Primer on Thermodynamics: Free Energies, Chemical Potentails, and all that.[1]

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February 5, 2020

In the next lecture, we will discuss one way that organisms can reduce errors during self-replication. However, in order to that we must first understand the basics of chemical kinetic and there relationship to thermodynamic quantities such as Free Energy. This lecture serves as a primer for basic thermodynamics. The core part of the lecture is to develop the machinery that will allow us to think about enzyme kinetics in two different way: a kinetic perspective and a thermodynamic perspective.

One the basic things that living things must do is transduce free energy – in other words extract energy from their environments. This is often done through chemical reactions that take a higher-free energy molecule and turn it into lower free-energy products. The problem with this process is that while *thermodynamically favorable*, they are often *kinetically extremely slow*. The reason for this is that there is often a "thermal barrier" that prevent the kinetics transition to the lower energy states. Cell exploit this fact to store energy and then use it when they need it.

A central aspect of all of living systems is that they control the kinetics by creating specialized catalysts that speed up chemical reactions (without changing the underlying thermodynamics). In the context of biology, these catalyst often take the form of specialized molecular machines called enzymes. In this class we will discuss the chemical kinetics from both a thermodynamic and kinetic perspective, and relate the two. It is essential that we can easily go back and forth between the thermodynamic and kinetic perspectives.

What is Free Energy

A full account of Free Energy is beyond the scope of these lectures. Here, we review the basics. A central quantity in the thermodynamics is of course the entropy of a system $S(E, N, V)$. The entropy is considered a function of the average energy E, number of particles N, and volume V and measures the number of available microscopic configurations available to the system when it has average energy E, particle number N, and volume V. The temperature of a system is defined in terms of the entropy as

$$\frac{1}{T} = k_B \left(\frac{\partial S}{\partial E}\right)_{V,N}, \tag{1}$$

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[1] Readings: Chapter 8, Nelson *Biological Physics*. Any undergraduate thermodynamics/stat mech book that discusses basic thermodynamics.

where $k_B = \approx 1.38 \times 10^{-23} J/K$ is the Boltzmann constant.

Equilibrium and Second Law (no particle, volume exchange)

Importantly, at equilibrium systems tend to *maximize* the entropy. We emphasize that at equilibrium systems do not occupy one particular microstate (microscopic) configuration, but rather represents a probability distribution over microstates (i.e the Boltzmann distrubution) that reflect physical constraints on the system (total energy, volume, particle number, etc.). Let us now review some thermodynamics.

Consider two systems that can exchange energies as shown in Figure . (but not particles or volume). Define the total energy of the system as $E = E_1 + E_2$ where $E_1 (E_2)$ is the energy of subsystem 1 (2). Note that we assume the combined system is *isolated* so that the total energy E is constant. In writing this we have ignore "boundary interactions" which are assumed to be small. Under the same assumption, we can write that the combined entropy of both systems as a sum of entropies of both systems [2]

$$S_{\text{tot}}(E, E_1) = S_1(E_1) + S_2(E_2) = S_1(E_1) + S_2(E - E_1) \tag{2}$$

A fundamental postulate of thermodynamics is that *entropy is maximized at equilibrium*. This is a direct result of the **Second Law of Thermodynamics** that says that the *entropy of an isolated system must always stay the same or increase*. Operationally, this means that at equilibrium the two system will exchange energy until the system 1 reaches an energy E_1 and maximizes S_{tot}. This implies that the derivative of S_{tot} with respect to E_1 must be zero. This gives the condition

$$0 = \left(\frac{\partial S_1}{\partial E}\right)|_{E_1} - \left(\frac{\partial S_2}{\partial E}\right)|_{E_2} \tag{3}$$

which implies that at equilibrium that temperatures must be equal.

$$T_1 = T_2. \tag{4}$$

Before proceeding, we point out a common misconception that is worth emphasizing. The second law applies only to *isolated systems*. If we consider a subsystem of the isolated system (say chamber 1 in the example above), *the entropy of this subsystem can still decrease without violating the second law* as long as the entropy of the remaining parts of the system increase so that S_{tot} increases or stays the same. [3]

Reformulating the Second Law in terms of Free Energies

Often, we consider a system that is hooked up to a thermal bath at temperature T. In this case, the whole universe whose energy we

[2] See HW problem for deriving a very interesting correction to this calculation.

[3] In fact, this is essentially the strategy that living systems use to maintain order and why Schrondinger classified life as having "negative entropy" (a confusing if intuitive term).

denote E consists of the system with energy E_1 and bath with energy $E_b = E - E_1$. Consider a process that changes the energy of the system a little $E_1 \to E_1 + \Delta E$. The system is then coupled to the bath and allowed to equilibrate. Since the bath is much bigger than the system, we assume that $\Delta E \ll E_b$ (This is really our definition of our bath. We know that this must increase the entropy S_{tot} of the system. Let us define $\Delta S = S_1(E + \Delta E) - S_1(E)$ and the temperature of the system/bath at $T = T_b = T_1$ [4]. We now perform some elementary mathematical manipulations

$$\begin{aligned} S_{\text{tot}}(E, E_1 + \Delta E) - S_{\text{tot}}(E, E_1) &\geq 0 \\ S_b(E - E_1 - \Delta E) + S_1(E + \Delta E) - S_b(E - E_1) - S_1(E) &\geq 0 \\ S_b(E - E_1) - \frac{\partial S_b}{\partial E}\Delta E - S_b(E - E_1) + \Delta S + \ldots &\geq 0 \\ \Delta S - \frac{1}{T}\Delta E &\geq 0 \\ -T(\Delta E - T\Delta S) &\leq 0 \\ \Delta F &\leq 0, \end{aligned} \tag{5}$$

where in the third line we have performed a Taylor series ignoring terms beyond first order in $\Delta E_1 / E_b$ and in the last line we have defined **Helmholtz free Energy**

$$\Delta F = \Delta E - T\Delta S. \tag{6}$$

In terms of this Free energy, the second law can be restates that the **Free energy of a system must always decrease when it relaxes coupled to a bath**. Furthermore, notice that the free energy depends only on the properties of the system we are measuring and makes no reference to the bath!! This is the magic trick that makes thermodynamics work. Furthermore, while we require $\Delta E \ll E_b$, ΔE can still be large compared to the energy of the system E_1

Deriving the Boltzmann distribution

We can also quickly derive the Botlzmann distribution. We however will have to evoke two basic facts from statistical mechanics.

- All microstates of an isolated system are equally probable. This is the fundamental postulate of statistical mechanics.
- The entropy S is related to the number of accessible configurations $\Omega(E)$ with energy E so that

$$S(E) = k_B^{-1} \log \Omega(E) \tag{7}$$

Consider again the situation shown in Figure **??** where we can consider the universe (i.e an isolated system) is divided into a system

[4] By assumption, system and bath are equilibrated.

and a bath that can exchange energy (but not particles and volume). Then, we can write the number of configurations accessible to the total system $\Omega_{\text{tot}}(E)$ as a product of the number configurations of the bath $\Omega_b(E - E_1)$ and the system $\Omega_1(E_1)$

$$\Omega_{\text{tot}}(E) = \Omega_b(E - E_1)\Omega_1(E_1). \tag{8}$$

Now choose a particular microstate s for the system with energy E_s. The number of configurations of the total system that are compatible with this state is just $\Omega_b(E - E_s)$ since this is the number of configurations available to the bath gives the microstate of the system. Thus, the probability of finding the system in this state is just given by

$$p_s = \frac{\Omega_b(E - E_s)}{\Omega_{\text{tot}}(E)}, \tag{9}$$

where we have used that fact that all configurations of the entire system are equally likely. Notice that the denominator is hard to calculate but does not depend on the state s. Thus, we can use the usual trick of statistics which is to consider the ratio of probabilities of two states, s and s' to get

$$\begin{aligned} \frac{p(s)}{p(s')} &= \frac{\Omega_b(E - E_s)}{\Omega_b(E - E_{s'})} \\ &= \frac{e^{S(E-E_s)/k_B}}{e^{S(E-E_{s'})/k_B}} \\ &= \frac{e^{-E_s/k_BT}}{e^{-E_{s'}/k_BT}} \end{aligned}$$

where in the last line we have used that to first order $S(E - E_s) \approx S(E) - \frac{\partial S}{\partial E} E_s$, Eq. 1, and the fact that $E_s \ll E$ [5]. It is common to rewrite this in terms of $\beta = 1/k_BT$. The quantity $e^{-\beta E_s}$ is often called the Botlzmann weight of state s.

This immediately gives us the **Botlzmann distribution** which states that the probability of a state s is just

$$p(E_s) = \frac{e^{-\beta E_s}}{Z} \tag{10}$$

where we have defined **the partition function** as a sum of the **Boltzmann weights** over all configurations

$$Z = \sum_{s'} e^{-\beta E_{s'}} \tag{11}$$

Systems that can exchange Energy, Volume, and Particles

In biological settings (and many physical settings), the system can not only exchange energy with the environment but also particles

[5] Again this is justified by saying energy of bath is much larger than energy of the system.

and "volume". [6] In this case, we do not have a well defined particle number or volume. Instead, we must work with fixed chemical potential and fixed pressure.

Defining pressure and Chemical Potential

Consider a system with many species of molecules. We'll call their populations N_α where $\alpha = 1, 2, \ldots$ runs over the kinds of species. There is a separate chemical potential for each of these

$$\mu_\alpha = -T \frac{\partial S}{\partial N_\alpha}|_{E,V,N_{\beta,\beta \neq \alpha}} \tag{12}$$

We can also define the thermodynamic pressure [7] as

$$P = T \frac{\partial S}{\partial V}|_{E,N_\alpha}. \tag{13}$$

You will show for HW that we can generalize the arguments above to show that in addition to the having equal temperatures, when two systems (1 and 2) are at equilibrium

$$\mu_{1,\alpha} = \mu_{2,\alpha} \tag{14}$$

and

$$P_1 = P_2. \tag{15}$$

Gibbs Free Energy and the Second Law

We can also generalize the Free Energy in the same way as we did above [8] to arrive at the Gibbs free energy

$$\Delta G = \Delta E - T\Delta S + \mu \Delta N - P\Delta V. \tag{16}$$

The second law then becomes that the Gibbs Free Energy always decreases as one relaxes to equilibrium

$$\Delta G \leq 0. \tag{17}$$

Generalized Boltzmann distribution and the Grand Partition Function

We can also easily generalize the arguments above to the case where the system exchanges both particles and volumes with its surroundings. In this case consider a state s with energy E_s, volume V_s, and N_s particles coupled to a bath (i.e environment) at a temperature T, pressure P, and volume V. In this case, using an analogous argument to above we can show [9]

$$p_s = \frac{e^{-\beta(E_s + \mu_s N_s - PV_s)}}{\mathcal{Z}}, \tag{18}$$

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[6] For example, a cell can expand or contract in response to changes in pressure, especially relevant through osmolarity.

[7] In equilibrium, one can show this is the same as the mechanical pressure (i.e. Force/Area). However, for systems that actively consume energy such as active materials this is not necessarily the case. See Solon, Alexandre P., et al. "Pressure is not a state function for generic active fluids." Nature Physics 11.8 (2015): 673.

[8] Reader is strongly encouraged to derive the expressions in these two sections.

[9] Please make sure you can derive these expressions

where $\mathcal{Z}$ is **the Grand Partition function**

$$\mathcal{Z} = \sum_{s'} e^{-\beta(E_{s'} + \mu_s N_s - PV_s)}. \tag{19}$$

This formula can be easily derived using the Boltzmann distribution and the fact that the kinetic energy

Chemical Potential for the the Ideal Gas

Thus, far everything we have done has been very abstract. One set of results we will rely on for understanding chemical kinetics are the thermodynamic potentials of an ideal gas of non-interacting particles. The reason is that we will often treat our chemical baths as non-interacting gases. The main result we will use is the form of the chemical potential for such gases.

The starting point for this is the Sakur-Tetrode formula for an ideal gas with N particles and volume V each with an internal energy ϵ:

$$S = k_B \log \left[\left(\frac{2\pi^{3N/2}}{(3N/2-1)!} \right) (2mE)^{3N/2} V^N \frac{1}{N!} (2\pi\hbar)^{-3N} \frac{1}{2} \right] \tag{20}$$

Here, $E = E_{kin} + N\epsilon$ refers to the total energy of the gas. Everything except the constants can be easily derived using the Boltzmann distribution [10].

Using the expression above, we can now use E q. 12 to calculate the chemical potential and get

$$\mu = k_B T \log c/c_0 + \mu_0(T), \tag{21}$$

where we have defined the concentration $c = N/V$, c_0 is a constant called the reference concentration and reference concentration-independent chemical potential

$$\mu^0(T) = \epsilon - \frac{3}{2} k_B T \log \frac{m k_B T}{2\pi\hbar^2 c_0^{2/3}}. \tag{22}$$

Notice that Eq. 21 says that **the chemical potential is directly proportional to the log of the concentration**. We will make use of this extensively when comparing thermodynamic and kinetics. '

Finally, notice that the difference of chemical potentials at a fixed temperature does not depend on $\mu^0(T)$ and the the difference in chemical potential depends only on the ratio of concentrations

$$\Delta\mu = \mu(c_1) - \mu(c_2) = k_B T \log c_1/c_2 \tag{23}$$

[10] See any elementary Stat Mech book or Chapter 3 of Nelson

Homework

1. Prove that if two systems A and B that can exchange energy and particles are at equilibrium, then $T_A = T_B$ and $\mu_{A,\alpha} = \mu_{B,\alpha}$.

2. **Mutual Information and Boundary Interactions** (optional for non-physics students). Let us define the probability that a system has energy E by $p(E)$. We can define the Shannon Entropy of a system as

   $$S[p(E)] = -\sum_E p(E) \log p(E). \tag{24}$$

   Denote the probability distribution of the systems 1 and 2 by $p_1(E_1)$ and $p_2(E_2)$. Furthermore, denote the joint distribution of both systems by $p(E_1, E_2)$.

   - Show that $S_tot = S_1 + S_2$ requires that the probability distribution of the whole system factorizes: $p_{1+2}(E_1, E_2) = p(E_1)p(E_2)$.
   - In general, we must use Bayes Rule, $p(E_1, E_2) = p(E_1|E_2)p(E_2) = p(E_2|E_1)p(E_1)$ to relate these probability distributions. Show that if the distribution does not factorize we must modify this expression to include the mutual information between energies of the system $I(E_1, E_2)$. Note that

   $$I(X,Y) = \sum_{X,Y} p(X,Y) \log \frac{p(X,Y)}{p(X)p(Y)} \tag{25}$$

   - Explain in words what this expression means. Why can we normally ignore this term safely? Discuss the relationship between information and thermodynamics here in physical terms.
   - Derive a new expression relating T_1 and T_2 at equilibrium. What is this correction mean and why can we ignore it safely in most large systems?
   - (Optional) Think about Boltzmann's Demon. How can we understand it qualitatively using this idea?

3. We can define the average energy of a system as

   $$\langle E \rangle = \sum_s E_s p(E_s) \tag{26}$$

   and the Hemholtz Free Energy as $F = \langle E \rangle - TS$. Using the expression for the Shannon entropy and the Boltzmann distribution in the last problem show that

   $$F = -k_B T \log Z, \tag{27}$$

   where Z is the partition function.