Tutorial : Self-limiting Assembly Thermodynamics and Kinetics

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The following exercises are adapted from a review article by Michael Hagan and Gregory Grason [1]

1 Equilibrium characteristics of Self-limiting Assembly

The free-energy for a self-assembling system of sub-units with a total mass fraction of Φ which form aggregates of sizes n with mass fraction ϕ_n respectively, is given by

$$f = \frac{F}{V/v_0} = \sum_{n=1}^{\infty} \phi_n \epsilon(n) + \frac{k_B T \phi_n}{n}\left(\ln\frac{\phi_n}{n} - 1\right) \tag{1}$$

where the first term in the RHS corresponds to the aggregation energy and the second term to a translational entropy of the sub-units. v_0 is known as the standard state volume of the subunit in the system and $\epsilon(n)$ is the per-subunit aggregation free energy in a cluster of size n.

(a) *Law of Mass-action* : Minimize the free energy with respect to the mass fractions $\{\phi_n\}$ under the mass-conservation constraint i.e.

$$\Phi = \sum_{n=1}^{\infty} \phi_n \tag{2}$$

and derive the relationship between the mass fraction ϕ_1 of monomers and the mass fraction ϕ_n of an n-mer.
Hint : This is typically done with a Lagrange multiplier that enforces the constraint as given below :

$$\frac{\partial}{\partial \phi_n}\left[f + \mu\left(\Phi - \sum_{n=1}^{\infty}\phi_n\right)\right] = 0$$

(b) *Equation of state for Self-limiting assembly :* Using the law of mass action in the mass conservation constraint determines the equation of state for the system. The specific form of the equation of state should depend on the form of the aggregation free energy per subunit $\epsilon(n)$. Assume that assembly leads to just one target size n_T for the resulting aggregate.

1. Sketch out a rough plot of the aggregation free energy $\epsilon(n)$ as a function of aggregate size n that leads to a single target size.
2. Write down the modified form of the mass conservation constraint(Eq. 2) under the assumption that you only manage to achieve assembly at an aggregate size n_* for assembly (recognize the caveat that n_* can possibly be different from n_T). Use the law of mass-action in this modified form to obtain the equation of state.
3. You can simplify the form of the equation of state by writing it in a non-dimensional form with a characteristic mass-fraction $\phi_* = \left[n_* e^{-n_*\beta\epsilon_*}\right]^{1/(n_*-1)}$. (**Hint : All mass-fractions should be in dimensionless form by scaling with respect to ϕ_***)
4. With the above form, comment on what mass fraction dominates the total mass fraction when $\phi_1 \ll \phi_*$ and when $\phi_1 \gg \phi_*$. Discuss the significance of ϕ_*

(c) *Optimal aggregate size and fluctuations in aggregate size :* While in the previous section we assume that only two states exist in equilibrium, we must recognize that there will be some finite dispersity in the size of the aggregate, arising from thermal fluctuations. We must hence construct the equilibrium distribution of aggregate sizes $\rho_n = \frac{\phi_n}{n}$ and make an approximate estimate of the fluctuations in the size from this distribution to determine how robust the assembly is.

1. Write down the aggregate distribution $\rho_n = \frac{\phi_n}{n}$ according to the law of mass action to obtain ρ_n as a function of n and $\epsilon(n)$

2. Write an approximate form for the per-subunit aggregation energy $\epsilon(n)$ in the vicinity of the target size n_T.
3. Use this form to determine an approximate form for the distribution ρ_n. Does the form look familiar ?
4. Based on the form derived above, can you calculate the relative dispersion in size $\frac{\langle \Delta n^2 \rangle^{1/2}}{n_T}$? how does it depend on $\epsilon(n)$ and n_T ? What does this tell us about reducing fluctuations in target aggregate size ?

2 (Optional) Stat Mech Primer for Assembly

The following is an optional exercise that will walk you through deriving the form of the free energy in Eq.1 : Consider N non-interacting particles in a volume V at temperature T.

(a) Assuming the particles have volume v_0, what is the total number of positional microstates accessible to a single particles, that is, how should it scale with V and v_0? And what about N indistinguishable particles? **Hint: imagine dividing your large volume V up into smaller volumes of size v_0.**

(b) Given the number of microstates available to the particles, write down the entropy and free energy. Recall that $F = -TS$ and $S = k_B \ln \Omega$, where Ω is the number of microstates (we ignore E since there are no interactions or external potentials). The Stirling approximation $\ln N! \approx N \ln N - N$ will come in useful. Note that $\Phi = N v_0 / V$ is the volume fraction of our particles. Also, write the free energy density $F/(V/v_0)$ in terms of Φ. This term captures the role of translational entropy.

For our purposes, we will have a certain number N of identical subunits that can bind to eachother to form assemblies composed of n subunits, which we call n-mers. For simplicity, we assume that all the n-mers are noninteracting and the only interactions are between binding subunits within each n-mer, which gives these n-mers a per-subunit free energy ϵ_n.

(a) Let N_n be the number of n-mers in the system. Write down the free energy of the n-mers $F_n = E_n - TS_n$ in the system, where E_n is the energy is the total energy of an n-mer related to ϵ_n and S_n is the same as derived above.

(b) Let us define $\phi_n = N_n n v_0 / V$ as the mass fraction of n-mers, which can be thought of as the total volume fraction of subunits inside n-mers. Rewrite the n-mer free energy density $F_n/(V/v_0)$ in terms of ϕ_n. Do you notice the extra factors of n^{-1}? Why do they appear in the translational entropy of n-mers?

(c) Finally, since we can have assemblies of size $n = 1, 2, 3, \ldots$, what is the total free energy of the system with a subunit mass distribution ϕ_n? If the total number of subunits in all the n-mers is fixed $\sum_n N_n n = N$, write down the constraint on the mass distribution ϕ_n if $\Phi = N v_0 / V$ is defined as the total subunit volume fraction.

References

[1] Michael F Hagan and Gregory M Grason. Equilibrium mechanisms of self-limiting assembly. *Reviews of modern physics*, 93(2):025008, 2021.