From sliding nucleosomes to twirling DNA motors

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The sliding of DNA-wrapped protein cylinders, so-called nucleosomes, along DNA is a mechanism presumably involved in exposing wrapped eucaryotic DNA to the molecular machinery. On the other hand, a self-propelling DNA minicircle is an example of a nanotechnological device that can be driven by temperature oscillations employing the ratchet effect. We show parallels between the two systems by demonstrating that a nucleosome in principle could also be turned into such an externally driven nanodevice; in this case the nucleosome would slide in directed fashion along DNA. We demonstrate, however, that the high friction between the DNA and the protein cylinder renders this idea unfeasible.
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I. INTRODUCTION

DNA – the carrier of the genetic information – is at the heart of many central life processes [1]. Replication, transcription and repair of the genetic material relies on special properties of DNA like the specific base pairing. In addition, one has to appreciate the fact that the substrate the molecular machinery has to deal with in eucaryotes (plants and animals) is not naked DNA but chromatin, a DNA-protein complex in which DNA is folded in a hierarchical fashion [2]. On the lowest level DNA is wrapped nearly twice around an octamer of histone proteins that form a cylinder of 6 nm diameter and height [3]. A short stretch of naked linker DNA connects to the next such protein spool. The resulting string of so-called nucleosomes folds into higher order structures, the details of which are still under debate.

The way DNA is folded, especially the density of the resulting complex, varies along the DNA chain and depends among other factors on biochemical modifications of the histone proteins [4]. This opens up the possibility for the chromatin complex to not only carry the genetic information in the basepair (bp) sequence of its DNA but also to prescribe which parts are open to the transcription machinery and which not. This is part of the so-called epigenetics that is a crucial feature in the differentiation of cells.

The fact that only around 1.5% of the human DNA encodes for proteins indicates the intriguing possibility that at least a fraction of the remaining 98.5% of "junk" DNA carries bp sequences that are chosen carefully to interact with the protein cylinders in a special way, namely such that they position them at specific locations. Such so-called positioning sequences make use of the fact that certain bp sequences are easier bendable in one direction than in the other. Note, however, that only $< 5\%$ of eucaryotic genomic DNA contains such positioning sequences [5].

Three quarter of eucaryotic DNA is wrapped onto octamers which leads to the puzzling question of how then the DNA is accessible to e.g. DNA binding proteins that bind at specific positions on the DNA. As long as the DNA is wrapped such proteins typically cannot bind [6]. To access the DNA it has to be freed at least temporarily, e.g. via a partial unwrapping of the wrapped portion [7, 8]. Another possibility is the sliding of the octamer along the DNA which is the subject of Section 2 of this paper.

But DNA is not only of interest due to its function as the carrier of genetic information. DNA is also an ideal material for nanotechnological applications. In fact it combines many important material features as stability, self-assembly ability, modularity, replicability, switchability and experimental tractability. In fact, assemblies based on DNA hybridisation chemistry [9–19] as well as on conformational DNA transitions [20–22] were successfully exploited to build periodically switchable nanodevices. Despite their beauty and conceptual originality these devices have certain limitations. The large kinetic barriers involved in the switching process boost their switching time per cycle to $\sim 10^3$ s, four orders of magnitude slower than their natural counterparts, the biological molecular motors. And – contrary to their macroscopic counterparts – such motors typically do not produce a continuous rotary motion but act as switches between two conformational states.

We have recently proposed a DNA nanomotor that in principle overcomes those limitations [23]: It achieves sub-second switching times, rotates in a continuous fashion and propels itself through the solvent with a speed of tens of nanometers per second. In Section 4 of this paper we outline the working principle of this nanoengine that is given in more detail in previous publications [23, 24].

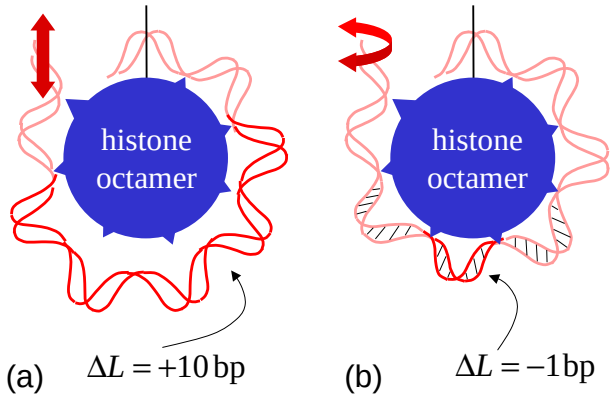

FIG. 1: Nucleosome repositioning, i.e., the sliding of the histone octamer along DNA, goes via thermally activated defects in the wrapped DNA. Two possible defect structures are: (a) bulge defects and (b) twist defects. Bulge defects contain typically an excess length of 10 bp whereas twist defects carry either an extra or a missing basepair.

The main purpose of the present paper is to fill the gap between the seemingly unrelated problems, that of the nucleosome sliding (which is presumably an important *in vivo* mechanism to expose wrapped DNA) and that of the self-propelling DNA nanomotor. As we show in Section 3 of this paper, the latter has in fact been inspired by the former. By posing the question whether we could drive the nucleosomes to slide along the DNA in a directed fashion, we are led to an answer that is already very close to our proposed nanomotor. That the nanomotor is made from pure DNA unlike the nucleosome, a DNA-protein complex, turns out to be an essential step in speeding up the motor onto a level where the proposed mechanism might be detected and used in a realistic nanotechnological application.

II. NUCLEOSOME DIFFUSION ALONG DNA

In nucleosomes DNA is wrapped in 1 and 3/4 turns of a left-handed superhelical wrapping path onto the histone octamer [3]. The DNA is bound at fourteen regions to the octamer surface, namely where the minor groove touches the protein cylinder. Each binding site, defined by charged groups and hydrogen bonds, contributes around $6k_BT$ adsorption energy that adds up to around $85k_BT$ on the whole nucleosome [25]. One should, however, be aware of the fact that a substantial part of this amount is cancelled by the bending energy required to wrap the DNA around the cylinder.

It has been observed under well-defined *in vitro* conditions that nucleosomes spontaneously reposition along DNA [26–29] transforming nucleosomal DNA into free DNA and *vice versa*. This mechanism is often referred to as "nucleosome sliding." Heat-induced repositioning turns out to be a rather slow process occurring on time scales of minutes to hours. The *in vivo* nucleosome repositioning has thus to be catalyzed by ATP consuming machines, so-called chromatin remodelling complexes [30, 31].

Repositioning experiments (reviewed in detail in Ref. [25]) have mostly been performed on short DNA fragments of lengths around 200 to 400 bp that contain one or two so-called positioning sequences. Repositioning is usually detected with the help of 2D gel electrophoresis making use of the fact that a complex with its octamer close to one of the DNA termini shows a higher electrophoretic mobility [26–28] than a complex with its octamer close to the center of the DNA fragment. These studies showed that heat-induced repositioning is a slow process that takes place on the time scale of minutes to hours [26, 29] at elevated temperatures (say 37°) whereas at low temperatures like 5° it is not observed. Another interesting feature is that the octamer is found at a preferred position (as mentioned above the DNA contains a positioning sequence) or multiples of 10 bp, the DNA helical pitch, apart [26, 29]. On longer DNA fragments no evidence for repositioning over larger distances along the DNA chain has been found [27].

What is the mechanism underlying this nucleosome mobility? An ordinary sliding of the DNA on the protein spool is energetically too costly since a bulk sliding motion would involve the simultaneous breakage of the 14 point contacts which amounts to $85k_BT$ desorption energy, i.e., this event does never occur spontaneously on any reasonable time scale. Also an alternative mechanism where the octamer "rolls" along the DNA makes no sense: The helical wrapping path would simply cause the cylinder to roll off the DNA.

Repositioning must thus rely on intermediate states with a lower energetic penalty. The two possible mechanisms [25, 32] are based on small defects that spontaneously form in the wrapped DNA portion and propagate through the structure: 10 bp bulges [33, 34] (cf. Fig. 1(a)) and 1 bp twist defects [35] (cf. Fig. 1(b)). The basic idea of the bulge

mechanism is the following: First some DNA unpeels spontaneously from one of the termini of the wrapped portion [7, 36]. Then that DNA stretch is pulled in before it readsorbs thereby creating an intranucleosomal DNA bulge that stores some extra length ΔL. This bulge diffuses then along the wrapped DNA portion and finally leaves the nucleosome at either end. If the loop comes out at the end where it was created one is back at the original state. If the loop leaves at the other end, the stored length ΔL has effectively been transported through the nucleosome and the octamer has made a step of length ΔL along the DNA. The quantitative analysis provided in Ref. [34] showed that the cheapest small loop has a length $\Delta L = 10$ bp, cf. Fig. 1(a). Other loops are much more expensive since they require twisting and/or stronger bending.

But even this cheapest loop with $\Delta L = 10$ bp is very expensive with a formation cost of about $20 k_B T$ that results from desorption and bending energy. Since the formation of such bulges is a very rare event, the resulting diffusion of the octamer along the DNA is very small with a diffusion constant on the order of $D \approx 10^{-16} cm^2/s$. Thus typical repositioning times on a 200 bp DNA fragment are on the order of an hour which is in reasonable agreement with the experimental observations [26, 29]. The strong temperature dependence and most strikingly the preference for 10 bp steps – corresponding to the extra length stored in the cheapest loops – is also in excellent agreement with the experiments. All these facts strongly support the bulge picture. There is, however, one serious caveat: We found that larger loops beyond one persistence length of DNA (roughly 150 bp) are easier to form than 10 bp bulges since such loops show a small curvature and have less desorbed binding sites [34]. For short DNA segments such loops cannot occur. But even in experiments with DNA segments of length $\approx$ 400 bp no signature of a long range nucleosome repositioning has been found [27].

This discrepancy led us to reconsider the underlying mechanism by analyzing whether nucleosome repositioning could be based on twist defects instead [35]. The basic idea is here that a twist defect forms spontaneously at either end of the wrapped DNA portion. Such a defect carries either a missing or an extra bp (Fig. 1(b) shows the case of a missing bp). A twist defect is typically localized between two neighboring nucleosomal binding sites, i.e., within one helical pitch (10 bp). This short DNA portion is stretched (compressed) and overtwisted (undertwisted). The energy of a ± 1 bp twist defects was estimated from the combined stretch and twist elasticity of DNA (including the twist-stretch coupling) to be on the order of $9 k_B T$ [35]. At any given time one should thus expect to find a twist defect only on one of around thousand nucleosomes.

A twist defect can diffuse through the wrapped DNA portion. The nucleosome provides between its 14 binding sites 13 positions for the defect. A defect – say a "hole" with a missing bp – moves from one position to the next similar to the earthworm creep motion. The bp that is in contact with a binding site moves towards the defect resulting in an intermediate state with the defect being stretched out over 20 bp. This state has a smaller elastic strain but costs desorption energy. Once the next bp has bound to the nucleosome the twist defect has moved to the neighboring location. During this process the kink crosses an energetic barrier on the order of $2 k_B T$ [35]. Not all twist defects that have formed will reach the other end of the nucleosome, most fall off at the end at which they have been created. Assuming that all 13 possible defect locations are energetically equivalent one can show that only 1/13 of the defects reach ultimately the other terminus contributing to the nucleosomal mobility. Once such a twist defect has been released, the octamer makes a step by one bp *and* a rotation by 36° around the DNA axis. One might also say that the DNA performs a corresponding corkscrew motion on the nucleosome.

Twist defects lead to a shorter step size of the octamer than the loop defects (1 bp *vs.* 10 bp) but this shorter length is dramatically overcompensated by the lower activation penalty involved (roughly $9 k_B T$ *vs.* $20 k_B T$). Putting all the above given points together we were able to estimate the diffusion constant of the nucleosome along DNA to be $D_0 \approx 580 bp^2/s \approx 7 \times 10^{-13} cm^2/s$ which – to our surprise – is 3 to 4 orders of magnitude larger than the one predicted by loop defects [35]. The typical repositioning times on a 200 bp DNA fragment are thus predicted to be on the order of seconds, times much shorter than in the experiments. Also the predicted dependence of the dynamics on temperature is much too weak. Finally, there is no "built-in" mechanism for 10 bp steps of the octamer. The experimentally observed preference for positions 10 bp apart manifesting itself in characteristic bands in the products of the gel electrophoresis [26, 27] seems to be inconsistent with this mechanism – at least at first sight.

Here comes into a play an important additional feature of the repositioning experiments, namely that they are typically performed with DNA segments containing strong positioning sequences, especially the sea urchin 5S positioning element [26–28], a sequence that shows a highly anisotropic bendability of the DNA. If repositioning is based on twist defect, then the DNA has to bend in the course of a 10 bp shift in all directions inducing a barrier for the corkscrew sliding. The elastic energy of the bent DNA is then approximately a periodic function of the nucleosome position with the helical pitch as its period. We approximated this energy by an idealized potential of the form $U(l) = (A/2)\cos(2\pi l/10)$ with l being the bp number and A denoting the difference in elastic energy between the optimal and the worst rotational setting [35]. In principle, these oscillations die out completely when the nucleosome leaves the positioning sequence, i.e., if it has moved around 140 bp. But since the templates are usually quite short (on the order of 200 bp) the nucleosome always feels the rotational signal from the positioning sequence and our elastic energy should provide a reasonable description. As a result the nucleosomal diffusion constant is reduced to

the value [35]:

$$D = \frac{D_0}{I_0^2\left(A/2k_BT\right)} \simeq \begin{cases} \frac{D_0}{1+A^2/8(k_BT)^2} & \text{for } A < k_BT \\ D_0 \frac{\pi A}{k_BT} e^{-A/k_BT} & \text{for } A \gg k_BT \end{cases} \quad (1)$$

where I_0 denotes the modified Bessel function and D_0 the diffusion constant for diffusion along isotropically bendable DNA, $D_0 \approx 580bp^2/s$.

The sea urchin 5S positioning element features a barrier $A \approx 9k_BT$ [37, 38] reducing the diffusion constant to $D \approx 2\times10^{-15}cm^2/s$. The typical repositioning times on a 200 bp DNA segment are now 2 to 3 orders of magnitude longer, i.e., they are on the order of an hour – remarkably just as the ones in the loop case. Equilibrium thermodynamics predicts that the probability of finding the DNA wrapped in its preferred bending direction is much higher than in an unfavorable direction. Thus also in the case of 1 bp defects we expect to find nucleosomes mostly at the optimal position or 10, 20, 30 etc bp apart corresponding to locations where still most of the positioning sequence is associated with the octamer and this in the preferred rotational setting. The bands in the gel electrophoresis experiments would just reflect the Boltzmann distribution of the nucleosome positions rather than an intrinsic step length of the underlying repositioning mechanism. In other words, both the 10 bp bulge and the 1 bp twist defect lead in the presence of a rotational positioning sequences to pretty much the same prediction for the experimentally observed repositioning – even though the elementary motion is fundamentally different.

This leads to the question whether there are experimental data available from which the underlying mechanism can be induced. The most straightforward way would be to use a DNA template without positioning elements but such experiments have not been performed up to now. A different experimental approach was taken by Gottesfeld *et al.* [39]. In this study repositioning on a 216 bp DNA fragment was analyzed, again with the sea urchin 5S rDNA nucleosome positioning sequence. The additional feature in this experiment was the presence of pyrrole-imidazole polyamides, synthetic minor-groove binding DNA ligands, that are designed to bind to specific target sequences. Experiments have been performed in the presence of one of 4 different ligands, each of which had one binding site on the nucleosomal DNA. It was found that a one-hour incubation at 37° in the absence of any ligand leads to a redistribution of the nucleosomes. The redistribution was completely suppressed in the presence of 100 nM ligands *if* the target sequence of this specific ligand faces outside (towards the solution) when the nucleosomal DNA is bent in its preferred direction. On the other hand, a ligand whose binding site faces the octamer in its preferred rotational frame had no detectable effect on the reposition dynamics.

Can this experiment determine the mechanism underlying repositioning? Since the ligands bind into the minor groove (as can be seen from the co-crystal complexes between nucleosomes and such ligands [40]) it is quite likely that a bound ligand will block the overall corkscrew motion of the DNA: The DNA can only rotate on the nucleosome up to a point where the bound ligand comes close to one of the 14 binding sites. The observed suppression of mobility through ligand binding is therefore consistent with the twist defect picture. The case of bulge defects is unfortunately not obvious. But at least in first approximation it seems plausible to assume that a bound ligand does not hinder bulge diffusion. Overall, the strong influence of ligand binding on nucleosome mobility supports the twist defect picture.

In Ref. [41] we calculated the nucleosome mobility along DNA in the various cases. In our model we assume that the nucleosome in the presence of a ligand can be in three states (cf. Fig. 2): Either the rotational setting of the wrapped DNA is such that its binding site is occluded (Fig. 2(a)) or it is facing the solution without a ligand (Fig. 2(b)) or with the ligand bound (Fig. 2(c)). Assuming thermodynamic equilibrium it is straightforward to determine the diffusion constant in the various cases. We find for the case of a rotational position sequence with $A \gg k_BT$ in the presence of a ligand whose binding site is exposed in the preferred rotational frame

$$D = \frac{\pi A e^{-A/k_BT}}{k_BT} \frac{D_0}{1+K} \quad (2)$$

For the case of a ligand whose binding site is preferentially occluded we obtain

$$D = \frac{\pi A}{k_BT} \frac{D_0}{e^{A/k_BT}+K} \quad (3)$$

In Eqs. 2 and 3 $K = [L]/K_d$ denotes the equilibrium constant of the ligand of concentration $[L]$ and dissociation constant K_d. In the absence of ligands $K = 0$ and Eqs. 2 and 3 reduce to Eq. 1.

Equations 2 and 3 provide an estimate of the influence of ligands on repositioning dynamics. In the following we define the typical equilibration time on a 216 bp long template (as used in Ref. [39]) as $T_{70bp} = (216-146)^2\, bp^2/(2D)$. For an isotropic piece of DNA we have $D = D_0 \approx 580bp^2/s$ leading to a typical equilibrium time $T_{70bp} = 4s$. For a positioning sequence with $|\Delta G_{12}| = 9k_BT$ one finds in the absence of ligands from Eq. 1 $D \approx 2bp^2/s$ and $T_{70bp} \approx 20min$. In such experiments repositioning is typically found on the time scale of an hour [26, 39]. In the

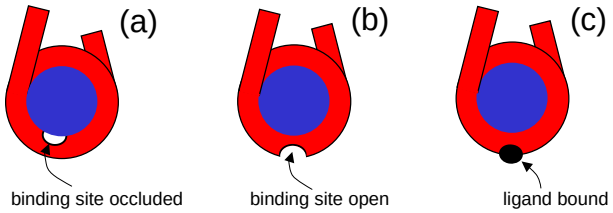

FIG. 2: Nucleosome repositioning in the presence of DNA ligands that bind to a specific target site on the wrapped DNA. The nucleosome can be in 3 different states, namely (a) with its ligand binding site occluded, (b) with its binding site open and (c) with a bound ligand. A nucleosome in state (c) cannot perform any corkscrew sliding.

presence of a ligand with $[L] = 100$ nM and $K_d = 1$ nM with its binding site open in the preferred rotational frame, Eq. 2 predicts a dramatic reduction of the diffusion constant by a factor of 100: $D \approx 2 \times 10^{-2} bp^2/s$ and $T_{70bp} \approx 34h$. In this case one does not observe any repositioning of the nucleosomes on the time scale of an hour which is in accordance with the experimental observations [39]. On the other hand, ligands with the same affinity and concentration but with the binding site in the unfavorable orientation have no appreciable effect on repositioning since the diffusion constant is only reduced by about one percent, cf. Eq. 3 and Ref. [39].

Concluding there is strong experimental evidence that autonomous repositioning of nucleosomes is based on twist defects. This process is slow in experiments since they are performed on DNA templates that contain nucleosome positioning sequences. However, as mentioned above only a small fraction of eukaryotic genomic DNA ($< 5\%$ [5]) seems to contain positioning sequences. This suggests a very dynamic picture of chromatin where the majority of nucleosomes are incessantly sliding along DNA – as long as they are not pinned to their location via linker histones [28].

Nucleosomal mobility has also profound consequences for the interaction of nucleosomes with motor proteins. Since most nucleosomes seem to be rather mobile, it might be that only positioned nucleosomes need the action of active (ATP consuming) remodelling mechanisms [42] making them switching elements bringing about e.g. gene activation or repression. Such chromatin remodelling complexes might catalyze the formation of twist defects or of bulges. In a recent experiment [43] it was found that a remodelling complex induced nucleosome repositioning even when the DNA was nicked and a torsion could not be transmitted – suggesting that at least for this specific example active repositioning might involve loop defects.

III. HOW TO INDUCE DIRECTED NUCLEOSOME SLIDING

As discussed in the previous section twist defects that form spontaneously on the nucleosomal DNA lead to a random diffusion of the protein cylinder along the DNA with the DNA double helix acting as a molecular corkscrew. In this section we pose the question whether it is possible to rectify this motion such that the nucleosome slides only in one direction along the DNA. We are looking for an "internal" mechanism causing the directionality instead of a directionality that is imposed from the outside (e.g. via the action of a transcribing RNA polymerase [41] or a chromatin remodelling complex [42]). How can we inscribe into a nucleosome a directionality? As we show in the following one can in principle use a DNA chain with an appropriate basepair sequence such that the DNA elastic bending energy stored in the nucleosome as a function of its position on the DNA shows a ratchet shape. Having a ratchet allows then to drive the nucleosome in one direction by applying e.g. periodic temperature oscillations in the spirit of the ratchet models [44, 45].

We have seen already before Eq. 1 that a nucleosome positioning sequences can lead to a periodic bending potential as a function of the nucleosome location. There we assumed a sinoidal potential as a reasonable description of the bending potential. Can one also choose a sequence that would lead to a ratchet? This is indeed possible. Crucial is here the fact that DNA – depending on its underlying bp sequence – can show quite exotic elastic properties. For instance, there are basepair sequences that lead to an intrinsic curvature of DNA. A nucleosome that slides in a corkscrew motion along such a DNA chain will feel a periodic elastic potential with the helical pitch of DNA (around $L = 10bp$) as periodicity (after a full corkscrew turn the DNA is again wrapped in the direction of its intrinsic curvature). There are other sequences that induce anisotropic bendability of DNA such that the chain is more easy bendable in one plane than in the plane perpendicular to it. A nucleosome sliding along such a chain will feel a periodicity of half a pitch (after half a corkscrew turn the DNA is again wrapped in its favorable bending plane around the nucleosome). As shown in the following a basepair sequence that combines both features (intrinsic curvature and anisotropic bendability) results typically in a ratchet shape of the elastic energy as a function of the

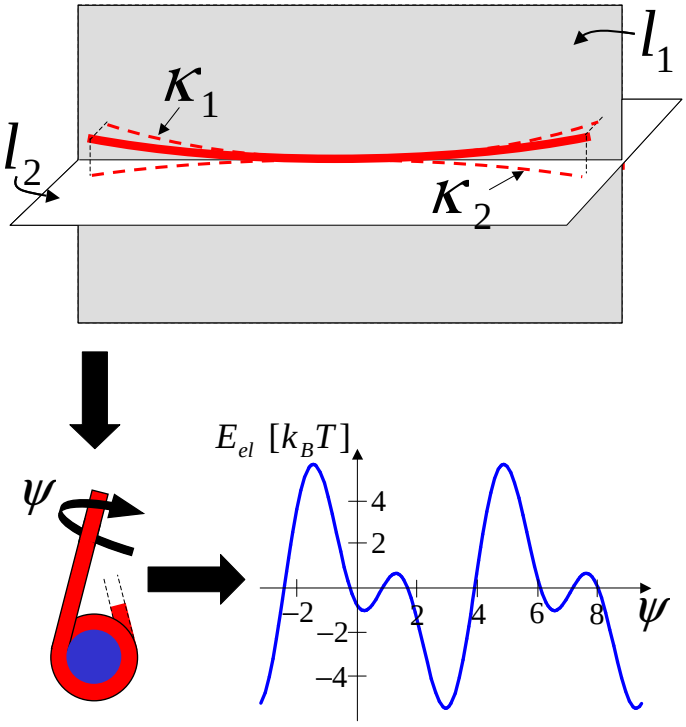

FIG. 3: Wrapping a stretch of a DNA chain with anisotropic bendability and bendedness onto a histone octamer leads in general to ratchet-shaped bending potentials. Shown are on top the two principal bending directions with persistence lengths l_1 and l_2 and the intrinsic curvatures κ_1 and κ_2 in the corresponding perpendicular directions. The plot on the bottom right gives the elastic energy, Eq. 4, as a function of the wrapping angle ψ for the following parameters: $l_1 = 45$ nm, $l_2 = 50$ nm and $\kappa_1 = \kappa_2 = (200\text{nm})^{-1}$.

nucleosome position.

We assume in the following that the elastic energy of such a DNA chain is quadratic in deviations from its ground-state. The anisotropic bendability is characterized by two principal bending persistence lengths l_1 and l_2 and the intrinsic curvature by its values κ_1 and κ_2 in the two corresponding perpendicular directions, cf. Fig. 3. For simplicity we assume these parameters to be independent of the arc-length throughout the chain [46]. The elastic distortion energy of the chain parametrized by the arc length parameter s is then described by three Euler angles $\theta(s), \phi(s)$ and $\psi(s)$ via $E_{el} = \frac{1}{2} k_B T \int_0^{2\pi R} \sum_{i=1,2,3} l_i (\omega_i - \kappa_i)^2 \, ds$ with $\omega_1 = \phi' \sin\theta \sin\psi + \theta' \cos\psi$, $\omega_2 = \phi' \sin\theta \cos\psi - \theta' \sin\psi$ and $\omega_3 = \phi' \cos\theta + \psi'$ [23]. l_3 denotes the twist persistence length and – for simplicity – we choose $\kappa_3 = 0$.

Assume now that a DNA stretch (of length l_{wrap}) is wrapped onto a histone octamer, Fig. 3. This leads then to the required ratchet potential acting on ψ:

$$\frac{E_{el}(\psi)}{k_B T} = \left[\frac{l_1 - l_2}{4R^2} \cos(2\psi) + \frac{l_1 \kappa_1}{R} \cos\psi - \frac{l_2 \kappa_2}{R} \sin\psi \right] l_{wrap} \tag{4}$$

where $R = 4.3$ nm is the radius of curvature of the bent DNA portion of length $l_{wrap} = 43$ nm around the nucleosome [25]. From Eq. 4 we see that for generating a ratchet potential we need both nonzero bending anisotropy, $l_1 - l_2 \neq 0$, as well as non-vanishing intrinsic curvatures, $\kappa_{1,2} \neq 0$. Fig. 3 demonstrates that reasonable small values of anisotropy and intrinsic curvature can induce a well-defined ratchet potential.

We have now indeed a directionality along the DNA chain. But having a ratchet alone will not induce a directed motion of the nucleosome. This can be achieved via non-equilibrium fluctuations exploiting the ratchet effect [44, 45]. Specifically, we might either periodically switch on and off the ratchet potential or we might periodically change the temperature. In both cases, the overall principle is the same. If the ratchet is switched on (or for low temperatures) the nucleosome is more or less stuck in one of the minima of the ratchet. If the ratchet is switched off (or for very high temperatures) the nucleosome is diffusing freely along the DNA. If the frequency of the switching (or of the temperature oscillation) is chosen properly, then the nucleosome should perform a directed motion. What is the optimal frequency? The idea is to choose the time during which the random walker is diffusing freely such that the width of the resulting probability distribution of the nucleosome position is just on the order of the period L of the

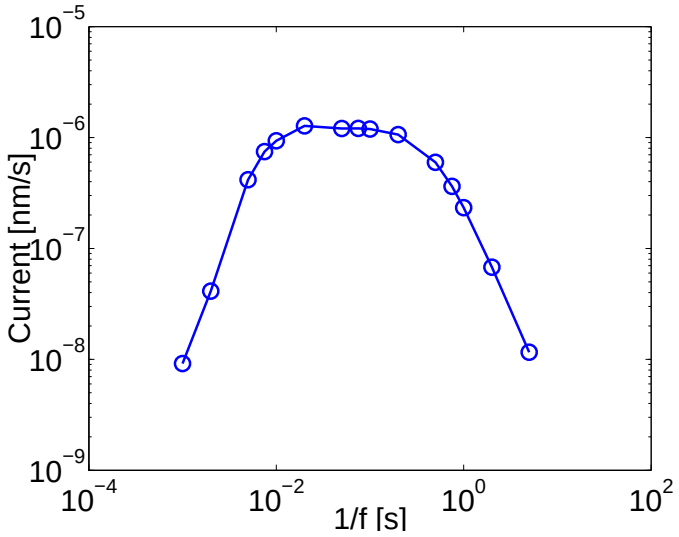

FIG. 4: Current per nucleosome along the DNA chain as a function of the inverse frequency, $1/f$, of the temperature oscillations given by Eq. 5 with $A_T = 1/30$. The elastic parameters of the DNA are chosen as in Fig. 3. Note the extremely slow maximal velocity on the order of $10^{-6} nm/s$ of the nucleosome that reflects the high friction between DNA and the protein cylinder.

ratchet potential. When after this time the ratchet (cf. Fig. 3) is switched on again, there are many more realizations where the random walker has managed to escape over the maximum to the right than over the maximum to the left. In other words, there will be a directed current to the right. Clearly, if the frequency is much larger or smaller than this optimal frequency the transport will be much less effective.

Let us give a very optimistic upper bound for the current that we might hope to achieve. The diffusion law tells us that the optimal frequency should be close to $f = 2D_0/L^2$ which leads for the nucleosomal diffusion constant $D_0 = 580 bp^2/s$ (see previous section) and a repeat length of 10 bp, i.e., 3.4 nm to an optimal frequency around $12 s^{-1}$. If during each time period the nucleosome would make a step to the next minimum to the right, the nucleosome would slide with a speed of around $40 nm/s$. This would indeed be quite an impressive directed motion.

Unfortunately our estimate is a few orders of magnitude too optimistic. In fact, we cannot hope to be able to switch the ratchet on and off or to achieve correspondingly strong temperature oscillations. Suppose we would manage to impose a temperature program of the form

$$T(t) = T_0 \left[1 + A_T \sin(2\pi f_T t)\right] \tag{5}$$

with a temperature amplitude of $\Delta T = \pm 10$ K, i.e., $A_T = 1/30$ (at room temperature $T_0 = 300$ K). In that case the barrier height of the ratchet in units of $k_B T(t)$ will vary only slightly and the nucleosome has on its corkscrew path to overcome substantial barriers – even at the elevated temperature.

The resulting flux of the nucleosome can be calculated numerically from the corresponding Fokker-Planck equation that describes the time evolution of the probability density $P(\psi, t)$ of the Euler angle ψ:

$$\zeta \frac{\partial P}{\partial t} = \frac{\partial}{\partial \psi}\left(\frac{\partial E_{el}}{\partial \psi} P + k_B T \frac{\partial P}{\partial \psi}\right) \tag{6}$$

with the twirling potential E_{el} given by Eq. 4 and the friction constant $\zeta = k_B T/D_0$ with $D_0 = 580 bp^2/s$. The sliding speed v follows then from

$$\langle \dot{\psi} \rangle = -\frac{1}{\zeta} \langle \frac{\partial E_{el}}{\partial \psi} P + k_B T \frac{\partial P}{\partial \psi} \rangle \tag{7}$$

via $v = (3.4 nm/2\pi)\, \langle \dot{\psi} \rangle$.

In Fig. 4 we plot the nucleosomal speed as a function of the inverse frequency of the above mentioned temperature oscillations. As can be seen there the maximal velocity occurs around a frequency of $50 s^{-1}$, i.e. around a similar value than the one we found in the simple argument given above. However, the maximal speed is with $v = 1.3 \times 10^{-6} nm/s$ extremely slow, in fact 10^7 orders of magnitude slower than we might have hoped for from our upper bound estimate.

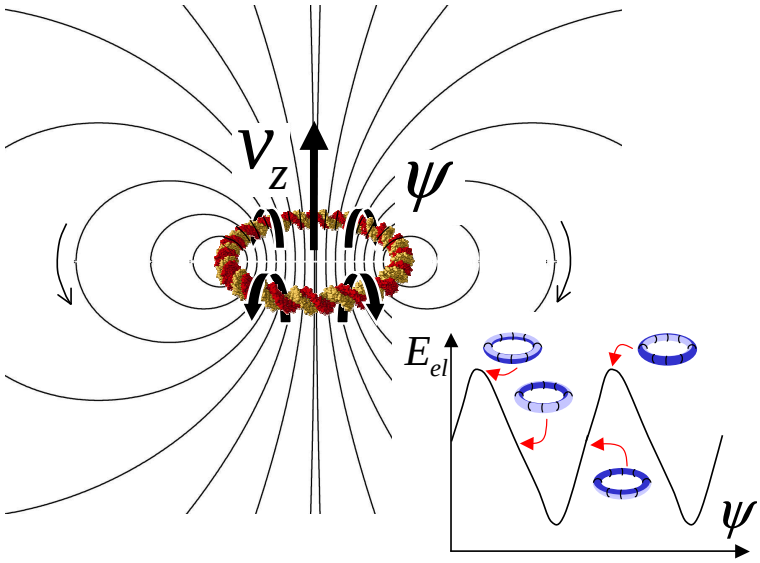

FIG. 5: The twirling DNA-minicircle together with the flowfield that induces its translational velocity v_z. The inset depicts schematically the elastic energy of the ring as a function of the twirling angle ψ that shows a ratchet shape for suitably chosen DNA sequences (cf. text for details).

Is there any possibility to improve the performance of the directed corkscrew sliding? The major problem is the very high friction between the DNA and the protein cylinder. The friction of the cylinder along the DNA is with $\zeta = 0.06pNnm/s$ much larger than the hydrodynamic friction of a Stokes sphere of the size of a nucleosome, $\zeta_{hydro} = 6\pi\eta R_0 = 10^{-7}pNnm/s$ with $R_0 = 5nm$ ($\eta = 10^{-3}$ Pa s, the water viscosity). This huge difference is due to the fact that a repositioning step of the nucleosome by 1 basepair requires the creation of a twist defect that costs $9k_BT$ and its subsequent diffusion around the nucleosome.

To achieve a motor with a reasonable speed we need to somehow "lubricate" the interface between the DNA and the histone octamer. This, however, seems to be difficult. In Ref. [23] we came up with a much simpler solution, namely to get rid of the protein cylinder altogether.

IV. SELF-PROPELLING DNA RING

The nanomotor proposed in Ref [23] is a DNA miniplasmid. Despite its structural simplicity this ring can be run as a motor, performing a continuous rotation with a frequency of $10^2 - 10^4$ Hz. The relevant degree of freedom is here the Euler-angle ψ (cf. Fig. 5). It is easy to show that provided that the plasmid length is smaller than the DNA persistence length l_P all other degrees of freedom besides the ψ motion can be neglected. The main idea is to induce a directed current $\langle\dot{\psi}\rangle$ – in a manner similar to the rotation of a closed rubber tube around its central circular axis. This is again achieved via non-equilibrium fluctuations exploiting the ratchet effect, cf. also the inset of Fig. 5. As a result the twirling ring generates a hydrodynamic flowfield (also shown in Fig. 5) that remarkably induces a self-propulsion of the motor as detailed below.

First let us calculate the elastic energy of the ring as a function of the twirling angle ψ. We assume again a piece of DNA with an anisotropic bendability and an intrinsic curvature that we now close into a circle. For the case of a DNA minicircle of short length, $2\pi R < l_i$ and with constant κ_i and l_i fulfilling the weak bending anisotropy condition $\max\{|l_1 - l_2|/R, l_1\kappa_1, l_2\kappa_2\} \ll l_3/R$ only the conformations close to the circular untwisted state will contribute, i.e., those close to $\theta(s) = \pi/2$, $\phi(s) = s/R$ and $\psi(s) = const.$ We find then from the generalized WLC Hamiltonian provided before Eq. 4 the required ratchet potential as a function of ψ:

$$\frac{E_{el}(\psi)}{\pi k_B T} = \frac{l_1 - l_2}{2R}\cos(2\psi) + 2l_1\kappa_1\cos\psi - 2l_2\kappa_2\sin\psi \tag{8}$$

In Ref. [23] we calculated the hydrodynamics of a twirling ring in the limit of low Reynolds numbers in the so-called slender body approximation [48]. We determined the full velocity profile, cf. also the stream lines around the rotating

ring shown in Fig. 5. The most interesting finding is that a twirling ring attains a net velocity:

$$v_z\left(\omega_{\mathbf{c}}\right) = \frac{r_0^2}{2R}\left(\ln\left(8\frac{R}{r_0}\right) - \frac{1}{2}\right)\omega_{\mathbf{c}} \tag{9}$$

where r_0 denotes the radius of the cylinder bent into a torus (here the radius of the DNA double helix). This velocity results from the fact that the outer surface area of the torus is larger than the inner one and that they move in opposite direction when the ring twirls. More generally by virtue of the linearity of the Stokes equations we derived in Ref. [23] the resistance matrix (M_{kl}) relating the angular velocity $\omega_{\mathbf{c}}$ (about the circular axis $\mathbf{c}$) and velocity v_z (in the z-direction) with the corresponding external torque $N_{\mathbf{c}}$ (about $\mathbf{c}$) and force F_z :

$$\begin{pmatrix} F_z \\ N_{\mathbf{c}} \end{pmatrix} = 4\pi^2\eta \begin{pmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{pmatrix} \begin{pmatrix} v_z \\ \omega_{\mathbf{c}} \end{pmatrix} \tag{10}$$

with $M_{11} = 2R\left(\ln 8/\varepsilon + 1/2\right)^{-1}$, $M_{22} = 2r_0^2 R$ and $M_{12} = M_{21} = r_0^2\left(\ln 8/\varepsilon - 1/2\right)\left(\ln 8/\varepsilon + 1/2\right)^{-1}$ where $\varepsilon = r_0/R$ is the small parameter. From Eq. 10 follows the angular friction constant in leading order

$$\zeta = N_{\mathbf{c}}\left(\omega_{\mathbf{c}}\right)/\omega_{\mathbf{c}} \approx 8\pi^2\eta r_0^2 R \tag{11}$$

Note that the latter is the same (in the $\varepsilon \ll 1$ leading order expansion) as for a straight cylinder with radius r_0 and length $2\pi R$.

Another interesting feature that can be read off Eq. 10 is the efficiency of the twirling ring propulsion. This defined as the ratio of the power $P_{rigid} = 2\pi^2\eta M_{11} v_z^2$ dissipated by a (for simplicity) rigid ring directly moved by a force as compared to the power $P_{twirl} = \frac{1}{2}N_{\mathbf{c}}\omega_{\mathbf{c}}$ dissipated by twirling propulsion at the same translational speed. For a ring with $R = 10$ nm we find $P_{rigid}/P_{twirl} \approx 0.8\%$, a number comparable to the efficiency of bacterial propulsion by a rotating flagellum [49].

The Fokker-Planck equation describing the time evolution of the probability density $P\left(\psi, t\right)$ of the Euler angle ψ of our twirling DNA motor is again given by Eq. 6 but now with the twirling potential Eq. 8 and the angular friction constant Eq. 11. To induce a directed twirling frequency $\omega_{\mathbf{c}} = \langle\dot{\psi}\rangle$ we choose a periodic time dependent temperature variation given by Eq. 5.

How fast can we operate the twirling DNA ring? Assume some realistic parameter values for a DNA minicircle, namely $R = 10$ nm, $r_0 = 1$ nm leading to $\zeta = 2 \cdot 10^{-7} k_B T$s. The characteristic relaxation time of the twirling degree of freedom is then given by $\tau_0 = 4\pi^2\zeta/\left(k_B T_0\right) = 8 \times 10^{-6} s$. Furthermore we chose the same bendabilities and intrinsic curvatures for the DNA as in the previous section, i.e., $l_1 = 45$ nm, $l_2 = 50$ nm, $\kappa_1 = \kappa_2 = (200\text{nm})^{-1}$. Equation 8 leads then to the ratchet displayed in the inset of Fig. 6. For the temperature variation amplitude we choose – as before – $\Delta T = \pm 10$ K, i.e., $A_T \approx 1/30$. Figure 6 provides a log-log plot of the rotational current and the corresponding drift speed of the ring as a function of the dimensionless frequency $\tilde{f} = f_T \tau_0$ of the temperature variation. The thin solid curve gives the numerical result obtained from Eq. 6, the two straight lines correspond to analytical results for the two asymptotic cases derived in Ref. [24] that show a $\tilde{f}^{-2}$ and $\tilde{f}^2$ dependence (cf. Eqs. 9 and 10 in that paper). The maximal rotational current is achieved in the crossover region, namely $\omega_{\mathbf{c}} \approx 200$rad/s for $\tilde{f} \approx 10^{-1}$. Following Eq. 9 this implies a translational velocity of $v_z = 50$nm/s.

Such fast temperature oscillations are technically feasible and might be generated by adiabatic pressure variations via ultrasound as nowadays employed in the field of sonochemistry and sonoluminescence [51]. Despite potentially large temperature oscillations (up to 3000 K on short timescales) achievable by this method, the shearing forces might however pose problems for the integrity of the DNA molecule. A more promising method might be to exploit the broad electromagnetic absorption spectrum of the DNA molecule (and its ordered water shell) ranging from UV to microwave frequencies and to heat the molecule selectively with short light pulses. The covalent modification of the DNA backbone with artificial fluorophores [52] and nanoncrystals [53] can expand the range of frequencies for electromagnetic heating. In fact, inductively heated gold nanoparticles attached to the DNA backbone have been successfully used to control the melting of DNA [54].

The latter might also point towards an alternative way of driving the ratchet, namely via a periodic variation of the elastic properties of the ring. Operating the system close to the DNA duplex melting temperature is likely to induce strong oscillations in the overall ring stiffness. Above the melting temperature of $50 - 70°$C [55] the DNA molecule dissociates into two single strands with negligible bending stiffness [56]. Therefore it is not unreasonable to assume that the oscillation of the bending potential amplitude becomes the major effect then varying by a factor of $\sim O(1)$ (in the vicinity of the melting temperature). The thick solid line in Fig. 6 shows the rotational current obtained when the elastic energy is varied as $\tilde{E}_{el}\left(\psi, t\right) = E_{el}\left(\psi\right)\left(1 + A_E \sin\left(2\pi f_E t\right)\right)$ where we chose the relative amplitude $A_E = 0.3$.

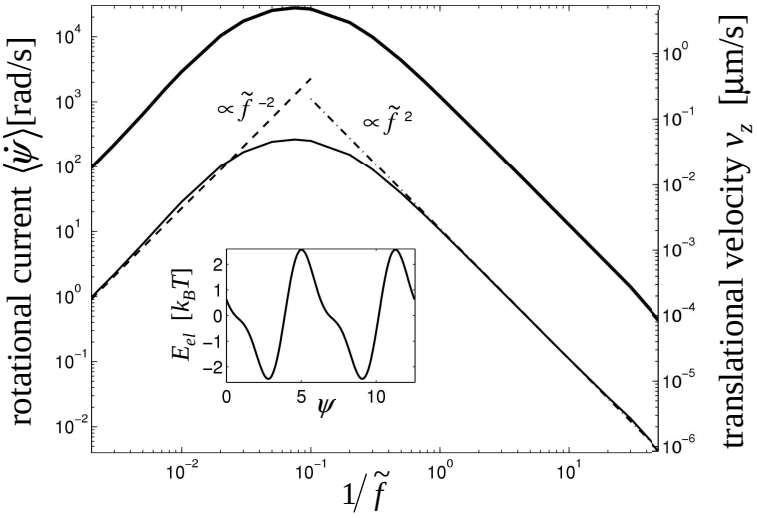

FIG. 6: The rotational current $\langle\dot{\psi}\rangle$ and the induced translational velocity v_z as a function of the dimensionless frequency $\tilde{f}$ of the temperature (potential) oscillations. The DNA ring has the following parameters: $R = 10nm$, $r_0 = 1nm$ (typical DNA minicircle), $l_1 = 45$ nm, $l_2 = 50$ nm, $\kappa_1 = \kappa_2 = (200\text{nm})^{-1}$ leading to the ratchet potential displayed in the inset. Displayed is the numerical solution of Eq. 6 (thin line) for a temperature ratchet with $A_T = 0.03$ together with the asymptotic expressions, Eqs. 9 (dashed line) and 10 (dashed-dotted line) of Ref. [24]. The thick solid line corresponds to an oscillating potential ratchet with $A_E = 0.3$. See text for details.

As can be seen from Fig. 6 the maximal current of this oscillating potential ratchet occurs roughly at the same frequency as that of the thermal ratchet but the value of $\omega_{\mathbf{c}}$ is much higher, namely on the order of 2×10^4rad/s which implies a quite notable translational velocity of $v_z = 5\mu$m/s. As a comparison a typical bacterium moves at 30μm/s. Our ring ratchet (with oscillating potential) with its nanoscopic size (radius 10 nm), swimming efficiency (0.8%) and speed (5μm/s) resembles in several respects "real" biological nanomotors. Note, however, that the produced forces are comparably small. Especially the net translational force is small due to cancellation of most of the stresses, namely according to Eq. 10 $F_z = 4\pi^2\eta M_{12}\omega_{\mathbf{c}} \approx 0.6$ fN. Stronger is the local torque $N_{\mathbf{c}} = 8\pi^2\eta r_0^2 R\omega_{\mathbf{c}} \approx 0.004 k_BT$ resulting in the force $F_{loc} = N_{\mathbf{c}}/r_0 = \zeta\omega_{\mathbf{c}}/r_0 \approx 16$ fN acting at the DNA surface.

How can one detect experimentally the effect of ring twirling? First of all one should be aware of the fact that a ring (twirling or non-twirling) looses its initial orientation almost instantaneously due to rotational diffusion. The typical relaxation time scale of this process is on the order $\eta R^3/(k_BT)$ which for a ring with $R = 10$ nm leads to 10^{-7} s. That means that a single twirling ring in solution will not perform any noticeable translational drift. A possible solution to the problem is to put the ring on a long DNA "track", e.g. to thread it on a straightened DNA chain. The DNA track can be stretched out by standard single molecule techniques and both the ring and the DNA track can be optically traced after fluorescent labelling, similarly to the DNA knot diffusion essays (cf. e.g. [57]). A ring with speed $v_{\max} = 5\mu$m/s will then overcome dispersion due to translational diffusion after 2 seconds and show significant changes in the concentration profile over distances $k_BT/F_z \approx 7\mu m$.

Another possible direction is to prepare semi-dilute or dense solutions of such rings and then study their response to an induced twirling. It is known that solutions of self-propelled particles show ordering as well as hydrodynamic instabilities [58], e.g. the low-Reynolds number turbulence observed for suspensions of bacteria [59]. The presence of the ratchet effect combined with the hydrodynamic coupling between twirling rings might induce detectable corrections to their pair-correlation function.

The fact that our minicircle nanomachine is fully based on DNA opens the intriguing possibility of finding the best sequences by exploiting the known methods of in vitro evolution (SELEX [60]). The experimental feasibility of finding the most agile DNA swimmers will strongly depend on the practical design of high yield assays for separation of the "good swimmer" fraction from the less mobile minicircle population.

V. SUMMARY

To conclude, we demonstrated that the experimental evidence points towards the fact that the autonomous repositioning of nucleosomes along DNA – as observed in *in vitro* setups – is based on twist defects that propagate through

the wrapped DNA portion. As a result a nucleosome diffuses along DNA in a corkscrew fashion. This motion can be suppressed by the addition of minor groove binding ligands that sterically block the corkscrew motion.

We posed then the question whether we could induce a directed motion of a nucleosome along DNA. To achieve directionality we proposed to use DNA with an anisotropic bendability and an intrinsic curvature. We demonstrated that in this case the bending energy of the wrapped DNA as a function of the nucleosome position shows in general a ratchet shape. We calculated typical velocities that could be induced via periodic temperature oscillations employing the ratchet effect and found that those are many orders of magnitudes too small to make this effect detectable. The high friction between the histone octamer and the DNA was identified as the major obstacle in this system.

We showed then that by removing the protein components one can construct a much faster nanomotor. To bend the DNA we simply suggested to close the chain into a minicircle. The induced twirling frequency shows then hundreds of turns per second. Moreover, we found that the ring propels itself tens of nanometers per second. The performance of the motor is satisfying considering the simplicity of the setup but the small size of the motor makes is very susceptible to thermal noise: A directed motion of the ring is not possible due to the very rapid rotational diffusion. We suggested to study solutions of motors where collective effects of the twirling rings might be easily detectable.

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[1] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson, *Molecular Biology of the Cell*, Garland, New York, **1994**.
[2] K. E. van Holde, *Chromatin*, New York, Springer, **1989**.
[3] K. Luger, A. W. Mader, R. K. Richmond, D. F. Sargent, and T. J. Richmond, *Nature* 389, 251 (**1997**).
[4] P. J. Horn and C. L. Peterson, *Science* 297, 1824 (**2002**).
[5] P. T. Lowary and J. Widom, *J. Mol. Biol.* 276, 19 (**1998**).
[6] J. L. Workman and R. E. Kingston, *Annu. Rev. Biochem.* 67, 545 (**1998**).
[7] K. J. Polach and J. Widom, *J. Mol. Biol.* 254, 130 (**1995**); 258, 800 (**1996**).
[8] I. M. Kulić and H. Schiessel, *Phys. Rev. Lett.* 92, 228101 (**2004**).
[9] B. Yurke, A. J. Turberfield, A. P. Mills, F. C. Simmel, and J. L. Neumann, *Nature* 406, 605 (**2000**).
[10] F. C. Simmel and B. Yurke B 2001 *Phys. Rev. E* 041913 (**2001**).
[11] H. Yan, X. Zhang, Z. Shen, and N. C. Seeman, *Nature* 415, 62 (**2002**).
[12] J. J. Li and W. Tan, *Nano Lett.* 2, 315 (**2002**).
[13] L. Feng, S. H. Park, J. H. Reif, and Yan H, *Angew. Chem. Int. Ed.* 42, 4342 (**2003**).
[14] A. J. Turberfield, J. C. Mitchell, B. Yurke, A. P. Mills, M. I. Blakey, and F. C. Simmel, *Phys. Rev. Lett.* 90, 118102 (**2003**).
[15] D. Liu and S. Balasubramanian, *Angew. Chem. Int. Ed.* 42, 5734 (**2003**).
[16] W. B. Sherman and N. C. Seeman, *Nano Lett.* 4, 1203 (**2004**).
[17] Y. Chen and C. Mao, *J. Am. Chem. Soc.* 126, 8626 (**2004**).
[18] J.-S. Shin and N. A. Pierce, *J. Am. Chem. Soc.* 126, 10834 (**2004**).
[19] Y. Tian Y and C. Mao, *J. Am. Chem. Soc.* 126, 11410 (**2004**).
[20] C. Mao, W. Sun, Z. Shen and N. C. Seeman, *Nature* 397, 144 (**1999**).
[21] P. Alberti and J.-L. Mergny, *Proc. Natl. Acad. Sci. USA* 100, 1569 (**2003**).
[22] Y. Chen, S.-H. Lee, and C. Mao, *Angew. Chem. Int. Ed.* 43, 5335 (**2004**).
[23] I. M. Kulić, R. Thaokar, and H. Schiessel, *Europhys. Lett.* 72, 527 (**2005**).
[24] I. M. Kulić, R. Thaokar, and H. Schiessel, *J. Phys.: Condens. Matter* 17, S3965 (**2005**).
[25] H. Schiessel, *J. Phys.: Condens. Matter* 15, R699 (**2003**).
[26] S. Pennings, G. Meersseman, and E.M. Bradbury, *J. Mol. Biol.* 220, 101 (**1991**).
[27] G. Meersseman, S. Pennings, and E.M. Bradbury, *EMBO J.* 11, 2951 (**1992**).
[28] S. Pennings, G. Meersseman, and E. M. Bradbury, *Proc. Natl. Acad. Sci.* 91, 10275 (**1994**).
[29] A. Flaus, and T.J. Richmond, *J. Mol. Biol.* 275, 427 (**1998**).
[30] R. D. Kornberg and Y. Lorch, *Cell* 98, 285 (**1999**).
[31] P. B. Becker, *EMBO J.* 21, 4749 (**2002**).
[32] A. Flaus and T. Owen-Hughes, *Biopolymers* 68, 563 (**2003**).
[33] H. Schiessel, J. Widom, R.F. Bruinsma, and W.M. Gelbart, *Phys. Rev. Lett.* 86, 4414 (**2001**); Erratum: *Phys. Rev. Lett.* 88, 129902 (**2002**).
[34] I. M. Kulić and H. Schiessel, *Biophys. J.* 84, 3197 (**2003**).
[35] I. M. Kulić and H. Schiessel, *Phys. Rev. Lett.* 91, 148103 (**2003**).
[36] J. D. Anderson and J. Widom, *J. Mol. Biol.* 296, 979 (**2000**).
[37] C. Anselmi, G. Bocchinfuso, P. De Santis, M. Savino, and A. Scipioni, *Biophys. J.* 79, 601 (**2000**).
[38] S. Mattei, B. Sampaolese, P. De Santis, and M. Savino, *Biophys. Chem.* 97, 173 (**2002**).
[39] J. M. Gottesfeld, J. M. Belitsky, C. Melander, P. B. Dervan and K. Luger, *J. Mol. Biol.* 321, 249 (**2002**).
[40] R. K. Suto, R. S. Edayathumangalam, C. L. White, C. Melander, J. M. Gottesfeld, P. B. Dervan, and K. Luger, *J. Mol. Biol.* 326, 371 (**2003**).
[41] F. Mohammad-Rafiee, I. M. Kulić, and H. Schiessel, *J. Mol. Biol.* 344, 47 (**2004**).

[42] Y. Lorch, M. Zhang, and R. D. Kornberg, *Cell* 96, 389 (**1999**).

[43] G. Längst and P. B. Becker, Mol. Cell. 8, 1085 (**2001**).

[44] A. Ajdari and J. Prost, *C. R. Acad. Sci. (Paris)* 315, 1635 (**1992**); M. O. Magnasco, *Phys. Rev. Lett.* 71, 1477 (**1993**); F. Jülicher, A. Ajdari, and J. Prost, *Rev. Mod. Phys.* 69, 1269 (**1997**).

[45] P. Reimann, *Phys. Rep.* 361, 57 (**2002**).

[46] The condition of constant κ_i and l_i will be fulfilled on a coarsegrained level (of a single helical turn) for sequences with 10bp periodicity. By symmetry a homopolymer (e.g. poly(A/T)) will have $\kappa_i = 0$ and $l_1 \neq l_2$. Additional requirements on the sequence composition of the basic periodic element like a nonrandom arrangement of A/T or G/C nucleotides have to be met in order to ensure $l_1 \neq l_2$ (bending anisotropy) and $\kappa_i \neq 0$ (intrinsic curvature). Phenomenological rules for the sequence selection with the desired properties can be extracted from known anisotropically bendable and curved nucleosome positioning sequences; cf. Refs. [37, 38, 47]. E.g. $l_1 \neq l_2$ can be achieved by placing A/T and G/C rich tract 5bp out of phase.

[47] S. C. Satchwell, H. R. Drew, and A. A. Travers, *J. Mol. Biol.* 191, 659 (**1986**); T. E. Shrader and D. M. Crothers, *Proc. Natl. Acad. Sci. U.S.A.* 86, 7418 (**1989**); *J. Mol. Biol.* 216, 69 (**1990**); S. Cacchione, M. A. Cerone, and M. Savino, *FEBS Lett.* 400, 37 (**1997**); H. R. Widlund et al. *J. Mol. Biol.* 267, 807 (**1997**).

[48] R. E. Johnson and T. Y. Wu, *J. Fluid Mech.* 95, 263 (**1979**).

[49] E. M. Purcell, *Proc. Natl. Acad. Sci. USA* 94, 11307 (**1997**).

[50] P. Reimann, R. Bartussek, R. Häussler, and P. Hänggi, *Phys. Lett. A* 215, 26 (**1996**).

[51] D. F. Gaitan, L. A. Crum, R. A. Roy, and C. C. Church, *J. Acoust. Soc. Am.* 91, 3166 (**1992**); L. H. Thompson and L. K. Doraiswamy, *Ind. Eng. Chem. Res.* 38, 1215 (**1999**).

[52] Lakowicz J.R., *Principles of fluorescence spectroscopy*, Kluwer Academic, New York, **1999**.

[53] W. J. Parak et al. *Nanotechnology* 14, R15 (**2003**).

[54] K. Hamad-Schifferli, J. J. Schwartz, A. T. Santos, S. Zhang, and J. M. Jacobson, *Nature* 415, 152 (**2002**).

[55] V. A. Bloomfield, D. M. Crothers, and I. Tinoco, *Nucleic acids: structures, properties, and functions*, University Science Books., Sausalito, **2000**; K. E. van Holde, W. C. Johnson, and P. S. Ho, *Principles of Physical Biochemistry*, Prentice Hall, **1998**.

[56] S. B. Smith, Y. J. Cui, and C. Bustamante, *Science* 271, 795 (**1996**).

[57] X. R. Bao, H. J. Lee, and S. R. Quake, *Phys. Rev. Lett.* 91, 265506 (**2003**).

[58] R. A. Simha and S. Ramaswamy, *Phys. Rev. Lett.* 89, 058101 (**2002**).

[59] C. Dombrowski et al., *Phys. Rev. Lett.* 93, 098103 (**2004**).

[60] S. J. Klug and M. Famulok, *Mol. Biol. Rep.* 20, 97 (**1994**).