Anomalous Diffusion, Spatial Coherence, and Viscoelasticity from the Epigenetic Energy Landscape of Human Chromosomes

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***Short Abstract* — Chromosome architecture originates from non-equilibrium, active processes that continuously rearrange chromatin over the lifetime of cells; optical experiments report sub-diffusive dynamics and spatially coherent motion. Using energy landscape theory, we built a model for chromosomes that takes into account biochemical interactions mediated by proteins and regulated by epigenetic markers. We study the dynamics of interphase human chromosomes as generated by this quasi-equilibrium energy landscape. Using numerical simulations of two interacting human chromosomes, we show that the epigenetic energy landscape naturally explains the physical mechanism leading to spatial coherence, viscoelasticity and sub-diffusive behavior in interphase chromosomes as observed in numerous experiments.**

Abstract

Chromatin consists of DNA and hundreds of associated proteins. In eukaryotic nuclei, the interactions between proteins and DNA generate organized structures, which are characteristic of both cell state and type [1,2]. This organization is a key element of transcriptional regulation, and its disruption often leads to disease.

Recently, we introduced a physical model for chromatin folding [3] that is able to predict the structural ensembles of human chromosomes using as input the sequence of epigenetic markings obtained by chromatin immunoprecipitation-sequencing. We exploited the idea that chromosomes encode a 1D sequence of chromatin structural types. Interactions between these chromatin types determine the 3D structural ensemble of chromosomes through a process similar to phase separation. Chromatin types are distinct from DNA sequence and change during cell differentiation, thus constituting a link between epigenetics, chromosomal organization, and cell development.

We demonstrated that it is possible to predict the sequence of chromatin structural types and, consequently, how a genome will fold, based on the epigenetic marks that decorate chromatin [4]. The structural ensembles resulting from this theory of genome folding were extensively validated by the results of DNA-DNA ligation assays and fluorescence microscopy.

Here, we revisit the results of several experimental observations regarding chromatin dynamics in light of the new theory for genome organization outlined above. By using molecular simulation, we analyze the implications of the model without any tuning and we show that it naturally explains and reproduces anomalous diffusion, viscoelasticity, and spatially coherent dynamics as observed in chromosomes. All of these phenomena were previously analyzed only through phenomenological models. We show that the very same interactions that account for genome organization in interphase also naturally explain several non-trivial features of genome dynamics, namely, spatial coherence, viscoelasticity and sub-diffusivity.

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References

[1] W. A. Bickmore, The Spatial Organization of the Human Genome. *Annual Review of Genomics and Human Genetics, Vol 14* **14**, 67-84 (2013).
[2] T. Cremer, C. Cremer, Chromosome territories, nuclear architecture and gene regulation in mammalian cells. *Nature Reviews Genetics* **2**, 292-301 (2001).
[3] M. Di Pierro, B. Zhang, E. L. Aiden, P. G. Wolynes, J. N. Onuchic, Transferable model for chromosome architecture. *P Natl Acad Sci USA* **113**, 12168-12173 (2016).
[4] M. Di Pierro, R. R. Cheng, E. L. Aiden, P. G. Wolynes, J. N. Onuchic, De novo prediction of human chromosome structures: Epigenetic marking patterns encode genome architecture. *Proceedings of the National Academy of Sciences*, 201714980 (2017)