Abstract

Physics-Based Modeling of Chromatin Organization and Epigenetic Stability

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Spatial organization of chromatin by epigenetic factors contributes to physical gene regulation, enabling diverse cell functions to be encoded by a shared genetic code. Epigenetic dysregulation can lead to aberrations in chromatin architecture, contributing to diseases like neurological disorders and cancers. Despite the known importance of chromatin organization on human health, the physical mechanisms governing chromatin folding remain underspecified. Using physics-based Monte Carlo simulation, we systematically build up a model of chromatin structure to evaluate how conditions in the nuclear environment and crosstalk between epigenetic marks affect genomic organization. By coupling structural simulation with a kinetic model of loop-based epigenetic mark conferral, we simulate the heritability of epigenetic marks between cell generations. Our work demonstrates the importance of reader protein concentration and binding site availability in dictating chromatin contact patterns. We reveal acquired interactions between reader proteins that emerge at high concentrations. We characterize a size dependence of heterochromatic and euchromatic domains that dictates epigenetic stability. By isolating the effects of physical factors on chromatin folding and stability, our work offers early guidance for future epigenetic therapeutics.