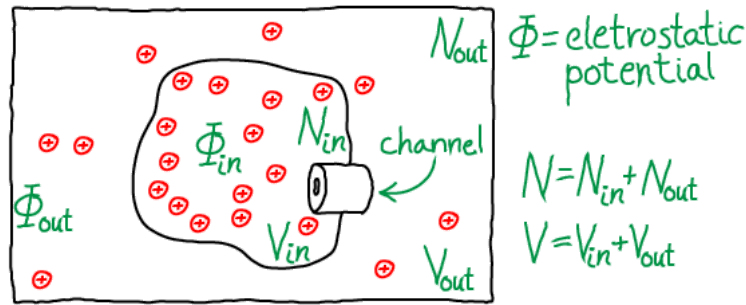


# Ionic Concentration Gradient Across a Bilayer

## A Half-Step Beyond Ideal: Ion Gradients and Transmembrane Potentials

One key way the cell stores **free energy** is by having different concentrations of molecules in different "compartments" - e.g., extra-cellular vs. intracellular or in an organelle compared to cytoplasm. The molecules playing this role are charged molecules, or ions, such as sodium ( $\text{Na}^+$ ), chloride ( $\text{Cl}^-$ ), potassium ( $\text{K}^+$ ), calcium ( $\text{Ca}^{++}$ ), and numerous nucleotide species. [A brief overview of trans-membrane ion physiology](#) is available.

Although the simplest way to study the physics of free energy storage in such a gradient is by considering **ideal particles all with zero potential energy**, the reality of the cell is that electrostatic interactions are critical. Fortunately, the most important non-ideal effects of charge-charge interactions can be understood in terms of the usual **ideal particles** (which do not interact with one another) that do, however, feel the effects of a "background" electrostatic field. Such a mean-field picture is a simple approximation to the electrostatic effects induced primarily by having an excess of one or more charged species on a given side of a membrane - for example, the excess of  $\text{Na}^+$  ions in the extracellular environment.



## Two semi-ideal gases of ions in different potentials

Unlike our examination of **two membrane-separated ideal gases**, the particles here are explicitly charged and they "feel" the electrostatic potential  $\Phi$ . The positively charged anions schematically represent  $\text{K}^+$  ions interacting with the field generated by the imbalance of  $\text{Na}^+$  ions - the extracellular or "outside" concentration of sodium is maintained at a high value relative to the cytoplasm or "inside" by constant ATP-driven pumping. However, *the effects of the  $\text{Na}^+$  concentration gradient will only be treated implicitly via the different values for  $\Phi_{\text{in}} < \Phi_{\text{out}}$ .*

To be precise, the model consists of  $N$  particles that do not interact with one another, but which interact with the external potential  $\Phi$  as if each had a charge of  $q$ , leading to potential energy  $q \cdot \Phi_X$  for each particle, where  $X = \text{"in" or "out"}$ . The total volume  $V$  is divided into inside and outside so that  $V_{\text{in}} + V_{\text{out}} = V$ , with  $N_{\text{in}} + N_{\text{out}} = N$  ions populating the two compartments. The whole system is maintained at constant temperature  $T$ . Particles can pass through the channel shown in the figure, but we assume it is closed so that  $V_{\text{in}}$  and  $V_{\text{out}}$  are constants: as shown in our discussion of **two membrane-separated ideal gases**, the assumption is a convenience and not an approximation because the total system volume  $V$  and particle-number  $N$  are truly constant.

## Deriving the free energy

We have two gases of ideal "ions" (that interact with the external potential but not with other ions). Mathematically, we can largely follow our discussion of **two membrane-separated ideal gases**. The total free energy is the sum of the two ideal gas free energies and the two electrostatic potential energies:

$$F(N_{\text{in}}, N_{\text{out}}) = F^{\text{idl}}(N_{\text{in}}, V_{\text{in}}) + F^{\text{idl}}(N_{\text{out}}, V_{\text{out}}) + N_{\text{in}} q \Phi_{\text{in}} + N_{\text{out}} q \Phi_{\text{out}} \quad (1)$$

where  $F^{\text{idl}}$  is defined in the [ideal gas page](#) and  $q$  is the ionic charge.

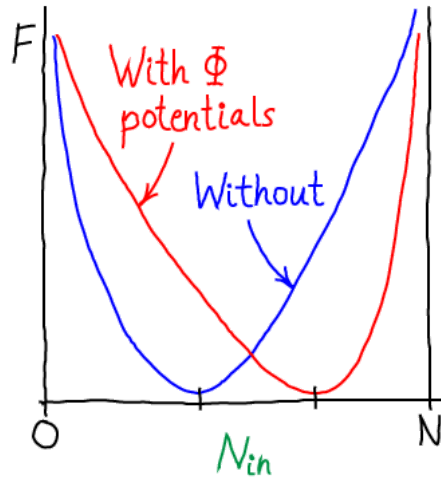
Substituting for  $F^{\text{idl}}$  and noting that  $N_{\text{out}} = N - N_{\text{in}}$ , we have

$$F(N_{\text{in}}, N - N_{\text{in}}) = N_{\text{in}} k_B T \ln \frac{N_{\text{in}} \lambda^3}{V_{\text{in}}} + (N - N_{\text{in}}) k_B T \ln \frac{(N - N_{\text{in}}) \lambda^3}{V_{\text{out}}} + N_{\text{in}} q \Phi_{\text{in}} + (N - N_{\text{in}}) q \Phi_{\text{out}}. \quad (2)$$

Because it is really the *difference* in electrostatic potential which governs the ionic behavior, we define  $\Delta\Phi = \Phi_{\text{in}} - \Phi_{\text{out}}$ . In terms of this quantity, we can rewrite the total free energy as

$$\begin{aligned}
 F(N_{\text{in}}, N - N_{\text{in}}) = & N_{\text{in}} k_B T \ln \frac{N_{\text{in}} \lambda^3}{V_{\text{in}}} \\
 & + (N - N_{\text{in}}) k_B T \ln \frac{(N - N_{\text{in}}) \lambda^3}{V_{\text{out}}} \\
 & + Nq\Phi_{\text{out}} + N_{\text{in}}q\Delta\Phi,
 \end{aligned} \tag{3}$$

Eq. (3) is the free energy as a function of the number of particles inside the membrane (in volume  $V_{\text{in}}$ ), which could be equivalently described using the [chemical potential](#). Inclusion of the electrostatic effects shifts the location of the most probable state, or free energy minimum.



### The most probable concentrations: The Nernst equation

If we open the channel and allow exchange of atoms between the compartments, the value of  $N_{\text{in}}$  can change. The probability of having  $N_{\text{in}}$  atoms in  $V_{\text{in}}$  is [proportional to the Boltzmann factor of the free energy](#):

$$p(N_{\text{in}}) \propto e^{-F(N_{\text{in}}, N - N_{\text{in}})/k_B T} \tag{4}$$

The most probable  $N_{\text{in}}$  value therefore can be found by determining the minimum of  $F$ . This will represent the [equilibrium](#) point in the thermodynamic limit (very large  $N$  - when fluctuations about the most probable  $N_{\text{in}}$  will be very small compared to  $N_{\text{in}}$  itself). We set  $\partial F / \partial N_{\text{in}} = 0$  in Eq. (3), then re-arrange and cancel terms to find

$$0 = k_B T \ln \frac{N_{\text{in}} \lambda^3}{V_{\text{in}}} - k_B T \ln \frac{N_{\text{out}} \lambda^3}{V_{\text{out}}} + q\Delta\Phi / k_B T \tag{5}$$

Combining the terms using the rules of logarithms, followed by exponentiation, we find the **Nernst equation**,

$$\text{Equilibrium: } \frac{N_{\text{in}}/V_{\text{in}}}{N_{\text{out}}/V_{\text{out}}} = e^{-q\Delta\Phi/k_B T} \tag{6}$$

where you should recognize the left-hand side as the ratio of concentrations.

In words, Eq. (6) shows that *the concentrations inside and outside vary according to the Boltzmann factor of the ionic charge times the potential difference*. Such an equilibrium is called a Donnan equilibrium. It should be comforting that when  $\Delta\Phi = 0$ , we recover [equal concentrations](#).

## Comparison to cellular behavior

As the exercise below will show, for some ions ( $\text{Cl}^-$ ,  $\text{K}^+$ ) the Nernst equation is a reasonable approximation. This suggests that such ions permeate the membrane [passively](#). For some ions ( $\text{Na}^+$ ,  $\text{Ca}^{++}$ ), the concentration ratios are very different from what would be predicted from the Nernst equation because the cell uses [active transport](#) to control them.

## Mass action and its limitations

It is always worthwhile to pursue both thermodynamic *and* kinetic analyses of any system you really care about, or just to train yourself to consider a problem from multiple perspectives. By comparison to the present case, some of the results from the [truly ideal \(uncharged\) two-compartment system](#) may seem puzzling.

In contrast to the uncharged system, we can see that the transport rates through the channel *cannot* be equal in the two directions. Let  $k_{io}$  be the inside-to-outside rate constant and  $k_{oi}$  be the reverse rate constant. Starting from [detailed balance](#), which says that the overall flows must be equal and opposite, and substituting the Nernst relation (6), we find that

$$\frac{k_{oi}}{k_{io}} = \frac{N_{\text{in}}/V_{\text{in}}}{N_{\text{out}}/V_{\text{out}}} = e^{-q \Delta\Phi/k_B T} \quad (7)$$

In other words, the ratio of rates for an ion channel depends on the potential difference. By itself, this does not contradict the [mass action viewpoint](#) (that rate constants are independent of concentrations) ... so long as  $\Delta\Phi$  is truly constant. But if, more generally,  $\Delta\Phi$  depends on the relative concentrations of the ion species moving through the channel, then the mass-action picture breaks down. Such a breakdown would occur, for example, if there were two species of ions, one of which could not permeate the membrane and hence was maintained at fixed inside and outside concentrations: in this case, flow of the permeable ion would change  $\Delta\Phi$  and, in turn, change the rate "constants".

The [brief overview of trans-membrane ion physiology](#) may help to clarify the bigger picture of ion/membrane behavior.

### References:

- R. Phillips et al., "Physical Biology of the Cell," (Garland Science, 2009).
- B. Alberts et al., "Molecular Biology of the Cell", Garland Science (many editions available).

### Exercises:

1. Derive Eqs. (5) and (6).
2. Use Eq. (6) to derive a concentration ratio for  $\text{Cl}^-$  using  $\Delta\Phi = -90 \text{ mV}$  (typical for skeletal muscle) and compare your result to the experimental value of  $\sim 1/30$ . This will require careful consideration of units when multiplying together physical constants.