Use of Nanomechanical Data to Validate a Supramolecular Multilayer Model That Explains the Dimensions, Topology, and Physical Properties of Condensed Metaphase Chromosomes

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Abstract

In the cell nucleus, genomic DNA molecules are associated with histone proteins and form long chromatin filaments containing many nucleosomes. The three-dimensional organization of these giant DNA molecules is undoubtedly the most challenging topological problem of structural biology. Previous TEM and AFM studies from our laboratory showed that, during cell division, chromatin filaments are folded into multilayer planar structures [1,2], in which DNA forms a two-dimensional network with a good flexibility and mechanical strength [3]. This discovery led to the thin-plate model in which we proposed that condensed chromosomes are formed by many stacked layers of chromatin oriented perpendicular to the chromosome axis [4]. More recently we found that multilayered plates can be self-assembled from chromatin fragments obtained by micrococcal nuclease digestion of metaphase chromosomes [5]. This finding, together with nanotechnology results showing that self-assembly of different structures of biological origin can produce complex micrometer-scale materials [6-8], suggested that chromosomes could be self-organizing structures. This communication shows that if chromosomes are considered as typical supramolecular assemblies, using the nanomechanical data obtained in other laboratories [9,10] and basic energetic considerations, it is possible to explain the geometry and physical properties of condensed chromosomes.

Metaphase chromosomes of different animal and plant species show great differences in size, ranging from 2 to 27 μm in length, and from 0.3 to 1.3 μm in diameter. The observed chromosome sizes are dependent on the amount of DNA that they contain (from 35 to 7450 Mb), but in all cases chromosomes are elongated cylinders that have relatively similar shape proportions: the average value of the length to diameter ratio (L/D) is 13. This study demonstrates that it is possible to explain this morphology by considering that chromosomes are self-organizing supramolecular structures formed by stacked layers of planar chromatin having different nucleosome-nucleosome interaction energies in different regions [11] (see figure). The nucleosomes in the periphery of the chromosome are less stabilized by the attractive interactions with other nucleosomes and this generates a surface potential that destabilizes the structure. Chromosomes are smooth cylinders (scheme a) because this morphology has a lower surface energy than structures having irregular surfaces (scheme b). The symmetry breaking produced by the different values of the surface energies in the telomeres and in the lateral surface ($\varepsilon_T > \varepsilon_L$) explains the elongated structure of the chromosomes.

The results obtained by other authors in nanomechanical studies of chromatin [9] and chromosome [10] stretching have been used to test the proposed supramolecular structure [11]. It is demonstrated quantitatively that internucleosome interactions (ε_{nn}) between chromatin layers (scheme c) can justify the work required for elastic chromosome stretching. Chromosomes can be considered as hydrogels with a lamellar liquid crystal organization. These hydrogels have outstanding elastic properties because, in addition to the covalent bonds of the DNA backbone, they have attractive ionic interactions between nucleosomes that can be regenerated when the chromosome suffers a deformation. This self-healing capacity has been observed in nanotechnology studies of other hydrogels stabilized by ionic interactions [12]. In the cell, this may be useful for the maintenance of chromosome integrity during cell division.

Finally, since early studies indicated that chromosomes are helically coiled [13], it is possible that each chromosome is formed by a single helicoidal plate [2,11]; the successive turns of a helicoid (scheme d) are equivalent to the stacked layers considered in the original thin-plate model. The flat plates seen in our micrographs and a helicoidal plate are topologically equivalent. They can be converted into each other without changing their mean curvature; the plane and the helicoid are both minimal surfaces (their mean curvature is zero). A continuous helicoidal plate has good mechanical properties and allows a homogenous organization of chromatin that precludes the random entanglement of the genomic DNA molecules. Furthermore, this chromatin organization can explain the morphology of the chromosome bands used in cytogenetic analyses for the diagnosis of cancer and hereditary diseases.

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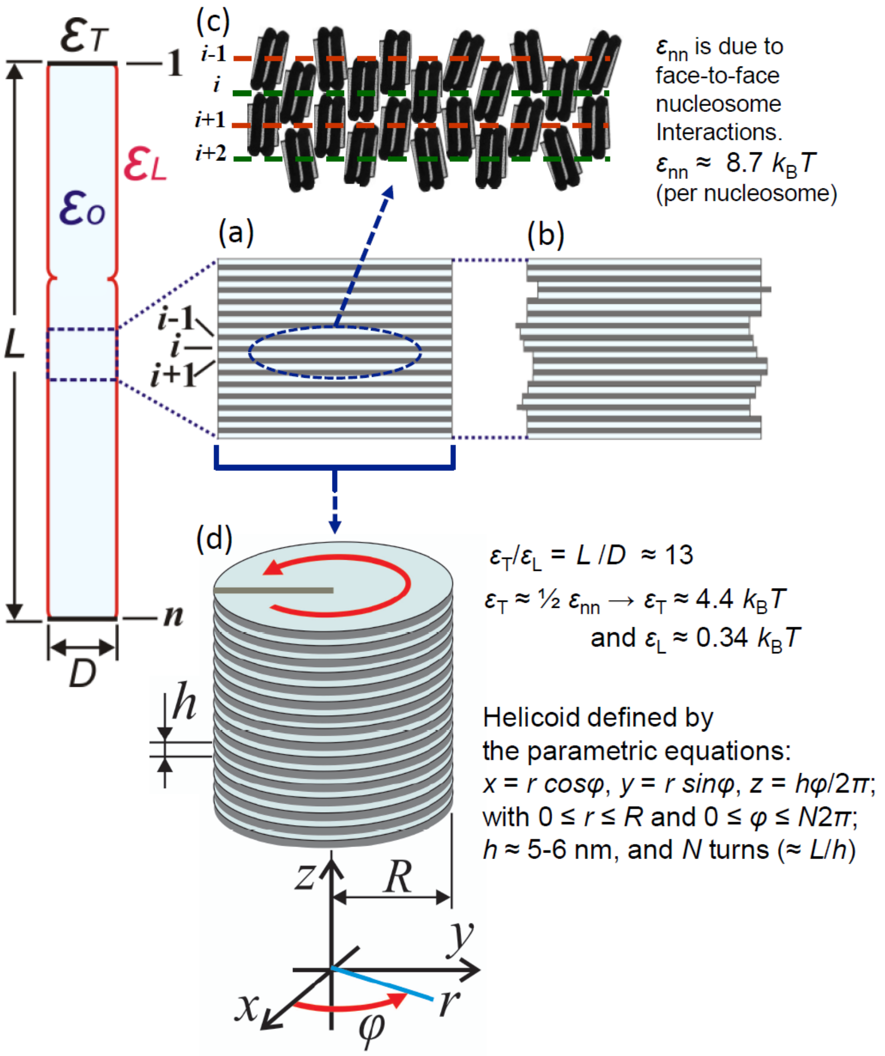
Figure



ε_{nn} is due to face-to-face nucleosome Interactions.
$\varepsilon_{nn} \approx$ 8.7 k_BT (per nucleosome)

$\varepsilon_T/\varepsilon_L = L/D \approx 13$

$\varepsilon_T \approx ½\, \varepsilon_{nn} \rightarrow \varepsilon_T \approx 4.4\ k_BT$
and $\varepsilon_L \approx 0.34\ k_BT$

Helicoid defined by
the parametric equations:
$x = r\cos\varphi$, $y = r\sin\varphi$, $z = h\varphi/2\pi$;
with $0 \leq r \leq R$ and $0 \leq \varphi \leq N2\pi$;
$h \approx$ 5-6 nm, and N turns ($\approx L/h$)