Quantitative Physiology I / Molecular and Cellular Systems; BMEN E4001x

Notes: 05 – Entropy

no text

Here, we investigate a complementary phenomenon to diffusion, namely entropy.

You've probably seen this in terms of the Gibbs free energy for a given reaction:

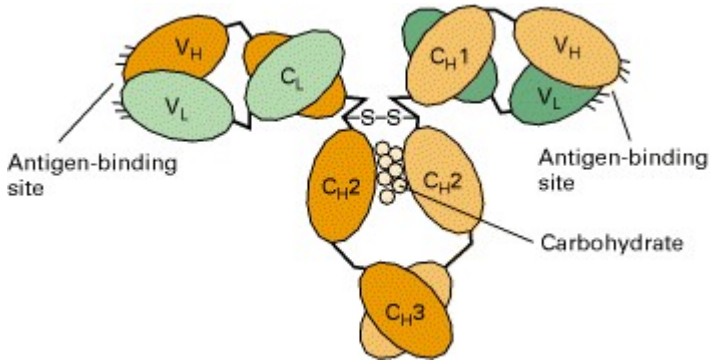
$$\Delta G=\Delta H-T\Delta S$$

but what does this mean? From earlier encounters with this term, it should increase. Vaguely, entropy is disorder, and it is an appropriate statement, as it really has different implications in different fields, and from different approaches. It is, to be sure, a thermodynamic property, such as temperature and enthalpy, but a bit harder to get a hold on. Temperature, it turns out, is equally intangible, but we interact with it on a more day-to-day basis.

Where will we see entropy in molecular biology? It is a force as equally important as diffusion in driving molecular recognition. In Biol 2005 and in subsequent places, you will see examples of proteins interfacing. This must happen quickly, and quite often, be reversible. Yes, covalent modifications are one route. But to take advantage of thermal fluctuations, the barriers to interaction must be much less than that associated with covalent binding. This is the realm of hydrogren binding, hydrophilic/hydrophobic forces, and entropy.

Antibodies:

Immunoglobulins. Proteins really important in the immune response. A major type of these proteins, IgG, has a Y-shape, with a very archetypical structure; two antigen binding sites (called Fab sites) and a constant region (Fc region). So why have two binding sites?



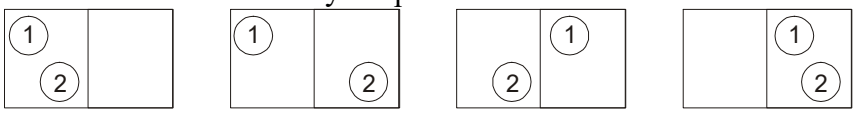
Microstates

We'll be following a microstate treatment, namely a lattice model following our discussion of diffusion.

Let's look at diffusion in a slightly different manner. Consider random motion of particles in a container composed of two boxes. For simplicity, consider two particles. As diffusion is additive, we can have more than 1 particle in each box. At any given moment, how are the balls distributed?

2 particles occupying a 2-compartment box. Each has a certain energy.

There are 4 ways to put these balls in this box



These are designated as microstates of the system. Each of these are equally probable. Under our model of diffusion, there are a limited number of direct transitions between these situations, but in general, we stand an equal chance of observing any one of these at any given look. However, we tend to look not at microstates, but groups of them, configurations that describe a property of the system and gloss over certain aspects, like which particle is specifically where.

So, look at this as three configurations: all balls in left box, all balls in right box, one ball in each box. The last one is most probable, as 2 out of 4 microstates describe having one ball in each box. If all microstates are equally probable, we are thus more likely to find one ball in each box than the cases (separately) of both particles in the left box or both particles in the right box. And if you compare configurations in which both balls are in the left box against all other situations, the probability of finding these other configurations is even greater.

If you expand this to three particles/balls in a three box chamber, there are:

27 microstates

1 in which all balls are in the left box (1 case of 2 boxes open)

3 in which 2 boxes are open (all in one box)

18 of these have 1 box open (two boxes filled)

6 in which each box has one particle (three boxes filled)

The number of microstates corresponding to a specific configuration is the multiplicity of the state. Note again, that the state encompasses all configurations; in our particle in a container system, the number of boxes and number of particles define the state. Systems tend towards the states with the highest multiplicity.

When an isolated system is left alone long enough, it evolves to equilibrium. Equilibrium is not one particular microstate. Rather, it's the probability distribution of microstates having the greatest possible disorder allowed by the physical constraints on the system.

Getting to equilibrium

Look at a different process, a chamber in which we first constrain particles to the left hand side, perhaps through a barrier, then release this constraint. Suddenly, there are many, many, many more microstates and configurations available.

It will take some time, but eventually all states will become populated through random motion. As before, at this equilibrium, our initial microstate will only rarely, vanishingly, be observed. This, in essence, is why entropy increases in a system.

Formal definition

$S=k_B\ln(\Omega)$; Ω=# of microstates or complexions consistent with a given system state

For the 3 particle / 3 box state:

- Initial, constrained configuration, all particles left side: $S=k_B\ln(\Omega)$; $\Omega=1$;$S=0$
- Balls anywhere in box: $S=k_B\ln(\Omega)$; $\Omega=27$; $S=k_B\ln(\Omega)$, higher entropy

So, we can give an example of the second law of thermodynamics:

> *Whenever we release an internal constraint on an isolated macroscopic system in equilibrium, eventually the system comes to a new equilibrium whose entropy is at least as great as before*

Work

In the last example, we released the constraint instantaneously, allowing a whole bunch of states to be repopulated. However, if we gradually moved the constraint, gradually increasing the number of possible states, we could have gotten some work out of this. From the mechanical point of view, this is exactly how a piston works. There is a corresponding statistical mechanics approach, which you'll get as needed in other courses. Here, the most important point is that the reverse is true; it takes energy to reduce the entropy of a system. Note that "reducing entropy" of a system must imply a open system, in which the entropy must go to some external source. Most biological systems can be considered open, so that it is possible to reduce entropy within a given system through interaction with external sources (with expenditure of energy).

Points

- State with the highest multiplicity is the one that is favored
- Must be communication or exchange between microstates. This is often supplied by thermal energy, k_BT.
- Work *can* be gained through an increase in entropy, work is needed to locally decrease entropy

In context for biology

This is an interesting discussion posed mainly in terms of an idea gas. But how does it apply to the two biological systems posed earlier and to biological systems in general?

In short, instead of looking at particle locations, generalize this to any parameter that allows multiple microstates. This, indeed, includes location of a given type of particle in a volume, but also its velocity, angle of flexible chemical bonds, etc.

Antibodies: multi-valent binding

Coming to the other question we posed, the key is that the antibody is multivalent. Let's make the following assumption that the antibody is rigid, and the other site precisely localized with another antigen without inducing stress.

For the binding of two antigens by a single, y-shaped antibody:

$$\Delta G_{bonds} \cong -73 \text{ kJ/mol}$$

$$\Delta G_s \cong 30 \text{ kJ/mol}$$

The key here is that in the multi-valent binding case, the entropy penalty is paid only once, whereas in the independent fragment case, the entropy penalty gets paid for each binding.

Let's put some numbers in it.

For a single headgroup (or Fab) binding to an antigen.

$\Delta G_{Fab}=\Delta G_{bonds}+\Delta G_s = -43$ kJ/mol

$\Delta G_{IgG}=2*\Delta G_{bonds}+\Delta G_s=2\Delta G_{Fab}-\Delta G_s=-116$ kJ/mol

Brief interlude to binding interactions.

Returning to the fundamental binding interaction:

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C$$

There's an interesting effect on the reverse case of dissociation. Let's start from the association constant, where

$$K_A = \frac{[C]}{[A]*[B]} = \frac{k_1}{k_{-1}}$$

This is related to the ΔG's:

$$K_A = \exp\left(-\frac{\Delta G}{RT}\right)$$

$\Delta G_{Fab}=\Delta G_{bonds}+\Delta G_s = -43$ kJ/mol

$K_{A,Fab} = 1.7 \times 10^7 \text{ M}^{-1}$

$\Delta G_{IgG}=2*\Delta G_{bonds}+\Delta G_s=2\Delta G_{Fab}-\Delta G_s=-116$ kJ/mol

So, $K_{A,IgG} = 3.5 \times 10^{19} \text{ M}^{-1}$

Now, many biological interactions are diffusion limited. That is, when A encounters B, they interact, so the reaction rate is limited by how often these molecules interact and that is limited by diffusion.

This gives a typical forward rate reaction of $k_1 \sim 1 \times 10^6$ M-1s-1

Now,

$$k_{-1} = k_1 / K_A$$

Consider that if we start with a pure population of complex, the dissociation can be written as:

$$C(t)=C(0)*\exp(-k_{-1}*t)$$

So, we can take the value $1/k_{-1}$ as a measure of how long the complex endures.

So, we get:

$K_{A,Fab} = 1.7 \times 10^{7}\ M^{-1}$ (association constant); lifetime = 17 sec
$K_{A,IgG} = 3.5 \times 10^{19}\ M^{-1}$ (association constant); lifetime = 3.5×10^{13} sec

Polymer length:

Although we draw many biomolecules in a straight-line configuration for simplicity, they are rarely found in this configuration, even in the absence of binding/interaction mechanism. Consider the angle and orientation of each bond as a degree of freedom. A fully extended configuration will require all bonds to be in very specific orientations, a situation for which few, or even a single, configuration satisfies. Many more configurations include single and multiple kinks, and these configurations all lead to a shorter molecular length; the configuration of a ball-like glob is comprised of a huge number of microstates, all of which are equally probable.

This gives rise to a Flory radius. Further effects, such as interactions with solvents, will change this characteristic.

Water:

Among the special properties of water is the hydrophobic effect. Water, being a highly electronegative atom and two very influenceable hydrogen atoms, likes to form hydrogen bonds with itself. Moreover, these bonds are continually made and broken between individual water molecules, to the point where the molecules are almost rotating and translating in a homogenous fluid.

This ability to rotate is a manifestation of entropy. If a surface is presented that cannot form hydrogen bonds, not only is that energy lost, but the water molecules must become ordered (thus, an entropic contribution). This exclusion of non-bonding molecules, which is both enthalpy and entropy driven, is the hydrophobic effect.