Entropy, free energy and entropic forces

Lecture notes, weeks 10–11. Nelson, chapters 6–7

Dag Kristian Dysthe

Biological question: if energy is always conserved, how can some devices be more efficient than others?
Physical idea: order controls when energy can do useful work, and order is not conserved.

What decides equilibrium?

In mechanics, a system at rest sits where the forces balance, $\sum_i \vec{F}_i = -\sum_i \nabla U_i = 0$: it minimizes its potential energy. In thermodynamics, an isolated system goes to the macrostate with the largest number of microstates: it maximizes its entropy $S = k_B \ln \Omega$.

Most biological systems are not isolated. A protein, a bead or a cell sits in water at fixed temperature T; the water is a huge heat reservoir. If the small system takes energy ΔU from the reservoir, the reservoir's entropy changes by $-\Delta U/T$. The total entropy change is

$$\Delta S_{\text{tot}} = \Delta S - \frac{\Delta U}{T} = -\frac{\Delta(U - TS)}{T} = -\frac{\Delta F}{T}.$$

So **maximizing the total entropy is the same as minimizing the Helmholtz free energy** $F = U - TS$ of the small system. At fixed pressure as well (an open test tube, a cell), the work $P\Delta V$ done on the atmosphere also counts, and the quantity to minimize is the Gibbs free energy $G = U + PV - TS$.

The two principles are tied together by the thermodynamic identity.

Thermodynamic potentials

Potential	Definition	Identity	Natural variables
Internal energy	U	$dU = T\,dS - P\,dV + \mu\,dN$	S, V, N
Enthalpy	$H = U + PV$	$dH = T\,dS + V\,dP + \mu\,dN$	S, P, N
Helmholtz free energy	$F = U - TS$	$dF = -S\,dT - P\,dV + \mu\,dN$	T, V, N
Gibbs free energy	$G = U + PV - TS$	$dG = -S\,dT + V\,dP + \mu\,dN$	T, P, N

Each identity gives the other variables as derivatives, for example $S = -(\partial F/\partial T)_{V,N}$, $P = -(\partial F/\partial V)_{T,N}$, and

$$\mu = -T\left(\frac{\partial S}{\partial N}\right)_{U,V} = \left(\frac{\partial F}{\partial N}\right)_{T,V} = \left(\frac{\partial G}{\partial N}\right)_{T,P}. \tag{1}$$

A useful way to read them: F is the energy needed to create the system, minus what the reservoir supplies as heat; G also includes the work of making room for it.

What can be measured? T, V, P, N (by weighing), heat (from a known dissipation, for example RI^2) and work. U follows from the first law and C_V from $\Delta U/\Delta T$. Entropy is never measured directly: it is an integral, $S(T_2) - S(T_1) = \int_{T_1}^{T_2} (C_V/T)\,dT$. The chemical potential is a derivative of S, and is found from equilibria, for example osmotic or electrical ones.

Chemical potential

μ is the free energy cost of adding one particle. **Particles move from high to low** μ, just as heat flows from high to low T. In equilibrium, μ of every species that can move between two regions is the same in both.

Ideal gas. At constant T and N, $dG = V\,dP = (Nk_BT/P)\,dP$, so $G - G_0 = Nk_BT\ln(P/P_0)$ and

$$\mu = \mu_0 + k_BT\ln\frac{P}{P_0} = \mu_0 + k_BT\ln\frac{c}{c_0}. \tag{2}$$

Statistical mechanics gives the same result with the constant filled in: $F = -Nk_BT\left[\ln\left(V/(Nv_Q)\right)+1\right]$, where v_Q is the quantum volume of one molecule, so $\mu = (\partial F/\partial N)_{T,V} = k_BT\ln(c\,v_Q)$.

Ideal mixtures and dilute solutions. Mixing two ideal gases at equal T and P increases the volume available to species 1 from V_1 to V_1+V_2. Then $\Delta\mu_1 = -k_BT\ln[(V_1+V_2)/V_1] = k_BT\ln x_1$, where $x_1 = N_1/(N_1+N_2)$ is the mole fraction:

$$\mu_i(P,T,x_i) = \mu_i^0(P,T) + k_BT\ln x_i. \tag{3}$$

For a dilute solute this is the same as Eq. 2 with c the solute concentration. **A dilute solute behaves like an ideal gas**, with the solvent playing the role of empty space. This is the basis of osmosis (see Processes at membranes).

Potential energy in the chemical potential

If each particle also has a potential energy U_{ext} (gravity, a centrifuge, an electric field), adding a particle costs that energy too:

$$\mu_{\text{tot}} = \mu_{\text{int}} + \mu_{\text{ext}} = \mu_0 + k_BT\ln\frac{c}{c_0} + U_{\text{ext}}.$$

In equilibrium μ_{tot} is the same everywhere. For air in gravity, $U_{\text{ext}} = mgz$:

$$\mu_0 + k_BT\ln\frac{P(z)}{P_0} + mgz = \mu_0 \quad\Rightarrow\quad \frac{P(z)}{P_0} = e^{-mgz/k_BT} = e^{-z/z_c}, \quad z_c = \frac{k_BT}{mg}.$$

For nitrogen at 288 K, $z_c \approx 8.7$ km; on top of Mount Everest the pressure is about a third of that at sea level. The same argument with the buoyant mass of a protein gives sedimentation equilibrium (Nelson 5.1, E4), and with $U_{\text{ext}} = ze\mathcal{V}$ for an ion it gives the Nernst potential (Processes at membranes).

The Boltzmann distribution

Put a small system in contact with a large reservoir with total energy E_0. The probability that the small system is in a particular microstate i with energy ε_i is proportional to the number of states the reservoir then has, $\Omega_R(E_0-\varepsilon_i) = e^{S_R(E_0-\varepsilon_i)/k_B}$. Since $\varepsilon_i \ll E_0$, expand S_R to first order, with $\partial S_R/\partial E = 1/T$:

$$P(i) = \frac{1}{Z}e^{-\varepsilon_i/k_BT}, \qquad Z = \sum_i e^{-\varepsilon_i/k_BT}. \tag{4}$$

The partition function Z normalizes the probabilities and contains all the thermodynamics of the small system: $\langle E\rangle = k_BT^2\,d\ln Z/dT$ and $F = -k_BT\ln Z$.

Every quadratic term in the energy, like $\frac{1}{2}mv_x^2$ or $\frac{1}{2}kx^2$, has average $\frac{1}{2}k_BT$ (equipartition). This is how you measure the stiffness of something you cannot pull on: watch its thermal fluctuations, $k = k_BT/\langle\Delta x^2\rangle$.

Two-state systems

Many molecular switches have two states: a channel is open or closed, a protein folded or unfolded, an RNA hairpin zipped or unzipped. If the two states differ by free energy $\Delta F = \Delta E - T\Delta S$ (each state is itself a group of many microstates, hence the entropy), then

$$\frac{P_2}{P_1} = e^{-\Delta F/k_BT}, \qquad P_2 = \frac{1}{1+e^{\Delta F/k_BT}}.$$

Pulling on a molecule. If state 2 is longer by Δz and we pull with a force f, the force does work $f\Delta z$ when the molecule opens, so $\Delta F \to \Delta F_0 - f\Delta z$:

$$P_{\text{open}}(f) = \frac{1}{1+e^{(\Delta F_0 - f\Delta z)/k_BT}}. \tag{5}$$

The molecule is open half the time at $f_{1/2} = \Delta F_0/\Delta z$, and the switch from mostly closed to mostly open happens over a force range of a few $k_BT/\Delta z$. Optical-tweezer experiments on a single RNA hairpin (Liphardt et al. 2001) find $\Delta z \approx 18$ nm and $f_{1/2} \approx 14$ pN. So $\Delta F_0 \approx 60\, k_BT$, and the transition width $k_BT/\Delta z \approx 0.2$ pN is sharp, as measured. One fit of a curve to Eq. 5 gives both a length and a free energy of a single molecule.

Entropic forces

A force is the derivative of a free energy, $f = -\partial F/\partial x$, not only of an energy. When the energy does not depend on x, all of the force comes from entropy, $f = T\,\partial S/\partial x$.

The ideal gas is the simplest example. A gas pushes on a piston although its molecules have no potential energy at all: $F = -Nk_BT\ln V + \text{const}$, so $P = -\partial F/\partial V = Nk_BT/V$. The gas pushes because larger volume means more microstates. **Osmotic pressure** is the same force, exerted by solute particles on a membrane they cannot cross.

A polymer as an entropic spring. Model a chain as N segments of length L, each pointing left or right (a one-dimensional random walk, Block A). Pulled with force f, each segment is a two-state system with energy $\mp fL$, so $\langle x\rangle = NL\tanh(fL/k_BT)$. For small forces $\langle x\rangle \approx (NL^2/k_BT)\,f$: the chain is a spring with stiffness $k = k_BT/(NL^2)$. Unlike a metal spring, **it gets stiffer when heated**, because the restoring force is the thermal drive back towards the many coiled states. Rubber bands behave this way.

The depletion force

Large objects in a suspension of smaller particles (proteins, polymers, micelles) are pushed together. Small spheres of radius R cannot get closer than R to a surface (their centres are excluded from a layer of thickness R). When two flat surfaces are closer than $2R$, no small particles fit between them. The osmotic pressure ck_BT of the small particles on the outside is then unbalanced, and pushes the surfaces together.

Equivalently: bringing the surfaces together removes the overlap of their excluded layers and **gives the small particles more room**. For surfaces of area A at separation $d < 2R$ the free volume gained is $A(2R-d)$, so

$$\Delta F = -c\,k_BT\,A\,(2R-d), \qquad d < 2R.$$

This is a purely entropic attraction, with range set by the size of the small particles and strength by their concentration. In the crowded cytoplasm, with about 30 % of the volume taken by proteins, it is strong enough to help assemble macromolecular complexes and filament bundles (E7).

Free energy transduction

A stretched spring, a concentration difference and an unequal distribution of ions all store free energy. How much useful work can be recovered depends on *how* the constraint is released. Releasing a big constraint all at once (the spring snaps back against a small load, the membrane ruptures) wastes most of it as heat. Releasing it in many small, controlled steps (a motor that takes one step per ATP, a pump that moves

one ion at a time) can come close to the full ΔF. Biology uses the second strategy. See Nelson section 6.5.3 and E6.