Chromosome Tethering to the Lamina Increases Chromosome Compartmentalization

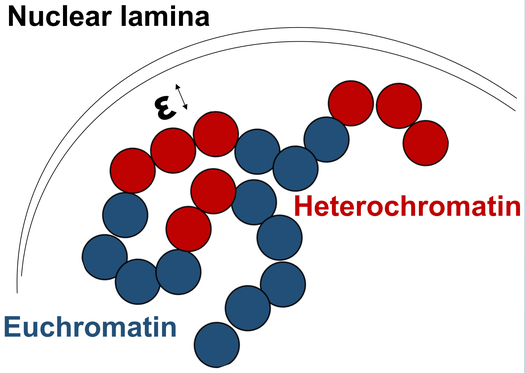
Kyle Lare*, Sumitabha Brahmachari# and Greg Morrison@

* @ Department of Physics, University of Houston, Houston, TX 77004, and #Center for Theoretical Biological Physics, Rice University, Houston, TX 77005

Introduction

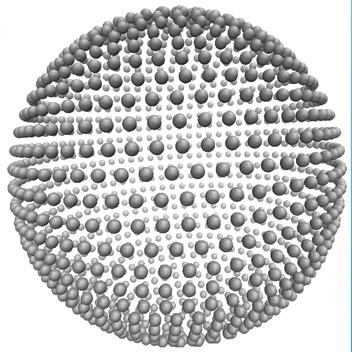
- Inside the nucleus of a cell, chromosomes are hierarchically folded due to various biochemical interactions
- Heterochromatin is known to "tether" to the nuclear lamina, a fibrillar network along the wall of the nucleus
- Aberrant nuclear lamina tethering has been implicated in various diseases such as progeria
- We were interested in finding out what effects lamina tethering can have on the overall structure of the genome

Nuclear lamina



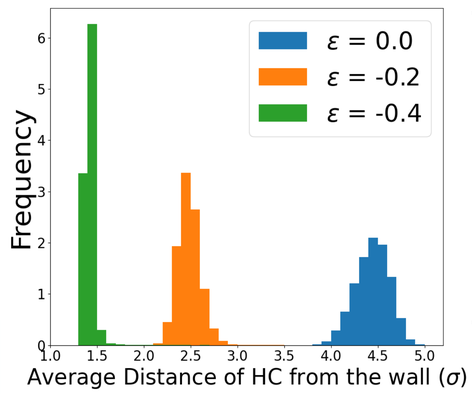
The Model

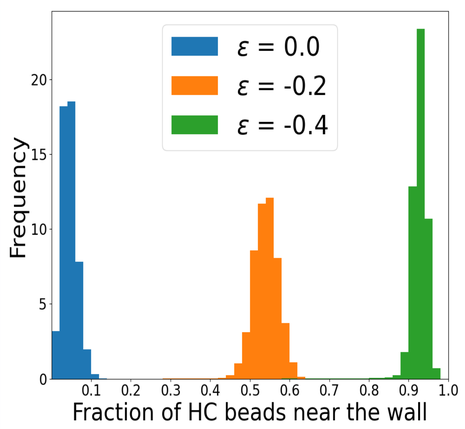
- We modeled chromosome twenty-one of human GM182878 lymphoblastoid cells[1]
- Chromatin was modeled as a block copolymer using the Minimal Chromatin Model (MiChroM) by Di Pierro, et al.[2]
- A spherical wall was implemented to mimic the nuclear lamina and its tethering effects



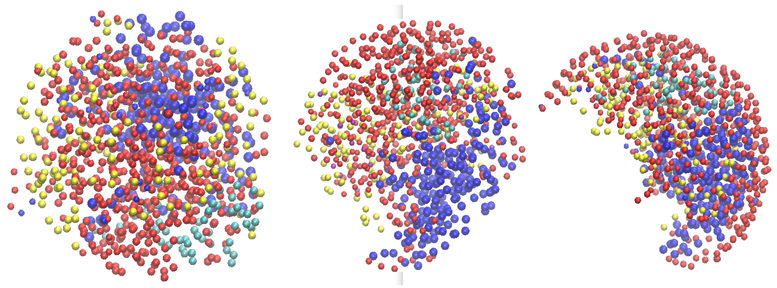
- Beads making up the wall represent proteins on the nuclear lamina, which are believed to be the driving force behind lamina-chromosome interactions

Lamina Interaction Pulls Heterochromatin Towards the Wall





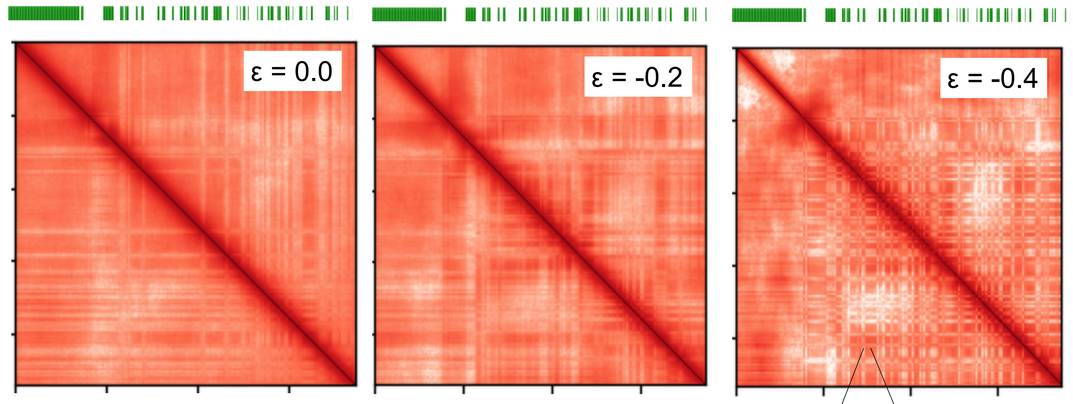
- A plot on the top left shows heterochromatin moving further from the lamina with decreasing interaction strength (ε). Distance is measured in sigma which is the diameter of each bead making up the wall.
- Another histogram in the middle left shows an increasing fraction of heterochromatin beads interacting with the wall
- These plots show that our model is capable of modeling lamina-chromosome interactions by successfully attracting heterochromatin to the nuclear lamina and keeping it there with a sticking propensity



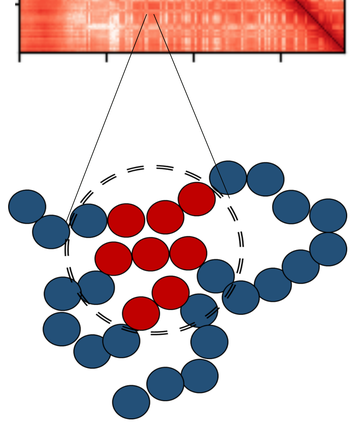
ε = 0.0 **ε = -0.2** **ε = -0.4**

- Simulation snapshots; red beads represent pieces of heterochromatin with a sticking propensity with the lamina (ε)

Hi-C Maps Show Enhanced Compartmentalization for Stronger Lamina-Chromosome Interaction

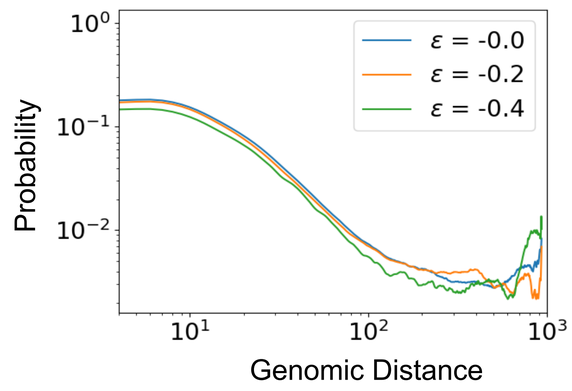


- In the Hi-C maps above, a chromosome is plotted on the x and y axis, and as we move along one line (representing one piece of chromatin) we find the probability of interaction between that piece of chromatin and every other piece of chromatin. The bright red diagonal represents the relatively high probability that each piece of chromatin will interact with its neighbors
- Blocks of chromatin that have a high probability of interacting in 3D space but are far along in genomic distance are called chromosome compartments (visualized on the right)
- We found that increased lamina-chromosome interaction lead to increased chromosome compartmentalization



Chromosome compartments

- By measuring probability of contact versus genomic distance we can get insight on the overall compaction of the chromosome
- We found that lamina tethering does not significantly change chromosome compaction



Conclusions and Outlook

- Compartmentalization increased as result of stronger lamina-chromosome interaction
- Because genomic compartments are essential for gene regulation, our work uncovers a possible role of the nuclear lamina in regulating gene expression
- Quantitative analysis of chromosome compartmentalization could provide meaningful results
- Simulating reinstated lamina-chromosome interactions for progeria cells is an interesting future possibility

References

1. Contessoto, et al. (2019) The Nucleome Data Bank: Web Based Resources to Simulate and Analyze the Three-Dimensional Genome. bioRxiv.
2. Di Pierro, et al. (2016) Transferable model for chromosome architecture. PNAS 113 (43) 12168-12173.

Acknowledgements

- FIS funded by NSF-PHY-1427654
- NOTS funded by NSF-CNS-1338099
- We thank Dr. Vinicius Contessoto for stimulating conversations