



STUDY OF PHYSICAL THEORY OF DNA COMPACTION

Dr. E.N. Ganesh

ABSTRACT

Chromatin fibers exist in dense and open states, presumably reflecting their corresponding genetic activity. Here we outline a physical theory that describes opening and closing of chromatin fiber as the result of the interplay between electrostatic attraction of nucleosomes and the elasticity of the DNA backbone of the fiber.

1. INTRODUCTION

The genomic DNA and the histone proteins compacting it into the chromatin complex comprise most of the contents of the nucleus. In every human cell, for instance, base pairs (bp) of DNA – corresponding to a total length of about 2 meters – must be packed to fit into a more or less spheroid nuclear volume about $10\ \mu\text{m}$ in diameter [1]. Not only has the DNA to be compacted, it also still needs to be accessible to enzymes acting on it, such as replication, transcription and repair machineries, and regulatory factors. Nature has solved this formidable task by compacting DNA in a hierarchical fashion as schematically depicted in Figure 1. Describing such a complex system with many different length-, time- and energyscales requires a multiscale approach to the problem. The purpose of this conference paper is to outline a first attempt for a self-consistent description of the first three length levels of this hierarchy (DNA, nucleosome, chromatin fiber).

of free linker DNA of 20-80 bp length. The histone octamer with the wrapped DNA, called nucleosome core particle (NCP), has been determined by X-ray

crystallography to atomic resolution [2]. At low ionic strengths, the polynucleosome chain forms a bead-on-a-string structure (“10 nm fiber”) that under physiological ionic conditions condenses into a fiber with approximately 30 nm diameter, cf. Fig. 1. Its detailed structure in this state is still under debate.

Two classes of models were proposed for the arrangement of the NCPs inside the 30 nm fiber: the solenoid models [3] and the zig-zag models [4]. In the solenoid model the NCPs are packed one by one along a solenoid helix in the same order as they follow along the chain. The linker DNA is bent in order to allow this geometric arrangement. In the zig-zag model straight linkers connect NCPs located on opposite sides of the fiber. The NCPs are also arranged in a helical order, but neighbors in space are second neighbors along the chain. We will argue that chromatin fibers feature geometries intermediate between those two.

2. CONDENSATION-DECONDENSATION TRANSITION

The fiber geometry of the zig-zag model can be quantitatively described in terms of two angles: the entry-exit angle $\pi - \theta$ of the linker DNAs at each NCP and the twist angle ϕ between successive NCPs on the chain [5]. For real chromatin fibers those angles vary along the fiber but certain values seem to be preferred. For constant angles we obtain regular fibers as shown in the diagram of states, Fig. 2, with the two axes representing the two angles. Example structures include planar structures for $\phi = 0$ (2-5) and $\phi = \pi$ (6,7), helical arrangements (9) and crossed linker fibers (10). The black area with the

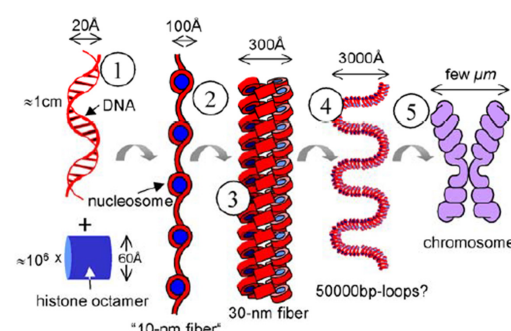


Figure 1: The hierarchical steps of DNA folding into chromatin:

(1) DNA (2) “10-nm fiber” and (3) 30-nm chromatin fiber. Details of the higher order structures are largely unknown. The first step in DNA compaction is the formation of the nucleosome, the elementary chromatin unit: 147 bp DNA wrapped in 1 and 3 4 turns around an octamer of histone proteins and a section

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intricate boundary corresponds to forbidden structures where NCPs would overlap.

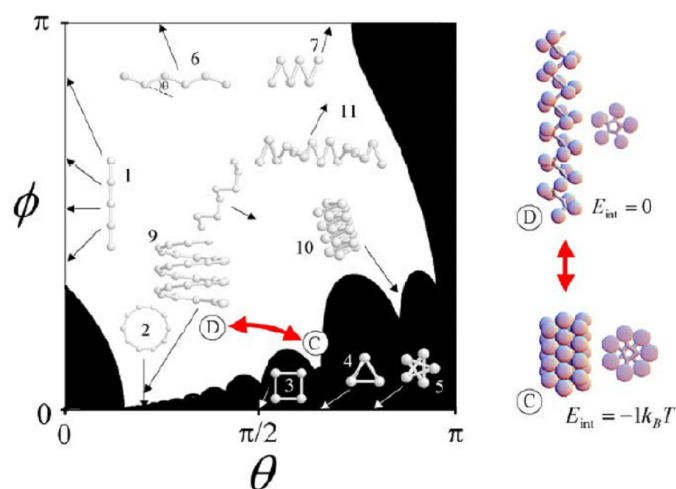


Figure 2: Left: Diagram of two-angle fiber geometries. Right: Fiber condensation/decondensation transition (see text for details).

The two-angle model is purely geometrical. No energies are involved. Clearly this is an oversimplification: NCPs are connected via bendable and twistable DNA linkers. For a given fiber geometry, i.e., a given set of angles (θ, ϕ) , one can analytically calculate all the linear elasticity constant of the DNA linker backbone [1]. A crossed-linker geometry, for instance, features lots of DNA sections crossing back and forth between the NCPs and one finds that such a fiber is extremely soft, e.g. around 1000 times more extensible than naked DNA (cf. the softness of a normal spring compared to that of the material it is made of). In addition NCPs show electrostatic attraction whose strength is under biochemical control via the acetylation (“uncharging”) and deacetylation (“charging”) of the histone tails, flexible extension of the eight histone proteins [6].

All this indicates that it is necessary to go beyond the simple purely geometric description of the two-angle model and to come to a model that self-consistently takes into account DNA bending, nucleosomal interaction and thermal effects. Here we sketch an approach that is still too naïve for the complexity of the problem but at least gives an idea of some basic issues. A more coherent approach will be presented in the MMM 2006 talk in Freiburg. For simplicity we here neglect thermal effects that could be brought in at a later stage by assuming a larger effective diameter of the NCPs. Now, even in the absence of thermal fluctuations, i.e. at zero temperature, the fiber geometries with straight linkers given in Fig. 2 do not correspond to ground states if the nucleosomes interact energetically with each other. Consider a fiber with a set of values (θ, ϕ) , where the NCPs are not in contact for unbent DNA linkers, corresponding to a structure away from the excluded volume boundary in Fig. 2. Without attraction between the NCPs this fiber is very soft, and would show large shape fluctuations at finite temperatures. Suppose that we switch now on an attraction between the

NCPs. Then, if this attraction is strong enough, the attraction overcomes the DNA linker stiffness and the fiber condenses into a dense fiber with the NCPs in contact, the fiber being located on the excluded volume boundary in Fig. 2. This fiber is very stiff since bending is costly due to the excluded volume of the NCPs. In addition this structure represents a “spring under tension”. Switching off the nucleosomal attraction will lead to a big jump back into the open and soft fiber. This is demonstrated on the rhs of Fig. 2 for a two-angle fiber with $(\theta, \phi) = (0.31\pi, 0.26\pi)$ and linker length l . The decondensed fiber (D) corresponds to the ground state for zero attraction. A condensed fiber (C) occurs for an attraction of 7.14nm $E_{int} = -1k_B T$ between NCPs in contact that is strong enough to induce a new ground state with densely packed NCPs at new effective angles $(\theta_{eff}, \phi_{eff}) = (0.67\pi, 0.24\pi)$. It is speculated that such dense fibers with deacetylated, i.e. sticky NCPs, correspond to silent regions without gene expression [7].

3. REFERENCES

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