

RESEARCH ARTICLE

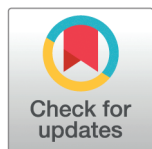
DNA spontaneously wrapping around a histone core prefers negative supercoiling: A Brownian dynamics study

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Abstract

In eukaryotes, DNA achieves a highly compact structure primarily due to its winding around the histone cores. The nature wrapping of DNA around histone core form a 1.7 left-handed superhelical turns, contributing to negative supercoiling in chromatin. During transcription, negative supercoils generated behind the polymerase during transcription may play a role in triggering nucleosome reassembly. To elucidate how supercoils influence the dynamics of wrapping of DNA around the histone cores, we developed a novel model to simulate the intricate interplay between DNA and histone. Our simulations reveal that both positively and negatively supercoiled DNAs are capable of wrapping around histone cores to adopt the nucleosome conformation. Notably, our findings confirm a strong preference for negative supercoiled DNA during nucleosome wrapping, and reveal that the both of the negative writhe and twist are beneficial to the formation of the DNA wrapping around histone. Additionally, the simulations of the multiple nucleosomes on the same DNA template indicate that the nucleosome tends to assemble in proximity to the original nucleosome. This advancement in understanding the spontaneous formation of nucleosomes may offer insights into the complex dynamics of chromatin assembly and the fundamental mechanisms governing the structure and function of chromatin.

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Author summary

The compacted organization of DNA within chromatin is primarily attributed to its intricate winding around histone cores. This winding process involves 1.7 left-handed superhelical turns around the histone core, contributing to the negative supercoiling within chromatin fibers. To gain deeper insights into how DNA supercoiling impacts the dynamics of DNA wrapping around histone cores, we first devised a novel computational model that simulates the intricate interplay between DNA and histone cores. The simulations reveal that both of the positively and negatively supercoiled DNA can

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spontaneously adopt the nucleosome conformation upon wrapping around the histone core, and demonstrated a strong preference for negative supercoiling during nucleosome wrapping. Additionally, the simulations of multiple nucleosomes assembling show that the nucleosome tends to assemble near original nucleosome. Finally, we examined that both the negative writhe and twist components are advantageous for the formation of the nucleosome. The studies shed light on the intricate dynamics underlying chromatin assembly and its functional implications.

Introduction

In eukaryotes, the primary step in the intricate folding of DNA into chromatin involves the wrapping of DNA strands around the histone core [1]. The crystal structure of the histone core particle of chromatin contains two copies of each histone protein, H2A, H2B, H3 and H4 being assembled into an octamer that accommodates approximately about 145 base pairs (bp) wrapped around it [2–5]. The negatively charged DNA wraps around the positively charged histone proteins about two turns in a counter-clockwise fashion [6,7]. The left-handed wrapping of DNA around the histone octamer results in the formation of approximately 1.7 superhelical turns [1,8]. The packaging of DNA within a robust nucleosome framework in eukaryotes physically obstructs the establishment of the initial replication and transcription complexes, as well as the subsequent activities of the respective machineries. Conversely, during transcription elongation, the positive supercoils generated in front of the RNA polymerase may destabilize the nucleosome while the negative supercoils behind the polymerase may aid in triggering the nucleosome reassembling [9,10]. Recent biochemical and molecular biological experiments have focused on stretching DNA molecules to investigate their mechanical or dynamical behaviors [6,11–14]. Meanwhile, some theoretical works have also explored the mechanical or dynamical properties of DNA and chromatin [15–17]. Along with experimental and theoretical studies of DNA and chromatin, numerous molecular dynamics simulation studies have been done on structures and stabilities of nucleosomes [18–25]. Recently, the Brownian dynamics methods have been developed to study the kinetics of DNA and nucleosome interactions, providing further insights into the dynamic nature of chromatin assembly and function [15,26–32].

In this study, we developed a Brownian dynamics model to investigate the dynamics properties of spontaneously nucleosome wrapping by supercoiled DNA. Our model integrates a discrete worm-like chain and a rotational sphere, for representing DNA and histone, respectively. Employing this model, we confirm that the interaction between histone and DNA is the primary driving force behind nucleosome wrapping, regardless of the supercoiling of the DNA. Importantly, our simulations have demonstrated that negative supercoils are much more beneficial to spontaneous nucleosome wrapping, which supports that negative supercoils facilitate the wrapping of DNA around histone octamers, thereby promoting the formation of nucleosomes. In addition, the simulations of the multiple nucleosomes on the same DNA template reveal that the histone core tends to assemble near the last nucleosome. Finally, we discussed the mechanisms underlying the preference for negative supercoiling during nucleosome wrapping. Our findings thereby offer insights into how DNA supercoiling affects chromatin structure, function, and assembly. Our model paves the way for studying how DNA manipulations by magnetic beads in single molecule techniques and supercoiling modifications by enzymes [13,14,33,34], such as polymerases, gyrase, and Topo II, influence and regulate chromatin properties.

Method

Our coarse grained model consists of a discrete worm-like chain and a rotational sphere, depicted in Fig 1, to simulate the supercoiled DNA and the histone core, respectively.

The discrete worm-like chain is comprised of N jointed discrete segments (cylinders) [35]. The conformation of this chain is described by $N + 1$ vertices $\{\mathbf{r}_i\}$. The i -th segment is defined by the vector $\mathbf{s}_i \equiv \mathbf{r}_{i+1} - \mathbf{r}_i$. The equilibrium length of each segment is $l_0 = 3.4$ nm, representing 10 bp. In addition, an orthogonal base vector frame $\{\mathbf{e}_i, \mathbf{f}_i, \mathbf{g}_i\}$ ($\mathbf{e}_i = \mathbf{f}_i \times \mathbf{g}_i$) is attached to

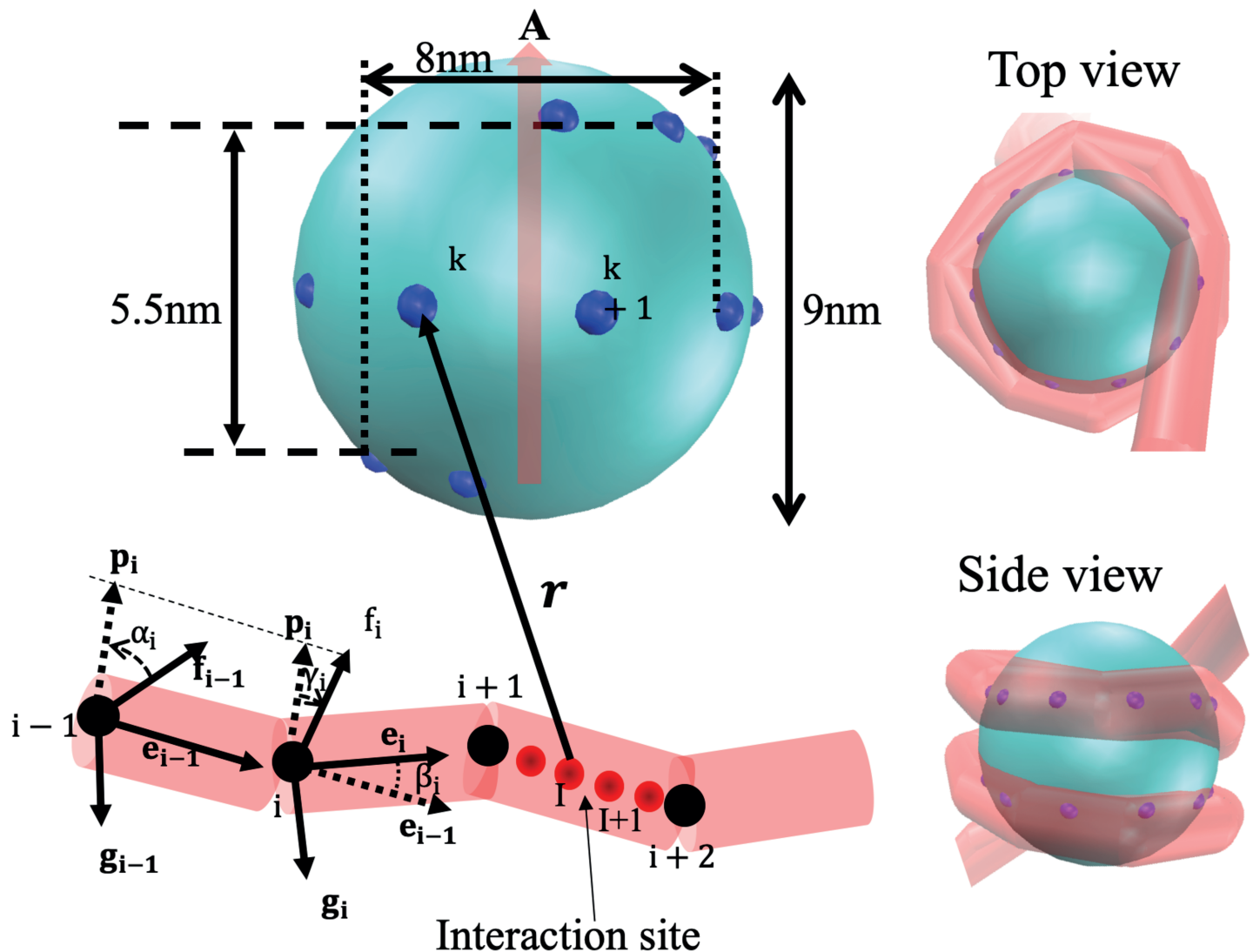


Fig 1. Schematic view of histone-DNA interaction model. The histone core is modeled as a sphere entity, possessing 22 interaction points along a left-handed helical path that enable the DNA to be wound around the histone core. The axial vector $\mathbf{A}$ of the helical path on the sphere describes the orientation of the histone core. The DNA is modeled as N discrete segments. The i -th segment is defined by vertices i and $i + 1$, attached by $\mathbf{f}_i$, $\mathbf{g}_i$ and $\mathbf{e}_i$. The vectors define the bending angle $\beta_i = \arccos(\mathbf{e}_{i-1} \cdot \mathbf{e}_i)$, and the twisting angle $\theta_i = \alpha_i + \gamma_i$ by introducing an auxiliary vector $\mathbf{p}_i = \mathbf{e}_{i-1} \times \mathbf{e}_i$. (Right) Two views of a nucleosome structure generated by VMD from the simulations.

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the segment (Fig 1), where $\mathbf{e}_i \equiv \mathbf{s}_i/s_i$, $\mathbf{f}_i$ and $\mathbf{g}_i$ describe a local rotational angle φ_i of the segment about its axis $\mathbf{e}_i$. The torsion of the chain is described by N rotational angles $\{\varphi_i\}$. The i -th bending angle β_i is defined as $\arccos(\mathbf{e}_{i-1} \cdot \mathbf{e}_i)$. The i -th twist θ_i depends on the two frames $\{\mathbf{f}_{i-1}, \mathbf{g}_{i-1}, \mathbf{e}_{i-1}\}$ and $\{\mathbf{f}_i, \mathbf{g}_i, \mathbf{e}_i\}$. By introducing an auxiliary vector $\mathbf{p}_i = \mathbf{e}_{i-1} \times \mathbf{e}_i$, the twist is $\theta_i = \alpha_i + \gamma_i$, where α_i is the rotation angle from $\mathbf{f}_{i-1}$ towards $\mathbf{p}_i$, γ_i is the angle from $\mathbf{p}_i$ towards $\mathbf{f}_i$.

The stretching, bending, twisting potential energies are all harmonic [35]. The electrostatic interaction is represented as the Debye-Hückel potential on the uniformly distributed point-like charges on the segments [36–38]. Thus the energetics of the DNA chain is

$$E = \sum_{i=0}^{N-1} \frac{k_B T}{2(l_0 \alpha_s)^2} (l_0 - s_i)^2 + \sum_{i=1}^{N-1} k_B T \alpha_b \beta_i^2 + \sum_{i=1}^{N-1} \frac{\alpha_t}{2l_0} \theta_i^2 + \frac{\nu^2 l_0^2}{\lambda^2 D_e} \sum_{I=0}^{\lambda N} \sum_{J=I+N_{near}+1}^{\lambda N} \frac{\exp(-\kappa r_{IJ})}{r_{IJ}}, \quad (1)$$

where the first term on the right-hand side is the stretching energy of each segment and α_s is a stiffness coefficient; the second term is the bending energy and α_b is a bending stiffness coefficient; the third one is the twisting energy and α_t is a torsional stiffness coefficient [35]; the last one is the electrostatics and ν and λ are the effective charge density on each segment and the number of the point-like charges per segment, respectively, D_e is the dielectric constant of water, N_{near} is the number of neighbor point-like charges of each segment, and κ is the inverse Debye length. Moreover, the impenetrability of DNA segments is guaranteed by introducing a repulsion force $F_{IJ}^{ex} = -F_{ex} \frac{r_{IJ}}{r_{IJ}}$ if $r_{IJ} < 2$ nm [36], where the indices I and J denote the point-like charges, not the vertices. All the simulation parameters used in this method are listed in the Table 1.

The histone core is considered as a rotational sphere with diameter 9 nm, on which 22 discrete interaction points are distributed along a left-handed helical path, spanning approximately 2 turns. The helical path of these interaction sites extends vertically for a height of 5.5 nm, while the diameters of the helix's apical and basal termini approximate 8 nm.

Table 1. Constants and parameters.

Parameter	Symbol	Value [35,37]
Number of segments	N	100
Temperature	T	298 K
Histone core radius	R_h	4.5 nm
Segment equilibrium length	l_0	3.4 nm
Stretching stiffness coefficient	α_s	0.1
Bending stiffness coefficient	α_b	7.32
Torsional stiffness coefficient	α_t	400 pN · nm ²
Monovalent salt concentration		150 mM
Dielectric constant	D_e	8.9×10^{-9} F/m
Effective charge density	ρ_e	8.01 e/nm
Inverse Debye length	κ	1.261 nm ⁻¹
Number of the point charges per segment	λ	5
Electrostatic cutoff distance	r_c	8 nm
DNA excluded volume force	F_{ex}	15 pN
Viscosity	η	0.001 kg/(m · s)
Hydrodynamic DNA radius	R_H	1.3 nm
Hydrodynamic DNA rotational radius	R_d	1.2 nm
Simulation time-step size	Δt	25 ps

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The interactions between the DNA and the points on the sphere are modeled as the Morse potential [29]

$$U_{DH} = \sum_{k,I} \epsilon \left[\left(e^{-\alpha(r-\delta)} - 1 \right)^2 - 1 \right] \quad (2)$$

where ϵ is the absorption energy, e.g., chosen as $5 k_B T$ (corresponding to the absorption energy density $8 k_B T \text{ nm}^{-1}$) [29,30], $\alpha \sim 1.26 \text{ nm}$, is the inverse decay length, $\delta = 1 \text{ nm}$, specifies the radius of the repulsive core of DNA, r is the distance between the I -th DNA binding site and the k -th site on the histone. The excluded volume effect between DNA and histone is considered by a half-harmonic potential, i.e., for $r < |a| + r_0$,

$$U_{ex} = \frac{1}{2} k (|a| + r_0 - R)^2 \quad (3)$$

where $k = 8 k_B T \cdot \text{nm}^{-1}$ is the rigidity coefficient, $|a| = 4.5 \text{ nm}$ is the radius of the histone, $r_0 = 1 \text{ nm}$ is the radius of DNA and R is the distance between the I -th DNA binding site and the center of the histone.

The Brownian dynamics (BD) can be performed using an integration, the second-order BD algorithm [35,37]. A tentative first-order displacement is

$$\begin{aligned} \mathbf{r}'_i(t + \Delta t) - \mathbf{r}_i(t) &= \sum D_{ij}(t) \frac{\mathbf{F}_j(t)}{k_B T} \Delta t + \mathbf{R}_i \\ \varphi'_i(t + \Delta t) - \varphi_i(t) &= D_{rot}(t) \frac{T_{q,i}^t(t)}{k_B T} \Delta t + \Phi_i, \end{aligned} \quad (4)$$

and the final half-step is

$$\begin{aligned} \mathbf{r}_i(t + \Delta t) - \mathbf{r}'_i(t + \Delta t) &= \sum D_{ij}(t) \frac{-\mathbf{F}_j(t) + \mathbf{F}'_j(t + \Delta t)}{2k_B T} \Delta t \\ \varphi_i(t + \Delta t) - \varphi'_i(t + \Delta t) &= D_{rot}(t) \frac{-T_{q,i}(t) + T'_{q,i}(t + \Delta t)}{2k_B T} \Delta t, \end{aligned} \quad (5)$$

where $\mathbf{r}'_i$ is the tentative position, D_{ij} is the Rotne-Prager tensor component [35], and for the computational efficiency, we chose $D_{ij} = D \delta_{ij} = \delta_{ij} k_B T / 6\pi\eta R_H$, and here R_H is effective radius of each segment [37,39], $\mathbf{F}_i$ and $\mathbf{F}'_i$ are the forces on the i -th vertex corresponding to the conformations $\mathbf{r}$ and $\mathbf{r}'$, respectively, $T_{q,i}$ and $T'_{q,i}$ are the torques on the i -th segment; $D_{rot} = k_B T / 4\pi\eta R_d^2 l_0$ is the rotational diffusion constant, here R_d is the diffusion radius of DNA, $\mathbf{R}$ and Φ are the thermal noises with the properties $\langle \mathbf{R} \rangle = 0$, $\langle \mathbf{R} \otimes \mathbf{R} \rangle = 2\mathbf{D} \Delta t$, $\langle \Phi \rangle = 0$, $\langle \Phi \otimes \Phi \rangle = 2\mathbf{D}_{rot} \Delta t$.

The center of mass of the histone protein moves following the Langevin equation under the protein-DNA interactions $U_{DH} + U_{ex}$,

$$\dot{\mathbf{R}}_{COM} = -\frac{1}{\zeta} \nabla_{\mathbf{R}_{COM}} (U_{DH} + U_{ex}) + \sqrt{\frac{2 k_B T}{\zeta}} \mathbf{w} \quad (6)$$

where $\zeta = 6\pi\eta|a|$ is the friction coefficient, with η the solution viscosity and $|a|$ the radius of the spherical protein, and $w(t)$ is the Gaussian noise with zero mean and unit variance. It should be noted that the BD (Eq. 6) can be performed using the second-order BD algorithm.

The orientational or rotational degrees of the histone core caused by thermal fluctuations and interactions are modeled by partitioning the rotations into the spatial rotation of the unit

axial vector $\mathbf{A}$ (axial vector of the helical path shown as Fig 1), $\Delta\Omega_A$ and the spinning about $\mathbf{A}$, Ψ [40]. Accordingly, the protein angular Langevin dynamic equations are formulated as (details in S1 Text).

$$\mathbf{A} \times \dot{\Omega}_A |\mathbf{a}| = -\frac{1}{\zeta_{rot}} \sum_i (\mathbf{a} \times \mathbf{F}_i) \times \mathbf{A} / |\mathbf{a}| + \sqrt{\frac{2 k_B T}{\zeta_{rot}}} (\mathbf{A} \times \mathbf{e}_\Theta w_1 + \mathbf{A} \times \mathbf{e}_\Phi w_2) \quad (7)$$

$$\mathbf{A} \cdot \dot{\Psi} |\mathbf{a}| = -\frac{1}{\zeta_{rot}} \sum_i (\mathbf{a} \times \mathbf{F}_i) \cdot \mathbf{A} / |\mathbf{a}| + \sqrt{\frac{2 k_B T}{\zeta_{rot}}} (w_3) \quad (8)$$

where $\zeta_{rot} = 8\pi\eta|a|$ is the friction due to rotation of the protein in solution, w_1 , w_2 and w_3 are the Gaussian noises with zero mean and unit variance. The source code is available at: <https://figshare.com/s/b38438c966505126910e>.

DNA supercoil can be quantified by linking number Lk and its two components, twisting number (Tw) and writhing number (Wr). A relaxed B-DNA consisting of N base pairs has a linking number $Lk_0 = N/10.5$. The excess DNA supercoils can be introduced by some enzymes, e.g. gyrase, Topo II, RNA and DNA polymerizes, or by rotating magnetic beads in single-molecule techniques. The resulting linking number difference is then $\Delta Lk \equiv Lk - Lk_0$. The components, excess twisting number (ΔTw) and writhing number (Wr) follow $\Delta Lk = \Delta Tw + Wr$ [41,42] (see examples in S2 Text). For the current model, ΔTw can be calculated as the sum of the twisting between neighbor segments of DNA

$$\Delta Tw = \frac{1}{2\pi} \sum_i \theta_i \quad (9)$$

Wr characterizes the spatial torsion of supercoiled DNA in terms of the sum of the crossings of all DNA segment pairs [43],

$$Wr = \frac{1}{4\pi} \sum_{i \neq j} \frac{(\mathbf{r}_{j+1} - \mathbf{r}_j) \times (\mathbf{r}_{i+1} - \mathbf{r}_i) \cdot (\mathbf{r}_j - \mathbf{r}_i)}{|\mathbf{r}_j - \mathbf{r}_i|^3} \quad (10)$$

Results

Spontaneously wrapping of DNA around histone

Similar to the supercoil turns added by magnets in experiments [14,44], the initial DNA conformation $\{\mathbf{r}_i, \mathbf{f}_i, \mathbf{g}_i, \mathbf{e}_i\}$ with a given ΔLk was obtained by rotating the end vectors $\mathbf{f}_N, \mathbf{g}_N$ about $\mathbf{e}_N$ at rate ± 5 turns/s while torsionally constraining the other end (Fig 2), where + denotes counterclockwise rotation. As the excess linking number reaches to the expected value, the rotation is stalled. In Fig 2, an extended and supercoiled DNA ($\Delta Lk = 3$) at length 1000bp stretched by $f = 0.3$ pN interacts with a histone. The interactions between DNA and histone with absorption energy $\epsilon = 5 k_B T$ can wind the DNA around the histone core, forming partially wrapped and mis-wrapped structures, and finally trigger the completion of the nucleosome wrapping. We accordingly define the first passage time (FPT) as the interval from the touching between the DNA chain and the histone to the completion of the nucleosome wrapping.

The DNA winding in the single nucleosome contributes to approximately -1 linking number difference, and consequently induces an extra $\Delta\Delta Lk = +1$ to the unconstrained DNA, which is energetically adverse. However, our simulation suggests that the positive supercoil is able to wrap a histone to form nucleosome.

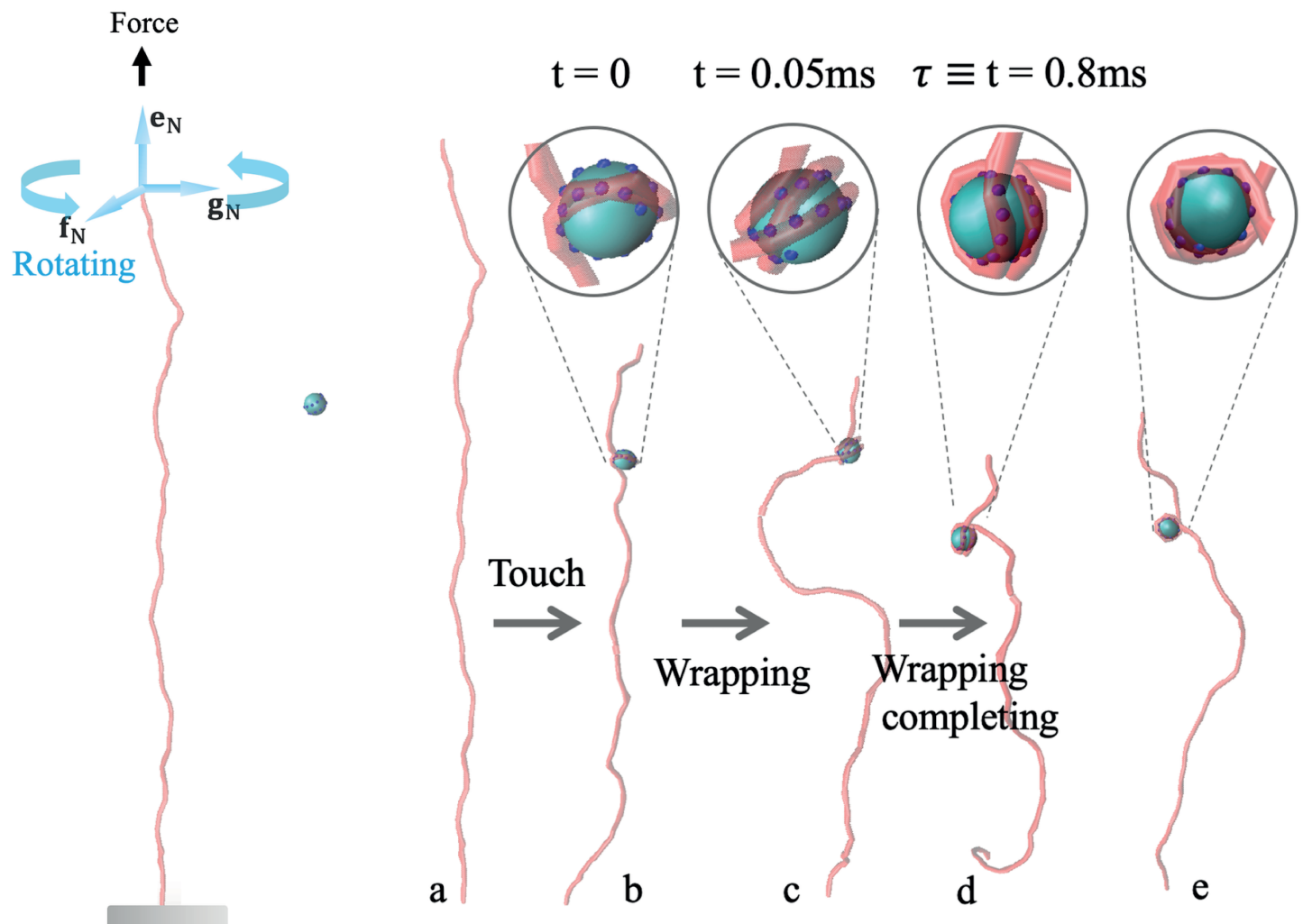


Fig 2. Generation of initial supercoiled DNA and representative snapshots of DNA winding around a histone core. (Left) The initial DNA supercoils were introduced by rotating the base vectors $\mathbf{f}_N$ and $\mathbf{g}_N$ about $\mathbf{e}_N$ attached to the end DNA segment. A single histone core interacts with a positively supercoiled DNA ($\Delta Lk = 3$) at length of 1000 bp (100 segments) under tension $f = 0.3$ pN. A complete simulation trajectory includes the sequential steps: histone core searching the DNA chain (a), the histone touching the DNA (b), DNA winding around histone (c) and finally completing the nucleosome wrapping (d and e). The first passage time (τ) of nucleosome-wrapping is defined by the time interval between (b) and (d).

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Strong interactions between histone and DNA promote the nucleosome wrapping

The DNA winding around the histone core is energetically costly. Hence, the interactions between the DNA and histone should be the primary factor for nucleosome wrapping. The conformations exhibited by the histone-DNA complex can be broadly categorized into three types: mis-wrapped (non-left-handed), partially wrapped and nucleosome wrapped states (Fig 3A). The typical pathways of the nucleosome wrapping are *mis-wrapped state* → *partially wrapped state* → *nucleosome state* and *partially wrapped state* → *nucleosome state* (see the S3 Text for the details).

Intuitively, the strong interactions can promote the completion of the nucleosome wrapping. This is confirmed by our simulations of spontaneously nucleosome-wrapping

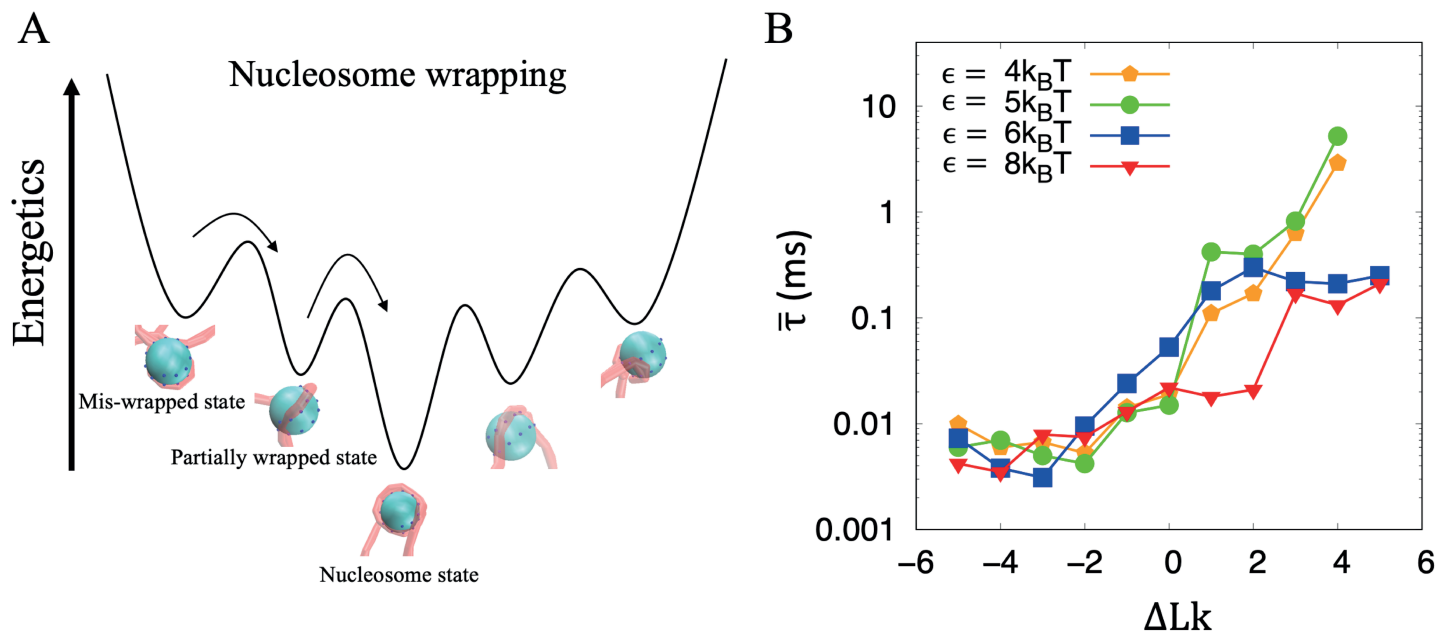


Fig 3. Nucleosome-wrapping driven by interactions between DNA and histone. (A) Schematic illustration of the nucleosome wrapping process. Before completely nucleosome wrapping (Energetic minimum), the system explores a vast number of conformations of the mis-wrapped state (out of left-handed helix path) and partially wrapped state. (B) The mean first passage time (MFPT) for the completion of the nucleosome wrapping depends on the interaction energy strength ϵ and the supercoil degree. Each dot was obtained from 20 simulations trajectories with 10ms of each (It should be noted that no data was captured for $\Delta Lk = 5$ and $\epsilon = 4, 5 k_B T$ within 10 ms). For each given linking number, the DNA is stretched under constant force $f = 0.3$ pN.

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with different DNA supercoils $-5 \leq \Delta Lk \leq 5$ and different adsorption energy strengths ϵ ($4 k_B T$, $5 k_B T$, $6 k_B T$ and $8 k_B T$, corresponding to the adsorption energy density from $6 k_B T \text{ nm}^{-1}$ to $11 k_B T \text{ nm}^{-1}$) under stretching force $f = 0.3$ pN (Fig 3B). The interactions from weak to strong correspond to the salt concentrations from high to low. Under all the conditions, both of the positively and negatively supercoiled DNAs can wrap around the histone to form nucleosome. Notably, the strong adsorption energy strength and the presence of negative supercoils serve to augment the efficiency of nucleosome wrapping.

Nucleosome-wrapping prefers negative supercoils

During transcription, the positive supercoils generated by the polymerases could dissociate the nucleosomes, while the negative supercoils behind might facilitate the re-assembly of the nucleosomes [9,10]. The transcription elongation can be stalled by the torque (about $5 \sim 11 \text{ pN} \cdot \text{nm}$) induced by the generated twin supercoils if the applied force is larger than 0.5 pN [33,45]. If the applied force is larger than the characteristic force (~ 0.08 pN), DNA can be extended [46]. Accordingly, we identify the forces larger than 0.08 pN and smaller than 0.5 pN as the small forces and define the forces larger than 0.5 pN as tensional forces. We have demonstrated that the nucleosome-wrapping process shows a strong preference for negative supercoils under a small force (Fig 3(B)). The efficiency of nucleosome-wrapping is supposed to be force-dependent. Hence, we have compared the mean first passage time (MFPT) of nucleosome wrapping for supercoiled DNAs under different forces. (Fig 4).

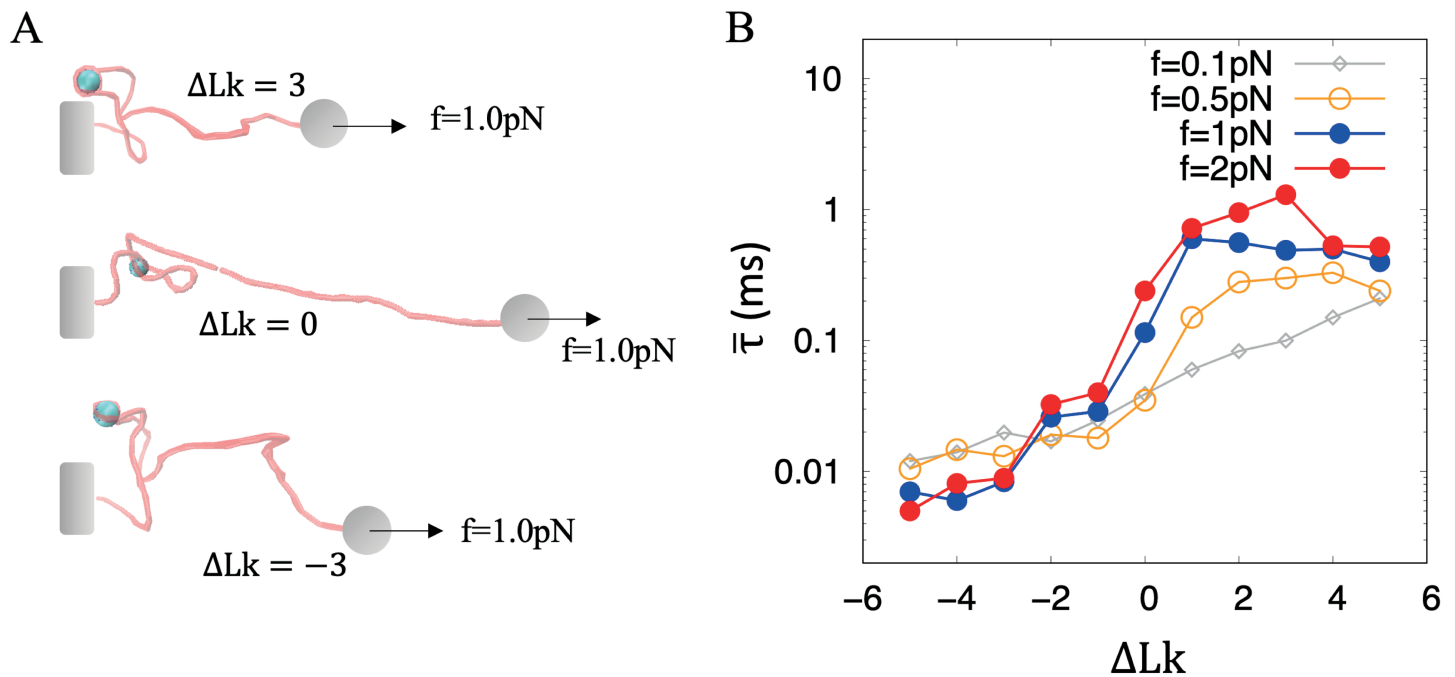


Fig 4. Preference for negative supercoiling. (A) Schematics for a single histone interacting with a supercoiled DNA under stretching force $f = 1.0 \text{ pN}$. (B) The MFPT for completing nucleosome wrapping with $\epsilon = 6 \text{ k}_B\text{T}$ is supercoiling-dependent and force-dependent. Each dot was obtained from 20 simulations trajectories with 10 ms of each.

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For all the cases of the applied forces, the MFPT for nucleosome wrapping by negative supercoiled DNA is significantly shorter compared to that achieved by positively supercoiled DNA. In addition, the applied force can amplify the preference. Indeed, for the case of $f = 1.0 \text{ pN}$ and 2.0 pN , the efficiency of nucleosome wrapping under negative supercoils is over two orders of magnitude higher than that under positive supercoils. In comparison, for the small force $f = 0.1 \text{ pN}$, the efficiency of nucleosome wrapping under negative supercoils is one order of magnitude higher than that under positive supercoils.

Nucleosome tends to assemble in proximity to the original nucleosome

Our model can be directly extended to the case of multiple nucleosomes on the same DNA template. We investigated how the distance between nucleosomes affects the nucleosome-wrapping. In Fig 5A, the first histone core is wrapped by DNA and pinned at $z = 20 \text{ nm}$. The end of the DNA chain under $\Delta Lk = -5$ is stretched by $f = 1.0 \text{ pN}$. Then the second histone randomly collides with any site along the DNA chain. Finally, the histone core interacts with DNA and form the second nucleosome. We performed the simulations and calculated the assembling distance d between the centers of the two histone cores. We noticed that the second histone tends to complete the assembly near the first one. The assembling probability is 0 if $d < 10 \text{ nm}$ due to volume excluding effect between the two histones. The most probable distance for nucleosome assembling is within $30 \text{ nm} < d < 50 \text{ nm}$, which may results from the substantial DNA bending induced by the first nucleosome.

Besides, we performed simulations of an initially naked DNA chain under $\Delta Lk = 0, -3$ or -5 simultaneously interacting with 6 histone cores as shown in Fig 5B. Our simulations shows that the histones are simultaneously wrapped by the same DNA and the average number of

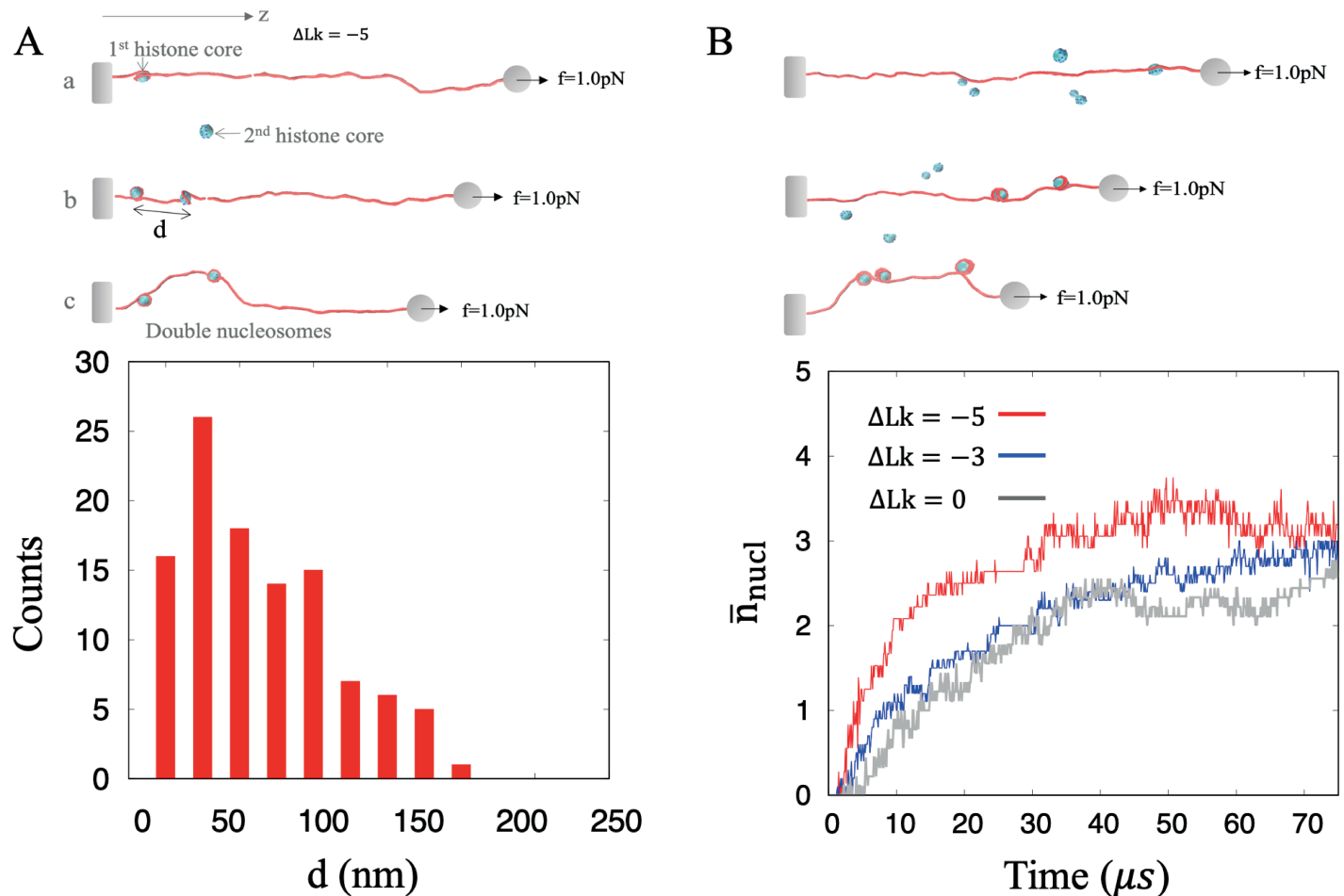


Fig 5. Multiple nucleosomes assembling. (A) Distribution of nucleosome assembling distance along a DNA chain at length of 1000 bp. The first nucleosome is constrained at $z = 20$ nm, and then the second histone is wound by DNA to form a new nucleosome. The second nucleosome tends to successfully assemble near the first nucleosome. The distribution of the distance d between two nucleosomes was obtained from 100 simulation trajectories of 100 μs each. (B) Average number of nucleosomes. An initially naked DNA chain with different linking numbers interact with 6 histone cores and form multiple nucleosomes. Compared with the DNA without supercoil ($\Delta Lk = 0$), the highly supercoiled DNA ($\Delta Lk = -5$) enhances efficiency of the nucleosome assembling. Each line is the average over 10 simulation trajectories with 75 μs of each.

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the nucleosomes increases with time. The average number of the nucleosomes on DNA with $\Delta Lk = -5$ reaches to $\bar{n}_{nucl} = 2$ in 10 μs . In comparison, $\bar{n}_{nucl} = 2$ for DNA with $\Delta Lk = 0$ takes about 30 μs . As above, the nucleosome wrapping favors negative supercoils. Indeed, as one nucleosome wrapping completes, $\Delta \Delta Lk = +1$ is induced on the unconstrained DNA, which in turn reduces the efficiency of following nucleosome assembling.

Discussion and conclusion

We examined the roles of DNA extension, twist and writhe played in nucleosome wrapping. Our simulations reveal that the change in DNA extension due to nucleosome-wrapping, $\Delta z \equiv (z_{nuc} - \bar{z})/L$, where $L = 340$ nm, depends on the supercoiling (see Fig 6A). The supercoiling-dependent

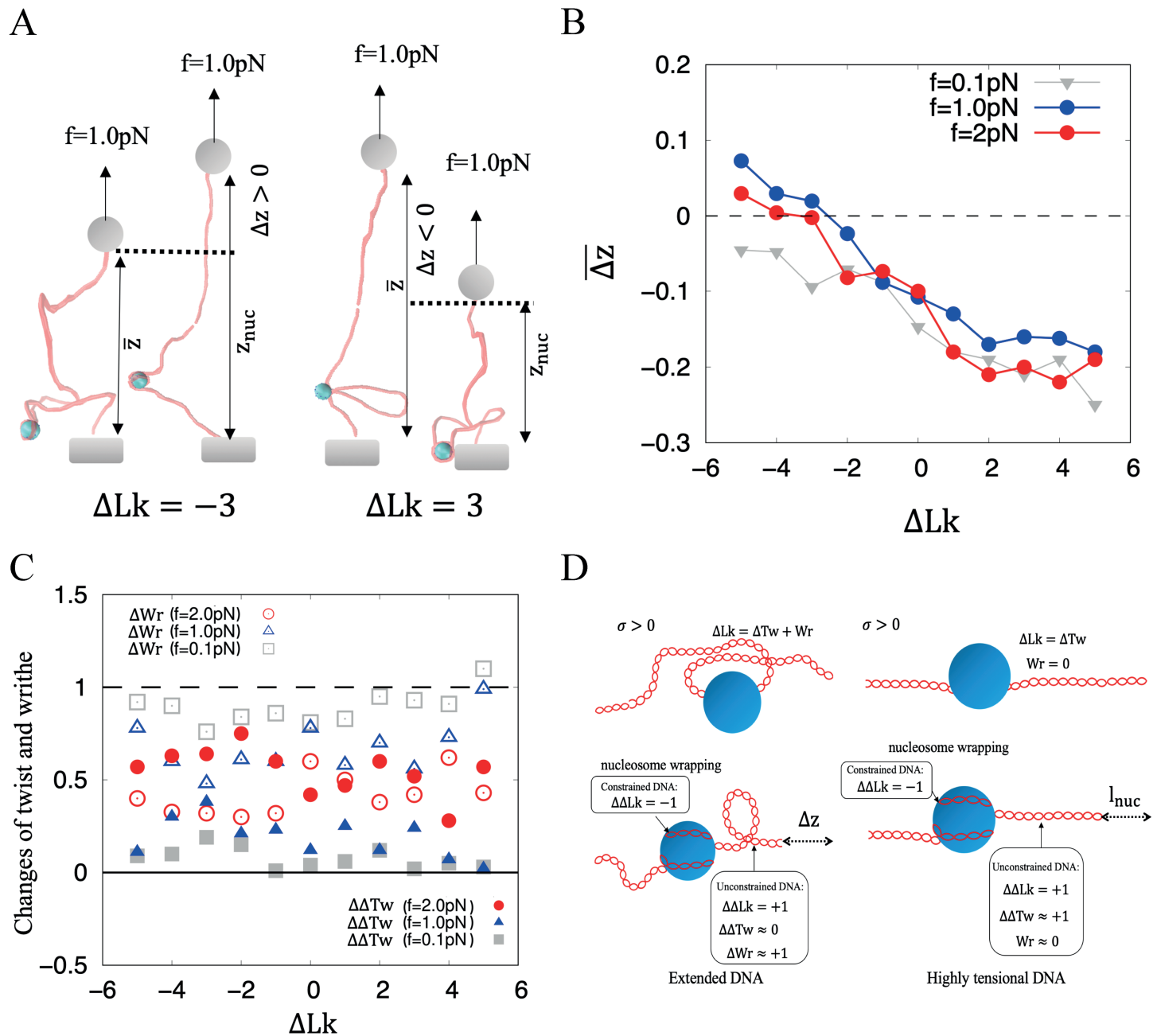


Fig 6. Extension, twist and writhe changes of DNA during nucleosome-wrapping. (A) The extension increment of the supercoiled DNA due to the nucleosome wrapping. Under tensional forces, the nucleosome wrapping increases the extension of the negatively supercoiled DNA while reducing the extension of the positively supercoiled DNA. (B) The mean extension increment resulting from nucleosome wrapping is a function of supercoil and stretching force. The positive increment in DNA extension due to nucleosome wrapping causes the decrease of the potential energy of the extended DNA, which is energetically favored. (C) Changes in the twist (ΔT_w) and writhe (W_r) of the unconstrained DNA due to nucleosome-wrapping. (D) The changes in twist and writhe of (positive supercoils) DNA during winding around histone core. (Left) Extendedly (+) supercoiled DNA wraps around a histone under small force, e.g., $f = 0.1$ pN. The induced +1 linking number is mainly attributed to writhe, which causes work done during nucleosome wrapping. (Right) Highly tensional (+) supercoiled DNA wraps around a histone under large force, e.g., $f = 10$ pN. The induced +1 linking number is mainly attributed to twist, which increases twisting energy during nucleosome wrapping.

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$\Delta z^{(+)} < \Delta z^{(-)}$ (Fig 6B), leads to the work done being $-f\Delta z^{(+)} > -f\Delta z^{(-)}$. The smaller work done by force f results in a reduced energy barrier for nucleosome wrapping. Therefore, nucleosome wrapping tends to occur preferentially for negatively supercoiled DNA.

For extendedly supercoiled DNA under $f = 0.1$ pN, the induced $\Delta\Delta Lk = +1$ on the unconstrained DNA is primarily attributed to writhe, with $\Delta Wr \approx +1$ and $\Delta\Delta Tw \approx 0$ (Fig 6C), where $\Delta Wr \equiv Wr^{un}(\tau) - Wr^{un}(0)$, $\Delta\Delta Tw \equiv \Delta Tw^{un}(\tau) - \Delta Tw^{un}(0)$, $\Delta\Delta Lk = \Delta\Delta Tw + \Delta Wr$ based on Eqs 9 and 10 and the superscript *un* stands for the unconstrained DNA. The increase in writhe rather than the change in twisting energy governs the dynamics. In other words, for positive writhe, $|Wr|$ increases due to nucleosome-wrapping. In contrast, for negative writhe, $|Wr|$ decreases due to nucleosome wrapping. The negative supercoiling results in comparatively lower amount of work-done by f , implying a decreased energy barrier for nucleosome wrapping.

In Fig 6(C), we observed that as the force f increases to 2.0 pN, there is a corresponding increase in $\Delta\Delta Tw$ and a decrease in ΔWr . For highly tensional DNA, such as those subjected to $f = 5, 10$ and 20 pN, which are commonly utilized for stretching chromatin [12,14], however, the increment of twist $\Delta\Delta Tw \approx 1$ meanwhile writhe $\Delta Wr \approx 0$ during nucleosome forming, giving a rise to a supercoiling-independent change in extension, $\Delta z = l_{nuc}$. The change of the twisting energy is supercoiling-dependent, i.e., $\Delta E_{\pm} = \frac{1}{2}C[(\Delta Lk \pm 1)^2 - (\Delta Lk)^2]$, where $C \equiv k_B T l_t (L - l_{nuc}) \Omega_0^2 / (Lk_0)^2$ is the stiffness of the whole unconstrained DNA [38]. Evidently, $\Delta E_+ > 0 > \Delta E_-$, meaning nucleosome-wrapping always prefers negative supercoils.

In both of the cases, the energy barrier associated with nucleosome wrapping under positively supercoiled DNA exceeds that of negatively supercoiled DNA, thereby the preference for negative supercoiling (Fig 6D).

In eukaryotic chromatin, DNA attains a highly compact structure due to its wrapping around histone cores, contributing to negative supercoiling. To elucidate the mechanism underlying the spontaneous wrapping of supercoiled DNA around histone proteins, we designed a Brownian dynamics model of the DNA-histone complex. We demonstrated that both the positively and negatively supercoiled DNAs can form the nucleosome conformation with appropriate absorption energies between DNA and histone. Furthermore, we observed that the preference for negative supercoiling during nucleosome wrapping becomes more evident with increasing force. Finally, our model has been extended to the case of multiple nucleosomes on the same DNA template and found that nucleosome favors assembling near the original nucleosome. Several improvements to our model are warranted for future studies. The first one is the over-twist on the constrained DNA that wraps around histone, which may mainly originates from interaction with the histone rather than DNA intrinsic property [47]. Secondly, the nucleosome filament requires histone H1, which associates with the entry and exit of DNA from the histone core [21,24]. The incorporation of the effects of the histone H1 allows nucleosomes to be arranged into a compact and stabilized array. In the large force regime, the dissociation of histone from DNA is dominating over re-assembling of nucleosome. Consequently, the net nucleosomes reassembling rate is determined by the difference between re-assembling rate and dissociate rate. Thus, the force-dependent kinetics of the nucleosome dissociation and re-assembling presents a promising research topic in the future. Finally, using some manipulations to supercoiled DNA and protein-DNA complexes, we can improve our model to study more intriguingly experimental and biological processes, e.g, DNA manipulations by magnetic beads in experiments and by certain enzymes that introduce supercoils to DNA, such as RNA polymerases, gyrase, and Topo II.

Supporting information

S1 Text. Dynamics of the rotational degrees.
(PDF)

S2 Text. Pathway of nucleosome wrapping and the intermediate states.

(PDF)

S3 Text. Quantitative measures of DNA supercoiling.

(PDF)

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