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Higher-order chromatin structure: bridging physics and biology

Geoffrey Fudenberg[1] and Leonid A Mirny[1,2,3]

Advances in microscopy and genomic techniques have provided new insight into spatial chromatin organization inside of the nucleus. In particular, chromosome conformation capture data has highlighted the relevance of polymer physics for high-order chromatin organization. In this context, we review basic polymer states, discuss how an appropriate polymer model can be determined from experimental data, and examine the success and limitations of various polymer models of higher-order interphase chromatin organization. By taking into account topological constraints acting on the chromatin fiber, recently developed polymer models of interphase chromatin can reproduce the observed scaling of distances between genomic loci, chromosomal territories, and probabilities of contacts between loci measured by chromosome conformation capture methods. Polymer models provide a framework for the interpretation of experimental data as ensembles of conformations rather than collections of loops, and will be crucial for untangling functional implications of chromosomal organization.

Addresses
[1] Graduate Program in Biophysics, Harvard University, Cambridge, MA, United States
[2] Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, United States
[3] Department of Physics, Massachusetts Institute of Technology, Cambridge, MA, United States

Corresponding author: Mirny, Leonid (leonid@mit.edu)

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Introduction

The organization of a long DNA molecule or a chromatin fiber inside a cell is rich with opportunities for the application of concepts from polymer physics. Recently developed experimental techniques and powerful computer simulations now make it possible to test whether various hypotheses about higher-order chromatin architecture are consistent with experiments [1••,2,3,4•]. Polymer models have the promise to unite diverse experimental observations into a coherent conceptual and physical framework. Moreover, insights from polymer physics call for a shift from the existing paradigm of regularly looped models of chromatin organization to a view where higher-order chromatin organization is considered in terms of probabilistic models, or ensembles, of polymer conformations. A conformational ensemble probabilistically describes contacts between genomic loci and distributions of spatial locations for individual loci. The view of chromatin in terms of ensembles highlights the importance of entropy for understanding nuclear organization (Figure 1). A similar physics-based approach revolutionized our understanding of protein folding [5].

The first level of eukaryotic chromatin organization, packing of DNA into an array of nucleosomes, is relatively well understood [6]. Building upon this consensus, recent studies extended our understanding of the nucleosomal array by considering the structural and functional implications of DNA-encoded sequence signals [7,8], active modifying and remodeling machinery [9], and the interplay between nucleosomes and gene expression [10,11].

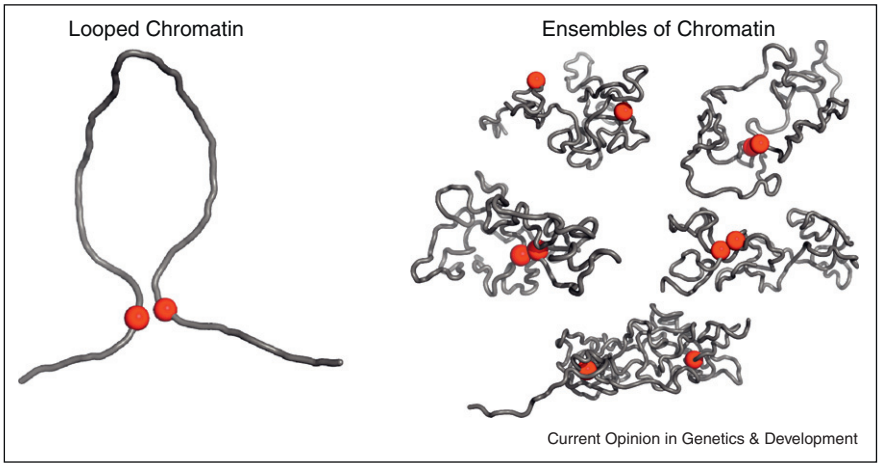
In the classical textbook view, nucleosomes are subsequently folded into a regular, 30 nm fiber [12]. However, recent experiments including cryo-electron microscopy, electron spectroscopy, and small-angle X-ray scattering have cast doubt on the pervasiveness of the 30-nm fiber during interphase and metaphase [13–15], and argue strongly against the genome-wide presence of any regular fiber beyond the 10 nm fiber formed by nucleosomal arrays in the majority of cell types.

Higher levels of chromatin organization have been traditionally thought of as various arrangements of loops formed by an underling fiber [12]. Here we argue that despite its visual appeal and simplicity, understanding high-order chromatin organization in terms of regularly folded loops falls short of explaining experimental observations. Locations of genomic loci in the nucleus and distances between genomic loci are highly variable [16,17], and individual genomic loci come in contact with a diverse set of genomic loci [1,18]. In light of the variability of high-order chromatin organization, ensembles of polymer conformations provide a natural framework for understanding chromatin organization.

Polymer physics

In polymer physics, three conformational ensembles: the random coil (random walk, RW), the swollen coil (self-avoiding walk, SAW), and the equilibrium globular state (EG), are the foundation for understanding more complex polymer systems [19–21]. These three ensembles are equilibrium states for an individual homopolymer (i.e. a polymer with identical monomers) in a solvent. These

Figure 1

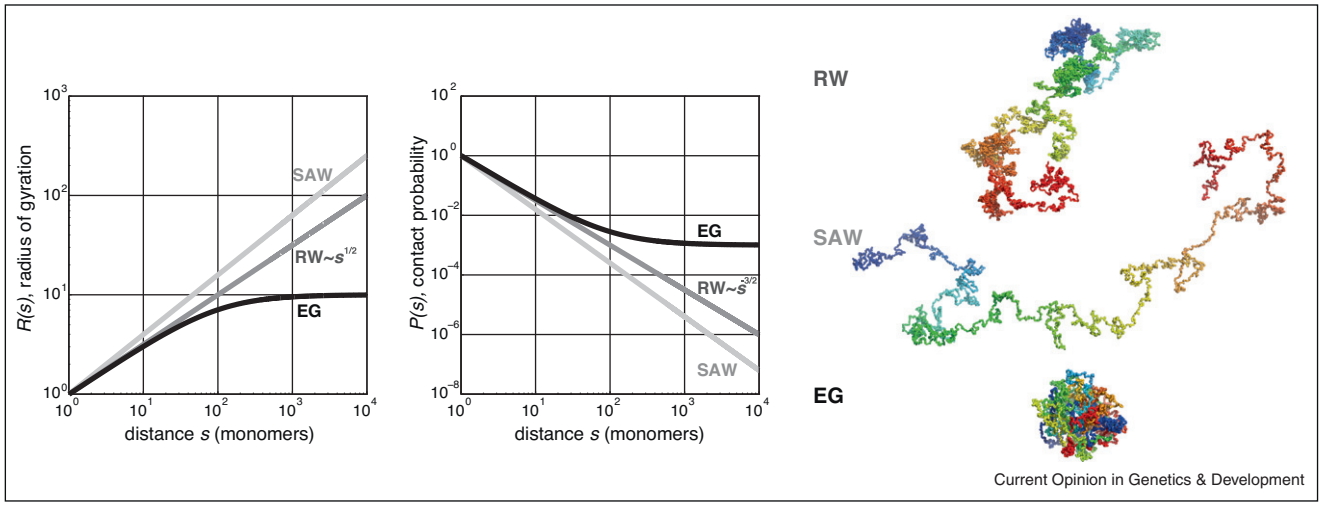


Looped versus ensemble view of chromatin organization. An ensemble view is important for capturing the experimentally observed variability in high-order chromatin organization. Looped chromatin and the conformations in the ensemble of chromatin both show the same small piece of a longer chromatin fiber; red spheres highlight two potentially contacting loci on the chromatin fiber.

ensembles are characterized by various relationships between their observable measures, or scalings, and include: the characteristic size of the whole polymer $R(N)$ (i.e. its root mean squared end-to-end distance $\langle R_{ee}^2 \rangle^{1/2}$, or a mean radius of gyration) as a function of its length N, the mean spatial distance between loci (subchain size) $R(s)$ as a function of distance s between these loci along the polymer (genomic distance), and the contact probability between loci $P(s)$ (Figure 2).

Random (Gaussian) coil: If steric repulsions between monomers of the polymer are negligible, balanced by interactions with the solvent, or screened by other polymers in a melt, and if topological constraints are disregarded, then a polymer adopts an ensemble of conformations equivalent to those of an unconfined polymer without steric interactions. A polymer with these properties is called an ideal chain, and its unconstrained conformations are well described by an ensemble of three-dimensional random walks. In the random coil state, a polymer of length N has a characteristic size of $R(N) \sim N^{1/2}$. Since any part of a random walk is also a random walk, any sufficiently long subchain of a polymer in the random coil state has a size $R(s) \sim s^{1/2}$, where s is the length of the subchain.

Figure 2



Basic polymer states. **(a)** Scaling for spatial distance $R(s)$ between two loci as a function of genomic distance s between them. **(b)** Scaling for the contact probability $P(s)$. **(c)** Sample conformations for each of the states. Conformations illustrate the random coil (random walk, RW) state, the extended swollen coil state (self-avoiding random walk, SAW) and the compact equilibrium globular state (EG). Scalings are exact for RW, and illustrated qualitatively for the SAW and EG.