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Current Opinion in Structural Biology

The chromatin fiber: multiscale problems and approaches

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The structure of chromatin, affected by many factors from DNA linker lengths to posttranslational modifications, is crucial to the regulation of eukaryotic cells. Combined experimental and computational methods have led to new insights into its structural and dynamical features, from interactions due to the flexible core histone tails or linker histones to the physical mechanism driving the formation of chromosomal domains. Here we present a perspective of recent advances in chromatin modeling techniques at the atomic, mesoscopic, and chromosomal scales with a view toward developing multiscale computational strategies to integrate such findings. Innovative modeling methods that connect molecular to chromosomal scales are crucial for interpreting experiments and eventually deciphering the complex dynamic organization and function of chromatin in the cell.

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Current Opinion in Structural Biology 2015, **31**:124-139

This review comes from a themed issue on **Theory and simulation**

Edited by **Claire Lesieur** and **Klaus Schulten**

For a complete overview see the Issue and the Editorial

Available online 5th June 2015

http://dx.doi.org/10.1016/j.sbi.2015.04.002

Introduction

Scientists by nature seek order and clarity. In the field of chromatin — the nucleoprotein complex that stores the genetic material in eukaryotes — such order has been difficult to describe. For a long time, a hierarchical helical model of chromatin organization has been envisioned, from the base-pair level of the DNA double helix to the megabase-pair level of states associated with chromosomes and nuclear DNA; the latter higher-order states are also known to alter flexibly throughout the cell cycle — from looser states at interphase (between cell division) to recognizable chromosomes at mitosis or meiosis (metaphase stage) in heterochromatin (see Figure 1).

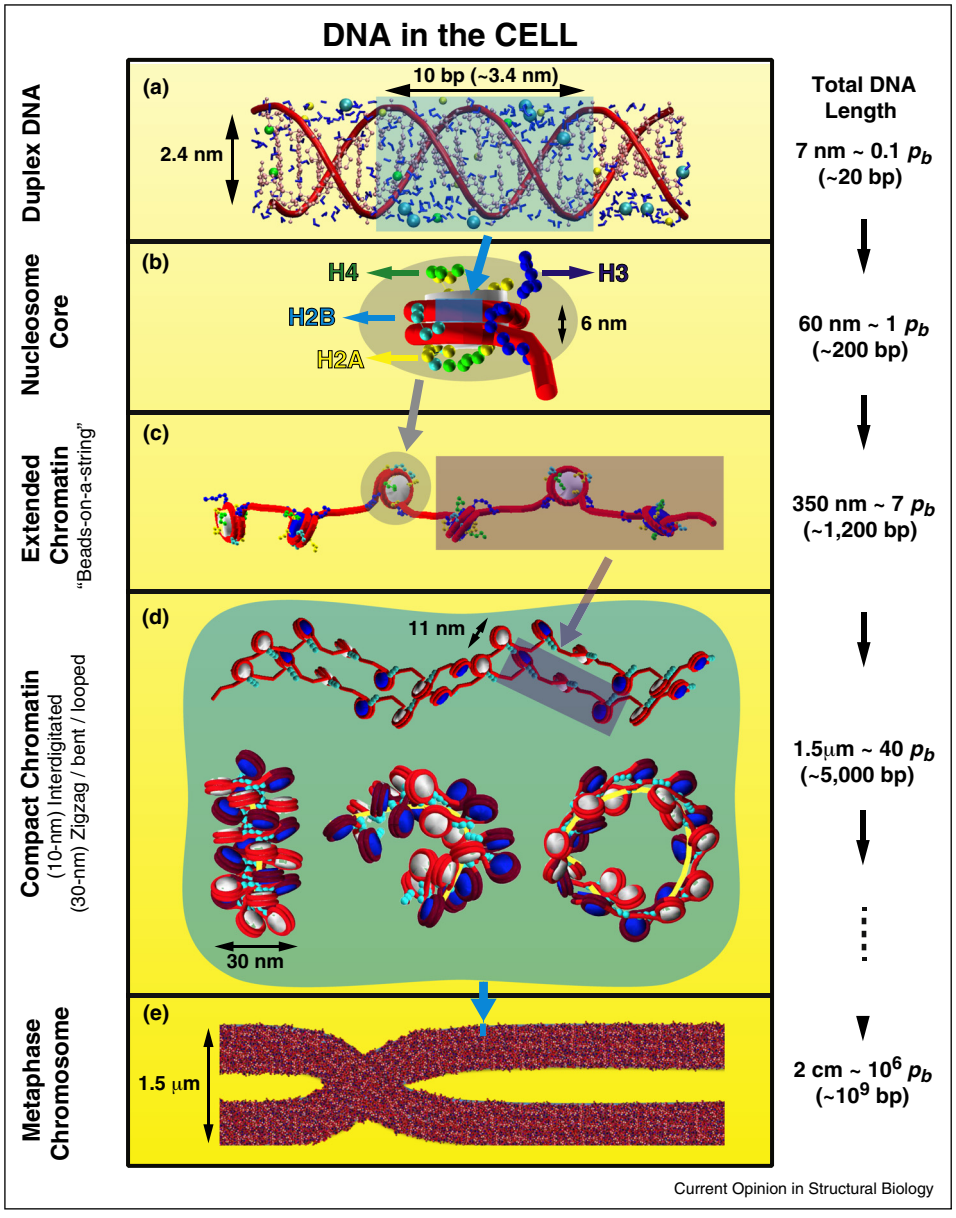
The compression involved in this DNA folding problem is enormous. In humans, for instance, the 2 m of stretched DNA corresponding to 23 pairs of chromosomes must fit into a cell nucleus of ~6 μm diameter. This translates into a compression ratio of up to 10 000, or three and four orders of magnitude for mammalian interphase and metaphase chromosomes, respectively.

The first level of packing consists of chains of DNA wrapped around nucleosome protein-octamer cores in ~1.7 left-handed superhelical turns, with linker DNA connecting successive nucleosomes (see Figure 1). Each of the nucleosome core histone proteins (two copies each of H2A, H2B, H3, and H4) has protruding N-terminal tails that are important targets for charge modulation and hence DNA regulation (see below). For a long time, a compact form of this polynucleosome polymer called the '30-nm fiber' lay at the heart of this initial helical coiling of the chromatin fiber. Yet a 30-nm compression represents only one order of magnitude condensation of the genetic material (Figure 1). The hierarchical helical folding model imagines successive coiling above such coiling to produce much thicker fibers in interphase and metaphase to accomplish the required condensation in eukaryotic cells (Figure 1).

Of course, such condensation is only one half of the mystery surrounding chromatin organization. The highly compact, transcriptionally silent states of chromatin must unravel through the influence and direct interactions with a host of accessory proteins and posttranslational modifications of the histone tails of the nucleosome-core proteins to allow DNA access to the cellular machinery for template-directed processes. Such covalent modifications — acetylation and methylation of lysine residues and phosphorylation of serines — destabilize the charge-screening residues of the DNA polyelectrolyte as well as attract specific regulatory proteins. These structural aspects of chromatin occupy another active branch of biological research surrounding the 'histone-code' [1–3].

Over the past decade, a plethora of experimental studies complemented by computational modeling has managed to puncture several holes in this idealized picture of chromatin's hierarchical helical folding. First, we now realize how the local structure of chromatin is variable

Figure 1



DNA's many levels of folding [99]. Various colored backgrounds/masks are used to illustrate the extent of DNA compaction from one stage to the next. **(a)** DNA is relatively straight for length scales smaller than its persistence length $p_b \sim 150$ bp. **(b)** In eukaryotic cells, DNA wraps around a core of eight histone proteins to form the nucleosome, the fundamental unit in chromatin. **(c)** Linker DNAs connect consecutive nucleosomes to form chromatin fibers, whose structures are unknown. The stretched 10-nm fiber, 'beads-on-a-string', is observed at low salt concentrations or when applying stretching forces to unfold the polymer. **(d)** At physiological conditions with multivalent ions and binding proteins such as linker histones, chromatin fibers condense. This can lead to side-by-side inter-digitated 10-nm fibers [11] (top), canonical 30-nm zigzag fibers with solenoid bent linker DNA motifs (bottom left), bent and looped fibers (bottom right) [12••]. The precise spontaneous secondary structure of chromatin depends on the cell type and other internal and external factors, and is still under debate [6,49••]. **(e)** Chromosomes are made up of dense chromatin fibers, shown here in the metaphase stage. Nuclear arrangements of chromatin in interphase stages are thought to be less ordered and more diverse (see polymer model in Figure 4). The blue strip of size ~80 × 120 nm on the metaphase chromosome of size ~1.5 × 10 μm helps illustrate the enormous compaction of DNA in the cell.

and pliant, depending critically on many factors, including the DNA linker length connecting successive nucleosomes, linker histone concentration, and the ionic environment [4], not to speak of sequence at the finer levels. Thus, for example, rather than speaking about a 'zigzag' versus 'solenoid' topologies, a heteromorphic structure — a compact state that blends features of both straight and bent DNA linkers [5•] — is more appropriate.