

ICFP Advanced Biophysics

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Notes and references for the gooey part

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The following objectives only cover the main lectures. You are additionally expected to be able to rederive the results presented in the tutorials.

1 Chromatin organization

Optional training exercises

1. Derive the Flory free energy in arbitrary dimension d .
2. Compute the swelling exponent in good and bad solvent in arbitrary dimension d . Is the coil larger or smaller in $d = 2$ compared to $d = 3$? Why?
3. In the polymer phase separation model, compute the critical value of the interaction parameter for phase separation.
4. Rederive the polymer phase separation free energy for polymers with different lengths ($N_A \neq N_B$).
5. Recompute the interaction parameter χ in the polymer phase separation model in a case where there are three distinct monomer-monomer interaction energies ϵ_{AA} , ϵ_{AB} , ϵ_{BB} .
6. Recompute the contact probabilities $P_{\text{contact}}(s)$ for the equilibrium and crumpled globule in two dimensions.
7. Predict the contact probability of a polymer in good solvent in $d = 3$.
8. Look at the Hilbert curve (or the related Peano curve), then redraw it yourself without looking.
9. Compute the probability that three points along a Gaussian chain at curvilinear coordinates s_1 , s_2 , s_3 find themselves at the same point in space with a tolerance a .
10. Same question if the chain has a ring topology.

Learning goals for this chapter

- Be able to explain the basic principle of Hi-C and perform a basic interpretation of the resulting data.
- Be able to rederive the Flory free energy.
- Be able to explain why polymers can phase separate even in cases where their interactions are very weak.

- Be able to explain qualitatively why a chain in molten globule locally behaves like a chain in theta solvent.
- Be able to explain the mechanism of polymer reptation and show through a scaling argument why the polymer reptation time is proportional to L^3 .
- Be able to formulate an argument that chromosomes should have few knots.
- Be able to qualitatively explain why the contact probability in crumpled globules decays more slowly than in equilibrium globules.
- Be able to qualitatively explain why a passive cohesin cannot explain the Hi-C data presented at the beginning of the chapter.
- Be able to establish and solve the survival probability equation used at the end of the chapter.

References

Original Hi-C reference [1]; Review on chromatin structuring mechanisms [2]; Review on the physics of epigenetic modifications (such as methylation) and their influence on chromosome structure through phase separation [3]; Book on scaling laws in polymers [4]; Book on formal approaches to polymer statistics and globules [5] and a review article [6]; Book on polymer dynamics, including a discussion of reptation [7]; Original microphase separation reference (used for the tutorial) [8].

2 Protein folding

Optional training exercises

1. Download and play the videogame “Foldit”.
2. Assume a particle is jumping in between wells whose depths ΔE are distributed according to $p(\Delta E) \propto \exp(-\Delta E/E_0)$. The escape rate from a well is given by Arrhenius’ law. Show that this famous “trap model” has a glass transition where the mean escape time diverges.
3. (more difficult) Now put this trap model in the context of a 1D spatial diffusion problem: Each time the particle jumps out of a trap, its position is incremented by a amount δ drawn from $p(\delta) \propto \exp(-\delta^2/2a^2)$. We assume that the particle visits a new trap at each jump. What is the mean variance of the particle position after $N \gg 1$ jumps? Now consider the time $T = \sum_{i=1}^N \tau_i$ that it takes to perform N jumps; below the glass transition temperature this time diverges faster than N , as discussed above. Interpret this divergence as a situation where the sum is dominated by the largest jump time. Show that the cumulative probability distribution of the energy barrier associated with this time is given by the Gumbel distribution $\mathcal{P}(\text{barrier} < E) \sim_{N \rightarrow \infty} \exp(-Ne^{-E/E_0})$. Deduce from this that below the glass transition, the particle moves subdiffusively, *i.e.*, that $\langle x^2 \rangle \propto t^\alpha$ with $\alpha < 1$.
4. Write down a nucleation model where the folded phase takes over the molten globule, and estimate the scaling of the resulting energy barrier as a function of the free energy bonus per volume for the folded state and the surface tension between the two phases.

Learning goals for this chapter

- Be able to explain the central dogma of molecular biology with proper terminology.
- Be able to explain the Levinthal paradox and its implications for protein folding.

- Be able to explain why a random energy model is a reasonable representation of a random heteropolymer.
- Be able to explain why folding in the random energy model should happen when the entropy vanishes, and to compute the corresponding folding temperature.
- Be able to qualitatively discuss the kinetic issues surrounding this folding.
- Be able to demonstrate that the mean folding time diverges at the folding temperature of the random energy model.
- Be able to explain the idea behind the minimal frustration principle, and what the physical and biological meaning of the minimally frustrated state is.
- Be able to estimate the time to jump out of a metastable state above the glass transition, and to explain why this time approaches the Levinthal time as the glass transition is approached. Mark the distinction between the origin of the Levinthal time in this and the “golf course” context.
- Be able to qualitatively discuss effects that will speed up folding beyond this estimate.

References

Anfinsen’s Nobel lecture [9]; Comprehensive review on the energy landscape theory [10, 11]; Original article on the random energy model [12]; Claim that protein folding is “solved*” (*sort of) [13]; Relatively recent perspective on the energy landscape theory of protein folding [14]; Description of Google’s AlphaFold machine learning-based protein folder [15]; Discussion of the Legendre transform in thermodynamics [16] (also available as arXiv:0806.1147).

3 Self-assembly

Optional training exercises

1. Write the Smoluchowski equation for the example of nonequilibrium dynamics proposed in the lectures. Assuming the reaction constants are all equal, compute the steady-state concentrations of each species. Demonstrate that there are some steady-state currents in the system.
2. Show from scratch that the Ansatz proposed in the lecture is a solution of the Smoluchowski equation in the case of a fiber ($z = 2$), and compute the associated extent of reaction over time. Does gelation ever occur?
3. Demonstrate using the Smoluchowski equation that the total mass $\sum k c_k$ is a constant over time.

Learning goals for this chapter

- Be able to rederive the size distribution of dilute polymorphic aggregates as a function of the energy associated with each aggregate size.
- Be able to re-write the Smoluchowski equation from scratch and explain each of its terms.
- Be able to explain and formulate the detailed balance condition for the reaction constants in the Smoluchowski equation.

- Be able to explain the difference between diffusion-limited and reaction-limited processes, and to qualitatively draw the spatial distribution of reacting objects in each case.
- Be able to rederive the associated association constants with a minimal indications.
- Be able to qualitatively explain the form of the Ansatz we used to solve the mean-field Smoluchowski equation in the case of equally reactive binding sites, and to discuss the onset of gelation as a function of the extent of reaction $\alpha(t)$.
- Be able to qualitatively explain why the mean-field assumption tends to fail near the gelation transition, and to explain why using percolation instead is a good idea.
- Be able to qualitatively explain why the mean-field assumption is not appropriate to describe diffusion-limited aggregation with irreversible binding, and to qualitatively explain why the resulting aggregates look like convoluted trees.
- Be able to cite some nonequilibrium assembly behaviors in cytoskeletal filaments.
- Be able to explain the biological advantage that viruses draw from being able to form large capsids out of a small set of proteins, and why this might motivate the formation of icosahedral capsids.
- Be able to explain why capsid proteins cannot assemble into a flat triangular lattice and expect to form a sphere; argue that vertices with a local pentagonal structure (a type of defects known as “disclinations”) are needed.
- Be able to explain how nucleation helps viruses form full capsids.
- Be able to explain how hierarchical self-assembly is useful to avoid mistakes in self-assembly.
- Be able to explain how a competition between curvature, twisting and lateral adhesion results in broad, underbent filament ribbons in twisted fiber self-assembly where none of the interactions are perfectly satisfied.

References

Experiments presented at the beginning of the chapter [17]; Detailed discussion of reversible gelation and the Smoluchovski equation [18]; Discussion of percolation as a better model for gelation (see Sec. V.2) [4]; Original article on diffusion limited aggregation [19]; Discussion of the various topologies of protein complexes [20]; Crick & Watson genetic economy [21]; Caspar-Klug classification of icosahedral viruses [22]; Recent review on the physics of viral capsids [23]; Discussion of the precise placement of pentagonal vertices on large icosahedral viruses through scaffolding [24]; Review on self-limiting assembly, including frustration effects and surfactants [25].

4 Cell compartmentalization

Optional training exercises

1. Compute the modified Laplace law for a large membrane spherical vesicle coated with the same type of proteins considered in Sec. 1.5 of the lecture.
2. Assume a system where droplets in solution (as in Sec. 2.3) coexist with droplets inside a gel (as in Sec. 2.4). The surface tension in solution and in the gel are different, but their density is the same. Write down the chemical potential of the solute in each type of droplet. When does Ostwald ripening proceed from the solution to the gel *vs.* the reverse?

3. Assuming a fixed waste concentration at the droplet of Sec. 2.4, compute the stable droplet size in a system that is limited by waste efflux rather than the influx of the functional molecule.

Learning goals for this chapter

- Be able to write down and explain every term in the Helfrich Hamiltonian.
- Be able to state the Gauss-Bonnet theorem for a closed surface and explain its implications for the (absence of) influence of the Gaussian curvature modulus in determining the shape of a vesicle.
- Be able to explain the geometry of a pipette microaspiration experiment.
- Be able to explain the two influences that compete to determine the shape of a membrane tube in such an experiment, and to give the scaling of the membrane tube radius.
- Be able to compute the tube force in such an experiment.
- Be able to state the unknowns and equations in a multicomponent phase equilibrium.
- Be able to explain the meaning of the cloud curve and the shadow curve.
- Be able to argue that the critical point in a two-phase equilibrium involving multiple species is not necessarily at the top of the cloud curve.
- Be able to justify the maximum number n of coexisting phases in a generic system with M conserved components.
- Be able to explain the phenomenon of Ostwald ripening.
- Be able to derive the scaling of the critical tension above which a linear elastic network cannot confine the droplets in a phase separation process.
- Be able to describe an active mechanism that allows to regulate the phase separated droplet size, and to derive the scaling of the associated radius.

References

Original reference for the Helfrich Hamiltonian [26]; Book on the physics of membranes [27]; Review on the role of phase separation in the cell [28]; Review on phase separation in multicomponent systems and the theoretical methods to tackle them [29]; Two nice papers trying to predict when and how systems with many components with randomly chosen interactions phase separate by looking at the spinodal with random matrix theory [30]; and at the cloud curve with numerics and a scaling argument [31]; Elastic constraints on phase separation [32]; Size limitation and division of active droplets [33].

References

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