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Modeling the coupling between epigenome regulation and 3D chromatin organization

The relation between the 3D chromosome organization and the epigenome (DNA methylation, histone modifications, etc.) has been long established. Several studies have demonstrated that epigenomic-driven interactions (mediated by architectural proteins like HP1 or PRC1) between loci sharing the same chromatin content are key drivers of the 4D Genome leading to (micro)phase separation and compartmentalization of active and repressive regions. However, on contrary, how genome folding impacts epigenome is still unclear. To explore the coupling between epigenome regulation and 3D chromatin organization, we introduce the "Living Painter"model incorporating 3D polymer dynamics and diffusing histone modifying enzymes (HMEs) along with architectural proteins (APs). The model elucidates how the concentration and kinetics of HMEs and APs impact the spreading and maintenance of epigenetic marks and at the same time as organize the 3D genome. We show that a limited number of enzymes does facilitate the formation of confined, stable chromatin state domains. Interestingly, favoring nucleation of APs at specific genomic recruitment sites (RSs) over their self-association creates multiple meta-stable nanodroplets localized around RSs, while favoring self-association of APs drives the system towards fully phase separated droplets englobing all RSs. These contrasting regimes provide mechanistic insights about how multiple nucleation sites can create local clustering of chromatin regulators.

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