Integrating Cohesin Loop Extrusion-Mediated Transcription into a Chromosome Model

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Introduction: Chromatin—the combination of protein and DNA that makes up the chromosome—exhibits a highly dynamic and complex structure that plays a central role in nearly all aspects of eukaryotic biology. Chromosomes have been shown to undergo dynamic reorganization in response to external stimuli, which can cause genome-wide changes in expression[1]. Epigenetic modifications like acetylation and methylation are thought to control these changes in packing, which influences which genes are suppressed and which are expressed by modulating their epigenetic state, such as heterochromatin or euchromatin, and in turn their accessibility to transcriptional machinery. However, active gene transcription has also been shown to affect the packing structure of DNA and reduce heterochromatic domain size[2]. Physical modeling of chromatin with molecular dynamics engines has shown significant promise in understanding chromatin structure[3], and we are interested in expanding these models to be able to predict how DNA structure changes in response to epigenetic and transcriptional dynamics. Here, we implement an implicit model for cohesin loop extrusion-mediated transcription into our model of the chromosome to recapitulate the effects of transcription on epigenetic dynamics and packing structure of chromatin.

Materials and Methods: In this work, we model the chromosome as a copolymer of two different epigenetic states, heterochromatin and euchromatin. These simulations are conducted in the Large Atomic/Molecular Massively Parallel Simulator (LAMMPS), an open-source molecular dynamics software package developed by Sandia National Laboratories[4]. Cohesin loop extrusion-mediated transcription was modeled implicitly by a probability described by equation 1, where P_{ext} is the probability of loop extrusion, h is the number of heterochromatin neighbors, Γ is the transcription rate, and h_{max} and Δh are parameters that can be optimized to fit experimental data.

$$P_{ext} = \Gamma\left(1 - \frac{\Delta h^{\left(\frac{h_{max}}{2} - h\right)}}{1+\Delta h^{\left(\frac{h_{max}}{2} - h\right)}}\right), \qquad (equation\ 1)$$

The model of the chromosome also incorporates the physics of chromatin-chromatin interactions, epigenetic diffusion, and epigenetic regulation, whose governing equations and models have been validated in previous work[1].

Results and Discussion: Culturing cells with Actinomycin D (ActD) results in transcriptional inhibition. Super resolution microscopy (STORM) images of transcriptionally inhibited cells demonstrate increased heterochromatic domain size compared to control cells. Qualitative comparison of STORM images with our model shows agreement where transcriptional inhibition reproduces this phenomenon (Figure 1a). Moreover, increasing transcription rate produces a relatively linear decrease in heterochromatic domain size (Figure 1b), which mirrors the behavior of our phase-field model of the chromosome (unpublished). We conclude that our model for cohesin loop extrusion could explain the link between increased transcription rate and decreased heterochromatic domain size observed in cells.

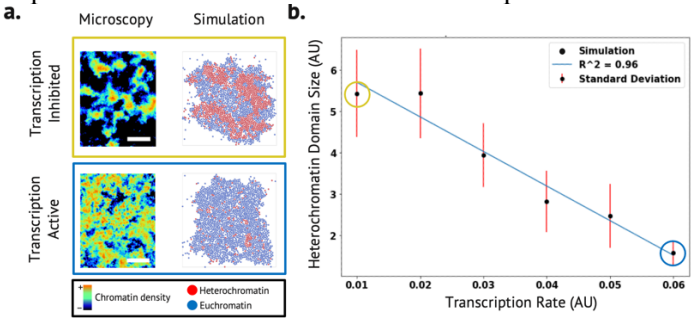

Figure 1. Our model for cohesion loop extrusion-mediated transcription recapitulates the observed phenomenon in cells in our model of the chromosome. (a) Cell images and model images from transcriptionally active and inhibited states. STORM imaging was used to produce cell images, where red represents the densest chromatin. Scale bar 1 μm. (b) Heterochromatic domain size from our simulation plotted against transcription rate, producing a linear trend.

Conclusion: Further utility from this model could arise from implementing our model for transcription into a full chromosome copolymer model, where initial epigenetic states are derived from ChIP-Seq data. Ultimately, these refinements would advance our model towards the ability to explain and predict epigenetics-controlled changes in gene expression, which could enhance our understanding of key biological processes such as embryonic development and metastasis of cancer.

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References: (1) Heo, S.J. *Nat. Biomed. Eng.*, 2022, 910. (2) Neguembor, M.V. *Mol. Cell*, (2021), 81(15), 3065-3081. (3) Shi G., *Nat. Commun.*, 2018, 9, 3161. (4) Thompson, A.P., *Comput. Phys. Commun.*, 2022, 271.