Modeling epigenome folding: formation and dynamics of topologically-associated chromatin domains

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Résumé

Genomes of eukaryotes are partitioned into domains of functionally distinct chromatin states. These domains are stably inherited across many cell generations and can be remodelled in response to developmental and external cues, hence contributing to the robustness and plasticity of expression patterns and cell phenotypes. Remarkably, recent studies indicate that these one-dimensional epigenomic domains tend to fold into three-dimensional topologically-associated domains forming specialized nuclear chromatin compartments. However, the general mechanisms behind such compartmentalization including the contribution of epigenetic regulation remain unclear. Here, we address the question of the coupling between chromatin folding and epigenome. Using polymer physics, we analyze the properties of a block copolymer model that accounts for local epigenomic information. Considering copolymers build from the epigenomic landscape of Drosophila, we observe a very good agreement with the folding patterns observed in chromosome conformation capture experiments. Moreover, this model provides a physical basis for the existence of multistability in epigenome folding at sub-chromosomal scale. We show how experiments are fully consistent with multistable conformations where topologically-associated domains of the same epigenomic state interact dynamically with each other. Our approach provides a general framework to improve our understanding of chromatin folding during cell-cycle and differentiation and its relation to epigenetics.

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