Boise State University
ScholarWorks

2021 Undergraduate Research Showcase | Undergraduate Research and Scholarship Showcases

4-23-2021

Modeling the Living Genome

Ethan Davis
Boise State University

Julianna Goelzer
Boise State University

Matthew Ferguson
Boise State University

Modeling the Living Genome

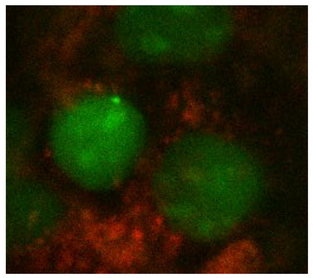
Abstract

Recent high-resolution contact mapping has made it possible to see the 3D organization of the nucleus on an unprecedented length scale (at 1kb resolution)[1,2]. Since the average human gene is 12kb, this information is finally below a critical limit, and we are now in a position to understand the principles underlying epigenetic programming. One of the challenges of understanding the regulation of gene expression is developing tools and protocols that capture the complex spatiotemporal dynamics of these functions without compromising sampling rates, timescales, visibility of the sample, and all within a single living cell. The goal of our project is to develop a protocol for using 3D orbital tracking microscopy and in vivo RNA labeling to provide measurements of the cooperative binding of transcription factors and reprogramming of the human genome at a single active transcription site within a living cell. Using coarse grained modeling, GPU acceleration and Hi-C data, we intend to develop a dynamic model of the human genome to test an enhancer promoter looping model for transcriptional bursting and epigenetic regulation.

This student presentation is available at ScholarWorks: https://scholarworks.boisestate.edu/under_showcase_2021/83

Modeling the Living Genome

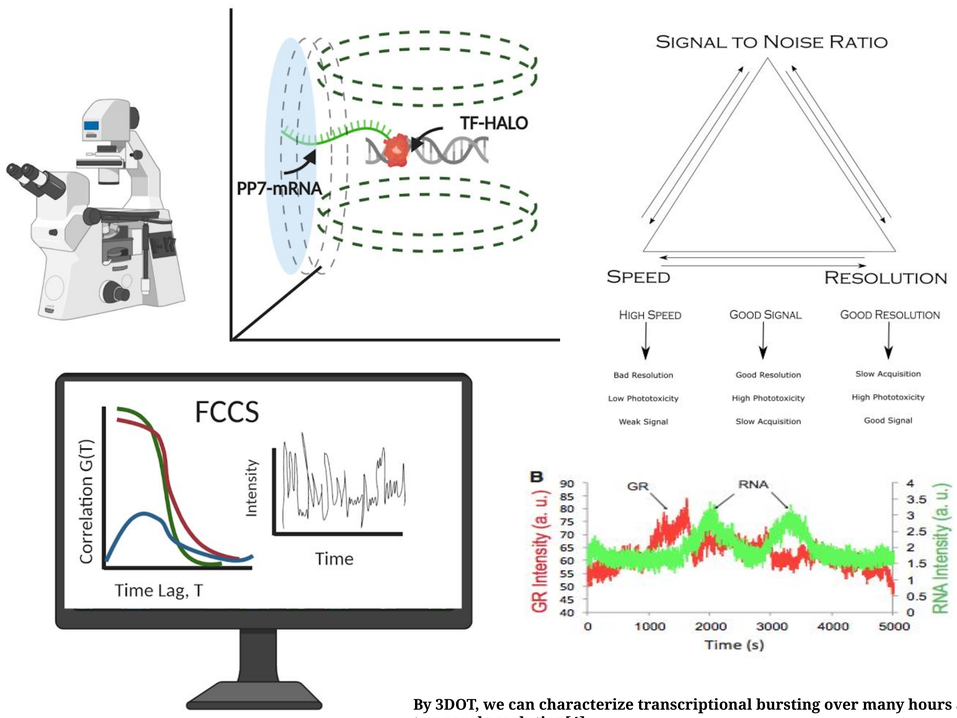
Ethan Davis[1], Julianna Goelzer[2], Matthew Ferguson[1,2]
1 Department of Physics, Boise State University, ID, 83725
2 Biomolecular Sciences, Boise State University, ID, 83725
ethandavis@u.boisestate.edu, mattferguson@boisetate.edu



Abstract

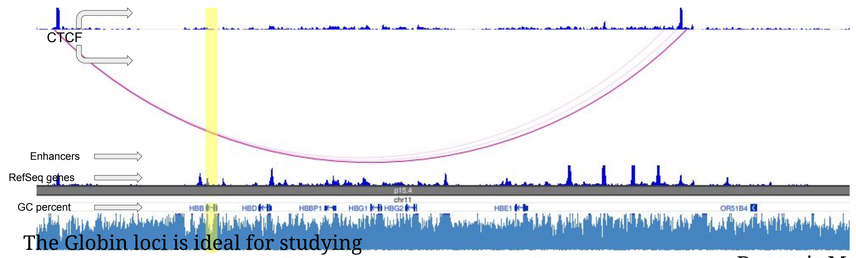
Recent high-resolution contact mapping has made it possible to see the 3D organization of the nucleus on an unprecedented length scale (at 1kb resolution)[1,2]. Since the average human gene is 12kb, this information is finally below a critical limit, and we are now in a position to understand the principles underlying epigenetic programming. One of the challenges of understanding the regulation of gene expression is developing tools and protocols that capture the complex spatiotemporal dynamics of these functions without compromising sampling rates, timescales, visibility of the sample, and all within a single living cell. The goal of our project is to develop a protocol for using 3D orbital tracking microscopy and in vivo RNA labeling to provide measurements of the cooperative binding of transcription factors and reprogramming of the human genome at a single active transcription site within a living cell. Using coarse grained modeling, GPU acceleration and Hi-C data, we intend to develop a dynamic model of the human genome to test an enhancer promoter looping model for transcriptional bursting and epigenetic regulation.

3DOT-FCCS

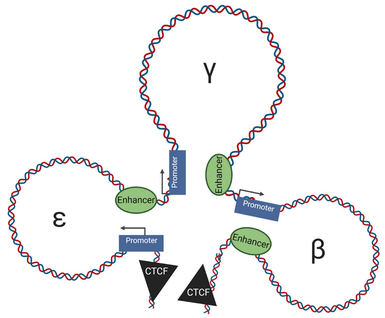


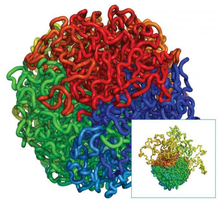
By 3DOT, we can characterize transcriptional bursting over many hours at high temporal resolution[4].

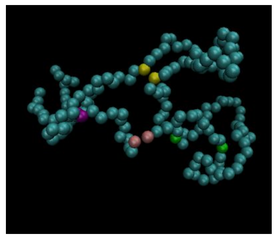
Chip-Seq and Chia-PET



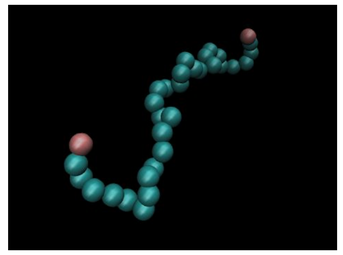
The Globin loci is ideal for studying enhancer promoter looping. The above Chip-Seq data was used to inform our models.

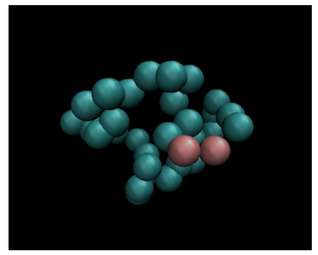






Modeling Loop Size

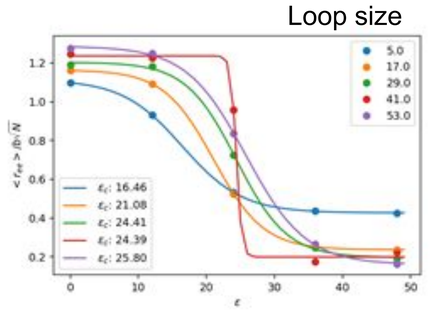


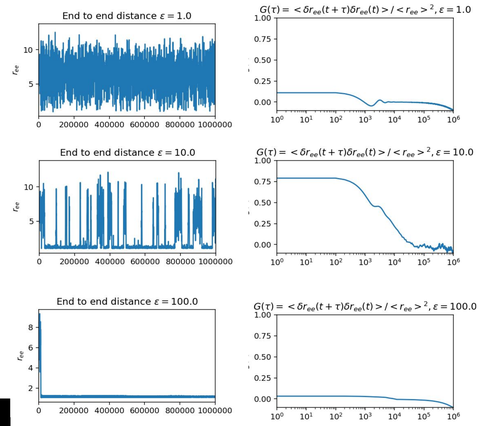


Dynamic Model

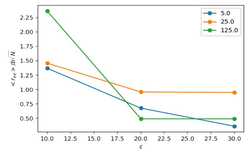
Enhancer-promoter looping characterizes the kinetics of chromatin and displays a correlation to gene activation

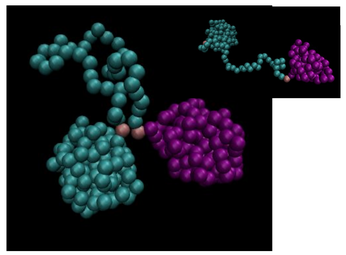
This model can further explore on regulation of alternative splicing, to identify possible processes in wider application such as cancer

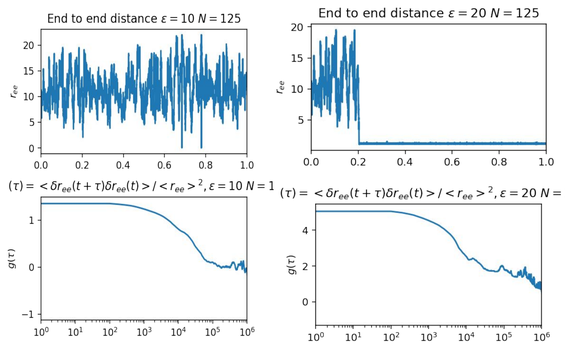




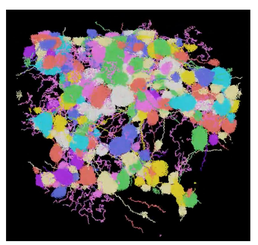
Modeling TADs







A dynamic high resolution polymer model of the Human Genome run in HOOMD-blue on an NVIDIA P100 GPU



Future Work

Through further understanding the genome and the rules that govern it we can begin to address diseases such as sickle cell anemia and cancer.

References

[1] Rao, S.S.P. et al., 2014. A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. Cell, 159(7), pp.1665–1680.
[2] Sanborn, A.L. et al., 2015. Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes. Proceedings of the National Academy of Sciences of the United States of America, 112(47), pp.E6456–65.
[3] Coulon, Ferguson et al. 2014. Kinetic competition during the transcription cycle results in stochastic RNA processing. eLife 2014;3:e03939 DOI: 10.7554/eLife.03939
[4] Donovan BT, Huynh A, Ball DB, Patel H, Poirier MG, Larson DR, Ferguson ML@, Lenstra TL@, Live-cell imaging reveals the interplay between transcription factors, nucleosomes, and bursting. EMBO Journal. 2019.
[5] Stavreva DA, Garcia DA, Fettweis G, Gudla PR, Zaki G, Soni V, McGowanA, Williams G, Huynh A, Palangat M, Schiltz RL, Johnson TA, Ferguson ML, Pegoraro G, Larson DR, Upadhyaya A, Hager GL, Transcriptional bursting and co-bursting regulation by steroid hormone release pattern and transcription factor mobility. Molecular Cell. 2019.
[6] Aiden, E. Untangling the Genome, Scientific American, March, 2019.
[7] Jameson, D. M. Introduction fo Fluorescence. CRC Press, 2014.

Acknowledgements

Our research is funded by Research Corporation for Science Advancement and the Gordon and Betty Moore Foundation through Grant GBMF5263.10 and by National Institute of General Medical Sciences through Grant 1R15GM123446.