# Gooey tutorial 1: Microphase separation 

ICFP M2 - Advanced Biophysics

Weak interactions - presumably mediated by histones and associated proteins - drive chromatin to phase separate and form distincts compartments in the nucleus. Here we discuss the physical basis of this phase separation by representing chromatin as a copolymer, i.e. a polymer with two types of monomers, denoted by A and B, which slightly repel each other. Denoting by $\rho_{A}(\mathbf{r})$ and $\rho_{B}(\mathbf{r})$ the local density of each type of monomer as a function of position $\mathbf{r}$, this results in the interaction Hamiltonian

$$
\begin{equation*}
\mathcal{H}_{\text {int }}=k_{B} T \chi \int \rho_{A}(\mathbf{r}) \rho_{B}(\mathbf{r}) \mathrm{d} \mathbf{r}, \tag{1}
\end{equation*}
$$

where $\chi$ is a scalar parameter with units of volume that quantifies the strength of the interactions and $k_{B} T=1 / \beta$ is the thermal energy. The resulting tendency towards phase separation is opposed by thermal agitation, as in the familiar example of oil and water demixing in a cup. Additionally, the polymer topology further hinders phase separation: while the molecules of oil and water can move arbitrarily far from one another, the monomers are tied together along the polymer chain. This may prevent them from achieving complete spatial separation, and result in interpenetrating regions respectively enriched in A and B.

Here we aim to compute the critical interaction strength leading to phase separation (more accurately: to spinodal decomposition), as well as the size of the resulting A and B domains. As discussed in the lectures, we will see that long chains can be driven to separate by very small interactions. We will also show that the precise sequence of A and B along the chain can strongly influence the system's final morphology.

In the following sections we follow a mean-field approach known as the "random phase approximation" by polymer physicists. This approach evaluates the entropic constraints on the polymer conformation in the absence of monomer-monomer interactions (Secs. 1. 2). It then introduces these interactions as an external field, similar to the Curie-Weiss "molecular field" formulation of the mean-field Ising model (Sec. 3), then sets a self-consistency condition on this field (Sec. 4). This allows to determine the stability of the homogeneous state (Sec. 5), which we further discuss in Sec. बW]

## 1 Monomer-monomer correlations in the absence of interactions

The extent to which the connection between monomers constrains their spatial location, and ultimately their phase separation, is readily expressed in the correlation between their local concentrations. Qualitatively, the concentration of A vs. B fluctuates more in a system where they are more loosely connected, and therefore more prone to phase separate. We consider one very long polymer with $N$ monomers in a box of volume $V$ in the limit $N, V \rightarrow \infty$ with $N / V$ fixed. Let us consider monomer $j$ and monomer $k$ of the chain $(j \in[1 . . N], k \in[1 . . N])$, and denote by $\rho_{j}(\mathbf{r}), \rho_{k}(\mathbf{r})$ their concentration at location $\mathbf{r}$.
1.1 Assuming that the box is large enough that its boundaries may be ignored, explain why the thermal average of these two concentrations is $\left\langle\rho_{j}(\mathbf{r})\right\rangle=\left\langle\rho_{k}(\mathbf{r})\right\rangle=1 / V$ irrespective of the location $\mathbf{r}$.
1.2 Show that the two-point density correlation function of these densities can be written as

$$
\begin{equation*}
\left\langle\rho_{j}\left(\mathbf{r}_{1}\right) \rho_{k}\left(\mathbf{r}_{2}\right)\right\rangle=\frac{1}{V} P\left(k, \mathbf{r}_{2} \mid j, \mathbf{r}_{1}\right), \tag{2}
\end{equation*}
$$

where $P\left(k, \mathbf{r}_{2} \mid j, \mathbf{r}_{1}\right)$ is the probability density for monomer $k$ to be in $\mathbf{r}_{2}$ knowing that monomer $j$ is in $\mathbf{r}_{1}$ (this density has units of $\mathrm{m}^{-3}$ ).

[^0]1.3 Use the results of our lectures to show that
\[

$$
\begin{equation*}
P\left(k, \mathbf{r}_{2} \mid j, \mathbf{r}_{1}\right)=\left(\frac{2 \pi}{3}|k-j| a^{2}\right)^{-3 / 2} \exp \left(-\frac{3\left|\mathbf{r}_{2}-\mathbf{r}_{1}\right|^{2}}{2|k-j| a^{2}}\right) . \tag{3}
\end{equation*}
$$

\]

and write the resulting two-point correlation function $\left\langle\rho_{j}\left(\mathbf{r}_{1}\right) \rho_{k}\left(\mathbf{r}_{2}\right)\right\rangle$.

## 2 Species correlations for a block copolymer

The correlation function of Eq. (2) tells us how likely monomers $j$ and $k$ are to be in the same location, which as we will see in Sec. 3 tells us how easy or difficult it is to pull them apart. That is not exactly the information we are looking for however, as phase separation really depends on how easy or difficult it is to separate A-type monomers from B-type monomers. This assessment requires the computation of a slightly different type of correlation functions, e.g., $\left\langle\rho_{A}\left(\mathbf{r}_{1}\right) \rho_{B}\left(\mathbf{r}_{2}\right)\right\rangle$, where the density of A- and B-type monomers are given by

$$
\begin{equation*}
\rho_{A}(\mathbf{r})=\sum_{j=1}^{N} \rho_{j}(\mathbf{r}) \theta_{j} \quad \text { and } \quad \rho_{B}(\mathbf{r})=\sum_{j=1}^{N} \rho_{j}(\mathbf{r})\left(1-\theta_{j}\right), \tag{4}
\end{equation*}
$$

where $\theta_{j}$ is a binary variable that is equal to 1 if monomer $j$ is of type A , and 0 if it is of type B . Physically, if $\theta_{j}=1$ for all $j<N / 2$ and $\theta_{j}=0$ for all $j \geqslant N / 2$, we have a so-called diblock copolymer with a monomer sequence ...-A-A-A-A-B-B-B-B-... This makes phase separation very easy: just put all the A monomers on the left side of the nucleus, and the B monomers on the right, with the small constraint that the midpoint of the polymer must be at the interface between the two regions. If on the other hand $\theta_{j}$ changes at every monomer, the sequence is ...-A-B-A-B-A-B-... In that case, segregating the monomers spatially is very difficult. Indeed, rather than forming two separate phases, similar monomers may regroup into finite-size droplets or layers.

Here we will consider two intermediate situations between these two extremes, as befits the physics of chromatin. In our two examples, a monomer tends to be of the same type as its neighbors, although these correlations only have a finite range $\ell$.

The first and computationally simpler case is that of a random copolymer, where the $\left\{\theta_{j}\right\}_{j \in[1 . . N]}$ are random variables. We denote by a bar $\uparrow$ the average with respect to their distribution. We consider the specific case where there is an equal number of $A$ and $B$ monomers on average, implying $\overline{\theta_{j}}=1 / 2$, and assume that the aforementioned correlations take the form

$$
\begin{equation*}
\overline{\theta_{j} \theta_{k}}-\overline{\theta_{j}} \overline{\theta_{k}}=\frac{e^{-a|k-j| / \ell}}{4}, \tag{5}
\end{equation*}
$$

implying that two monomers are very likely to be identical if their distance along the chain $a|k-j|$ is much smaller than $\ell$, and that their types are uncorrelated if it is much larger.
2.1 We first aim to compute the disorder-averaged A-A correlation function in Fourier space, namely

$$
\begin{equation*}
\overline{\left\langle\rho_{A}\left(\mathbf{q}_{1}\right) \rho_{A}\left(\mathbf{q}_{2}\right)\right\rangle}=\iint_{-\infty}^{\infty} \overline{\left\langle\rho_{A}\left(\mathbf{r}_{1}\right) \rho_{A}\left(\mathbf{r}_{2}\right)\right\rangle} e^{i \mathbf{q}_{1} \cdot \mathbf{r}_{1}} e^{i \mathbf{q}_{2} \cdot \mathbf{r}_{2}} \mathrm{~d} \mathbf{r}_{1} \mathrm{~d} \mathbf{r}_{2} . \tag{6}
\end{equation*}
$$

Using the above and the equality $(2 \pi)^{3} \delta(\mathbf{q})=\int e^{\mathbf{q} \cdot \mathbf{r}} \mathrm{d} \mathbf{r}$, show that this function is equal to

$$
\begin{equation*}
\overline{\left\langle\rho_{A}\left(\mathbf{q}_{1}\right) \rho_{A}\left(\mathbf{q}_{2}\right)\right\rangle}=(2 \pi)^{3} \delta\left(\mathbf{q}_{1}+\mathbf{q}_{2}\right) S_{A A}\left(\mathbf{q}_{1}\right), \quad \text { where } \quad S_{A A}(\mathbf{q})=\frac{1}{V} \sum_{j, k} \overline{\theta_{j} \theta_{k}} e^{-|k-j|(q a)^{2} / 6} . \tag{7}
\end{equation*}
$$

2.2 For a very long polymer, you may convert the sums to integrals: $\sum_{i} \rightarrow \int \frac{\mathrm{~d} s_{1}}{a}$, where $s_{1}=a j$ is the coordinate along the polymer. Neglecting the contributions of the ends of the polymer to the resulting integrals, prove that if $\xi=q^{2} a \ell / 6$ then

$$
\begin{equation*}
S_{A A}(\mathbf{q})=S_{B B}(\mathbf{q})=\frac{N \ell}{2 V a}\left(\frac{1}{\xi}+\frac{1}{1+\xi}\right) . \tag{8}
\end{equation*}
$$

2.3 Likewise, show

$$
\begin{equation*}
S_{A B}(\mathbf{q})=S_{B A}(\mathbf{q})=\frac{N \ell}{2 V a} \frac{1}{\xi(1+\xi)} . \tag{9}
\end{equation*}
$$

## [Optional] Species correlations for fixed-length blocks

Now consider a deterministic polymer with a periodic sequence with period $2 \ell$ defined by $\theta_{j}=1$ for $a j \in[0, \ell]$ and $\theta_{j}=1$ for $a j \in[\ell, 2 \ell]$. Denoting $\xi=q^{2} a \ell / 6$, show that

$$
\begin{equation*}
S_{A A}(\xi)=\frac{N \ell}{V a}\left(\frac{1}{\xi}-\frac{1}{\xi^{2}} \tanh \frac{\xi}{2}\right) \quad \text { and } \quad S_{A B}(\xi)=\frac{N \ell}{V a} \frac{1}{\xi^{2}} \tanh \frac{\xi}{2} \tag{10}
\end{equation*}
$$

## 3 Response to an external field

In the following we consider a state where the monomer density across the whole system is constant, and assess the stability of that state. To understand the strategy that we will use, first consider the following example: a bead with horizontal coordinate $x$ is trapped in a harmonic potential $U=k x^{2} / 2$, where the sign of $k$ is unknown. To determine the stability of the potential, we apply an external field $h$ on the bead, which adds a term $+h x$ to its Hamiltonian. Minimizing the total energy reveals that the displacement of the bead is $x_{h}=-h / k$. The stability of the original potential can be determined by assessing the sign of this displacement: if $x_{h}$ has a sign opposite (identical) to the sign of $h$, then the potential is stable (unstable).

Returning to our polymer problem, we first consider a simplified case where there is only one type of monomer with a density $\rho(\mathbf{r})$ subjected to a field $h(\mathbf{r})$, which implies a total energy $\mathcal{H}=\mathcal{H}_{\text {int }}+$ $\int h(\mathbf{r}) \rho(\mathbf{r}) \mathrm{d} \mathbf{r}$. Computing the response of the monomer density in the presence of an interaction of the type of Eq. (11) is unfortunately exceedingly difficult in this case. We thus resort to a mean-field approximation, which consists in imitating the combined effect of the interaction with the neighboring monomers and the field $h(\mathbf{r})$ as a "molecular field" $H(\mathbf{r})$. This is a very similar strategy to the one used in the Curie-Weiss approach to the Ising model, and we similarly fix the value of $H(\mathbf{r})$ self-consistently later (Sec. 4). For now, the partition function for our interaction-less polymer reads

$$
\begin{equation*}
Z_{0}(\{H\})=\sum_{\text {configs }} e^{-\beta \int H(\mathbf{r}) \rho(\mathbf{r})}, \tag{11}
\end{equation*}
$$

where the sum runs over all the possible configurations of the polymer and the index ${ }_{0}$ denotes the absence of interactions.
3.1 Prove that the average density of monomer $\psi_{\{H\}}(\mathbf{r})=\langle\rho(\mathbf{r})\rangle_{\{H\}}$ under the field $H(\mathbf{r})$ is equal to $\frac{\delta F_{0}}{\delta H(\mathbf{r})}$, where the free energy is defined as $F_{0}(\{H\})=-\beta^{-1} \ln Z_{0}(\{H\})$. (If you need a refresher on functional derivatives, denoted as $\delta$ here, go look at Sec. 6 of
http://lptms.u-psud.fr/membres/mlenz/teaching/ICFPstat-prerequisites.pdf)
3.2 Expand $\psi$ to first order as a function of $H$ to prove that

$$
\begin{equation*}
\psi_{\{H\}}(\mathbf{r}) \underset{H \rightarrow 0}{\sim} \frac{N}{V}+\left.\int \frac{\delta \psi(\mathbf{r})}{\delta H\left(\mathbf{r}^{\prime}\right)}\right|_{H=0} H\left(\mathbf{r}^{\prime}\right) \mathrm{d} \mathbf{r}^{\prime} \tag{12}
\end{equation*}
$$

where

$$
\begin{equation*}
\left.\frac{\delta \psi(\mathbf{r})}{\delta H\left(\mathbf{r}^{\prime}\right)}\right|_{H=0}=-\beta\left[\left\langle\rho(\mathbf{r}) \rho\left(\mathbf{r}^{\prime}\right)\right\rangle_{H=0}-\langle\rho(\mathbf{r})\rangle_{H=0}\left\langle\rho\left(\mathbf{r}^{\prime}\right)\right\rangle_{H=0}\right] \tag{13}
\end{equation*}
$$

is a function of the difference $\mathbf{r}^{\prime}-\mathbf{r}$ only.
3.3 Going to Fourier space, show that the Fourier transform of the quantity presented in Eq. (13) can be written as $G\left(\mathbf{q}, \mathbf{q}^{\prime}\right)=-\beta S(\mathbf{q})(2 \pi)^{3} \delta\left(\mathbf{q}+\mathbf{q}^{\prime}\right)$ for $\mathbf{q} \neq \mathbf{0}$, where the Fourier transform is defined through $\tilde{f}(\mathbf{q})=\int f(\mathbf{r}) e^{i \mathbf{q} \cdot \mathbf{r}} \mathrm{~d} \mathbf{r}$.
3.4 Conclude that $\psi_{\{H\}}(\mathbf{q}) \sim_{H \rightarrow 0}-\beta S(\mathbf{q}) H(\mathbf{q})$ for $\mathbf{q} \neq \mathbf{0}$.
3.5 Going back to a system with two different types of monomers, convince yourself (full proof not required) that this generalizes to

$$
\begin{align*}
& \psi_{A}(\mathbf{q})=-\beta S_{A A}(\mathbf{q}) H_{A}(\mathbf{q})-\beta S_{A B}(\mathbf{q}) H_{B}(\mathbf{q})  \tag{14a}\\
& \psi_{B}(\mathbf{q})=-\beta S_{B A}(\mathbf{q}) H_{A}(\mathbf{q})-\beta S_{B B}(\mathbf{q}) H_{B}(\mathbf{q}) \tag{14b}
\end{align*}
$$

and write the definitions of the new quantities thus introduced.

## 4 Mean-field interactions

From the point of view of the A monomers, the full interaction Hamiltonian of Eq. (1) can be written as $\mathcal{H}_{\text {int }}=\int H_{A}^{\text {fluct }}(\mathbf{r}) \rho(\mathbf{r}) \mathrm{d} \mathbf{r}$, where we have defined a fluctuating field $H_{A}^{\text {fuct }}(\mathbf{r})=\beta^{-1} \chi \rho_{B}$. The mean-field approximation consists in approximating this field by its average value, namely $\beta^{-1} \chi\left[N / 2 V+\psi_{B}(\mathbf{r})\right]$.

Here we write the full Hamiltonian as

$$
\begin{equation*}
\mathcal{H}=\mathcal{H}_{\text {int }}+\int h(\mathbf{r})\left[\rho_{A}(\mathbf{r})-\rho_{B}(\mathbf{r})\right] \mathrm{d} \mathbf{r}+\int \lambda(\mathbf{r})\left[\rho_{A}(\mathbf{r})+\rho_{B}(\mathbf{r})\right] \mathrm{d} \mathbf{r}, \tag{15}
\end{equation*}
$$

where the field $h$ favors the presence of B-monomers over that of A-monomers and plays the same role as the field of the same name discussed in the beginning of Sec. 3. The field $\lambda$ is a Lagrange multiplier that ensures the incompressibility of the system as a whole; in practice this means that you should treat is as an unknown that will take whatever value is required to ensure that for $\mathbf{q} \neq \mathbf{0} \psi_{A}(\mathbf{q})+\psi_{B}(\mathbf{q})=0$ throughout the system (which derives from the incompressibility condition $\rho_{A}+\rho_{B}=N / V$ ).
4.1 Apply the mean-field approximation strategy described above to express the fields $H_{A}$ and $H_{B}$ introduced in Eq. (14) as functions of $\psi_{A}, \psi_{B}, h$ and $\lambda$.
4.2 Use this result to show that

$$
\begin{align*}
\left(1+\chi S_{A B}\right) \psi_{A}+\chi S_{A A} \psi_{B} & =-\left(S_{A A}+S_{A B}\right) \beta \lambda-\left(S_{A A}-S_{A B}\right) \beta h  \tag{16a}\\
\chi S_{B B} \psi_{A}+\left(1+\chi S_{B A}\right) \psi_{B} & =-\left(S_{B A}+S_{B B}\right) \beta \lambda-\left(S_{B A}-S_{B B}\right) \beta h \tag{16b}
\end{align*}
$$

4.3 Along with the incompressibility condition, Eqs. (16) form a linear system of three equations. What are the three corresponding unknowns? Solve the system to prove that

$$
\begin{equation*}
\psi_{A}(\mathbf{q})=\frac{2 \beta h(\mathbf{q})}{2 \chi-\frac{S_{A A}(\mathbf{q})+S_{A B}(\mathbf{q})+S_{B A}(\mathbf{q})+S_{B B}(\mathbf{q})}{S_{A A}(\mathbf{q}) S_{B B}(\mathbf{q})-S_{A B}(\mathbf{q}) S_{B A}(\mathbf{q})}} \tag{17}
\end{equation*}
$$

## 5 Stability of the homogeneous phase

Following the strategy described for the toy model at the beginning of Sec. 3:
5.1 Use Eq. 17) to express the condition for the system to be stable at wavevector $\mathbf{q}$.
5.2 Considering a random copolymer and using the expressions of Eqs. (8) and (9), what is the most unstable wavelength? What is the threshold at which the homogeneous system becomes linearly unstable?
5.3 Same questions for the periodic polymer and Eq. 10.

## 6 Discussion of phase separation

6.1 How does the critical $\chi$ scale with $\ell / a$ and with $N$ ? Relate this to the discussion of the main lecture about phase separation in polymers.
6.2 Over what typical length scale do you expect each polymer to phase separate? Beware though: here we have looked at spinodal decomposition, and binodal decomposition can be somewhat different.


[^0]:    ${ }^{1}$ Some equations may still have some small typos... Sorry and don't get too hung up on it while preparing the tutorial.

