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Polymer physics reveals a combinatorial code linking 3D chromatin architecture to 1D chromatin states

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Recent technologies, such as Hi-C [1], have revealed that the mammalian genome has a complex, far from random three-dimensional (3D) organization, intimately linked to vital biological processes. To rationalize the complexity of experimental data, polymer models from Statistical Physics and a variety of computational methods have been developed [2,3]. However, they typically cannot explain data at the scale of the full genome. In this talk, I will present the first genome-wide extension of PRISMR [4], our approach that combines Machine Learning and Polymer Physics to infer the different types of DNA binding sites determining genome 3D structure. The genome-wide study allowed us to develop a code linking chromosome 3D structure to chromatin states through our inferred binding domains. Interestingly, they have an overlapping, combinatorial organization along chromosomes necessary to accurately explain contact specificity. The binding domains and the associated architectural code were tested by making predictions on the changes of the 3D structure caused by a set of genomic mutations at the Sox9 locus linked to human diseases and our predictions were confirmed by independent data from cells carrying such mutations. Finally, in a reverse approach based on the discovered code, we predicted de novo the 3D structure of an independent set of chromosomes from only their 1D chromatin marks, thus validating the inferred epigenetic-architecture code [4]. Overall, our results shed light on how 3D information is encrypted in 1D chromatin via the specific combinatorial arrangement of binding sites.

References

[1] R. Kempfer, A. Pombo, Nature reviews Genetics 21 (2020) [2] Barbieri et al. Proc. Natl. Acad. Sci. USA 109 (2012) [3] Bianco et al. Nat. Genet. 50 (2018) [4] Esposito et al. Cell Reports 38 (2022)

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