Notes on Israelachvili's *Intermolecular and Surface Forces*

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Israelachvili's book is pretty famous; everyone has heard about it. Prof. Adam Cohen recommended it to me. Unfortunately, it's really boring. I only read the parts which had to do with biology. The main points I took away from my cursory reading are as follows.

- Self-assembly is a process which depends intimately on geometry, temperature, and concentration.
- Different biological molecules are shaped differently, so their self-assembled superstructures take different geometries.
- Biological superstructures are highly dynamic (i.e. fluid mosaic model). Things are always falling off the superstructure, merging with the structure, or moving around inside the structure.

Ch 19. Thermodynamic principles of self-assembly

Soft structures, i.e. those made of amphiphilic molecules, are *fluid-like*, like the "fluid mosaic model." Contrast this to, say, globular proteins or DNA, which are rigid. Amphiphilic structures are soft because the forces that hold them together are weak: the relevant forces are H-bonds and van der Waals, rather than covalent or ionic bonds.

Equilibrium condition for self-assembly

In thermal equilibrium, the chemical potential of all species must be the same. We claim this leads to the following equilibrium condition:

Claim: In thermal equilibrium,

$$\mu = \mu_N = \mu_N^0 + \frac{kT}{N}\log(\frac{X_N}{N}) = \text{const} = \text{same for all} N.$$

X_N is the concentration of molecules in aggregates of number N. N tells us how many molecules are in the aggregate. $N = 1$ corresponds to a *monomer*, $N = 2$ to a *dimer*, $N = 3$ to a *trimer*, and so on. μ_N^0 is the free energy *per molecule* of an aggregate and is the most important quantity

here. We will learn more about it later.
Proof: Let x_N be the concentration of N-aggregate, which means $X_N = Nx_N$. It takes N molecules to make one N-aggregate. By the law of mass action,

$$N\text{-aggregate creation rate} = k_1 X_1^N, N\text{-aggregate dissociation rate} = k_N x_N = k_N \frac{X_N}{N}.$$

The reason we write this in terms of X_N instead of x_N is that this allows us to use particle-number conservation. Specifically, the equilibrium constant K is defined

$$K = \frac{k_1}{k_N} = e^{-N(\mu_N^0 - \mu_1^0)/kT},$$

and the result of equating reaction rates is

$$X_N = N[X_1 e^{(\mu_N^0 - \mu_1^0)/kT}]^N.$$

This is the same relation as above.

There is another constraint: conservation of *total particle number*. In other words, we should have the same number of total particles regardless of what N-aggregates they happen to be in:

$$C = \sum_{N=1}^{\infty} X_N = \text{const.}$$

In real life, there will only be some values of N that give aggregates.

Forming aggregates (i.e. what is μ_N^0?)

Aggregates form only when there is a difference in the cohesive energies between molecules in the aggregated and dispersed (monomer) states. From the above equilibrium condition,

$$\mu_1^0 + kT\log(X_1) = \mu_N^0 + \frac{kT}{N}\log(\frac{X_N}{N}),$$

we see that X_N will be appreciable, compared to X_1, only if $\mu_N^0 < \mu_1^0$. You can also see this from $X_N = N[X_1 e^{(\mu_N^0 - \mu_1^0)/kT}]^N$ and note that $X_1 < 1$ (usually we work in mole fraction units, or volume concentration units, but anyway, X_i never exceeds unity).

From the preceding discussion, we may say that, all things being equal (i.e. $\mu_1^0 = \mu_N^0$), molecules prefer to be dispersed. This makes sense because of entropy. We have to lower the free energy of the N-aggregate to make it thermodynamically plausible.

μ_N^0 for some simple structures: To get a better understanding of what this free energy is, let's look at some simple structures in low dimensions.

- 1D aggregates (rods, cylinders): A 1D aggregate could look like a chain of molecules. Let $-\alpha kT$ be the monomer-monomer bond energy relative to isolated monomers in solution. $\alpha > 0$ so this is an attractive bond, i.e. the energy is negative. We can say that

$$\alpha kT = \mu_1^0 - \mu_N^0 \text{ for large } N.$$

For an N-aggregate, there are $N-1$ bonds, so

$$N\mu_N^0 = -(N-1)\alpha kT \implies \mu_N^0 = -(1-\frac{1}{N})\alpha kT.$$

The free energy decreases with N.

- 2D aggregates (discs, sheets): Consider a circular disk of molecules. The number N of molecules goes as πR^2, where R is the radius of the disk, and the number of unbonded molecules on the circumference goes as $R \sim \sqrt{N}$. So,

$$\mu_N^0 = \mu_\infty^0 + \frac{\alpha kT}{\sqrt{N}}.$$

The $N^{-1/2}$ behavior comes from taking $\sqrt{N}$ and dividing it by N, since we are looking for a free energy per molecule.

- 3D aggregates (spheres, droplets): By similar arguments,

$$\mu_N^0 = \mu_\infty^0 + \frac{\alpha kT}{N^{1/3}}.$$

Let's estimate α in terms of γ, the interfacial free energy per unit area (i.e. surface tension). We can write

$$\text{total free energy of sphere} = N\mu_\infty^0 + 4\pi R^2\gamma,$$

and matching with the above gives the estimate

$$\alpha \approx \frac{4\pi r^2\gamma}{kT},$$

where $Nr^3 = R^3$, so r is the effective radius of a molecule.

Critical micelle concentration

There is a **critical micelle concentration** (CMC), denoted $(X_1)_{\text{crit}}$, at which adding more monomers results in the formation of more aggregates, leaving the monomer concentration roughly unchanged at $(X_1)_{\text{crit}}$. You can think of $(X_1)_{\text{crit}}$ as the *solubility* of monomers in the solution. Once you put more than the CMC in solution, stuff piles up and you get a new phase separated from the solvent. More on this later.

Claim: Let the bonding energy be αkT. In other words, let

$$\mu_1^0 - \mu_\infty^0 = \alpha kT,$$

where μ_1^0 is the free energy of a lone molecule and μ_∞^0 is the free energy of a molecule surrounded by an infinite number of other molecules in aggregate. Then

$$\boxed{(X_1)_{\text{crit}} = \text{CMC} \approx e^{-\alpha}}.$$

Reasoning: Depending on the dimensionality of the aggregate, we found above that

$$\mu_N^0 = \mu_\infty^0 + \alpha kT/N^p,$$

where p depends on the kind of aggregate. This means that

$$\mu_1^0 - \mu_N^0 = (\mu_1^0 - \mu_\infty^0) + (\mu_\infty^0 - \mu_N^0) = \alpha(1 - N^{-p}) \to \alpha, \text{ for large} N.$$

Using $X_N = N[X_1 e^{(\mu_N^0 - \mu_1^0)/kT}]^N$ gives the approximate concentration

$$X_N = N[X_1 e^{\alpha}]^N.$$

For $X_1 e^\alpha < 1$, this makes sense. However, it doesn't make sense for $X_1 e^\alpha > 1$: the concentration of particles in the large-N aggregates would increase with N! So, we have an upper bound on X_1.

How can we think about this? Mathematically, $X_N = N[X_1 e^\alpha]^N$ undergoes a very wild transition when $X_1 e^\alpha \approx 1$. What I mean is, if you take $X_1 e^\alpha$ and change it from 0.99 to 0.995, the change in X_N will be very large. So this equation doesn't *break down*, per se, it's just that the input (X_1) needs to evolve only infinitesimally for the output (X_N) to change *a whole lot*. Physically, we can think of it like we "saturated" the solution. When you have a container of salt water and stir enough salt into it, crystals start to form (not right away, you have to wait for it to reach equilibrium). I guess a chemistry way of thinking about it is with Le Chatelier's principle,

$$X_1 + \cdots + X_1 \to N X_N.$$

If you increase $[X_1]$, then $[X_N]$ increases in response.

Infinite vs. finite aggregates: The creation of an **infinite aggregate** is called **phase separation**, like the separation of oil and water. The creation of a **finite aggregate** is called **micellization**, like the creation of a free-floating phospholipid membrane. The former is much more common than the latter. Why?

Let's put the finite size-dependence back in to our formula for X_N; namely, expand $e^{\alpha(1-N^{-p})} \approx e^\alpha e^{-\alpha N^{-p}}$. We get

$$X_N = N[X_1 e^\alpha]^N e^{-\alpha N^{1-p}},$$

which shows that X_N decays with N. So, there are no big aggregates for $p < 1$, where $p = 1/d$ from above, where d is the dimension of the aggregate. Instead, if you keep putting monomers in solution, they go to a whole different phase, like oil separating from water. In this new phase, there is no notion of comparing μ_N and stuff like that. They are just not in contact (except at the interface).

Nucleation: Now that we know that phase separation will happen, we need to ask *how* it happens. Ignoring supersaturated solutions and the like, there are two basic kinds of nucleation processes,

- Coalescence: If the forces between the solute droplets are monotonically attractive, they just run to each other and give their buddies a big hug.
- Ostwald ripening: This one is kind of complicated. Israelachvili says "individual solute molecules are exchanged between the droplets by diffusion through the solvent." Let's try to decode what he means.

  First, there is a diffusion process occuring in the solvent, by which solute molecules can travel to and from solute bubbles. You can think about this like the intermolecular forces holding bubbles of solute together are not strong enough to prevent solute molecules from escaping from the surface and traveling away, or coming in and lodging on the surface.

If the long-range colloidal forces between the droplets are repulsive, which they often are, the bubbles can't just run to each other. The Laplace pressure of a bubble,

$$P(R) = \frac{2\gamma_i}{R},$$

is greater for small bubbles than for large bubbles. So, solute tends to diffuse away from small bubbles and towards the larger ones. Over time, the small droplets will disappear and we will be left with the large droplets.

Size distributions

We would like to know why, when we look at a bunch of vesicles under a microscope, they are all roughly the same size. If the distribution is narrow, it is called **monodisperse**; if it is wide, it is called **polydisperse**. What controls this size, and what controls the standard deviation of size, i.e. the polydispersity?

First, note this idea of polydispersity does not apply for $p < 1$. This is because there is an abrupt phase transition to a single infinitely-sized aggregate and hence no concept of size distribution. Heuristically, we can understand this by noting

$$X_N = N[X_1 e^{\alpha}]^N e^{-\alpha N^{1-p}}$$

decays exponentially with N, *regardless of how close we are to the critical micelle concentration.*

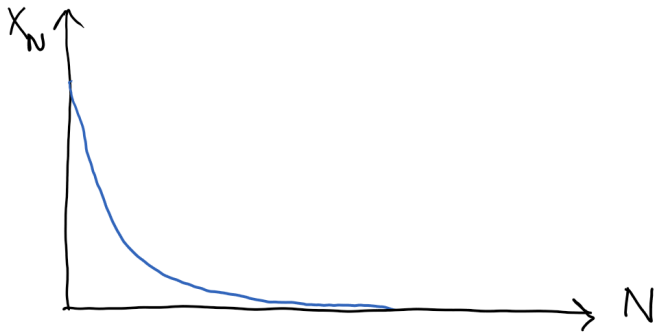


Figure 1: For $p < 1$, the distribution always looks like this.

However, for $p = 1$, the distribution goes as $X_N \propto N$ near the CMC. So, these results apply to 1D structures like microtubules and chain-like aggregates. This gives us a nontrivial distribution with a maximum for $N > 1$:

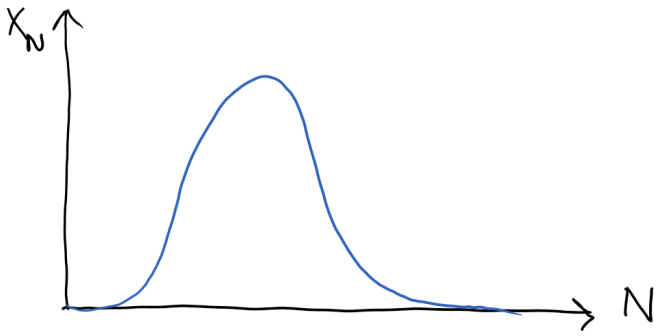


Figure 2: For $p = 1$ and $X_1 \approx$ CMC, we get a nontrivial distribution.

To solve for this distribution, note that for $p = 1$, we have $X_N = N[X_1 e^{\alpha}]^N$. Enforcing $C = \sum_N X_N$ and performing a sum gives us the mean. The result is $N_{\max} = \sqrt{Ce^{\alpha}}$. In fact, there is a very interesting result

$$\langle N \rangle = \frac{\sum_N N X_N}{\sum_N X_N} = \sqrt{1 + 4Ce^{\alpha}}.$$

Below the CMC, $\langle N \rangle \approx 1$. Above the CMC, $\langle N \rangle \approx 2\sqrt{Ce^{\alpha}} = 2N_{\max}$. Conclusion: the *size* of 1D aggregates grows with the concentration of solute, C, at least above the CMC. We obtained this result from thermodyanmic considerations only!

Ch 20. Soft and biological structures

The equilibrium structures of amphiphilic molecules are soft or fluid-like: the molecules are in constant thermal motion within each aggregate. They twist and turn, diffuse in and out, etc.

The major forces that govern the self-assembly of amphiphiles are (1) the hydrophobic attraction, which induces the molecules to associate and (2) the hydrophilic attraction, which preserves contact with water. The first tends to decrease the interfacial area a per molecule exposed to the aqueous phase; the second tends to increase it.

Optimal headgroup area

Consider the following diagram of a micelle (the packing factor is defined as $V/a_0 l_c$, where l_c is the length of the tail:

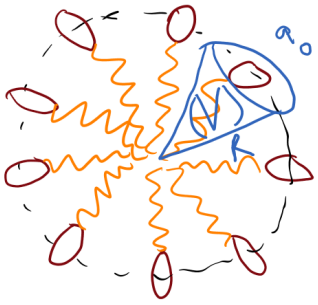


Figure 3: Micelle with headgroup area a_0, volume per amphiphile V, radius R.

Let's write the interfacial free energy per molecule in this micelle. There is a contribution from the surface tension and also a contribution (containing steric, hydration force, and electrostatic double-layer terms) that can simply be written as $\propto a^{-1}$, proportional to inverse area. This is because we expect the first term in any energy expansion to be inversely proportional to the surface area, such as in the van der Waals equation of state. (Why? I need to think more about this.)

So, the total interfacial free energy per molecule is, to leading order,

$$\mu_N^0 = \gamma a + \frac{K}{a} \implies a_0 = \sqrt{\frac{K}{\gamma}}.$$

a_0 is the optimal surface area per molecule at the hydrocarbon-water interface. The interfacial energy per molecule is

$$\mu_N^0 = 2\gamma a_0 + \frac{\gamma}{a}(a - a_0)^2.$$

Heuristically, we can change a by squishing the same amount of molecules into a smaller sphere.

Packing

We still have to determine which structures are preferred, now that we know the optimal head area. The preferred structure will depend on the packing factor $v/a_0 l_c$, which depends on the maximum length l_c of a hydrocarbon chain.

In order of increasing packing factor, the preferred structures are: spherical micelles, ellipsoidal micelles, cylindrical/rod-like micelles, vesicles and extended bilayers, "inverted" structures.

Let's study some of the more important of these structures.

- Spherical micelles: For the spherical micelle to be a viable packing arrangement, the radius of the micelle, R, must not exceed the critical chain length l_c. That is because $R > l_c$ is thermodynamically unfavorable because there would be "empty space" in the middle, and what would it be filled by (not water!)? The number of hydrocarbons in the micelle gives us a condition on the radius, R:

  $$\frac{4\pi R^2}{a_0} = \frac{4\pi R^3}{3v} \implies R = \frac{3v}{a_0}.$$

  Because $l_c > R$, this gives $\boxed{v/a_0 l_c < \frac{1}{3}}$. Typically, lipis that form spherical micelles have charged headgroups, since this leads to a large headgroup area, a_0. If there are too many micelles to be spherical, sometimes it deforms slightly and becomes elliptical.

- Cylindrical micelles have $\frac{1}{3} < v/a_0 l_c < \frac{1}{2}$. There is an unfavorable end energy associated with the hemispherical caps at the ends of the cylinders, so sometimes the cylindrical micelles bend together to form a toroid! But, there are extra elastic energy costs associated with this as well.

- Bilayers are typically made of hydrocarbons with more chains. For example, hydrocarbons with only one CHCHCHCHCH chain tend to form micelles and cylindrical micelles. Hydrocarbons with two CHCHCHCH chains tend to form bilayers, because there is more stuff to pack inside and we would like more space to do so. Because these hydrocarbons (i.e. with more chains) are much more hydrophobic on their tail ends, they are much less likely (i.e. 10^{-8} times as likely) to leave the bilayer and shoot out into the aqueous solution. They can, however, trade places with their partners in the bilayer.

  We can easily estimate the compressibility modulus k_a of the bilayer. By definition,

  $$\Delta E := \frac{1}{2}k(a - a_0)^2/a_0 = 2\gamma(a - a_0).$$

  The first $=$ sign is a definition; the second $=$ sign is just the definition of surface tension. I multiplied γ by 2 because there are *two* layers. This gives $k = 4\gamma$.

- Vesicles: Bilayers have an energy cost associated with the edges, where the phospholipids have lower coordination. In vesicle, which is a bilayer closed on itself, there are no edges and no problems (other than the curvature).

  Critical radius: We would like to find the radius of the smallest vesicle that may be formed without forcing the headgroup area a in the *outer* monolayer to exceed a_0 (the inner monolayer is safe because the headgroup area tends to decrease there). The result for $1/2 < v/a_0 l_c < 1$ is

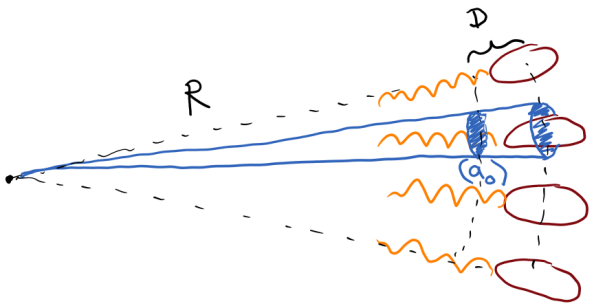
  $$R_c = l_c \frac{3 + \sqrt{3(4v/a_0 l_c - 1)}}{6(1 - v/a_0 l_c)} \approx \frac{l_c}{1 - v/a_0 l_c}.$$

  Proof: Note that the aggregation number of a vesicle of radius R and bilayer thickness $t \approx 2v/a$ is $N = 4\pi(R^2 - (R-t)^2)$.

  In the critical (i.e. boundary) case, we set $4\pi R_c^2 = a_0 \times N/2$. This gives a self-consistent quadratic equation for R_c; we may take $t = 2l_c$. The solution of this equation is the above critical radius.

Bending energies and elasticities

There is an energy cost associated with bending a membrane, due to three effects: (1) between the headgroups (2) between the chains (3) betwen the heads and the aqueous solution.



Let R be the radius of curvature of the surface and let D be how far we are above the interface. For example, $D > 0$ for head-head interactions and $D < 0$ for chain-chain repulsion. It's not very correct to assume a single D, i.e. since chains are extended objects, but typically we can find a reasonable D that describes the numbers well. Often, only one of the three effects listed above is important, and we can take D to describe that single effect. We add an additional contribution

$$\Delta\mu_N^0 = (2\gamma a_0)(-D/R)$$

to the molecular free energy due to this curvature. This is because of changing geometry; recall that the free energy per molecule was $\mu_N^0 = \gamma a + \frac{K}{a} \implies a_0 = \sqrt{\frac{K}{\gamma}}$. Here, we're concerned with the Laplace bubble pressure, $\Delta P = 2\frac{\gamma}{R}$. The extra energy of the molecules due to this pressure is

$$-\text{force} \times \text{distance} = -(\frac{2\gamma}{R} a_0) \times D,$$

which is what we got. We know the sign is correct because if the relevant bonding center of the molecule is "inside the bubble," or $D < 0$, we expect it to be at higher energy because the interior

of the buble is always at higher pressure. You can also think of this as a PV energy term, like in a gas.

Hence, $\mu_N^0 = 2\gamma a(1 - \frac{D}{R})$ per molecule in a spherical vesicle. For cylindrical vesicles and such, the geometry is a bit different.

For a spherical *bilayer* vesicle, we have to add two opposing contributions and worry about different radii of curvature, etc. The result is

$$\mu_N^0 = \mu_\infty^0 - \frac{\gamma a_0 D t}{2R^2} \implies \frac{\Delta E}{\Delta \text{area}} = -\frac{\gamma D t}{2R^2}.$$

This D is positive if the headgroup repulsion dominates for both monolayers and is negative if the tail-tail interactions dominate.

Generally, if $D > 0$, the vesicles will be smaller than if we had not accounted for the Laplace bubble pressure correction. This is because it is now energetically favorable to have a small radius R, as this drives down the free energy μ_N^0. If $D < 0$, the vesicles will be larger.

Biological membranes

Most biological membranes are made of double-chained phospholipids or glycolipids, with 16-18 carbons per chain, one of which is unsaturated/branched. These ensure that (1) biological lipids will self-assemble into thin bilayer membranes that can compartmentalize different areas of a cell (2) have an extremely low CMC, so they remain intact even when there are not many other free lipids insolution (2) because of unsaturation or branching, are fluid at physiological temperatures.

Interestingly, different kinds of lipids can pack together. This gives vesicles made of lipids of varying composition different properties (i.e. small/large, spherical/cylindrical, etc). For example, adding cholesterol, which is an inverted-cone lipid ($v/a_0 l_c > 1$), increases the radius of bilayers, straightens the hydrocarbon chains, and reduces their fluidity. This causes the stiffening of membranes.

Membrane proteins can float around in the lipid bilayer, in what Singer and Nicholson proposed as the "fluid mosaic model." Membrane-associated proteins are usually amphiphilic, which is why they can live in the amphiphilic bilayer. Soluble proteins are typically hydrophilic on their entire surface.

How does a cell maintain and regulate the structural integrity of its membranes? The answer seems to be that the heterogeneous lipid mixture should be able to self-assemble into bilayers, but individual species should not. This is a very precarious and intimate result of many energetic conditions that have to be simultaneously satisfied.

Ch 21. Interactions of biological membranes and structures

Biomolecular assemblies generally cannot be described by such a simple free energy, $\mu^0 = \gamma a + \frac{K}{a}$. In fact, most biological membranes are never at equilibrium. So, we must consider the non-equilibrium (i.e. dynamical) aspects of their interactions.

Some more forces

We have already considered these forces or their corresponding energies: surface tension, curvature, and the "other" part, K/a, which contained steric, hydration, and electrostatic double-layer contributions.

Israelachvili considers some of these in more detail. I think it is intolerably boring, so let's skip it. Let's get to some real biology.

Biospecific interactions

Some cell-cell contacts in signaling, for example, are totally specific for one and only one molecule. Early models proposed a "lock-and-key" kind of picture; this has been updated to an "induced-fit" model.

Some important points:

- The biospecific bonds are usually not very strong. They are just a little bit stronger than H-bonds and much weaker than covalent bonds.
- Due to their weak bonding, biospecific bonding is short-lived. The molecule comes in, sits on the surface, and detaches relatively quickly. However, the process is long enough for the molecule to perform its function.
- Due to the exponential nature of thermal excitation $e^{-\beta E}$, adding one or two more H-bonds can exponentially increase the lifetime of the ligand-receptor (LR) bond. A site with only four bonds may have lifetime of less than 1s; adding two more bonds may increase the lifetime to hours!
- The specificity of the bond arrangement is due not to the strength of the bonding, but rather the directionality.

Bioadhesion

Suppose we have two soap (or lipid) bubbles. Why could it be energetically favorable for them to adhere and kiss each other on a flat circular surface? The answer is that this decreases the contact area between the bubbles and air, thus reducing the energy cost of surface tension. However, this is counteracted by the energy of bending.