + \frac{z_j\mathcal{F}}{RT}C_j\frac{d\varphi}{dx}\right]$$
$$\equiv -\frac{D_j}{RT}C_j(x)\frac{d\mu_j}{dx}. \quad (2)$$

The electrochemical potential $\mu_j(x)$ of ion species j is discussed in Chapter 26, $\mu_j(x) \equiv z_j\mathcal{F}\phi(x) + RT \ln C_j(x)$. The current I (amp) through a channel of radius r is simply $I = \pi r^2 \cdot \Sigma_j z_j \mathcal{F} J_j$, see Section 29.6. Note that in this simple first treatment ions behave ideally, with no excess chemical potential, and thus have the same activity coefficient and standard chemical potential in the bulk solution and in the channel (see Chapters 25 and 26, e.g., Eqs. 26.7–26.12). It is extraordinary that a theory with such an unlikely assumption fits so many data.

Simplified boundary conditions specify both (1) the concentrations of each species $C_j(L)$ and $C_j(R)$ in the solutions outside the channel and also (2) the potential difference $V_{applied}$ (inside – outside) maintained by the voltage clamp apparatus. The original publications (Eisenberg, 1996) describe the more realistic (and complex) boundary conditions that are needed to fit experimental data.

The Nernst–Planck equations can be integrated only once analytically, using integrating factors, to give an explicit expression for the concentrations $C_j(x)$ as functions of the boundary conditions and the entire potential profile across a channel $\Phi(x) = \Phi(x)\mathcal{F}/RT$ of length d:

$$C_j(x) = \frac{C_j(L)\cdot e^{z_j[V_{applied}-\Phi(x)]}\cdot\int_x^d e^{z_j\Phi(\zeta)}d\zeta}{\int_0^d e^{z_j\Phi(\zeta)}d\zeta}$$
$$+\frac{C_j(R)\cdot e^{-z_j[V_{applied}-\Phi(x)]}\cdot\int_0^x e^{z_j\Phi(\zeta)}d\zeta}{\int_0^d e^{z_j\Phi(\zeta)}d\zeta}. \quad (3)$$

This expression is less helpful than it seems because the potential profile $\Phi(x)$ is not known. The profile of potential can only be determined by solving the Poisson equation (1). But the Poisson equation contains the concentration of mobile charges $C_j(x)$, and that concentration is not small. The concentration of counter ions (ions with charge opposite to that of the nearby fixed charge of the channel protein) is always of the same order as the fixed charge, because the combined system of channel wall and channel pore is fairly close to electrically neutral. Thus, the Poisson equation cannot be solved until the Nernst–Planck equation is solved. In other words, Eqs. 1 and 2 or Eqs. 1 and 3 must be solved simultaneously; the Poisson and Nernst–Planck equations form a coupled system.

The system of Poisson and Nernst–Planck equations is called the *PNP* equations in channology or the drift-diffusion equations in solid state physics (where they are universally used to describe current flow in semiconductor devices such as transistors). Note that neither the channel's pore, nor the channel plus surrounding baths, nor for that matter, a transistor, is electrically neutral. The number of positive charges does not precisely equal the number of negative charges in any region. The potential profile in the channel's pore $\Phi(x)$ could not vary (i.e., Φ would be spatially uniform) and even the transmembrane potential $V_{applied}$ could not exist if the system were strictly electrically neutral. Nonetheless, electrical neutrality is approximately satisfied and the total fixed charge lining the channel wall and the total mobile charge within the channel are within say 20% of each other.

Another integrated form of the Nernst–Planck equations is helpful, particularly in making links to work on chemical reactions, because it can either be derived from the Nernst–Planck equations or from the stochastic theory of chemical reactions (Eisenberg et al., 1995). In fact, the integrated expression for flux J_j can be written as a form of the law of mass action, allowing a rigorous derivation of the forward and backwards rate constants for flux over any shape potential barrier $\Phi(x)$. The integrated flux equation is

$$J_j = \overbrace{D_j\frac{C_j(L)\exp(z_jV_{appl})}{\int_0^d \exp[z_j\Phi(\zeta)]\,d\zeta}}^{Unidirectional\ Efflux} - \overbrace{D_j\frac{C_j(R)}{\int_0^d \exp[z_j\Phi(\zeta)]\,d\zeta}}^{Unidirectional\ Influx}. \quad (4)$$

The flux is best written as the sum of two unidirectional fluxes: As we shall see, each component of flux has a much simpler physical meaning and dependence on experimental variables than the sum.

It is important to note that the flux depends on the integral of the potential profile in the integrated Nernst–Planck Eq. 4, and the potential depends (speaking roughly) on the second integral of the fixed charge distribution, according to the Poisson Eq. 1. The fixed charge profile contains most of the information concerning the structure of the protein. The current through the channel has a highly integrated (and thus smoothed) dependence on fixed charge and so is expected to be rather independent of the details of charge distribution, at least if the charge distribution has one sign and never gets too close to zero.

Each unidirectional flux is carried by ions from a source concentration on the *cis* side (say on the left side of the channel) to the *trans* side (here the right side), when the *trans* side is held to zero concentration (even in the presence of flux) by experimental apparatus or by the metabolism of a biological cell. The *trans* side is then made into an absorbing boundary, by the apparatus or cell, if we use the words of stochastic processes and probability theory.

Each unidirectional flux can be written neatly, without further approximation, as the product of a "source" concentration; "diffusion velocity," (D_j/d), sometimes called "the permeability" in the channology literature; and the appropriate conditional probability,

$$J_j = d[k_f C_j(L) - k_b C_j(R)]$$
$$\equiv \overbrace{C_j(L)\left(\frac{D_j}{d}\right)Prob\{R|L\}}^{\text{Unidirectional Efflux}} - \overbrace{C_j(R)\left(\frac{D_j}{d}\right)Prob\{R|L\}}^{\text{Unidirectional Influx}}. \quad (5)$$

Source Concentration; Diffusion Velocity; Conditional Probability

The same system can be written (for any shape of potential profile) as a chemical reaction linking ions on the *L*eft and on the *R*ight side of the channel, without making any further approximations.

$$L \underset{k_b}{\overset{k_f}{\rightleftarrows}} R$$
$$k_f \equiv k\{R|L\} = (D_j/d^2)\, Prob\{R|L\}$$
$$k_b \equiv k\{L|R\} = (D_j/d^2)\, Prob\{L|R\} \quad (6)$$

$Prob\{R|L\}$ is conditional probability that an ion starting a trajectory on the *L*eft side of the channel (with right-going velocity) eventually appears on the *R*ight, when a reflecting boundary condition is imposed at the left boundary and an absorbing boundary condition is imposed on the right boundary. This probability is essentially the same as the coefficient specifying the transmission probability that appears in Eq. 31.21.

The trajectories can be described by other statistics besides conditional probabilities. The time an ion takes to go from L to R is a statistic called $T\{R|L\}$, the (conditional) first passage time; the number of $\{R|L\}$ trajectories within the channel is the conditional contents of the channel $[\{R|L\}]$, the unidirectional flux $J\{R|L\}$ is the flux carried by the $\{R|L\}$ trajectories, and not surprisingly,

$$J\{R|L\} = \frac{[[R|L]]}{T\{R|L\}}. \quad (7)$$

Equations for *un*conditional probabilities, passage times, or total fluxes are awkward to write, at best, because they often contain infinite quantities (that are difficult to compute) even in systems that are entirely finite. For example, no simple relation exists between the (total) contents of the channel, the net flux, and the mean first passage time of all ions. Simple relations exist between these variables only if the trajectories are first separated (i.e., "conditioned") into the subsets $\{R|L\}$ or $\{L|R\}$.

The conditional probabilities, and other statistics of equations, can be determined numerically (Barcilon et al., 1993; Elber et al., 1993) at various resolutions. For example, they can be determined by computing a random walk, or by simulating a full or reduced Langevin equation (see Section 29.3) or from simulations of molecular and atomic dynamics.

When friction is large (as in channels on the biological time scale) and simple (characterized by a single number D_j for each ionic species j), the statistics can be determined analytically. The probabilistic analysis reduces then to studying the Langevin equation of Section 29.3 and the conditional probabilities satisfy a Fokker–Planck partial differential equation. In that case, the rate constant $k\{R|L\}$ and conditional probability $Prob\{R|L\}$ (of the integrated Nernst–Planck equation and chemical reaction) can be written exactly for any shape of potential barrier $\varphi(x)$ (Barcilon et al., 1993),

$$k\{R|L\} \equiv \frac{D_j}{d^2} Prob\{R|L\}$$
$$= \frac{D_j}{d^2} \cdot \frac{\exp(z_j F V_{appl}/RT)}{\frac{1}{d}\int_0^d \exp[z_j \varphi(x)/RT]\, dx}. \quad (8)$$

In this way, permeation can be described *exactly* both as a chemical reaction and as stochastic transport over a potential barrier of any shape. Permeation through a channel can be described as a reaction along a coordinate more precisely, less metaphorically, than chemical changes can be in many more traditional situations.

The PNP Equations

The *PNP* equations are deceptively simple both in their physics and in their form. Physically, they are mean-field equations like those of other mean field theories and they depend on the same assumptions. But the *PNP* equations differ from many mean field theories because they explicitly and self-consistently allow flux. This is very different from theories that are confined to equilibrium, where no flux flows.

Systems at equilibrium have much simpler behavior than nonequilibrium systems; in particular, systems at equilibrium do not have the behaviors characteristic of (what engineers call) devices, the motors of our technology that we use every day to help us with our lives. For example, an automobile engine without gasoline is not a motor; it cannot move. A transistor at equilibrium (without current flowing into its terminals) is not a device; it cannot switch, amplify, or perform logic functions. In fact, one could measure and understand every physical property of a transistor at equilibrium and still be unaware that away from equilibrium it can be a switch, amplifier, memory element, or indeed a part of an integrated circuit that remembers a number or name.

The *PNP* equations describe the rich behavior of semiconductor devices, such as switches, amplifiers, and mem-

ory elements, for example, even though they look like (linear) differential equations that yield only much more ordinary behavior. The equations are not linear, however, and in fact describe much richer behavior. Only the potentials at the terminals of a transistor need to be changed to convert the device from a linear amplifier to a logarithmic amplifier or even a nonlinear switch. The theory has the same properties as the physical system. Only the boundary values have to be adjusted to give this richness of behavior. *Neither the differential equation nor its parameters have to be changed in any way.*

The *PNP* equations are deceptive in this way, giving a rich repertoire of well-determined behavior from a simple pair of equations. They are deceptive in other ways as well, because they cannot be integrated by the normal numerical recipes widely available in packaged programs. Those integration schemes do not work on these equations, even approximately, for fundamental reasons that are well understood mathematically.

Solving the PNP Equations: The Gummel Iteration

Integration of the *PNP* equations is difficult if recipes for standard systems of equations are used, but integration is easy if a particular method called the Gummel iteration, or its equivalent, is used. The Gummel iteration was discovered some decades ago by the semiconductor community and is a general method for producing a self-consistent solution of coupled equations closely related to the self-consistent field methods used in quantum chemistry to compute molecular orbitals, which we have discussed previously, in Part I.

The Gummel iteration starts with an initial guess of the potential profile, often as just a linear function of position connecting the boundary values of potential. That initial profile is substituted into the right-hand side of the integrated concentration Eq. 3. This substitution determines the congruent initial guess of the concentration profile $C_j(x;$ initial guess). That guess is substituted into the right hand side of Poisson's equation (1), which is then trivially solved. The resulting estimate of potential $\phi(x;$ first iterate) identically satisfies the boundary conditions, as do all other estimates of the potential profile. The potential profile $\phi(x;$ first iterate) is substituted into the integrated NP Eq. 3 and so determines a first-iterate of concentration profiles $C_j(x;$ first iterate). These two iterates are consistent with each other and the boundary conditions. The two first-iterates $\phi(x;$ first iterate) and $C_j(x;$ first iterate) are then substituted into the right hand side of Poisson's Eq. 1, which is again solved, now to determine the second-iterate $\phi(x;$ second iterate), an updated, hopefully better approximation to the potential profile. The second-iterate of potential determines a second-iterate of concentration by Eq. 3; together, the two second-iterates determine the third-iterate of potential, and so on for ten iterations (which is more than enough for good convergence in almost all cases), that take only milliseconds on a typical personal computer.

The *PNP* equations form a map between the structure of the channel protein, represented crudely by the function $P(x)$ and the *I–V* curves measured experimentally. Different types of channels have different pores made with linings of different charge. A useful and productive working hypothesis assumes that the only difference between different types of open channels is their different distributions of fixed charge $P_k(x)$, where the subscript k identifies the type of channel protein, e.g., a voltage activated Na–channel, a stretch–activated channel and so on. Of course, this working hypothesis cannot always be true: specific chemical interactions, not captured in this simple mean field theory, will no doubt be important in ways we do not yet understand. Nonetheless, as we write these words, the *I–V* relations of some seven types of channels in a wide range of solutions can be predicted by simple distributions of fixed charge $P_k(x)$. In one particular kind of channel (from cardiac muscle), a fixed charge $P_{cardiac}(x) = P_0$ independent of position, with P_0 equal to $-1e$, predicts the currents measured in pure solutions, and most mixtures, of all the monovalent cations (i.e., Li^+, Na^+, K^+, Rb^+, Cs^+) from 20 mM to 2 M, and potentials of ±150 mV, assuming each ion has a different diffusion coefficient. The value of the diffusion coefficients are estimated by fitting theoretical predictions to the experimental data. Typically, the diffusion coefficients are some ten times smaller than in free solution.

The figures show a few *I–V* relations from three types of channels with quite different characteristics. Fig. 1

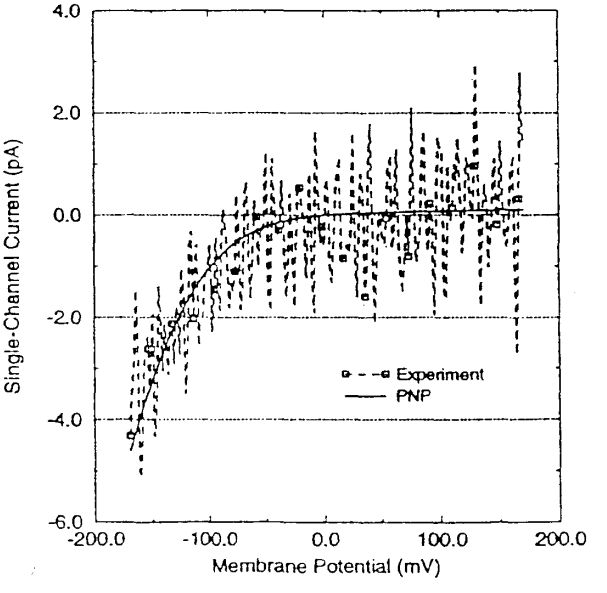

Figure 1 PNP fit to current voltage relations of LS-channel for $[KCl]_N = 0.545$, $[KCl]_C = 0.563$ M.

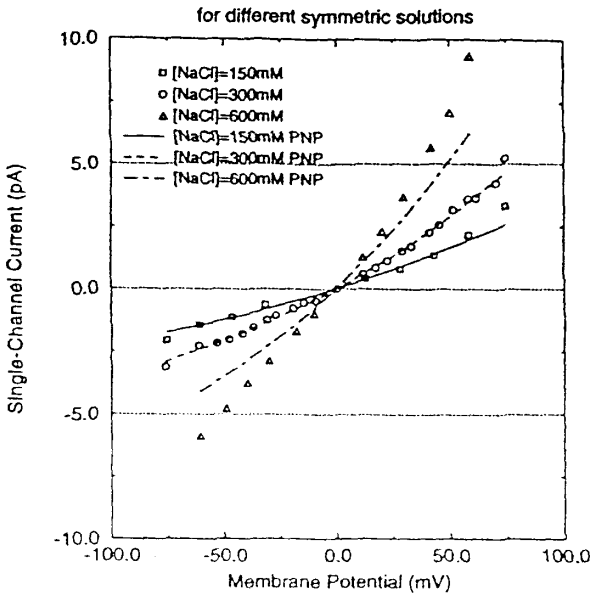

Figure 2. PNP fit to *I/V* of NBAK channel.

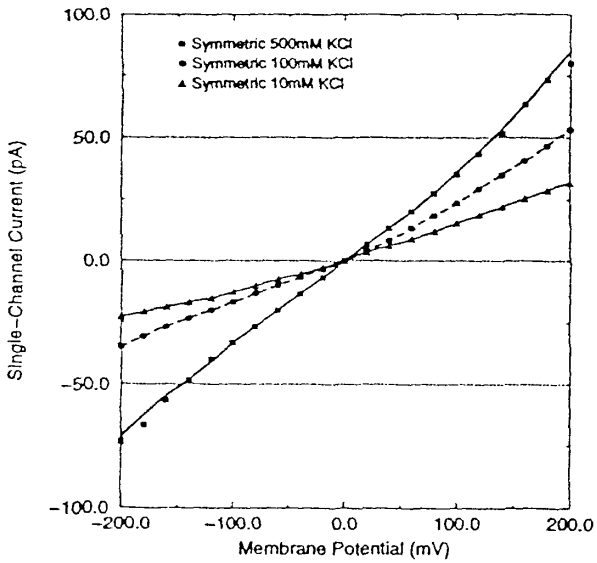

Figure 3 Current-voltage relations for G119D Porin.

shows that the *LS* channel (Chen et al., 1997) is highly rectifying—incidentally, the *NBAC* channel rectifies in the other direction (Chen et al., 1995). Fig. 2 shows that the *CRC* channel is nearly linear (Chen et al., 1997) and Fig. 3 demonstrates that a porin channel (Tang et al., 1997; Tang et al., 1997) has still different behavior. The data from the porin channels are of particular interest because the locations of the atoms of that protein are known by x-ray crystallography (Cowan et al., 1992; Jeanteur et al., 1994; Schirmer et al., 1995).

Nonequilibrium Effects

Nonequilibrium effects in channels are profound. These arise in at least two different ways. First, the flow of current and the flux of ions is accompanied by a significant change in electrochemical potential, a change in both the profiles of electrical potential and concentration. This is the voltage drop or change in concentration gradient given by either Ohm's or Fick's law in simple uncoupled systems (Section 29.6 and Sections 20.2, 29.2).

The other effect of moving away from equilibrium states is more subtle but at least as important. A nonequilibrium system can exist for a very wide range of boundary conditions but equilibrium systems can exist (i.e., make sense, and satisfy the equations that define themselves) only under very special circumstances, e.g., when boundary conditions are spatially uniform so no flux flows in the system. For example, a channel and its mathematical model are nonequilibrium systems that can function (biologically) and exist (mathematically) *no matter what the concentrations and what the electrical potentials in the baths,* or in the boundary conditions used to describe the baths. But an equilibrium theory of a channel (e.g., Poisson–Boltzmann models, or most simulations of the molecular dynamics of a channel) can only describe situations in which no flux of any species flows anywhere. If the concentrations and electrical potentials present in the baths (and boundary conditions) do in fact produce flux, (say) because they are not spatially uniform, an equilibrium model or simulation cannot be computed, if it is programmed correctly, because the equations in fact have no solution in that case. If an equilibrium simulation or computation gives a result, that result must have zero flux everywhere, because that is what equilibrium means. If an equilibrium simulation or computation seems to give a result when bath and boundary conditions are nonuniform, the simulation must not have converged to a solution to the equations defining the system, because no solution to the equations exists, and thus no numerical procedure can find one, in that case.

It is possible, of course, that an equilibrium model may be a decent approximation to a nonequilibrium model, or that it may give important physical insight into the properties of the nonequilibrium system. But this must be shown to be so, it cannot be assumed, and indeed is unlikely to be the case very often in systems like channels that function nearly always away from equilibrium, with potential and concentration gradients larger than $RT/\mathcal{F}$.

These abstract words have consequences for nearly all channels, because most channels carry flux under all conditions. Only a perfectly selective channel can be placed in solutions and at electrical potentials in which there is no flux of any species. Only a perfectly selective channel has gradients of potential and concentration across it that satisfy the Nernst equation of electrochemistry (Section 26.2), the Nernst equation is an algebraic equation defining a potential, not to be confused with the Nernst–Planck

differential that describes diffusion) for the permeable ion. Most channels are not so selective and allow biologically and experimentally significant flux of several types of ions at all potentials and concentration gradients. Even when the potential and concentration gradients are arranged so that one ion is at equilibrium (i.e., the potential and concentration gradients across the channel satisfy the Nernst equation for that one ion), and so the flux of that ion is zero, other ions are away from equilibrium, and do not satisfy their own Nernst equation and do carry flux that cannot be ignored. Thus, most channels cannot be analyzed under any experimental conditions by an equilibrium theory. They cannot be simulated by a molecular dynamics calculation that has spatially uniform boundary conditions.

Implications

Open channels provide a link among the communities of scientists who study electrochemical systems, who study enzymes and who study transistors. It will be interesting to see if the physical insights of the semiconductor community—used to study charge transport in macroscopic systems with complex structure and (spatially nonuniform) boundary conditions, far from equilibrium, in atomic detail, on femtosecond time scales (Hess et al., 1991; Hess, 1991)—can be applied to the study of the atomic and molecular dynamics of electrolyte solutions, proteins, and channels.

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