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Unraveling the principles regulating chromosome spatial organization during differentiation

Chromosomal structural organization contributes to fundamental processes in the cell nucleus, including DNA transcription, replication, and repair. Experimental and theoretical works unveiled that chromosome organization consists of a complex aggregate of layers: entire chromosomes occupy distinct regions of the nucleus, called territories; below, at the tens of Mega-bases (Mb) scale, active and repressed regions form (A/B) compartments; and at the intermediate Mb scale, local domains (TADs) and loops may bring in contacts gene promoters with enhancers. However, the forces regulating this organization and its interplay with transcription activity are still elusive. Here, I present a project where we study these organizing principles at the *Zfp608* locus in mouse embryonic stem cells (ESC), where *Zfp608* is transcriptionally inactive, and neural progenitor cells (NPC), where the gene is active. By applying biophysical structural 3D modeling, we focus on epigenomic-driven interactions between chromatin of the same type (e.g., active chromatin attracting other regions with the same chromatin marks), loop-extrusion dynamics, and the effect of promoter-enhancer interactions. Furthermore, we perform extensive quantitative analysis and comparison with Capture Hi-C experimental data to drive model parameterization. This project shows that biophysical models can help explain how experimentally observed structures are formed and unravel potential factors and molecular mechanisms regulating chromosome organization in different cell types.

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