Coupled enhancer-promoter condensates

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1 Free energy functional

$$
\begin{aligned}
F(\phi_{\mathrm{P}}(\vec{x},t),\phi_{\mathrm{R}}(\vec{x},t)) = \int \mathrm{d}\vec{x} \Bigg[& \rho_{\mathrm{P}}(\phi_{\mathrm{P}}-\alpha)^2(\phi_{\mathrm{P}}-\beta)^2 + \rho_{\mathrm{R}}\phi_{\mathrm{R}}^2 \\
& - \chi\phi_{\mathrm{P}}\phi_{\mathrm{R}} + c\phi_{\mathrm{P}}^2\phi_{\mathrm{R}}^2 \\
& + \frac{\kappa}{2}|\nabla\phi_{\mathrm{P}}|^2 \\
& - \chi_{\mathrm{Pe}}\phi_{\mathrm{P}} \exp\left\{-\frac{(\vec{x}-\vec{x}_e)^2}{2\sigma^2}\right\} \Bigg] \\
& + \frac{1}{2}k(|\vec{x}_e-\vec{x}_p|-R_r)^2
\end{aligned}
$$

The functional incorporates protein-protein double-well potential (phase separation), RNA-RNA electrostatic repulsion, protein-RNA electrostatic intreaction (re-entrant phase behaviour), interfacial surface-tension, protein-DNA interaction (enhancer locus, Gaussian is ϕ_{e}).

2 Chromatin

- Packaging and extrusion of DNA complicates the persistence length. The equilibrium rest length (end-to-end distance) is not necessarily countour length.
- End-to-end distribution of Gaussian chain is the same as the Boltzmann weight of a Hookean spring
- $\vec{R} \leq 10^3$ nm (Cho et al. 2018)
- $l_c \sim 10^4$ nm estimated from linker DNA lengths
- Worm-like chain for $l_c \gtrsim l_p$
- Gaussian chain for $l_c \gg l_p$

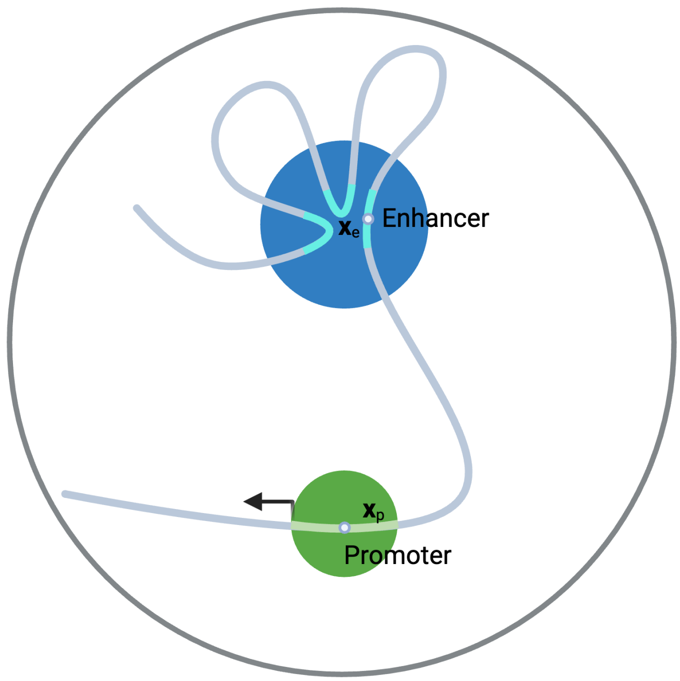

Figure 1: Enhancer and promoter regions on chromatin

2.1 Gaussian chain

Rod length a, Kuhn length $b = 2l_p$, Kuhn segments $N_k = \frac{Na}{b} = \frac{l_c}{b}$.

$$\langle R \rangle = 0$$

$$\langle R^2 \rangle = N_k b^2$$

The probability distribution of the end-to-end distance is a 3D Gaussian, following the CLT for random walk of N_k independent rods.

$$P\left(\vec{R} = \sum_{i=1}^{N_k} \vec{u}_i\right) = \left(\frac{2\pi\langle R^2\rangle}{3}\right)^{3/2} \exp\left(-\frac{R^2}{2\langle R^2\rangle}\right) \sim \frac{1}{Z}\exp\left(-\frac{U}{k_BT}\right)$$

$$U = \frac{1}{2}k_BT$$

$$k = \frac{3k_BT}{N_kb^2} = \frac{3k_BT}{2l_cl_p}$$

$$F_{\mathrm{C}}(\vec{R}) = \frac{1}{2}kR^2 = \frac{3k_BT}{4l_cl_p}R^2$$

Enhancer-to-promoter chromatin has a non-zero rest length.

$$F_{\mathrm{C}}(\vec{R}) = \frac{1}{2}k(R - R_r)^2$$

$$R = |\vec{x}_e - \vec{x}_p|$$

3 Dynamic equations

3.1 Protein

- Model B (diffusivex) dynamics with conserved quantity.

$$\frac{\partial \phi_{\mathrm{P}}}{\partial t} = M_{\mathrm{P}}\nabla^2\left(\frac{\delta F}{\delta \phi_{\mathrm{P}}}\right) = M_{\mathrm{P}}\nabla^2\mu_{\mathrm{P}}$$

3.2 RNA

$$\frac{\partial \phi_{\mathrm{R}}}{\partial t} = M_{\mathrm{R}}\nabla^2\phi_{\mathrm{R}} + k_p(\vec{x})\phi_{\mathrm{P}} - k_d\phi_{\mathrm{R}}$$

$$k_p(\vec{x}) = \frac{k_T}{2\pi\sigma^2}\exp\left\{-\frac{(\vec{x} - \vec{x_p})^2}{2\sigma^2}\right\}$$

3.3 Enhancer

- Model A (gradient descent) dynamics.
- Overdamped Langevin equation without noise.
- Gradient of free energy functional withμ respect to the vector $\vec{x}_e$

$$\frac{\partial \vec{x}_\mathrm{e}}{\partial t} = M_\mathrm{D} \nabla_{\vec{x}_e} F$$

Cho, Won-Ki, Jan-Hendrik Spille, Micca Hecht, Choongman Lee, Charles Li, Valentin Grube, and Ibrahim I. Cisse. 2018. "Mediator and RNA Polymerase II Clusters Associate in Transcription-Dependent Condensates." *Science* 361 (6400): 412–15. https://doi.org/10.1126/science.aar4199.