

# Biology 3550: Physical Principles in Biology

## Fall Semester - 2016

### Notes on Thermodynamics III

#### Entropy Continued, the Second Law and Free Energy

#### I. More on the statistical definition of entropy

A. In the previous section, we introduced both the classical and statistical definitions of entropy.

1. Classical definition of the entropy change for a system at constant temperature:

$$\Delta S = \frac{q_{rev}}{T}$$

where  $q_{rev}$  is the heat absorbed by the system for the reversible process that generates the maximum amount of work.

2. Statistical definition of entropy of a state made up of  $\Omega$  microstates with equal probability:

$$S = k \ln \Omega$$

where  $k$  is Boltzmann's constant.

3. We used both definitions to calculate the entropy change for expansion of a gas and arrived at the same result:

$$\Delta S = nR \ln \left( \frac{V_2}{V_1} \right)$$

where  $n$  is the number of moles, and  $V_1$  and  $V_2$  are the volumes of the gas at the beginning and end of the process.

4. Note that the entropy changes calculated so far refer only to the *system* (in this case the gas), and do not include entropy changes for the surroundings, which we will come to today.

B. Entropy change for a bimolecular reaction.

Consider the reaction:  $A + B \rightleftharpoons C$

Intuitively, we imagine this to be the sort of reaction that leads to a reduction of entropy, since the individual molecules of A and B have more freedom than a single molecule of C. We can use a statistical argument to estimate this reduction in entropy.

As in the example of gas expansion, we begin by dividing up the volume of interest into small cubes with volume  $V_c$ . The total volume is  $MV_c$ , where  $M$  is the number of small cubes.

Considering just one molecule each of A and B, the number of ways of placing these two molecules in the lattice of cubes,  $\Omega_{A,B}$  is  $M^2$ . This again assumes that the number of cubes is much larger than the total number of molecules. Because, the two molecules are assumed to be different,  $M^2$  is not divided by two, since swapping the positions of A and B results in a distinct arrangement. If the two reacting molecules were identical, then  $\Omega_{A,B}$  would equal  $M^2/2$

The number of arrangements of a single molecule of C in the volume is  $\Omega_C = M$ . The entropy change for a single pair of A and B molecules being converted to C is then given by:

$$\begin{aligned}\Delta S &= k \ln \left( \frac{\Omega_C}{\Omega_{A,B}} \right) = k \ln \left( \frac{M}{M^2} \right) \\ &= -k \ln M\end{aligned}$$

This result indicates that the entropy decreases for the reaction, as we expect. But, the result is also somewhat problematic, because the number of cubes,  $M$ , does not cancel out, as it did for the example of a gas expansion. Therefore, the size of the cubes does matter in this case.

Though there is no absolutely certain way to define the size of the cubes, we can at least make a reasonable estimate. The cubes should be just big enough to hold one of the reactant or product molecules. The product is probably larger than either of the reactants, making it difficult to specify a single size, but a reasonable estimate would be a cube 2 nm on each side, or a volume of  $8 \text{ nm}^3$ . The number of cubes is then calculated by dividing the reaction volume,  $V$ , by the volume of a single cube,  $V_c$ . We will specify that the total volume is given in liters. Taking into account the necessary conversion factors,  $M$  can be expressed as:

$$M = \frac{V \text{ L}}{8 \text{ nm}^3} \times \frac{10^{-3} \text{ m}^3}{L} \times \left( \frac{10^9 \text{ nm}}{\text{m}} \right)^3 \approx V(\text{L}) \times 10^{23}$$

The entropy change is then:

$$\Delta S = -k \ln(M) = -k \ln(V(\text{L}) \times 10^{23})$$

Note that the entropy change is closely related to the reaction volume,  $V$ , and becomes more negative with larger volume. This can be understood by recognizing that all of the molecules gain entropy when the volume is increased, but the two reactant molecules, together, lose more than the single product molecule.

For one mole each of A and B converted to C, the result above is multiplied by Avogadro's number:

$$\begin{aligned}\Delta S &= -N_A k \ln(V(\text{L}) \times 10^{23}) \\ &= -R \ln(V(\text{L}) \times 10^{23})\end{aligned}$$

If the volume is specified as 1 L, a numerical result can be calculated:

$$\begin{aligned}\Delta S &= -R \ln(10^{23}) = -8.31 \text{ J/K} \times 53 \\ &= -440 \text{ J/K}\end{aligned}$$

We can express this result in terms of energy by recalling the classical definition of entropy:

$$\Delta S = \frac{q_{\text{rev}}}{T}$$

The heat associated with the reversible process at a specified temperature, 298 K for instance, is then:

$$q_{\text{rev}} = T \Delta S = -130 \text{ kJ}$$

For an isothermal reversible process, the work,  $w_{\text{rev}}$ , is 130 kJ, a quite large amount of energy. This represents the amount of energy, in some form, that would have to be put into the system to compensate for the entropy loss and make the reaction favorable.

This simple calculation shows that the change of entropy associated with a reaction in which the number of molecules changes can be very significant. It is particularly significant in the context of biological systems, where very large molecules, such as proteins, nucleic acids and polysaccharides, are assembled from small building blocks (amino acids, nucleotides and sugars). However, accurately calculating these entropy changes is challenging and a source of some controversy. The calculation above considers only the loss of translational degrees of freedom, and a large reduction in rotational freedom is also to be expected in a bimolecular reaction. Other factors, including the changes in internal motions (bond rotations and vibrations) and interactions with solvent molecules may also contribute to the total entropy change. Among various estimates, the one above represents the lower range of calculated entropy changes for the association of two molecules.

### C. Microstates with different probabilities

(This section was not covered in class but is worth thinking about.)

What if the state is defined by microstates that do not all have equal probabilities? For instance, what if we were to divide up the total volume into cubes of different sizes, so that they had different probabilities of being occupied. Would the calculated entropy be different? More significantly, what if we were considering a more complicated environment, like the interior of a cell, where certain molecules have specific affinities for different compartments. Could we still use this approach to calculate entropy, or at least entropy changes?

The more general expression for the statistical entropy is:

$$S = -k \sum_{i=1}^N p_i \ln p_i$$

where  $N$  is the number of microstates, and  $p_i$  is the probability of microstate  $i$ . We won't try to prove this, but we can consider a couple of extreme cases. At one extreme, if we have  $N$  states with equal probabilities, the probability of each state must be  $p_i = 1/N$ . The entropy is then calculated as:

$$\begin{aligned} S &= -k \sum_{i=1}^N p_i \ln p_i = -k \sum_{i=1}^N \frac{1}{N} \ln \frac{1}{N} \\ &= -kN \frac{1}{N} \ln \frac{1}{N} \\ &= k \ln N \end{aligned}$$

consistent with the original expression for  $\Omega$  microstates with equal probabilities. At the other extreme, if there is only a single state, its probability must be 1, and the entropy is:

$$\begin{aligned} S &= -k \sum_{i=1}^N p_i \ln p_i \\ &= -k1 \ln(1) \\ &= 0 \end{aligned}$$

So, this state has an entropy of zero. In general, for a given number of microstates, if some of the microstates are more probable than others, the entropy will be lower than if all of the microstates have equal probabilities. So, for instance, if some configurations of a molecule are more probable because certain atoms tend to interact with each other, the molecule will have a lower entropy than if all of the possible conformations had equal probabilities.

## II. Entropy and the second law

Now that we have defined this new state function, entropy (twice in fact), we can state the second law of thermodynamics. There are several equivalent ways to state this law, but the most common one is probably the following:

For a spontaneous process, the total entropy of the system and its surroundings increases.

This leaves us with two questions, though:

- What do we mean by spontaneous?
- How do we define, measure or calculate the entropy change for the surroundings?

By spontaneous, we mean that the process will occur without any mechanical work being applied to the system. In other words,  $w \leq 0$ . If  $w < 0$ , then we can actually

use the process to *do* work. A gas expansion is an example of a spontaneous process, and one that can do work. Compressing a gas, on the other hand, requires work.

For a specified process, the entropy change for the surroundings is defined as:

$$\Delta S_{\text{surr}} = -\frac{q}{T}$$

The important point here is that  $q$  is the heat absorbed by the system for the actual process, *not* the maximum-work reversible process. The entropy of the surroundings is *not* a function of the state of the system.

The entropy of the surroundings increases whenever heat flows from the system outwards. This only occurs when the system is warmer than the surroundings, and the flow of heat represents an increase in the disorder of the surroundings. If the system has a lower temperature than the surroundings, heat will flow inward, and the entropy of the surroundings will decrease. These are the only ways that the system can affect the entropy of the surroundings.

If there is a net flow of heat from the system to the surroundings, the entropy of the system can *decrease* in a spontaneous process.

Consider two cases for the expansion of an ideal gas:

1. Adiabatic expansion with no work.  $\Delta E = 0$ ,  $q = w = 0$ .

$$\Delta S_{\text{univ}} = \Delta S_{\text{sys}} + \Delta S_{\text{surr}} = nR \ln \left( \frac{V_2}{V_1} \right)$$

So long as  $V_2 > V_1$ ,  $\Delta S_{\text{univ}} > 0$ , and the process is spontaneous, which we knew already! But, now we have a way of quantifying the tendency of the gas to expand.

2. Reversible isothermal expansion with maximum work.  $\Delta E = 0$ ,  $q = q_{\text{rev}}$

$$\begin{aligned} \Delta S_{\text{univ}} &= \Delta S_{\text{sys}} + \Delta S_{\text{surr}} \\ &= \frac{q_{\text{rev}}}{T} + \frac{-q_{\text{rev}}}{T} \\ &= 0 \end{aligned}$$

So, the reversible process is right on the edge of being spontaneous, which we can take as the meaning of a reversible process.

### III. Enthalpy and Free energy

The entropy functions (for the system and the surroundings) and the second law can tell us whether or not a particular process will be spontaneous and how much work we can obtain from it (or have to put into it to make it occur). But, it is awkward having to think about the heat flow to the surroundings, which is not a state function.

Instead, we usually apply the second law using an approach developed by Josiah Willard Gibbs (1839–1903), who was arguably the first really great American physical or theoretical scientist. Gibbs, working mostly on his own, put together the ideas of

thermodynamics into a consistent system. He spent his entire career at Yale University, and published all of his work in the Transactions of the Connecticut Academy of Sciences. His work was very slow to be fully appreciated.

One of Gibbs' major accomplishments was formulating the application of thermodynamics to chemical reactions. In doing so, he introduced two new state functions, enthalpy ( $H$ ) and what we now call the Gibbs free energy ( $G$ ).

The change in enthalpy,  $\Delta H$ , is the heat that is absorbed by a process when it is carried out reversibly at a constant pressure and temperature:

$$\Delta H = q_p$$

where the subscript  $p$  indicates constant pressure. Although  $q$  does not, in general, represent a state function, the value of  $q$  for a specific process interconverting two states does represent a change in state function. This is similar to the use of  $q_{\text{rev}}$  to define the entropy change.

If  $w_p$  represents the work associated with the constant-pressure process, then the relationship between  $\Delta E$  and  $\Delta H$  is given by:

$$\Delta E = q_p + w_p$$

$$\Delta E = \Delta H + w_p$$

$$\Delta H = \Delta E - w_p$$

If there is no change in volume, and no work, during the process, then  $\Delta H = \Delta E$ . On the other hand, if the volume increases acting against the fixed pressure  $P$ , then  $w_p < 0$ , and  $\Delta H$  will be greater than  $\Delta E$ . For most chemical reactions, the volume change at constant pressure is very small, and  $\Delta E$  and  $\Delta H$  can be considered almost interchangeable.

The major advantage of working with  $\Delta H$  is that this quantity can be directly measured, for instance using a calorimeter to directly measure the flow of heat into or out of a chemical reaction.

The change in Gibbs free energy for a process is defined as:

$$\Delta G = \Delta H - T\Delta S_{\text{sys}}$$

Because  $\Delta H$ ,  $T$  and  $\Delta S_{\text{sys}}$  are all state functions,  $\Delta G$  must be a state function as well. From the definition of  $\Delta H$ , the expression for  $\Delta G$  can also be written as:

$$\Delta G = q_p - T\Delta S_{\text{sys}}$$

Since the entropy change for the surroundings,  $\Delta S_{\text{surr}}$ , is defined as  $-q/T$ ,  $q$  for the constant-pressure process is equal to  $-T\Delta S_{\text{surr}}$ , and we can write:

$$\begin{aligned}\Delta G &= -T\Delta S_{\text{surr}} - T\Delta S_{\text{sys}} = -T(\Delta S_{\text{surr}} + \Delta S_{\text{sys}}) \\ &= -T\Delta S_{\text{univ}}\end{aligned}$$

and

$$\Delta S_{\text{univ}} = -\Delta G/T$$

Thus,  $\Delta G$  and  $\Delta S_{\text{univ}}$  are directly related to one another, and  $\Delta G$  contains the information to determine whether or not a process will be spontaneous or not.

If  $\Delta G < 0$ , then  $\Delta S_{\text{univ}} > 0$  and the process will occur spontaneously. If  $\Delta G > 0$ , then  $\Delta S_{\text{univ}} < 0$ , and the reverse process will be spontaneous. If  $\Delta G = 0$ ,  $\Delta S_{\text{univ}} = 0$ , which defines a reversible process that can be pushed in either direction by a small amount of work. This defines a state of equilibrium for the system.

The Gibbs free energy change is also related to the maximum amount of work that can be obtained from a process. As discussed earlier, the maximum work that can be obtained from the conversion of one state to another is defined by the reversible (infinitely slow) process. From the first law, we can write:

$$\Delta E = q_{\text{rev}} + w_{\text{rev}}$$

Earlier it was shown that  $\Delta E = \Delta H + w_p$ , where  $w_p$  is the work under conditions of constant pressure. Using this relationship, along with the relationship  $\Delta S_{\text{sys}} = q_{\text{rev}}/T$ , gives:

$$\Delta H + w_p = q_{\text{rev}} + w_{\text{rev}}$$

$$w_{\text{rev}} = \Delta H - q_{\text{rev}} + w_p$$

$$w_{\text{rev}} = \Delta H - T\Delta S_{\text{sys}} + w_p$$

$$w_{\text{rev}} = \Delta G + w_p$$

$$\Delta G = w_{\text{rev}} - w_p$$

Thus, if  $\Delta G < 0$ , so that the process will occur spontaneously, the value of  $-\Delta G$  represents the maximum amount of work that can be obtained from the process, minus the amount of work due to the change in volume at constant pressure (often referred to as “ $PV$ -work”). If  $\Delta G > 0$ , then the value of  $\Delta G$  represents the minimum amount of work required to drive the process, minus  $w_p$ .

#### IV. The Helmholtz free energy

Another free energy function, called the Helmholtz free energy,  $F$ , was mentioned in an earlier section of these notes. The change in this free energy function is defined as:

$$\Delta F = \Delta E - T\Delta S_{\text{sys}}$$

The close relationship between  $\Delta F$  and  $\Delta G$  should be apparent, with  $\Delta E$  taking the place of  $\Delta H$  found in the definition of  $\Delta G$ . More specifically, the relationship between  $\Delta F$  and  $\Delta G$  is

$$\begin{aligned}\Delta F &= \Delta E - T\Delta S_{\text{sys}} \\ &= \Delta H + w_p - T\Delta S_{\text{sys}} \\ &= \Delta G + w_p\end{aligned}$$

In the previous section, it was shown that  $\Delta G = w_{\text{rev}} - w_{\text{p}}$ , so that we can now show that  $\Delta F$  represents the work for the reversible process:

$$\begin{aligned}\Delta F &= \Delta G + w_{\text{p}} \\ &= w_{\text{rev}} - w_{\text{p}} + w_{\text{p}} \\ &= w_{\text{rev}}\end{aligned}$$

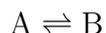
In this respect,  $\Delta F$  is somewhat easier to interpret than  $\Delta G$ , because it does not include the  $w_{\text{p}}$  term. However,  $\Delta E$  is not an easily measured quantity, which is why  $\Delta H$  and the Gibbs free energy are the functions most commonly used in chemistry and biochemistry.

## V. Free energy changes for chemical reactions

Most of the transformations of energy in biology involve chemical reactions. When we considered gas expansion problems, one of our underlying assumptions was that the internal energy of the system was only a function of temperature. But, when chemical reactions are involved, there is usually a change in the internal energy of the molecules. Forming and breaking chemical bonds almost always involves a change in potential energy. Bonds form because the atoms involved find a lower energy state in which they “share” electrons. The changes in internal potential energy must be accompanied by either changes in the thermal (kinetic) energy of the system, heat flow to or from the surroundings or mechanical work, or some combination of the above.

In biological systems, the energy changes associated with reactions are almost always coupled to other processes. In that way, the energy change for a favorable process can be used to drive an unfavorable one. The most commonly used tool for keeping track of, and understanding, these energy conversions is the Gibbs free energy.

For the simple case of the interconversion of one compound to another, we can write a generic chemical reaction as:



In principle, any chemical reaction is reversible, in that there is a finite probability that it can occur in either direction. The probability that any molecule of A will be converted to B is the same as for any other molecule of A. As a consequence, the rate of conversion of A to B will be proportional to the number of A molecules, or equivalently, their concentration. Similarly, the rate of conversion of B to A will be proportional to the concentration of molecules of B. We can write this as a differential equation:

$$\frac{d[A]}{dt} = -\frac{d[B]}{dt} = -k_f[A] + k_r[B]$$

where  $k_f$  and  $k_r$  are rate constants that relate the probability of each reaction to the concentration of the molecules. We won't worry about solving this equation just now, except to note that if we start out with all A, some of it will be converted to B. As the concentration of A decreases, the rate of conversion to B will decrease, and the rate of

conversion of B to A will increase. At some point, the flow in each direction will be equal, and the rate of change in concentration will be zero. At this point:

$$\frac{d[A]}{dt} = 0$$

$$k_f[A] = k_r[B]$$

$$\frac{[B]}{[A]} = \frac{k_f}{k_r}$$

At this point, we say that the reaction is at equilibrium, and we can define an equilibrium constant:

$$K_{eq} = \frac{k_f}{k_r} = \frac{[B]_{eq}}{[A]_{eq}}$$

where it is understood that the concentrations are those that are measured at equilibrium. This is not the most rigorous derivation of an equilibrium constant, but it will do.

One of the implications of the equilibrium state is that there is no way in which to obtain work from the reaction. If the system is at equilibrium, then an infinitesimal amount of work could shift it in either direction, by an infinitesimal amount. Looked at another way, if we were to have an immense volume of the reactants at the equilibrium concentrations, one mole of A could be converted to one mole of B (or vice versa) without doing any work, provided that the concentrations didn't change significantly. Therefore, the free energy change for the reaction must be zero.

Suppose, though, that we were to change the concentrations from their equilibrium values, say by adding one or the other of the reactants. Then, we would expect the concentrations to shift back to those that would satisfy the equilibrium constant, and during this process we could, at least in principle, extract some work. This work would represent the free energy change for the transition from the new conditions to the equilibrium concentrations. It is convenient to define a standard state for measuring and reporting free energy changes, and the most widely used standard is to specify that the initial concentrations are all 1 M. (Or, for the gas phase, that the pressures of each component is 1 atm.) The free energy change associated with the conversion from these concentrations to the equilibrium concentrations is called the standard free energy change,  $\Delta G^\circ$ .

At any other set of concentrations, the free energy change can be calculated as:

$$\Delta G = \Delta G^\circ + RT \ln \frac{[B]}{[A]}$$

We won't go through the derivation, but this very important equation comes directly from the expression we derived for the maximum work derivable from a change in

concentration. If the concentrations are at their equilibrium values, then  $\Delta G = 0$ , and:

$$0 = \Delta G^\circ + RT \ln K_{eq}$$

$$\Delta G^\circ = -RT \ln K_{eq}$$

This then provides a link between the standard free energy change and the equilibrium constant. Both represent essentially the same thing: the extent to which one side of the reaction is favored. If the forward reaction ( $A \rightarrow B$ ) is favored, then  $K_{eq} > 1$  and  $\Delta G^\circ < 0$ . A negative value of  $\Delta G^\circ$  also implies that work can be obtained from the reaction if the reactants are initially at their standard-state conditions.

Measuring the equilibrium constant is generally the most straight forward way of measuring  $\Delta G^\circ$ . Once this value is known, the free energy change for other concentrations can be easily calculated. If  $\Delta H$  is also known, for instance by measurement with a calorimeter, the entropy change,  $\Delta S$ , and then be calculated from the relationship  $\Delta G = \Delta H - T\Delta S_{sys}$ .