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Physical properties of the chromatin fiber

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1 Introduction

In the eukaryotic genome DNA is organized in chromatin fibers. The primary chromatin function is to pack DNA to fit in the cell. Other important functions are to strengthen DNA to allow mitosis and meiosis and to control gene expression and DNA replication. Chromatin is made of nucleosomes which are fundamental repetitive chromatin units. Nucleosome is made of DNA (147 bp) wrapped around octamer histone core which consists of two copies of the histone proteins H2A, H2B, H3 and H4. There is also H1 (or H5) histone situated out of octamer core. Two nucleosomes are connected by 20 to 60 bp of linker DNA and they fold into chromatin fibers with a diameter of approximately 30 nm. The main unsolved issue in the chromatin structure is the one of the higher-order structured chromatin. Electron microscopy studies and spectroscopy measurements lend support to a one-start solenoidal model. However, the tetranucleosome crystal structure indicates a cross-linker two-start zig-zag model. In the solenoid model it is assumed that nucleosome forms helical structure with the linker DNA bent in between while the zig-zag model assumes the straight linkers that connect nucleosomes that are located on the opposite sites of the fibre. Different models are used to explain the structure of the $30-$ nm fiber. In this seminar I'll explain physical properties of the chromatin fiber obtained using different approaches: single-molecule force spectroscopy, computational modeling and theoretical approach but first I'll give brief introduction about physical properties of the single nucleosome complex.

2 Single nucleosome

The structure of the nucleosome core particle is well known from the X-ray crystallography, the crystal structure is resolved at 1.9 Åresolution. It is composed of the octamer core and linker histone H1 or H5. Core particle is composed of the 2 molecules of each histone protein: H2A, H2B, H3 and H4 and they all have similar central domain composed of three α -helices connected by two loops. The proteins are put in the octamer in such way that they follow a cylinder with $\sim$ 65 Ådiameter and $\sim$ 60 Åheight and they form a left-handed superhelix. 147 bp of DNA are wrapped around core in 1.7 turns with a $\sim$ 28 Åpitch. Schematic view of the nucleosome core particle is on (Figure 1). There are 14 sticking points on the octamer surface where wrapped DNA contacts the

octamer core. Adsorption energy per sticking point is measured to be of order $\sim 1.5 - 2\ k_B$T. It is the energy which is left after DNA has been bent around the octamer to make contact with the sticking point. A rough estimate of the deformation energy can be made if we take DNA as semiflexible chain with the persistence length l_P of $\sim$ 500 Å. Then the elastic energy needed to bind 127 bp of DNA (10 bp at each terminus are straight) around the octamer is given by

$$\frac{E_{elastic}}{k_BT} = \frac{l_P l}{2R_0^2} \tag{1}$$

where l is the bent part of the wrapped DNA and R_0 is the radius of curvature of the wrapped DNA which is $\sim$ 43 Å. By substituting all known qantities we get the bending energy per sticking point of order $E_{elastic}$ = 58 k_BT / 14 $\sim$ 4 k_BT. Together with the observation that the net gain per sticking point is 2 $\sim$ k_BT it is concluded that the pure adsorption energy is on average $\sim$ 6 k_BT per binding site [5].

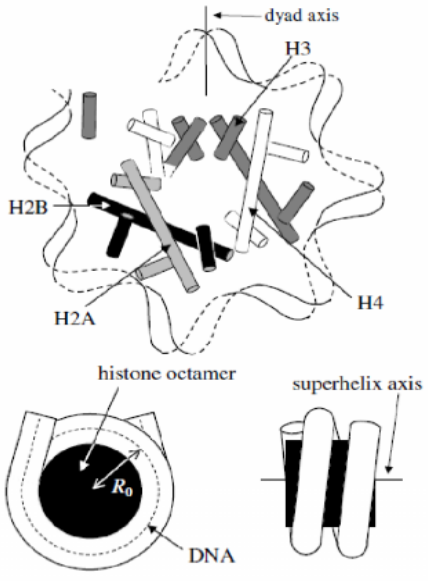

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Figure 1: Schematic view of the nucleosome core particle. Top: upper half of the 8 core histones and the nucleosomal DNA. Bottom: a simplified model where the octamer is replaced by the cylinder and DNA by the worm-like chain (WLC). Also indicated are dyad axis and DNA superhelix axis.

2.1 The net charge of the nucleosome complex

The histone octamer contains 220 basic side chains (arginine and lysine) of which 103 are part of nucleosome tails which extend out of the nucleosome structure and 31 of them are exposed to solvent. On the other hand, there are 147 bp of DNA wrapped around octamer and each bp has attributed two phosphate groups. In total, there are 294 negative charges of DNA versus 220 positive charges of the octamer which suggests that nucleosome complex is overcharged by the DNA. This fact was a starting point for developing simplified models containing charged spheres and oppositely charged chains. The experimental and theoretical studies have shown that the complexation of DNA is governed by electrostatics mechanism called counterion release [5].

In order to obtain the physical description of the counterion release we start with the simple description of the system. Lets consider the homogenously charged eZ sphere of radius R_0 around which is wrapped the rod of contour length L $\gg R_0$. They are both put in salt solution which is characterized by the Bjerrum lenght l_B and with concentrations c_S. The entropic contribution to electrostatic charging free energy of the isolated chain in the salt solution is given by

$$\frac{F_{chain(L)}}{k_B T} \sim \frac{l_P l}{2R_0^2} \tag{2}$$

and the corresponding electrostatic free energy of the spherical macro-ion is given by

$$\frac{F_{sphere}(Z)}{k_B T} \simeq \begin{cases} \dfrac{l_B Z^2}{2R_0} & \text{for } |Z| < Z_{max} \\ |Z|\tilde{\Omega}(Z) & \text{for } |Z| \gg Z_{max} \end{cases}$$

The total free energy of the sphere-chain complex can be devided in several parts: the free energy of the sphere with a wrapped part of lenght l of the chain and the free energy of the remaining chain of lenght L-l. The total free energy of the sphere-rod complex is then approximately given by

$$F_1(l) = F_{compl(l)} + F_{chain(L-l)} + F_{compl-chain}(l) + E_{elastic}(l) \tag{3}$$

The first two terms are already described, the third term is the electrostatic free energy of the electrostatic interaction between the complex and the remainder

of the chain and the forth term is elastic energy of the wrapped part of the chain.

The aim is to determine the relation between wrapping length and counterion release. We need to consider two cases for wrapping lengths, $|Z(l)| < Z_{max}$ and $|Z(l)| > Z_{max}$ where Z(l) is equal to Z(l) = Z − l/b, l is the length of the wrapped part of chain and b is the unit length of rod and $Z_{max} \approx \Omega \frac{R_0}{l_B}$ is effective sphere charge. These two cases have to be treated separately. The first case is for wrapping length l between $l_{min} = l_{iso} - bZ_{max}$ and $l_{max} = l_{iso} - bZ_{max}$, where $l_{iso} = bZ$ is the *the isoelectric wrapping lenght*, at which $Z(l_{iso}) = 0$. Now the free energy has a form

$$\frac{F_1(l)}{k_B T} \simeq \frac{l_B}{2R_0}\left(Z - \frac{l}{b}\right)^2 + \frac{Cl}{b} + \text{constant}$$

the second case, when $|Z(l)| > Z_{max}$ formula has this form

$$\frac{F_1(l)}{k_B T} \simeq \frac{B^{\mp} l}{b} + \text{constant}$$

With this equations we can refer complexation to chain stiffness. By increasing l_P there is no wrapping and free energy is minimized for l=0. The $l_P = 0$ is referred to fully flexible chain and complex is always overcharged then.
The conclusion is that the release of the counterions from the chain drives the overcharging. What opposes this is the charging energy of the complex, the repulsion between the chain and the overcharged complex and bending stiffness of the chain. But this is simplified model which does not take in account the real nucleosome structure and it neglects the existence of linker histone. The sphere – chain system helps us to understand the behavior of nucleosome under changing ionic conditions. The lower the ionic strength the bigger is the importance of the electrostatics [5].

2.2 DNA unwrapping in mononucleosomes

Before analyzing the F-D curves of the chromatin fiber it is informative to evaluate the streching behavior of a single nucleosome. Recently with the help of the single-molecule force spectroscopy it was shown that with increasing force DNA unwraps from the octamer core in two separate stages. It reveals a force

induced DNA unwrapping at two steps, at 3 and 8 pN (Figure 2) that is moderately dependent on salt concentration. In 50 mM KaAc and 10 mM Mg^{2+} first reversible transition occurred at $\sim$ 3 pN which is assigned to the unwrapping of the first turn of the DNA and increased end-to-end length in 21 nm. The free energy of the first unwrapping is estimated to 12 kBT. At $\sim 8-9$ pN, second rapture happens with a size of 22 nm. Similar results were obtained in 2 mM Mg^{2+} solution where the first unwrapping occurred at 2 pN and second between 5 and 25 pN. In 200 mM KAc the first unwrapping transformed from a well defined rupture to the gradual plateau whereas the second turn of unwrapping featured multiple intermediate levels of unwrapping. This indicates that electrostatic interactions are the most responsible for DNA unwrapping. The free energy of DNA wrapping was not much affected with increasing ionic length [1].

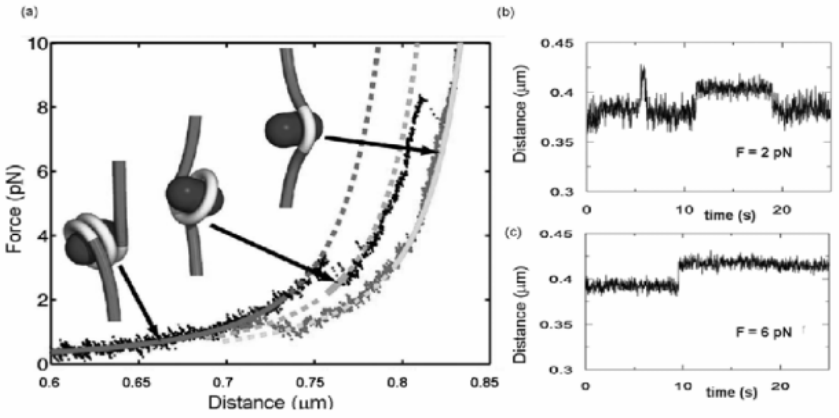

Figure 2: Stepwise induced DNA unwrapping of a mononucleosome. (a) The F-D curve shows two distinct steps that can be attributed to the DNA unwrapping. (b) Reversible unwrapping of the first turn of DNA at 2 pN and (c) irreversible unwrapping of the second turn of the DNA at 6 pN.

3 30 − nm fibre

When stretched DNA − histone complex looks like 'beads-of-string'. This structure is also known as '10 nm fibre' and can be easily seen when chromatin is exposed to low salt concentrations. By increasing the salt concentrations toward physiological conditions (100 mM), the fibre thickens and appears as '30 nm fibre'. Its structure represents disagreement among scientist. There are

two suggested models, the zig-zag (the crossed-linker) and the solenoid model. Electron microscopy studies and force spectroscopy measurements support one-start solenoidal model. The tetranucleosome crystal structure and in vivo cross-linking studies follow crossed-linker two-start model [2]. In both models linker histones (H1 or H5) play an important role in compaction mechanism: depending on their presence or absence fibres form more or less open structures. However, neither method allows us to detect the linker geometry at physiological conditions, so it is still unknown does the fibre fold upon solenoid or upon zig-zag model. In order to obtain true structure, there was performed variety of the experimental measurements. Here, I will present the two-angle model which was the first model describing the nucleosome complexation. I will also present two approaches which lead support to one of the models depending on the geometric and steric constraints. One approach was to measure folding of the $30-$ nm fiber by $single-$ molecule force spectroscopy and the other approach uses geometry parameters obtained from experimental measurements to computationally model the most stabile structures depending on the linker lenght.

3.1 The two $-$ angle

Two $-$ angle model proposed by Woodcock et al. describes chromatin geometry in the terms of the entry-exit angle of the nucleosomal DNA and the rotational settings of the neighboring nucleosomes.It represents a mathematical description of different possible folding pathways. Model built in this way with the constant linker length results in a family of fiber- and ribbon-like structures. It is assumed that the geometric structure of the 30 nm fibre can be obtained from the single nucleosome structure. The roles of linker elastic energy, nucleosome $-$ nucleosome interactions, preferred binding sites etc. are then considered as corrections to this basic model.

147 bp of DNA are wrapped around nucleosome in case of no H1 histone. This implies that incoming and outgoing linker chains make an angle θ with respect to each other; the entry-exit angle π-θ is non-zero. In the presence of the H1 (or H5) histone these two chains are glued together along short section resulting in a stem-like structure. However, there is also rotational (dihedral) angle ϕ between the axes of neighboring octamers along the necklace (Figure 3).

Adsorption of DNA on the octamer core always begins with minor groove turned

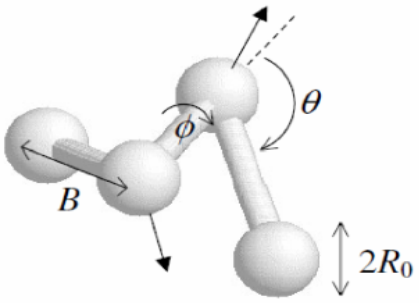

Figure 3: The part of a two-angle fibre containing four nucleosomes. Here are depicted two angles: θ − deflection angle and π − dihedral angle together with the nucleosome diameter 2 R_0 and the linker length B.

in toward the first histone binding site. There is experimental evidence that the linker length shows preferential quantization which means that there is preferred value of ϕ. Using the pair of angles and linker length (θ, ϕ and B) as given physical properties it can be entirely determined the geometrical structure of the necklace. The model assumes that the core particles are pointlike at the joints of the linkers and that the linkers are straight. By taking in the account all these constraints one can obtain two-phase (θ, ϕ) diagram as shown on (Figure 4) from which can be seen preffered fibre structures depending on the θ and ϕ value. If one of the angles is 0 or π then the resulting structure is planar as in '1'. In the case $\phi = \pi$ and θ is arbitary it corresponds to 2D zig-zag-like structure as shown in '6' and '7'. For small values $\theta >> 1$ and $\phi << 1$ structures resemble solenoids as in '9'. Structures where ϕ is small and θ large ($\pi - \theta << \pi$) form fibres with crossed linkers. Finally, structures with large rotational angle ϕ lead to twisted zig-zag structures as '11'.

This model assumes that the core particles are spherical with diameter 2 R_0. There are two types of interactions between the particles. One is between monomers at positions i and $i \pm 2$ (also called short-range interaction) and it requires that the entry angle must be sufficiently small: $\theta < 2arccos(R_0/B)$. This condition excludes structure '8 'on the right side of the diagram. There are also long-range interactions which excludes volumes with small values of ϕ. By increasing the value of ϕ, starting with the circular structure '1', we have to increase it above some critical value so that the pitch angle of the solenoid is large enough that neighboring loops does not interact with each other. It leads to condition $d > 2a$ where d is vertical distance between loops. Two conditions

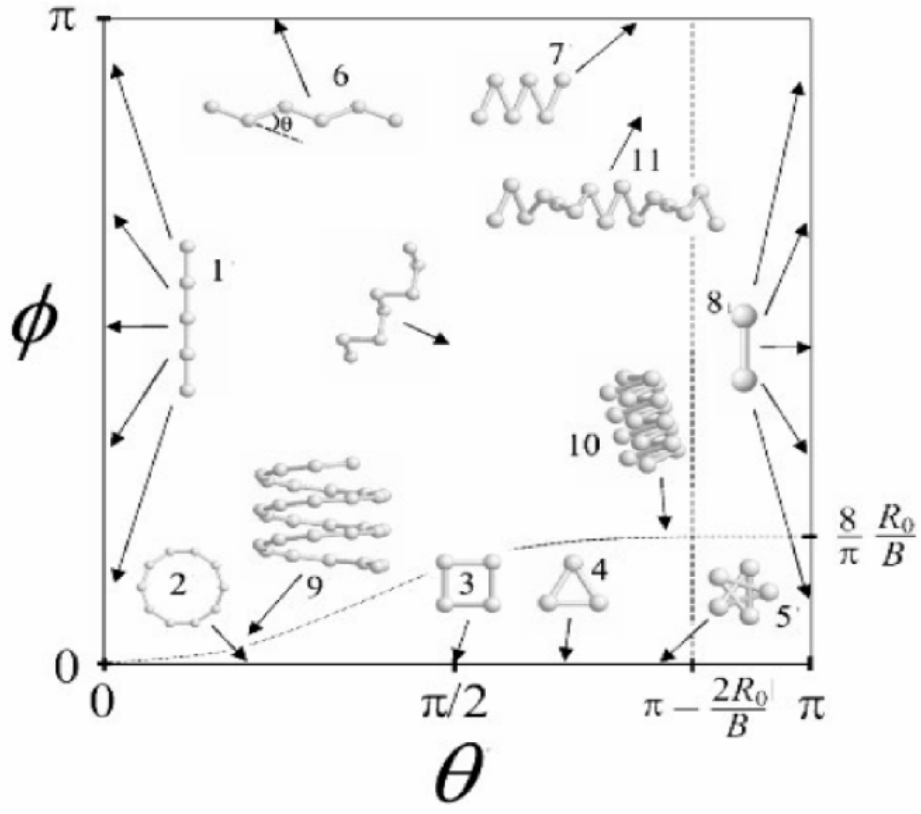

Figure 4: Diagram of geometries of two-angle fibres in the (θ, ϕ)-plane. Shown are some example structures with the arrows denoting their position in the plane. The lines give the boundaries to the forbidden structures due to short-range excluded volume (large θ values) and long-range excluded volume (small ϕ values).

must be satisfied and they are shown schematically as dotted curve on (Figure 4). The problem with the structure diagram is that it doesn't favor any of the chromatin structures because it's purely geometrical model. But it can be used to explain physical properties of the 30-nm fiber such as for exemple fiber streching. Elastic stress of the chromatin fiber can be of the external and internal factors. External stresses are exerted on the chromatin during the cell cycle when the mitotic spindle separates chromosome pairs. The 30-nm fiber should be very stretchable and flexible to survive this stress. The fiber is also exposed to internal stresses such as attractive or repulsive forces between nucleosomes. Repulsive electrostatic interactions are due to the net charge of the nucleosome core particles and attractive interactions are mediated by the lysine-rich core

histone tails.

Here we will see the role of the internucleosomal attractions U_{inter} on the stretching elasticity of a fibre. U_{inter} is taken to be short-range attraction of strength $-U_{min}$ and it acts only when the nucleosomes are in close contact, i.e., at a distance $x \approx 2R_0$ of the order of the core diameter. For i-th nucleosome, closest ones in the space are i+2 and i-2. The interaction between other pairs is disregarded, so the elastic energy is of following form

$$U_{elastic}(x) = \frac{3}{sin^2(\theta/2)} \frac{A}{B^3}(x - x_0)^2 \tag{4}$$

where $x_0 = 2Bcos(\theta/2)$ denotes the distance between nucleosomes i and i+2 for straight linkers. Total interaction nucleosomal potentials equals

$$U(x) = U_{inter}(x) + U_{elastic}(x) \tag{5}$$

and it is plotted as a function of θ (Figure 5, a). It is assumed that the interaction energy U_{inter} remains the same. Curve '1' shows U(x) for small θ value where the global minimum of U(x) is located at $x = x_0$ denoted by 'S' (swallen state). Curve '2' corresponds to an intermediate value of θ at which the minima at 'S' and 'C have the same value. For this value of θ, $\theta = \theta_C$ the energy minumum shifts from 'S' to a new minimum 'C' (condensed) state. The change in θ produced *structural transion* from the swollen to condensed state. Curve '3' depicts $U(x)$ for a deflection angle $\theta > \theta_C$ with a minimum at 'C'.

The corresponding F-D graph is shown on (Figure 5, b) and it has coexistence plateau. If the imposed end-to-end distance is smaller than L_0 (the contour length of the condensed fiber) than the restoring force is entropic. For $L_0 < L < L_1$ the force rises sharply with increasing L. This elasticity is governed by nucleosomal interaction potential. At $L = L_1$ the coexistence plateau is reached. Between $L = L_1$ and $L = L_2$ parts of the fibre are in the 'S' state and parts are in the 'C' state. For larger extensions, $L > L_2$, the fibre shows soft elasticity due to the bending and twisting of the linkers.

The role of the linkers is to bring the nucleosomes in the contact. The nucleosomes experience then in addition an attractive force where U_{min} has been chosen to be of order k_BT. This leads to dense structure with the nucleosomes in contact so that there is hardly any space for fibre bending. The fibres stiffen very strongly as soon as the dense state is reached. This all shows that the nucleosome − nucleosome attraction is a crucial element determining the mechanical properties of the fiber [5].

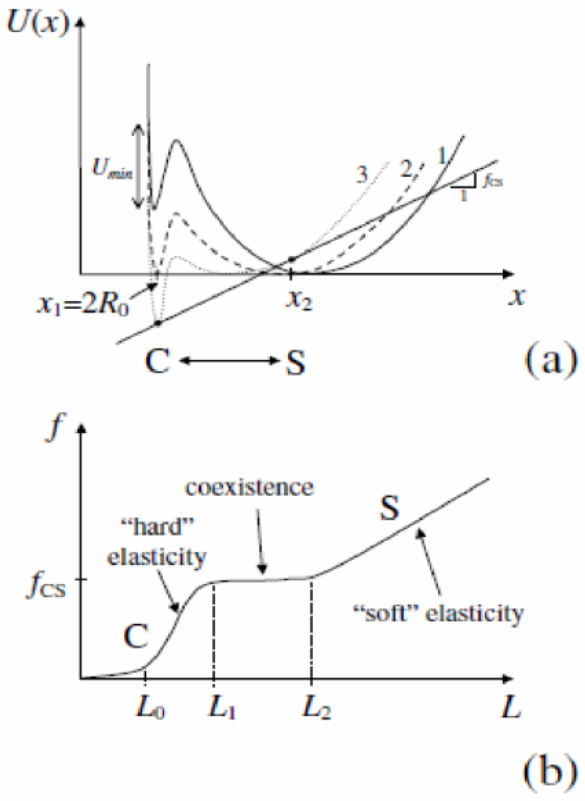

Figure 5: (a) Internucleosomal interaction potential U between nucleosomes i and i+2 as a function of distance x. Different curves correspond to different values of angle θ. Curve '1' has the global minimum at large x ('S' state) whereas curve '3' has the minimum for nucleosomes in close contact (condensed state 'C'). Curve '2' corresponds to transition point. (b) Force-extension curve of the condensed fibre.

3.2 Mechanical properties of the 30-nm fiber

To understand the chromatin compaction we need to know dimensions of the fiber components. One of the parameters that define chromatin structure is the length of the linker DNA which can be expressed in terms of the nucleosome repeat length (NRL). NRL varies between 165 bp and 212 bp, but the most common ones are between 188 bp and 196 bp. It is also known that long NRLs can be found in the transcriptionally silent cells while the short NRLs are connected with the transcriptionally active chromatin.

In the single-molecule force experiment[3] chromatin fibers were reconstructed from the chicken erythrocyte histone octamers and DNA arrays consisting of

25 repeats of the 167 bp and 197 bp of 601 DNA were used. The nucleosomes in the 197 NRL fibers without linker histones are connected by 50 bp of DNA. The total contour length of this 30-nm fiber is approximately 150 nm. They

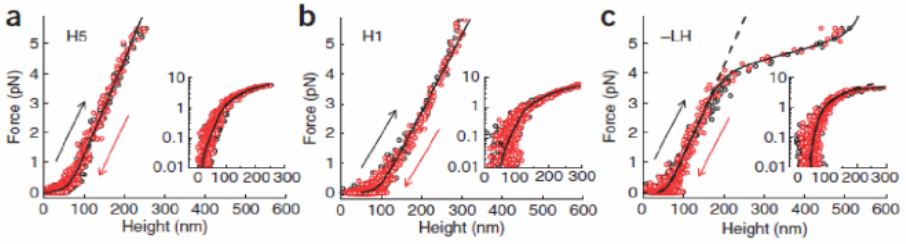

Figure 6: Chromatin fibers stretch like a Hookian spring. F-D curvatures of chromatin fiber containing (a) stoichiometric concentrations of H5 and (b) H1. (c) F-D curves of fiber without linker histone. The dashed line shows data fit to Hookian spring in series with WLC.

performed force-distance (F-D) experiments and measured extension both of the chromatin fiber and the flanking DNA. The graph depicted four major stages of the extension at increasing forces: an extension of the DNA flanking the fiber fallowing a Worm-Like-Chain (WLC), a linear extension of the chromatin fiber up to three times its resting length, a plateau corresponding to the rupture of the internucleosomal interactions at 4 pN, and a WLC-like extension of the beads-on-a-string fiber with reduced persistence length relative to DNA (Figure 6, a). The nucleosome interaction energy was found to be 14 k_BT [3].
Measured stiffness and extension were related to the structure of the 30-nm fiber. The small spring constant of the chromatin fiber is consistent with stacks of nucleosomes arranged in helical structure. But when the linker lenght was decreased from 50 bp to 20 bp, a longer and stiffer fiber was obtained, hinting at a two-start arrangement. The inclusion of the stoichometric amounts of linker histone didn't affect the lenght nor the stiffness of the fiber (Figure 6, a, b), but stabilized nucleosome stacking up to 7 pN [1].

3.2.1 DNA unwrapping in nucleosome arrays

In contrast to the results obtained with mononucleosome, bigger forces must be applied on the nucleosome arrays to unwrap DNA. The rupture force for DNA unwrapping is between 3 and 7 pN. This shows that the unstacking of the nucleosome and DNA unwrapping are two separate invents - nucleosome unstacking is happening at lower force regime than DNA unwrapping. In re-

constituted chromatin fiber from the chicken histones and 27 repeats of the 601 positioning elements the length of the fiber below 10 pN is similar to the one expected corresponding to the first turn DNA unwrapping and above 10 pN there is a stepwise length increase corresponding to the second turn of the DNA unwrapping. Similar curvature was obtained with reconstituted chicken histones and 17 repeats of the 5S rDNA positioning elements [1]. Certain modifications to the histones themselves, such as tail acetylation are belived to facilitate the unwrapping of the DNA [2].

3.3 Computational modeling

Computational modeling can also help in finding 30-nm fiber structure. By using minimal number of parameters (in this case - nucleosome geometry and DNA elastic moduli), all of which can be taken from experimental data, the nucleosome interaction energies required for stabile fiber structure were estimated [2]. There were defined six geometric parameters in the fiber from which the position and orientation of the nucleosomes in the fiber can be fully defined. They are (Figure 7):

1. Height (h) per nucleosome along fiber axis.
2. Angle (θ) per nucleosome around fiber axis.
3. Radius (R) of the helix.
4. Euler angles (α, β, γ) defining the orientation of the first nucleosome relative to the fiber coordinate system.

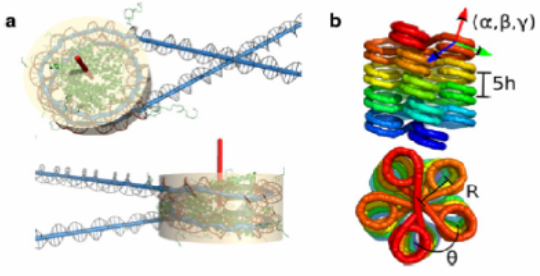

Figure 7: (a) Nucleosome geometry obtained from crystallographic structure. (b) The six coordinates used to specify regular fiber structure.

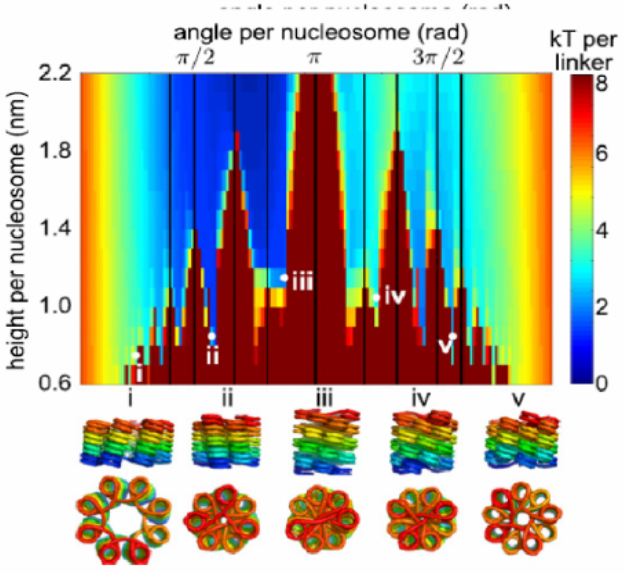

Figure 8: Fiber structures with linker length of 50 bp. Minimal energy is plotted as function of height and angle per nucleosome. The energy cost of each possible pair combination is indicated on the right vertical column.

For each pair (h, θ) of height and angle per nucleosome, the minimal energy graph was plotted (Figure 8). The form of the elastic energy graph depends upon

- the twist registry of the nucleosome – which defines the set of preferred helix coordinates
- the linker length – which affects the fiber flexibility by setting the minimum value of the low-energy basin.

On (Figure 9) the angle between the nucleosome symmetry axis and the fiber axis was plotted. It was shown that nucleosomes separated by integer multiples of DNA pitch pack with their symmetry axis aligned along fiber axis ($\beta = 0, 2\pi$). Whereas nucleosomes separated by half-integer multiples of DNA pitch align perpendicular to the fiber axis ($\beta \approx \pi/2$).

The purpose of the all described methods is to construct candidate fiber structures that match experimental geometric parameters. For different fiber lengths (between 30 and 80 bp) with the height and diameter fixed values, they run basin-hopping calculation. Arrays with 10 to 40 bp of linker DNA all produce fibers with diameter of 33 nm with 11 nucleosomes per 11 nm and arrays 50

to 70 bp of linker DNA all produce 44 nm wide fibers with 15 nucleosomes per 11 nm [4]. The resulting structures are shown on (Figure 10) from which it can be seen that fibers with 30-bp linkers assume solenoidal structure. Fibers with longer linkers prefer to form crossed-linker structures when given experimental constraints. The bending of linker DNA to such fibers can be accommodated without significantly changing the experimentally defined fiber diameter by tilting the nucleosomes [2].

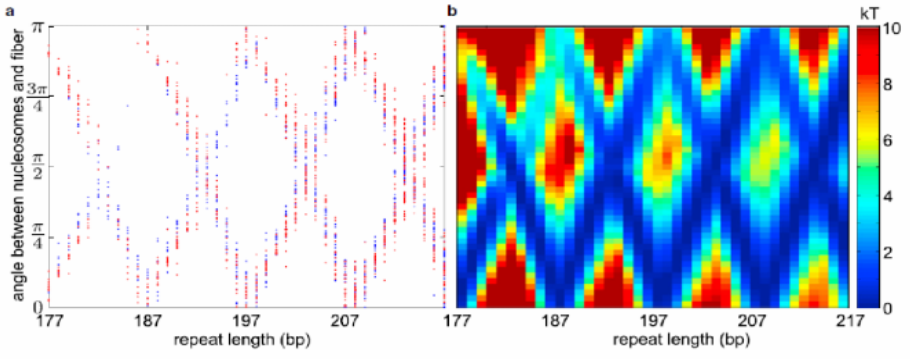

Figure 9: (a) Angle (β) between nucleosome and fiber axis is plotted as a function of repeat lengths for all candidate structures. (b) Minimal energy for all structures is also plotted as a function of repeat lengths for a given β-angle.

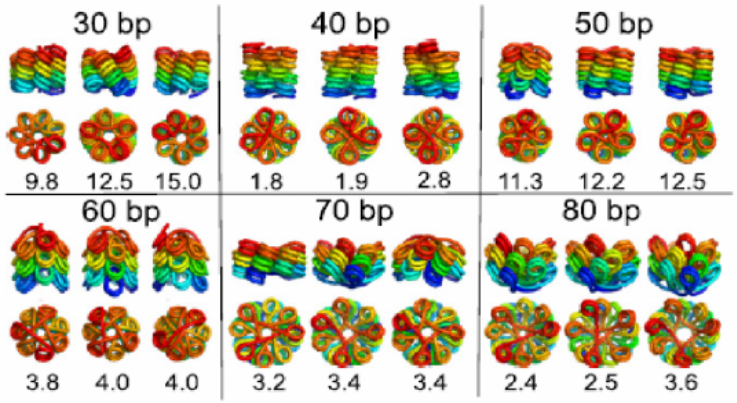

Figure 10: Three structures for each fiber length with fixed height and diameter. The energy for each locally optimized structure is given in kT per linker.

4 Conclusion

The structure of the 30-nm chromatin fiber remains unsolved even after more than 10 years study only with the force spectroscopy. To the humans it is still unknown how nature has managed to pack DNA in such structures to fit into eukaryotic cell. Different approaches are used to reveal this mystery, including different types of experiments, computational modeling and theoretical assumptions. In this seminar there were shown newest achievements in resolving 30-nm fiber structure all of them obtained by considering its physical properties. It was shown that the fiber acts like a simple spring with linear force − distance dependence. The spring constant, in this case the fiber stiffness is independent of the presence of the linker histone although it increases the fiber compaction by stabilizing nucleosome stacking. Linker length has important role in resolving chromatin structure. For repeat lengths where the straight-linker helix is highly extended, stable structures are formed with low elastic energy cost per linker and for shorter linkers it is necessary to invest energy higher than 10 k_BT per nucleosome to rotate it. It was also shown that higher-order folding is driven by nucleosome stacking with interaction energy of approximately 15 k_BT. An interaction energy of a few k_BT has been the basis model for zig-zag conformation. For energy of 15 k_BT it is favorable helical folding.

In computational studies they wanted to see the effect of the local geometry factors and linker length on the compact fiber structure. The linker histone or internucleosome electrostatic interactions weren't included in the study but only the experimentally obtained parameters. What they showed is that the twist registry of the consecutive nucleosomes along DNA, as set by the internucleosome repeat length, effects linker length quantization. The nucleosomes position in the chromatin fiber was described in terms of β angle. There are two classes of nuclesome positioning which are expected to respond differently to perturbations of fiber structure. For fibers where nucleosomes are positioned perpendicular to fiber axes, twisting parts of fiber would require breaking face-to-face histone contacts whereas linear extension of the fiber would only involve deformation of the linker DNA. And for nucleosomes which are symmetrical to fiber axis, there is separation of fiber faces and twist is resisted by DNA elasticity alone. The conclusion is that the preference for specific configuration depends on the exact local geometry, so unwrapping of even few basepairs can

change the energetic preference for the number of nucleosome stacks in the fiber. Chromatin fiber presents exciting field of research to both physicists and biologists and over last years there have been done big progress in understanding its properties. Experimental studies study the behavior under changing ionic conditions and/or under externally applied tensions whereas computational studies capture the energy and timescales occurring in chromatin fiber. There are also theoretical treatments of the fiber complex which try to identify physical properties underlying fiber compaction. The aim of all of them is to get clearer picture of the working of the chromatin.

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