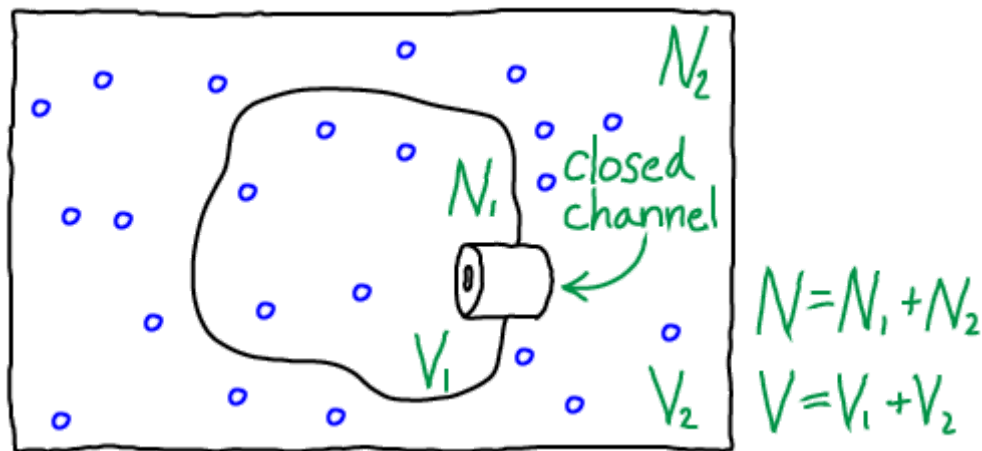


# Simple Concentration Gradient Across a Bilayer

## The Free Energy in a Concentration Gradient

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. Here, we will study the simplest example of such a *gradient*, differing concentrations of **ideal gas** molecules across an idealized rigid membrane. Elsewhere, we consider **a simple model of ion concentration gradient across a membrane**.

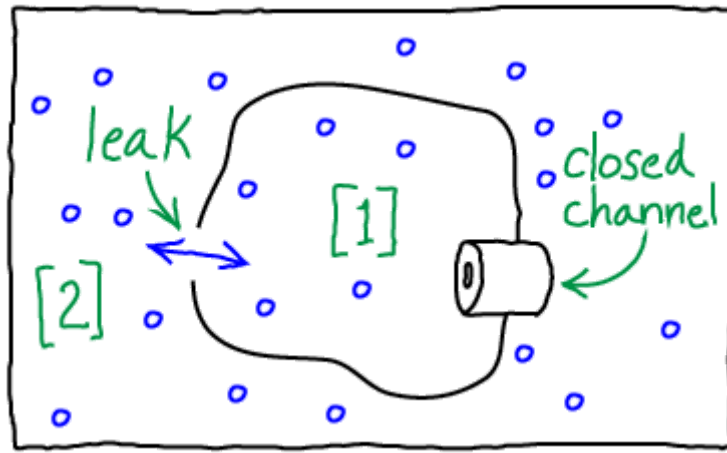
### Two ideal gases separated by a barrier



Analyzing the model depicted above will enable us to understand free energy storage in a concentration gradient, but the basic ideas generalize to **activated carriers** as well.

To be precise, the model consists of  $N$  non-interacting atoms in the volume  $V$  maintained at constant temperature  $T$ . Beyond **the simple ideal gas studied elsewhere**, our present system is divided into two compartments by a rigid "membrane," with  $V_1$  the volume of the inner compartment and  $V_2$  the outer volume such that  $V_1 + V_2 = V$ . Similarly, there are  $N_1$  atoms in the inner compartment and  $N_2$  outside, with  $N_1 + N_2 = N$ . Although particles could pass through the channel shown in the figure, we assume it is closed so that  $N_1$  and  $N_2$  are constant.

### A quick mass-action analysis



We can derive the key result for this system very quickly using a [mass action](#) "thought experiment". Our simple kinetic analysis will provide a key reference when we delve into some specific [limitations of the mass-action picture in the context of ionic gradients](#).

Instead of our original system, we consider the leaky cell or organelle shown above. The leak should be considered a simple hole (unlike a channel, which is expected to interact strongly with molecules passing through it). Hence the inside-to-outside rate constant  $k_{12}$  for the leak/hole must be equal to the outside-to-inside rate constant  $k_{21}$ . After all, if the hole is large enough the "atoms" will not interact with the membrane at all - or if they do, the effects should be symmetric.

In [equilibrium](#), we know that the total number of events in each direction will match:  $[1] k_{12} = [2] k_{21}$ . Cancelling the equal rates on both sides of this relation, we find that the **equilibrium concentrations must be equal inside and outside**:

$$[1]^{\text{eq}} = [2]^{\text{eq}}. \quad (1)$$

Deriving this result thermodynamically in a careful way requires more effort (see below).

This equilibrium result for the leaky condition actually tell us something about the channel rates. Because the channel is a passive element that uses no energy, it cannot change the (equal) equilibrium concentrations just derived. Hence, applying the principle of [detailed balance](#) to the channel (which implies the flows through the channel must be equal and opposite) we see that the *channel rate constants must be equal in both directions*. This perhaps obvious result only holds for a channel separating two systems with no driving force or external field applied - a condition which breaks down in the case of [trans-membrane ionic gradients](#).

## Deriving the free energy

Because we have non-interacting ("ideal") particles which cannot exchange across the membrane, the total free energy for the combined systems  $F^{\text{comb}}$  is simply the sum of the two free energies calculated independently for the two systems. (From the probability point of view embedded in the calculation of a partition function - see below - the lack interactions implies statistical independence and hence factorizability of the full-system partition function

into those for the two systems.) We have

$$F^{\text{comb}}(N_1, N_2) = F^{\text{idl}}(N_1, V_1, T) + F^{\text{idl}}(N_2, V_2, T), \quad (2)$$

where  $F^{\text{idl}}$  is defined in the [ideal gas page](#). We have omitted the  $V_1$ ,  $V_2$ , and  $T$  dependence in  $F^{\text{comb}}$  because these will be held constant throughout.

Substituting in for  $F^{\text{idl}}$ , we have

$$F^{\text{comb}}(N_1, N_2) = N_1 k_B T \ln \frac{N_1 \lambda^3}{V_1} + N_2 k_B T \ln \frac{N_2 \lambda^3}{V_2}. \quad (3)$$

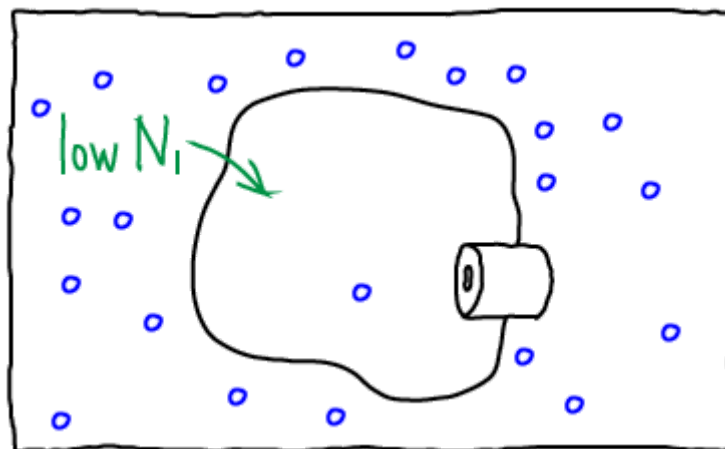
Noting that

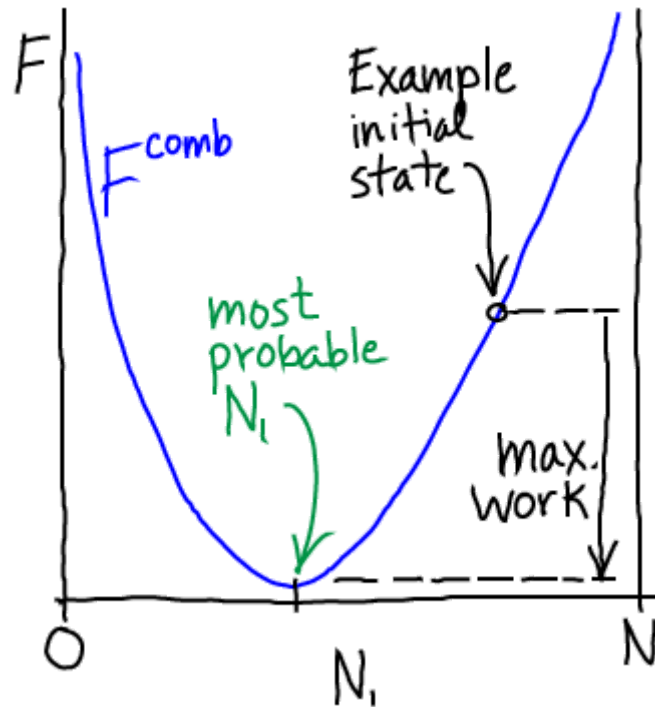
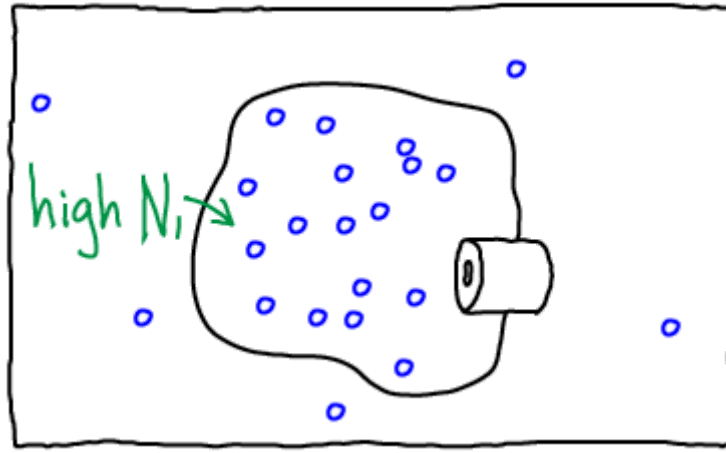
$$N_2 = N - N_1,$$

we can rewrite this further as

$$F^{\text{comb}}(N_1, N - N_1) = N_1 k_B T \ln \frac{N_1 \lambda^3}{V_1} + (N - N_1) k_B T \ln \frac{(N - N_1) \lambda^3}{V_2}. \quad (4)$$

Eq. (4) is the free energy as a function of the number of particles inside the membrane (volume  $V_1$ ).





If we open the channel and allow exchange of atoms between the compartments, the value of  $N_1$  can change. The probability of having  $N_1$  atoms in  $V_1$  is proportional to the Boltzmann factor of the free energy:

$$p(N_1) \propto e^{-F^{\text{comb}}(N_1, N-N_1)/k_B T} \quad (5)$$

The most probable  $N_1$  value therefore can be found by determining the minimum of  $F^{\text{comb}}$ . This will represent the **equilibrium** point in the thermodynamic limit (very large  $N$  - when fluctuations about the most probable  $N_1$  will be very small compared to  $N_1$  itself). We set  $\partial F^{\text{comb}}/\partial N_1 = 0$  in Eq. (4), then re-arrange and cancel terms to find

$$0 = k_B T \ln \frac{N_1 \lambda^3}{V_1} - k_B T \ln \frac{(N - N_1) \lambda^3}{V_2} \quad (6)$$

Combining the terms using the rules of logarithms, followed by exponentiation, we find that

$$\text{Equilibrium: } \frac{N_1}{V_1} = \frac{N - N_1}{V_2} = \frac{N_2}{V_2}, \quad (7)$$

where we substitute  $N_2 = N - N_1$  to obtain the last equality.

In words, Eq. (7) shows that *the concentrations inside and outside the membrane must match in equilibrium*. You probably knew that already, but we have derived it from statistical/thermodynamic principles.

## The next step: Considering ions

[Ion concentration gradients](#) can also be analyzed in a similar way.

## Work that can be performed

As we move from higher to lower free energy, the system can perform work - if it is coupled to a suitable mechanism for harvesting the work. The [maximum amount of work that can be extracted](#) is equal to the decrease in free energy as sketched above. In a simple gas system, work could be extracted by placing a turbine at the "channel"/nozzle as the gas flows toward equilibrium. Models of work extraction which are more pertinent to cell biology are discussed in the [transport](#) section.

## Passive Transport

In the simplest kind of [passive transport](#), molecules flow down a gradient (from high to low concentration) and that flow is not coupled other processes. In our technical language, such a process would involve moving from a state of higher to lower free energy (see sketch above) or from lower to higher probability - see Eq. (5).

## A deeper look at partition functions and probabilities

A partition function  $Z$  is simply a sum of Boltzmann factors for all possible states (configurations - and velocities if considered) of a system. Because a Boltzmann factor represents a weight (an un-normalized probability),  $Z$  is the sum of weights. Many times, partition functions are easier to work with mathematically, compared to free energies. Our system is such a case.

## Factorizability

Our combined system consists of two independent sub-systems. That is, the state of one system will not affect the other. Hence the probability for a configuration of the combined system is simply the *product* of the probabilities for the individual system configurations, and this also holds for the Boltzmann weights summed in  $Z$ .

If  $U_1$  is the potential energy of the configuration of system 1 and  $U_2$  is the energy of system 2, these two are

independent, so we have

$$e^{-U_{\text{tot}}/k_B T} = e^{-(U_1+U_2)/k_B T} = e^{-U_1/k_B T} e^{-U_2/k_B T} \quad (8)$$

We can extend this reasoning to calculate the partition function of the combined system, building on what was done for a simple [ideal gas](#). Denoting the configuration of the combined system by  $(\mathbf{r}_1^N, \mathbf{r}_2^N)$ , the partition function is

$$\begin{aligned} Z^{\text{comb}}(N_1, N_2) &= \frac{\lambda^{-3N_1}}{N_1!} \frac{\lambda^{-3N_2}}{N_2!} \int_{V_1} d\mathbf{r}_1^N \int_{V_2} d\mathbf{r}_2^N e^{-U_{\text{tot}}(\mathbf{r}_1^N, \mathbf{r}_2^N)/k_B T} \\ &= \left[ \frac{\lambda^{-3N_1}}{N_1!} \int_{V_1} d\mathbf{r}_1^N e^{-U_1(\mathbf{r}_1^N)/k_B T} \right] \left[ \frac{\lambda^{-3N_2}}{N_2!} \int_{V_2} d\mathbf{r}_2^N e^{-U_2(\mathbf{r}_2^N)/k_B T} \right] \quad (9) \\ &= \frac{\lambda^{-3N_1}}{N_1!} V_1^{N_1} \frac{\lambda^{-3N_2}}{N_2!} V_2^{N_2} = Z^{\text{idl}}(N_1, V_1) Z^{\text{idl}}(N_2, V_2) \end{aligned}$$

where we evaluated the integrals in the last line, noting  $U_1 = U_2 = 0$  for ideal particles, so that each atom's integration yields a factor of  $V_i$  depending on which volume  $i$  is occupied.

## Connecting $Z$ and $F$ to probability

A partition function is the sum of all probability (weights) consistent with the conditions/constraints - such as constant  $T$  or  $V$ . This allows us to compare the (summed) probabilities consistent with different constraints, such as different  $N_1$  values in  $Z^{\text{comb}}$ . More specifically, recalling that  $N_2 = N - N_1$ , we have

$$p(N_1) \propto Z^{\text{comb}}(N_1, N - N_1). \quad (10)$$

Because the free energy is nothing other than the log of the partition function ( $F = -k_B T \ln Z$  or  $Z = \exp(-F/k_B T)$ ), we see that Eqs. (10) and (5) are equivalent.

## The total partition function

Advanced readers may have considered the possibility of the *total* partition function  $Z^{\text{tot}}$ , which not only sums over all configurations consistent with a given  $N_1$  value - *but which also sums over all possible  $N_1$  values from 0 to  $N$* . The outcome is rather neat. We write

$$\begin{aligned}
Z^{\text{tot}} &= \sum_{N_1=0}^N Z^{\text{comb}}(N_1, N - N_1) \\
&= \sum_{N_1=0}^N \frac{1}{N_1!} \left( \frac{V_1}{\lambda^3} \right)^{N_1} \frac{1}{(N - N_1)!} \left( \frac{V_2}{\lambda^3} \right)^{(N-N_1)} \\
&= \frac{1}{N!} \sum_{N_1=0}^N \frac{N!}{N_1! (N - N_1)!} \left( \frac{V_1}{\lambda^3} \right)^{N_1} \left( \frac{V_2}{\lambda^3} \right)^{(N-N_1)} \\
&= \frac{1}{N!} \left( \frac{V}{\lambda^3} \right)^N
\end{aligned} \tag{11}$$

where the last line derives from recognizing the [binomial expansion](#) for  $(V_1 + V_2)^N$  implicit in the previous line.

You should recognize Eq. (11) as the partition function for a [simple ideal gas](#) of  $N$  atoms in volume  $V = V_1 + V_2$ . Indeed, once the channel is open, all atoms can access both volumes and this is the correct result.

#### References:

- J. Kuriyan, B. Konforti, and D. Wemmer, *The Molecules of Life: Physical and Chemical Principles* (Garland Science, 2013).
- 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. (6) and (7).