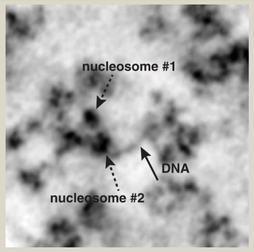
Nucleosome Heterogeneity Governs Chromatin Elasticity

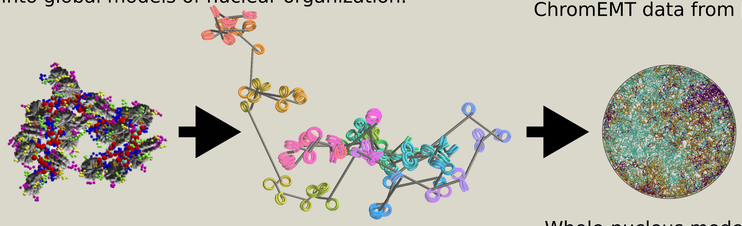
Bruno Beltran, Deepti Kannan, Quinn Macpherson, Andrew Spakowitz
Stanford University

Modeling Chromatin

- *In vivo* chromatin is extremely heterogeneous.
- Detailed models of chromatin often include nucleosome geometry and heterogeneity.
- However, it is difficult to isolate the effects of nucleosome localization in these complex models.
- Using a purely analytical approach, we can construct an intuitive picture for how nucleosome positioning affects chromatin structure.
- This allows us to incorporate nucleosome positioning into global models of nuclear organization.

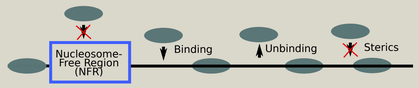


ChromEMT data from [4].

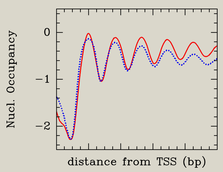


Detailed model [2]. Simplified model (this poster). Whole-nucleus model (MacPherson et. al., *in preparation*).

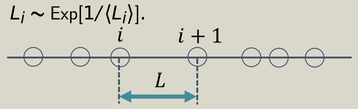
Realistic Nucleosome Positioning



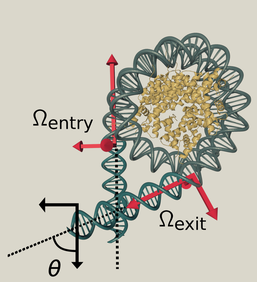
- Random binding explains nucleosome ChIP, even at transcription start sites [1].



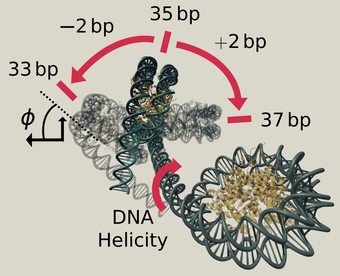
- Uniformly-binding nucleosomes lead to exponentially distributed linkers.
- $L_i \sim \text{Exp}[1/\langle L_i \rangle]$.



Nucleosome Geometry



- A human nucleosome [5] with entry (Ω_{entry}) and exit (Ω_{exit}) orientations of the bound DNA labeled.
- The amount of DNA wrapping the nucleosome dictates the spherical angle θ.



- Two adjacent nucleosomes pictured.
- The histone octamer must align with the major groove of the double helix.
- Therefore, the relative angle ϕ between nucleosomes is determined by linker length.

Kinked WLC

- The energy of a twistable wormlike chain (tWLC) is

$$\beta\mathcal{E} = \frac{l_p}{2}\int_0^L \omega_1^2 + \omega_2^2 ds + \frac{l_t}{2}\int_0^L (\omega_3 - \tau)^2 ds,$$

where $\partial_s \vec{t}_i(s) = \vec{\omega}(s) \times \vec{t}_i(s)$ and $\tau = 10.5\,\text{bp}^{-1}$.

- Its Green's function

$$G(\vec{R}, \Omega|\Omega_0; L) = \int_{\Omega(s=0)}^{\Omega(s=L)} \mathscr{D}[\Omega(s)] \exp[-\beta\mathcal{E}]\, \delta(\vec{R} - \int_0^L \vec{t}_3 ds)$$

has an exact solution in Wigner D-functions [3].

- We rotate the Green's function by Ω_{kink} using

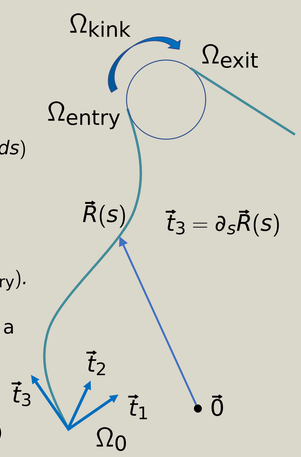
$$\mathcal{D}_l^{mj}(\Omega_{\text{entry}} \cdot \Omega_{\text{kink}}) = \sum_k \sqrt{\frac{8\pi}{2l+1}} \mathcal{D}_l^{mk}(\Omega_{\text{kink}}) \mathcal{D}_l^{kj}(\Omega_{\text{entry}}).$$

- Concretely, we compute a matrix $\mathcal{B}$ representing a (linker, nucleosome) pair in Fourier space

$$\hat{G}(\vec{k}, \Omega|\Omega_0; L) = \sum_\mu \sum_{\mu_0} \mathcal{B}_{\mu_0}^{\mu} \mathcal{D}^{\mu}(\Omega) \mathcal{D}_{\mu_0}(\Omega_0).$$

- Linkers combine via convolution (multiplying $\mathcal{B}$'s)

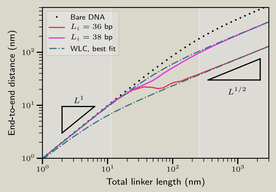
$$G(\vec{R}, \Omega|\Omega_0; L_1, L_2) = \int G(\vec{R} - \vec{R}_1, \Omega|\Omega_1; L_2) G(\vec{R}_1, \Omega_1|\Omega_0; L_1) d\vec{R}_1 d\Omega_1.$$

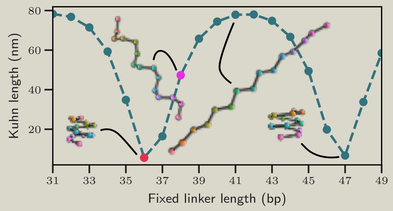


End-to-end Distance

We compute the end-to-end distance $\langle R^2 \rangle$ using $\lim_{k\to 0} \frac{\partial^n \mathcal{B}_0^0}{\partial k^n} = i^n \langle R^n \rangle$.

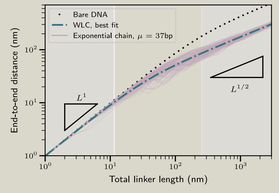
- Constant linker length chains will have specific helical geometries.



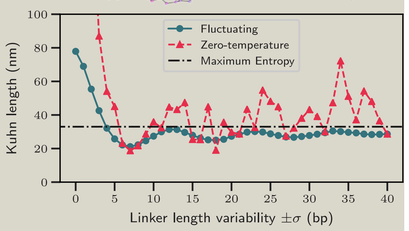


- As linker variability increases, the zero-temperature structure becomes a random walk.
- The "diffusivity" of this random walk determines the structure of heterogeneous chains.
- Very little linker length heterogeneity is need to create a random walk at zero temperature.

- Exponential nucleosome chains fluctuate about an effective WLC.

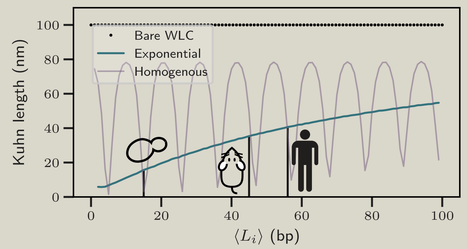


- Long length behavior can be summarized by Kuhn length .
- The Kuhn length for constant linker length is simply determined by its zero-temperature structure.



Heterogeneous Chain Elasticity

- Kuhn length depends only on the mean linker length for exponential chains.
- Heterogenous chains are less sensitive to changes in average nucleosome spacing.
- The chromatin chain's Kuhn length approaches bare WLC Kuhn length like $\sim 1/\langle L_i \rangle$.

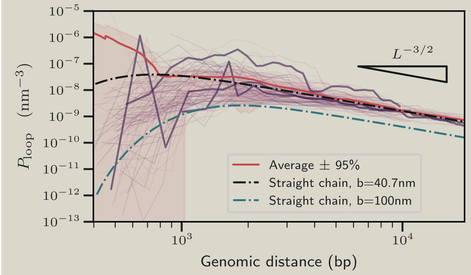


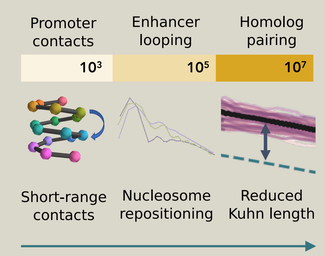
Looping Probabilities

We compute the looping probabilities as a modified J-factor, ignoring orientational contributions:

$$P_{\text{loop}}(L) = G(\vec{0}|L) = \frac{1}{2\pi^3}\int G(\vec{k}|L) \exp(-i\vec{k}\cdot\vec{R}) d\vec{k}\Big|_{\vec{R}=0} = \frac{1}{2\pi^2}\int k^2 j_0(0) \mathcal{B}_0^0(k; L) d\vec{k}.$$

- For $\langle L_i \rangle = 56\,\text{bp}$:





- As suggested by the $\langle R^2 \rangle$, the average looping probability matches an effective wormlike chain with increased elasticity.
- Nucleosome repositioning can change the looping probability by **up to 6 orders of magnitude**.
- Nucleosome repositioning is implicated in enhancer loop formation.

Conclusions

Heterogeneous nucleosome binding → Random chromatin geometry → Enhanced flexibility, looping

- Our work suggests that heterogeneity in nucleosome positioning plays a major role in the local and global behavior of chromosomal DNA.
- Chromatin is an effective WLC with reduced persistence length.
- Even one base pair of linker length variance can be sufficient to create this modified WLC.
- Nucleosome repositioning can expedite looping out to tens of kilobases.

Citations

[1] G. Chevereau, L. Palmeira, C. Thermes, A. Arneodo, and C. Vaillant. Thermodynamics of Intragenic Nucleosome Ordering. *Physical Review Letters*, 103(18), Oct. 2009.
[2] R. Collepardo-Guevara and T. Schlick. Chromatin fiber polymorphism triggered by variations of DNA linker lengths. *PNAS*, 111(22):8061–8066, June 2014.
[3] S. Mehraeen, B. Sudhanshu, E. F. Koslover, and A. J. Spakowitz. End-to-end distribution for a wormlike chain in arbitrary dimensions. *Physical Review E*, 77(6), June 2008.
[4] H. D. Ou, S. Phan, T. J. Deerinck, A. Thor, M. H. Ellisman, and C. C. O'Shea. ChromEMT: Visualizing 3D chromatin structure and compaction in interphase and mitotic cells. *Science*, 357(6349):eaag0025, July 2017.
[5] M. Wakamori, Y. Fujii, N. Suka, M. Shirouzu, K. Sakamoto, T. Umehara, and S. Yokoyama. Intra- and inter-nucleosomal interactions of the histone H4 tail revealed with a human nucleosome core particle with genetically-incorporated H4 tetra-acetylation. *Scientific Reports*, 5:17204, Nov. 2015.