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Out of register: How DNA determines the chromatin fiber geometry

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Abstract – We present a model that predicts the geometry of chromatin fibers as a function of the DNA repeat length. Chromatin fibers are widely observed *in vitro* and are typically posited as the second level of the hierarchical organization of chromatin in the nuclei of cells. We postulate that the major driving force for fiber formation is the dense packing of the underlying DNA-protein spools, the nucleosomes, allowing for fibers with four possible diameters. We show that the diameters observed in experiments on reconstituted regular fibers correspond to the geometries that minimize the elastic energy of the DNA linking the nucleosomes.

Introduction. – DNA of eukaryotic cells have macroscopic lengths (*e.g.*, 2 m for the human genome) but need to fit into micron-sized nuclei. This is achieved by packaging the DNA with the help of proteins into the hierarchical chromatin complex [1]. As a first step DNA is wrapped 1 3/4 turns around protein cylinders, corresponding to 147 basepairs (bp). The resulting complexes, called nucleosomes, are connected via unwrapped portions of about 50 bp length, the linker DNA. As the next level of folding, the condensation of the string of nucleosomes into a 33 nm thick chromatin fiber is typically posited. Whereas the structure of the nucleosome is known at atomic resolution through X-ray cristallography [2], the structure of the chromatin fiber remains poorly understood, despite more than three decades of experiments and intense model building.

We know from the experiments that chromatin extracted from a cell nucleus or reconstituted from its pure components forms under physiological conditions 33 nm wide dense fibers whose structure cannot be resolved with electron microscopy. However, all the models published so far cannot be checked against this fact since they do not predict the diameter. Instead —starting in 1976 with Klug's solenoid model [3]— modeling typically consists of placing nucleosomes into a fiber with the desired diameter. The insight is then rather limited due to the huge number of possible configurations and hardly any experiments to distinguish between them.

Since the groundbreaking study of the Rhodes lab [4] there is, however, more to explain than that single diameter. In these experiments regular fibers were reconstituted by placing about 50 nucleosomes equally spaced onto a piece of DNA using a DNA template containing positioning sequences with a higher affinity to nucleosomes. The group studied repeat lengths from 187 to 237 bp in steps of 10 bp. The experimental findings were surprising (fig. 1): for the three shorter repeat lengths fibers with 33 nm diameter were reported. Even more remarkably, for the larger three repeats thick fiber with a non-canonical 44 nm diameter were observed. These findings point towards a discrete set of optimal nucleosome configurations that act as the main driving force for fiber formation. This leads to two questions: 1) Which principle underlies that discrete set of optimal nucleosome arrangements? 2) Why does the rather stiff DNA double helix not affect the fiber diameter when the repeat length is varied over a range of at least 20 bp for the 33 and 44 nm wide fibers, respectively? These two questions remain unanswered by the fiber model proposed in ref. [4] and by models built upon the results of ref. [4], like ref. [5], where, as in Klug's solenoid model, the fiber diameters are set *ad hoc*. In particular, question (2) remains unanswered by the two-angle models that predict fiber diameters that depend linearly on the DNA linker length (see for example refs. [6–10]).

The model published by Depken and one of the authors gives a possible answer to the first question [11]: Chromatin fibers result from a packing problem. We know from the crystal structure that nucleosomes are cylinders

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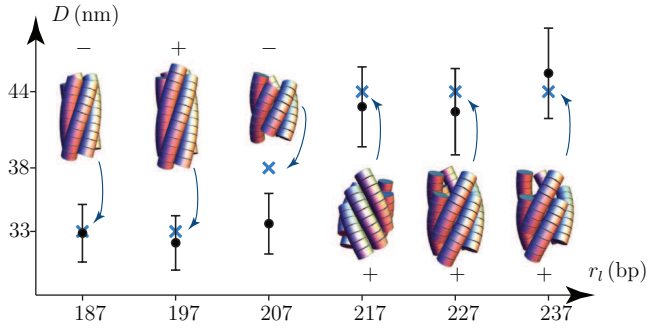


Fig. 1: (Colour on-line) Fiber diameter as function of repeat length: experimental data [4] in black, our theoretical prediction for $(x, y, z) = (2.5, 0.5, 0.1)$ nm in blue.

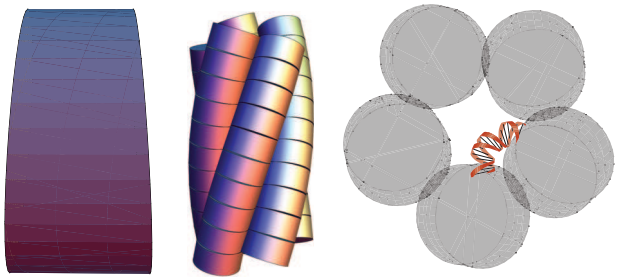


Fig. 2: (Colour on-line) (a) Side view of a nucleosome with the $\beta = 8.1°$-wedge angle. The DNA leaves the nucleosome on the top. (b) Fiber made from 5 stacks of nucleosomes, $N_{\rm rib} = 5$. (c) Cross-section of (b) showing one of the DNA linkers. In this example nearest stacks are connected, $N_{\rm step} = 1$ and the wrapped portion of DNA is hidden for clarity.

with top and bottom surfaces not parallel to each other but showing a wedge angle (fig. 2(a)). Disconnected particles consisting only of wrapped DNA plus protein core are known to have a tendency to stack into circles with a $\beta \approx 8°$ splay angle reflecting their microscopic wedge shape [12]. It has been speculated that nucleosomes can increase their wedge angle through a gaping mechanism [13]; the energetic cost of such a deformation is, however, estimated to considerably exceed the energy scales encountered in our model so that we can assume a fixed nucleosome shape.

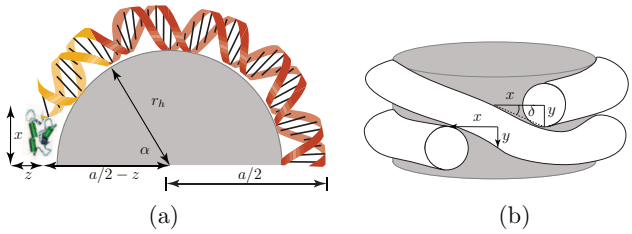
In ref. [11] possible dense packings of nucleosomes were characterized. They consist of several stacks of nucleosomes twisting around each other. For any of those geometries the centerline of each ribbon is a helix of radius $R = (D - a)/2$ and pitch angle $\pm\gamma$. Here D is the diameter of the resulting fiber, $a = 11.5$ nm is the effective nucleosome diameter and γ is determined by the number of ribbons [11]. The value of D needs to be chosen such that the splay in each stack is $\beta \approx 8°$. This leads to 5 to 8 ribbons as possible dense packings. For the 33 nm wide fibers the dense packing requirement leads to a nucleosome line density of 11 nucleosomes/11 nm [11]. This value has indeed been observed for fibers formed from perfectly spaced nucleosomes [4]. Lower line densities of around 6 nucleosomes/11 nm, as typically observed for natural fibers *in vitro* [14] and *in situ* [15], indicate non-dense fibers and are not considered in our current study.

An example of a dense fiber with 5 ribbons is displayed in fig. 2(b). Its diameter is 33 nm whereas a fiber of 7 stacks has 44 nm. This strongly suggests that the fibers observed in the Rhodes lab correspond to these two dense packings. But why are these optimal while the other dense packings, namely 6 stacks with $D = 38$ nm and 8 stacks with $D = 52$ nm [11] have not been observed?

Whereas all these fibers feature densely packed nucleosomes, they might show vastly different conformations of the linker DNA that connect them. A fiber can be characterized by two numbers: $N_{\rm rib}$, the number of its stacks, and $N_{\rm step}$, the distance across stacks between connected nucleosomes. *E.g.*, for $N_{\rm step} = 1$ neighboring stacks are connected and for $N_{\rm step} = 2$ next-nearest stacks. An example with $N_{\rm rib} = 5$ and $N_{\rm step} = 1$ is displayed in fig. 2(c). Obviously there is just one repeat length for which the DNA fits perfectly into such a configuration. To add, *e.g.*, 10 or 20 bp while maintaining the same nucleosome positions, the DNA needs to bend strongly. Here we describe the DNA by the worm-like chain model with a persistence length $l_P = 50$ nm [16]. This allows to estimate the elastic energy per bent DNA linker; we found that energies lie typically in the range of 30 to $40 k_B T$ —even if one does not enforce a particular DNA entry-exit angle at the nucleosomes. This would clearly overrule the stacking energy, the energy gain from putting one nucleosome on top of another, that has been estimated from chromatin fiber stretching experiments [17], theory [7] and simulations [18] to be on the order of $3 k_B T$. The independence of the fiber diameter on the repeat length observed experimentally over a wide range seems thus to be inconsistent with any theoretical model.

We demonstrate in this paper how to solve this problem. Keeping the dense nucleosomal packing intact, the nucleosomal stacks can be shifted "out-of-register" in a way that reduces the elastic energy per linker to about one $k_B T$ without changing the stacking energy. The predictions of our model —based only on geometrical constraints and DNA elasticity— agree remarkably well with the experimental data from ref. [4]. Our model applies to dense fibers that only form for perfectly spaced nucleosomes but not for native fibers like in ref. [19]. Also fibers with regularly spaced nucleosomes were excluded if the linker length was too short [20,21], the total number of nucleosomes too small [20,22–25], or if there were no linker histones present [20,23,26].

Results. – We discuss first in more detail the geometry of the nucleosome to identify the locations where the linker DNA enters and leaves the nucleosome since the elastic energy of the linker is quite sensitive to the distance it spans by going from one nucleosome to the next. Figure 3(a) shows a top view of a nucleosome half. The



(a) (b)

Fig. 3: (Colour on-line) (a) Half-nucleosome with the nucleosomal DNA (red), the stem (orange), and the linker histone (green). Here $r_h = 3.75\,\mathrm{nm}$ and $\alpha = 0.33\pi$. (b) A cartoon of the nucleosome from another perspective. For simplicity, the linker histone is omitted. x and y are the distances between the centerline of the DNA and the dyad axis of the nucleosome.

DNA exits the wrapped part to the left. The linker histone, close to the entry-exit point, binds the two DNA linkers together forming a stem region [27]. The tip of the stem has a distance $r = D/2 - a + z$ from the centerline of the fiber. Moreover, the centerline of the DNA is shifted from the dyad axis of the nucleosome by an x- and y-offset (see fig. 3(b)). Then the distance d that a linker has to span to connect two consecutive nucleosomes is given by

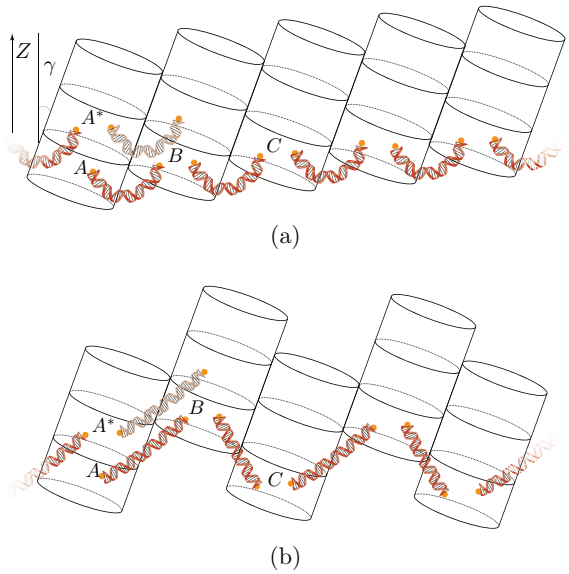
$$d(\Delta, N_{\mathrm{rib}}, N_{\mathrm{step}}) = \left\{\Delta'^2 + 2r^2\left[1 - \cos\left(2\pi\frac{N_{\mathrm{step}}}{N_{\mathrm{rib}}} + \Delta'\tan\frac{\gamma}{R} - 2\frac{x'}{r}\right)\right]\right\}^{\frac{1}{2}} \quad (1)$$

with

$$\begin{aligned}\Delta'(\gamma) &= \Delta + 2y'\,\mathrm{sign}(\Delta)\,\mathrm{sign}(\gamma),\\ x'(\gamma) &= \sqrt{(x^2+y^2)}\cos(\delta+\gamma),\\ y'(\gamma) &= \sqrt{(x^2+y^2)}\sin(\delta+\gamma).\end{aligned}$$

Here Δ is the vertical offset between the two nucleosomes and $\delta = \tan^{-1} y/x$. Note that γ and R in eq. (1) depend on N_{rib} [11].

The vertical offset Δ is not a free parameter. Starting from some arbitrary nucleosome we require that after N_{rib} steps one has visited every ribbon once and ends up at the starting ribbon, just one nucleosome above or below. The helicity of the linker path is determined by where the DNA ends. The sum of all the N_{rib} offsets between the connected ribbons must equal $h = \pm b\cos\gamma$ where $b = 6\,\mathrm{nm}$ is the height of a nucleosome and h its height projected on the fiber axis. The sign of h determines the helicity of the linker path. We choose the geometry such that a positive h-value leads to a positive helicity. The most obvious choice is $\Delta = h/N_{\mathrm{rib}}$ for every vertical offset. But, as mentioned above, this would increase the bending energy too much, making the stacking of nucleosomes too costly. However, a vertical offset alternating between positive and negative values (still adding up to h after one round) circumvents this problem. Starting from a fiber with uniform offsets and highly bent linkers, see fig. 4(a), one can arrive, by shifting stacks up and down, at a conformation where the linkers are almost straight, see fig. 4(b). Note that this geometry is different from the canonical solenoid and crossed linker models [1].



(a) (b)

Fig. 4: (Colour on-line) The 5-ribbon fiber rolled out in a plane, omitting the wrapped DNA in the figure for clarity. (a) A constant vertical offset $b\cos\gamma/N_{\mathrm{rib}}$ between connected nucleosomes (*e.g.*, A-B) leads to highly bent linkers. (b) A zig-zag geometry with vertical offsets $\Delta_\uparrow$ for A-B and $\Delta_\downarrow$ for B-C can have nearly straight DNA linkers, except close to the entry/exit points where we assume denaturation. Note that the fiber connectivity does not change from (a) to (b) and that the Z-axis indicates here the axis of the fiber and is not related to the z in fig. 3.

Before computing the energies let us make the assumption that a small DNA portion at the point where it exits the linker histone is denaturated. This allows the linker DNA to point in any direction and to twist without further cost. Obviously the denaturation comes at some cost, typically about 1–3k_BT per basepair [28]. As a few basepairs need to be denatured, this might cost about $10k_BT$ in total. We justify this assumption by the fact that the resulting elastic energy per linker is substantially reduced, namely be several tens of k_BT. We furthermore speculate that the linker histone might facilitate the formation of the denaturation region, lowering its free energy cost. Recent experiments showing how the linker histone enhances the conformational flexibility of the DNA at the entry/exit point of the nucleosome [29] might support this idea.

Using the Euler's theory on elastica [30] we compute the mechanical energy to bend the linker DNA of length l over a distance d:

$$\begin{aligned}E(d(\Delta), l) &= E(m(d), l)\\ &= \frac{8A\mathrm{K}(m)}{l}\left[\mathrm{E}\left(\frac{\pi}{2}\middle|\, m\right) - (1-m)\mathrm{K}(m)\right]. \quad (2)\end{aligned}$$

Here $A = k_BTl_P$ is the bending modulus of the DNA, K is the complete elliptic integral of the first kind, E is the

Table 1: Number of nucleosome stacks, $N_{\rm rib}$, in dense fibers together with their diameters in nm. The diameters follow from the geometry of the nucleosomes that are wedge shaped with a wedge angle of $\beta = 8.1°$.

$N_{\rm rib}$	5	6	7	8
D	33	38	44	52

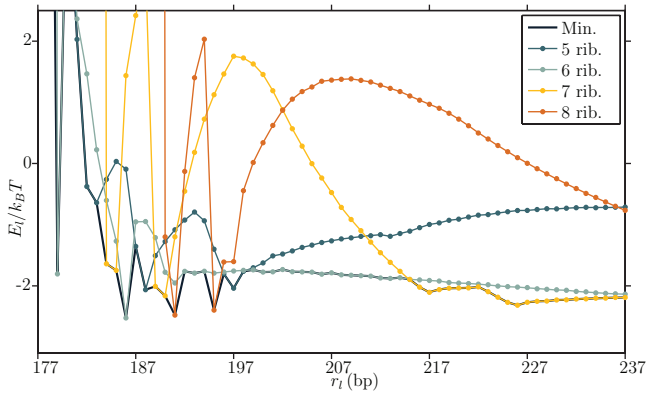


Fig. 5: (Colour on-line) Energy E_l per linker, eq. (3), as a function of repeat length r_l for the four possible $N_{\rm rib}$. We assume infinitely long fibers with $E_{\rm stack} = -3k_BT$ and $(x, y, z) = (2.5, 0.5, 0.1)$ nm. We note that changes in the helicity of the fiber manifest themselves in kinks, as for the 7-ribbons structure at 222 bp (see also fig. 1).

elliptic integral of the second kind, and m, the parameter of the elliptic functions, is a function of d, obtained numerically. From eq. (2) we can calculate the average energy per linker DNA, $E_l(\{\Delta_i\}) = \sum_{i=1}^{N_{\rm rib}} E(\Delta_i, l)/N_{\rm rib}$. Together with the stacking energy, $E_{\rm stack} \approx -3k_BT$, this leads to the total energy of the fiber per nucleosome:

$$E_l(\{\Delta_i\}, n) = E_l(\{\Delta_i\}) + E_{\rm stack}\frac{n - N_{\rm rib}}{n}. \qquad (3)$$

Here $E_{\rm stack}$ is multiplied by a factor that accounts for a finite size effect. For a sufficiently small number n of nucleosomes, fibers with less ribbons might be favored because they have less end nucleosomes. When comparing our model to experimental data we account in our calculations for this finite size effect.

Assuming that every fiber seen in the experiments corresponds to the energetically most favorable geometry, we numerically minimize the total energy per nucleosome, eq. (3), with respect to $\{\Delta_i\}$, $N_{\rm rib}$ and $N_{\rm step}$. For each set we have to consider four cases since the ribbons and the linkers can be right- or left-handed, independent from each other. For an even number of ribbons the number of positive vertical offsets is the same as the number of negative ones. For an odd number of stacks and a positive (negative) helicity of the linker backbone, the number of positive vertical offsets exceeds the number of negative offsets by one (minus one). Moreover, for a given set of Δ_i that minimizes the energy, offsets with the same sign have equal values.

Table 2: Optimal fibers for given number n of nucleosomes and repeat length r_l chosen as in the experiment [4]. The energy E_l per linker, eq. (3) with $E_{\rm stack} = -3k_BT$, and the positive vertical offset $\Delta_\uparrow$ are presented for the case $(x, y, z) = (2.5, 0.5, 0.1)$ nm.

n	52	61	47	55	66	56
r_l (bp)	187	197	207	217	227	237
E_l (k_BT)	−1	−1.8	−1.4	−1.7	−2	−1.8
$\Delta_\uparrow$ (nm)	2.2	5.9	7.7	11.2	12.6	15.1

The dense fibers considered in our minimization are summarized in table 1. We only account for the case $N_{\rm step} = 1$ since for any $N_{\rm step} > 1$ one has strong steric interactions between the linkers. Also in the case $N_{\rm step} = 1$ overlap between linkers can occur when the vertical offsets become too large. We consider in our minimization only allowed configurations. Having set $N_{\rm step} = 1$ we have —for a given helicity of the ribbons and of the backbone— only one remaining degree of freedom, the amount by which the ribbons are shifted with respect to each other. The energies per linker for infinite fibers with $E_{\rm stack} = -3k_BT$ and $(x, y, z) = (2.5, 0.5, 0.1)$ nm are displayed in fig. 5 in one bp steps between 177 and 237 bp repeat length. We show the energies for all possible numbers of ribbons. Curves for given $N_{\rm rib}$-values are not smooth since the optimal helicity varies with the repeat length, see also fig. 1. Note that for the chosen (x, y, z)-values there is no difference in structure between the infinite fibers and the finite ones from fig. 1. The only role of the stacking energy is to make the energies negative, and therefore the fiber stable. Changing its value produces only a vertical shift in fig. 5 (up to finite size effects).

The results for the six experimentally studied fibers [4] are presented in fig. 1 along with table 2 for $(x, y, z) = (2.5, 0.5, 0.1)$ nm. Since these microscopic values are not known precisely we performed the minimization for a range of values (in nm) $0 < x < 3.5$, $0 < y < 2.5$ and $0 < z < 1$. For every set of (x, y, z)-values that gives the blue crosses in fig. 1, the length of DNA in contact with the linker histone is about 10 bp (*i.e.*, 20 bp per nucleosome), the length that has been shown to be strongly bound to the globular domain of H1 [27]. We assume that H5, the linker histone used in [4], engages the same length. The helicity of each fiber can be seen directly from the artwork in fig. 1, while the helicities of the linker paths are indicated by + and − signs.

The predictions of our model are in agreement with the experiments, except for $r_l = 207$ bp, see fig. 1. However, the electron micrographs from fig. 1 of [4] might indicate that fibers with $r_l = 207$ bp are thicker than the fibers with shorter repeat length and thinner than the ones with larger repeat length. From the five micrographs per repeat length shown in that figure we estimate $D \approx 33$ nm for

$r_l = 197\,\mathrm{bp}$, $D \approx 38\,\mathrm{nm}$ for $r_l = 207\,\mathrm{bp}$ and $D \approx 44\,\mathrm{nm}$ for $r_l = 217\,\mathrm{bp}$. Moreover, the variations in the diameters for fibers of the same repeat length are much smaller than the error bars, see fig. 1. We speculate that the displayed fibers are examples of very regular and dense fibers for which our theory works best. The whole ensemble of fibers shows larger variations in diameter, presumably reflecting less regular nucleosomal packings, and the average of the 207 bp repeat is even shifted close to 33 nm.

As can be seen from fig. 5, formation of dense fibers for $r_l = 177\,\mathrm{bp}$ is very expensive and might be even sterically impossible, depending on microscopic parameters. In fact, the Rhodes group found in a new study that 177 bp repeats form non-canonical 30 nm wide fibers [31].

We stress that short fibers, *i.e.* fibers with a small number of nucleosomes, might show different fiber geometries than long ones. *E.g.*, the energies of the 6- and 7-ribbon fibers with $r_l = 237\,\mathrm{bp}$ are so close (see fig. 5) that $N_{\mathrm{rib}} = 6$ becomes cheaper already for $n = 50$. Very short fibers like *e.g.* $n = 10$ [22] and $n = 12$ [25] seem to prefer $N_{\mathrm{rib}} = 2$ compromising on perfect packing to have less end nucleosomes.

Discussion. – We have presented a chromatin fiber model that predicts the fiber diameter as a function of the linker length. It is important to note that all the parameters that entered our model, the nucleosomal wedge angle and the DNA elastic modulus, were extracted from experiments that were performed on components of chromatin fibers, disconnected nucleosomes (so-called nucleosome core particles) and naked DNA, but not on chromatin fibers themselves. The first assumption of our model, the dense packing of the nucleosomes, leads to four different possible geometries. This together with a second assumption, namely that the experimental fibers are those with the lowest elastic energy per linker DNA, are already sufficient to predict the fiber diameters seen in the experiment.

To achieve constant fiber diameters over an extended range of linker length, it is necessary that the nucleosome stacking energy dominates over the elastic energy for linker bending. According to our study, this can only be achieved when two points are fulfilled. The first one is that the DNA is locally denatured close to the entry-exit region. This assumption might sound rather extreme, but according to our estimates it helps to lower the elastic energy by several tens of k_BT per linker. As the nearest-neighbor basepair free energy depends strongly on the basepair step, one might ask whether stretches with low cost for denaturation are typically found just next to nucleosome positioning sequences. Linker histones are indeed known to preferably bind to AT-rich regions [32].

A second requirement for having low enough elastic energies is that nucleosomes are equally spaced. Only then one can achieve small energies through "out-of-register" sliding. If just two neighboring nucleosomes are connected by a shorter linker length than the rest, the stacks belonging to these two nucleosomes will not be able to shift by the optimal amount. In that case either the fiber cannot form, or a nucleosome has to disintegrate to allow the rest of nucleosomes to pack. On similar grounds we expect that optimal fibers are very stable against thermal fluctuations even though for certain linker lengths different fibers have similar energies. A thermal excitation in the form of a short fiber stretch with non-optimal geometry would be too costly to spontaneously occur as different sliding lengths would cause steric clashes at the boundaries.

That strict requirement of equal spacing of nucleosomes for the formation of dense fibers might have implications for living cells. Our model suggests, dense fibers would only form for equally spaced nucleosomes. Since linker lengths typically vary along DNA, perfectly dense fibers, as discussed in this paper, can hardly be formed. Instead one should expect less dense and less regular fibers as typically found when chromatin is isolated from cells, see, *e.g.*, [14]. Such less dense fiber stretches interdigitate with neighboring fibers, making them harder to detect *in vivo*. In the dense environment of the cell nucleus they may even disintegrate into a nucleosomal melt [33]. Nevertheless there are mechanisms that can cause an approximately equal spacing of nucleosomes *in vivo*, namely directly through mechanical signals in the underlying DNA sequence [34], or indirectly through statistical ordering in the vicinity of barriers [35–37]. Furthermore, one might speculate that the action of chromatin remodellers like ISWI that are known to repress transcription by forming equally spaced nucleosomes [38], make use of this phenomenon. Once they have equally spaced an array of nucleosomes, a dense fiber can form and the corresponding DNA stretch can no longer be accessed.

To conclude, we presented a chromatin fiber model with nucleosomal stacks "out-of-register" that predicts the fiber geometry as a function of the repeat length in agreement with existing experimental data. We hope that our model will guide future experiments to find various structural transformations between the various fibers, including a not-yet observed 52 nm fiber.

* * *

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