Removal of DNA-bound proteins by DNA twisting

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We present a simple model of how local torsional stress in DNA can eject a DNA-bound protein. An estimate of the torque τ^* required to eject a typical DNA-bound protein is made through a two-state model of the equilibrium between the bound and unbound states of the protein. For the familiar case of a nucleosome octamer bound to double-stranded DNA, we find this critical torque to be $\approx 9k_BT$. More weakly bound proteins and large (≈kilobase) loops of DNA are shown to be destabilized by smaller torques of only a few k_BT. We then use our model to estimate the maximum range $R_{\max}$ at which a protein can be removed by a transient source of twisting. We model twist strain propagation along DNA by simple dissipative dynamics in order to estimate $R_{\max}$. Given twist pulses of the type expected to be generated by RNA polymerase and DNA gyrase, we find $R_{\max} \approx 70$ and 450 bp, respectively, for critical torques of $\approx 2k_BT$.

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I. INTRODUCTION

DNA inside the cell is found predominantly in the form of double-stranded B-DNA, which consists of two polynucleotide strands wrapped around each other in a right-handed sense. In its relaxed form, the double helix has 10.5 base pairs per right-handed turn, and a contour length of 0.34 nm per base pair. B-DNA's double-helical structure gives rise to a *twist modulus*. The twist modulus of DNA leads to many new phenomena including the supercoiling of DNA under torsional stress [1,2], twist dynamics [3,4], and twist transport [5,6].

There are many mechanisms known that either constrain or modify the twisting of DNA in the cell. Constraints on DNA twisting are generated by any attachment of two points along the double helix to large cell structures (e.g., nuclear envelope), or DNA-DNA connections that from DNA loops. One particularly well-known example of the class of cellular machines that actively change DNA twisting is RNA polymerase, which is known to generate positive twisting (overtwisting) upstream of transcription, and compensating negative twisting downstream [7]. A second example of a twist-modifying enzyme is DNA gyrase, a bacterial enzyme that breaks double helix DNA and then passes DNA through itself, changing DNA linking number by -2 for each cycle of the enzyme.

This paper will examine the interplay between twisting of DNA generated by active DNA-twisting enzymes, and the stability of proteins that, in their binding to DNA, constrain DNA twist. Our aim will be to estimate conditions under which twist-constraining proteins bound to DNA can be removed by torque. Our general approach will be to simplify the treatment of the DNA conformations, and to largely ignore the partition of linking number into twisting and writhing [1]. Instead we will consider relatively short DNA segments where DNA twist and linking number will be treated essentially interchangeably.

Figure 1 shows examples of DNA-protein structures where DNA twisting is constrained. Torques are imagined to be applied at the left-hand side of the structures shown, and at the right-hand side, the DNA is imagined to be anchored so as to be unable to rotate. The simplest and most obvious case [Fig. 1(a)] is the typical situation of a protein that binds to some specific short (8–20 bp) DNA sequence. Because of the defined shape of the protein that must interact with the DNA bases, the twist of the bound region is constrained. A rather extreme example of this situation is the case of DNA

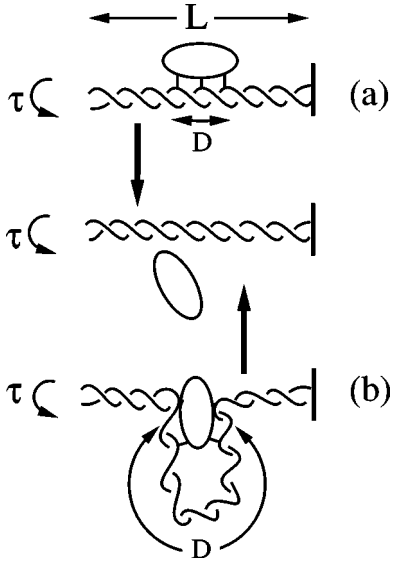

FIG. 1. Ejection of DNA-bound protein (oval) by applied torque τ for different DNA-protein binding geometries. (a) Length D of DNA is used up when protein binds; the remaining length $L-D$ must absorb the imposed twist strain since D has its twist fixed to 10.5 bp/turn. For $\tau < \tau^*$, inability of D bp to absorb some of the excess twist is compensated by the protein-binding free energy μ. But for $\tau \geqslant \tau^*$ the protein-DNA complex dissociates since ΔF can be lowered by spreading out the extra twist strain over the remaining length D. In nucleosomes, D is the length of DNA wrapped around the histone core. (b) DNA-bound protein captures length D of DNA in a loop. Since the length of the loop is much bigger (typically 1 Kb) than the protein-DNA interaction region, we expect a lower τ^* than above. The lac repressor bound to DNA is an example. The heavy arrows in (a) and (b) signify that the dissociated state of the DNA-protein complex is more favored when $\tau \geqslant \tau^*$.

bound to the octamer of histone proteins in the nucleosome, where 146 bp of DNA are twist constrained [8]. In this case, one can imagine that an applied torque has to be quite large to change the equilibrium in favor of the protein being dissociated, since the free energy of binding of such proteins is typically $10k_BT-20k_BT$. On the other hand, one might imagine the DNA to respond by partially unbinding from the proteins, possibly leading to gradual transfer of twist *through* a protein-DNA complex [9].

Figure 1(b) shows a variation of the first case, where a DNA loop is formed by interaction of one protein (or protein complex) with two (or more) DNA sites. There are many examples known where loops of thousands of bases of DNA are stabilized in this manner, for example, the bacterial lac-repressor protein complex, and DNA loop-protein complexes formed by other transcription factors [10]. DNA loops are also hypothesized to be stabilized by chromosome-folding protein complexes such as SMC elements [11]. In all these cases, one can imagine that the binding of the DNA loop could be controlled by either static or transient torsional stress. In the case of twisting generated by RNA polymerase, this would provide an example of transcription-generated chromosome ''remodeling,'' and could be part of regulation of genes near the transcription site [9].

Another situation close to that shown in Fig. 1(b) is the binding of a double-stranded DNA (dsDNA) to a surface; twisting DNA on either side of this binding site could then drive unbinding. If the binding surface is fixed in space (e.g., the nuclear envelope or some other large cell structure) the far end of the DNA need not be constrained in order for the twisting to drive unbinding of the DNA.

In Sec. II of this paper, we estimate the static torque necessary to free a DNA-bound protein that constrains DNA twist over some contour length, such as a histone octamer core wrapped around DNA as in chromatin. We do this by using a simple two-state model of the equilibrium between a protein-DNA complex, and dissociated protein + ''bare'' DNA. Roughly speaking, dissociation occurs when the reduction in twist elastic energy realized by protein release is comparable to the binding free energy. This computation is analogous to the release of proteins that bind DNA ''loops'' expected to occur when the DNA is put under linear tension [12].

In Sec. III we apply our static results to study how transient twist-strain perturbations injected at one point along a DNA affect proteins bound some distance away. We investigate how the subsequent twist-strain relaxation will affect the ability of distant proteins to bind to DNA. The dissipating twist pulse will propagate out from the origin of the strain and at each point along the DNA contour that the pulse visits a finite amount of torque will be generated. If a protein is bound some distance away from the source of the strain, this raises the question: at a given location on the DNA molecule, will the twist pulse produce large enough torques to dislodge a bound protein?

In Sec. III A, we describe the proteins RNA polymerase and DNA-gyrase, two prominent examples of torque-producing protein machines. In Sec. III B, we describe the simplest model for the spreading of an initially localized twist pulse based on local balance of torques produced by the viscous drag of the medium and the local twist elastic strain. In Secs. III C and III D, we present results for two types of initial twist perturbations that either conserve linking number as is appropriate for RNA polymerase, or change linking number as in DNA gyrase. Finally, in Sec. III E, we use our twist-propagation results to estimate the range $R_{\max}$ for protein removal. Our main result is that pulses of torque generated by cell machinery will be able to locally remove relatively weakly bound proteins, but not disrupt strongly bound protein structures such as nucleosomes.

II. DRIVING PROTEINS OFF DNA WITH APPLIED TORQUE

In this section, we analyze the stability of a protein which, when bound to DNA, constrains DNA twist (Fig. 1). We consider a segment of DNA of length L, the ends of which can be subject to a total twist Θ. In between the ends, we suppose a protein may be bound by binding free energy μ (ideal-gas entropy of the proteins in solution is included in μ). When bound, we suppose that the protein constrains the twist of a length D of DNA to be the equilibrium DNA twisting (constraint of twist to a different value is a straightforward generalization).

The length D of DNA with fixed linkage may be the linear sequence of base pairs covered up by the protein when it binds to DNA [Fig. 1(a)], or, in the case of a protein that can simultaneously bind two different parts of a single DNA molecule and form a loop, D is the contour length of the loop. We note that a loop-forming protein need not necessarily bind both strands of the double helix at each of the two DNA binding sites to constrain DNA twist; indeed, two single-strand protein-DNA attachments are sufficient to fix the topology of the intervening DNA.

We take the twisting energy of bare DNA to be

$$\frac{E}{k_BT}=\frac{C}{2}\int_0^L ds\left(\frac{d\theta}{ds}\right)^2, \tag{1}$$

where C is the twist persistence length of DNA, which has been determined to be between 75 and 100 nm from supercoiling and micromanipulation experiments [1,13]. The excess local twist angle $\theta(s)$ is measured relative to the equilibrium DNA twisting (i.e., the elastic equilibrium state is $d\theta/ds=0$). The total twisting angle along the bare DNA is

$$\Theta=\int_0^L ds\,\frac{d\theta}{ds}. \tag{2}$$

Assuming uniform twisting, the twist energy is simply

$$\frac{E}{k_BT}=\frac{C}{2L}\Theta^2. \tag{3}$$

If our protein is bound, the twisting imposed at the DNA ends must be made up by the remaining length $L-D$ of free DNA, since a length D stuck to the protein has its $d\theta/ds$

fixed at zero. Equilibrium between the bound and unbound states is described by the fixed-twist partition function

$$Z(\Theta)=\sum_{n=0}^{1}\exp\left[-\left(\frac{C}{2(L-nD)}\Theta^2-\frac{n\mu}{k_BT}\right)\right], \qquad (4)$$

where $n=0$ stands for the protein removed from the DNA and free to move about in the solution and $n=1$ stands for the protein complexed with DNA.

In the absence of imposed torque τ, the binding free energy μ will favor protein attachment to DNA. With external twist, there is competition between the lower twist energy of the protein-off state ($n=0$) due to the additional length D released by the dissociated protein, versus the gain of binding free energy μ in the protein-bound state ($n=1$). The critical torque value τ^* at which these contributions balance can be roughly estimated from Eq. (4) to be

$$\tau^*=\sqrt{2k_BT\mu C/D}, \qquad (5)$$

which, for a μ of $20k_BT$ (for a nucleosome) and $D=150$ bp, gives a τ^* of about $9k_BT$.

The probability for the protein to be unbound as a function of imposed twist is

$$P_{\rm off}(\Theta)=\left[1+\exp\left(-\frac{\Delta E}{k_BT}\right)\right]^{-1}, \qquad (6)$$

where $\Delta E=E_{\rm on}-E_{\rm off}$ and the torque $\langle\tau\rangle=-k_BT\partial_\Theta\ln Z(\Theta)$ is

$$\frac{\langle\tau\rangle}{k_BT}=\frac{C\Theta}{L(L-D)}[L-DP_{\rm off}(\Theta)]. \qquad (7)$$

We want to calculate the critical torque τ^* required to remove a protein that is already bound to DNA. This is easily done in the fixed torque ensemble. The τ-dependent partition function is

$$\Xi(\tau)=\int_{-\infty}^{+\infty}d\Theta\, Z(\Theta)\exp\left(\frac{\tau\Theta}{k_BT}\right). \qquad (8)$$

The average twist $\langle\Theta\rangle=\partial_\tau\ln\Xi(\tau)$ in this ensemble is related to the applied torque by

$$\langle\Theta\rangle=\frac{\tau}{k_BTC}[L-DP_{\rm on}(\tau)], \qquad (9)$$

where

$$P_{\rm on}(\tau)=(\sqrt{2\pi(L-D)/C})\times\exp[\mu/k_BT+(L-D)\tau^2/2C(k_BT)^2]/\Xi(\tau).$$

Our theory also applies to the case where torque is applied to one end of a DNA molecule that is pinned to a surface at two places separated by a length D of DNA, whose twist is fixed, even while the end with no applied torque is free to flip-flop in solution. The DNA-surface connection closer to the source of torsional stress will unbind at a torque described by the above theory.

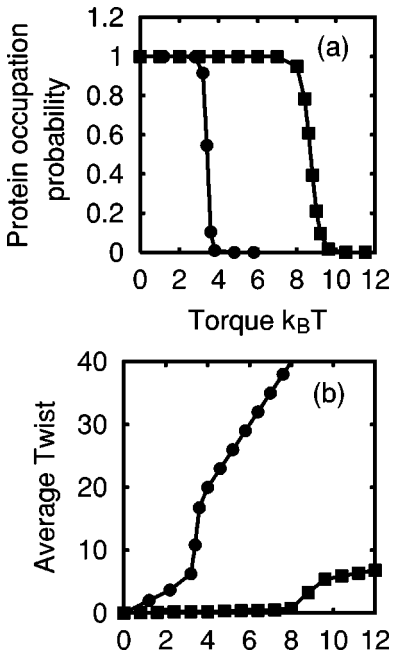

FIG. 2. The probability for a DNA-bound protein to remain bound as applied torque (in k_BT units) is ramped up in a two-state model of DNA-protein complex (a) and the corresponding twist-torque distribution (b). (a) We consider two cases: a single nucleosome particle (line-square) with $D=150$ bp, $L=170$ bp, and $\mu=20k_BT$ and a DNA-bound loop forming protein (line-circle) with $D=1000$ bp, $L=1500$ bp, and $\mu=20k_BT$. The larger stored length of the loop favors dissociation of the complex at lower torques, which happens at $\tau^*\approx3k_BT$. In comparison, the stored length D is much smaller for nucleosomes, implying a larger τ^* of $\approx9k_BT$. In each case, the DNA-protein complex becomes unstable in a narrow region of width $\Delta\tau\approx1k_BT$. (b) The corresponding twist-torque isotherms are linear away from τ^* with different slopes above and below τ^*. Near τ^*, the sudden step from one linear regime to the other corresponds to strong fluctuations between protein-on and protein-off states. Above τ^*, we recover the twist elasticity of bare DNA. We have used a $\mu\approx20k_BT$ for loops to demonstrate the reduction in τ^* for increasing amounts of stored frozen twist. In practice, the loop formation free energy will be much lower (see text) so that our τ^* clearly represents an upper bound. $C=300$ bp.

In Fig. 2 we show results for two cases where a DNA-binding protein constrains the twist of some region of the substrate DNA. The square-line curves concern nucleosomes, where the DNA that directly contacts the positively charged histone octamer surface has its twist frozen. Figure 2(a) (square-line) shows the probability $P_{\rm on}(\tau)$ for a histone octamer to remain bound to the DNA when a torque τ is applied. In a region of width $\approx1k_BT$ centered around $\tau^*\approx9k_BT$, the protein occupation probability drops from 1 to 0. This is our estimate for the nucleosome destabilization torque, and agrees with Eq. (5). Our calculation was done for DNA$\approx$200 bp long with 150 bp in direct contact with the octamer, in the form of approximately 1.75 turns of the

double helix around the disk-shaped histone core [8]. We ignore, in our simple model, the protein histone $H1$ that acts a ramp for the overhanging DNA to pass over when it completes (or enters) its turns over the octameric protein core. The binding free energy of each nucleosome is taken to be $\approx 20 k_B T$ (roughly, the enthalpy of nucleosome binding as measured in physiological $0.15M$ univalent salt solution [14]).

The dot-line curves of Fig. 2 concern loop-forming proteins. Such proteins can store a lot of DNA with frozen twist without requiring a large μ since the actual protein-DNA interaction region is only a few to 10 bp in length. For instance, the binding affinity of lac repressor is $\approx 10^9$ m^{-1} [15] and cro repressor is $\approx 10^{12}$ m^{-1} [15]. Each protein upon binding typically uses up $\approx$1000 bp of DNA in the loop [10]. In comparison to nucleosomes, since much more length D of stored DNA can be released at a lower cost μ, we expect that the protein-DNA complex will become unstable at a lower τ. Indeed, even when μ is kept fixed at $20 k_B T$ in Fig. 2(a) (dot-line), $P_{\rm on}(\tau)$ jumps from 1 to 0 at around $\tau^* \approx 3 k_B T$ for $L = 1500$ bp and $D = 1000$ bp.

Corresponding to each of the two cases considered above, in Fig. 2(b), we show the associated equilibrium twist-torque response curves (square-line for nucleosome and dot-line for loop). Away from τ^*, $\langle \Theta \rangle$ evolves linearly with τ. Close to τ^*, fluctuations of the protein on or off the DNA+protein complex give rise to a steplike torque response with a width $\Delta\tau = 1 k_B T$. Beyond τ^*, the protein on or off come off the DNA and we recover the twist elasticity of bare DNA.

The computed critical torque is insensitive to L over a wide range of choices for L: a tenfold change in L leads to $<$10% shiftup in τ^*. The twist-torque response curves show a more pronounced dependence on the total DNA length, reflecting a change in the distribution of twist with increasing L. For the same tenfold jump in L, the two segments of the response curve merge with one another approaching the limit of uniform distribution of twist over a linear segment of DNA. The critical torque τ^*, on the other hand, is still well described by Eq. (5) for long DNA segments so that only small corrections to τ^* are needed when $L \to \infty$.

III. DYNAMICS OF DNA TWISTING

The previous section presented an equilibrium calculation that gives an estimate for the torque at which release of a protein that constrains DNA twisting becomes thermodynamically favorable. We now consider the dynamical problem of propagation of twist along a DNA to address the question of whether it is feasible for *transient* torque pulses injected at one point into dsDNA to remove proteins at a second, distant point.

In this section, we study the spreading dynamics of such a twist packet and use the result to estimate the range to which sufficient torque is propagated that a bound protein can be knocked off DNA. In Sec. III A we discuss twist distortions introduced by two DNA-modifying protein ''machines,'' RNA polymerase, and DNA gyrase. Then, in Sec. III B, we describe the model for twist propagation along a DNA. In Secs. III C and III D, we examine simple solutions for time evolution of initially localized twist distortions, where $\Delta Lk = 0$ and $\Delta Lk \neq 0$, relevant to the action of RNA polymerase and gyrase, respectively. In Sec. III E we use these results to numerically obtain estimates for $R_{\rm max}$.

A. Actions of DNA-twist-modifying enzymes

1. RNA polymerase

Many of the DNA-processing machines inside cells may be able to generate initially localized twist ''packets.'' To consider a concrete example, it is known that RNA polymerase (RNAP) tracks along the DNA double helix during transcription, producing a net positive linking number buildup ahead of the enzyme, and a balancing net negative linking number deficit behind it [7]. If we consider a single step of the enzyme, the burst of twisting generated ahead and behind the RNAP will spread out over the length of DNA and eventually settle down to a value consistent with the molecule boundary conditions. The dynamics of the twist packet is determined by balance of the local elastic strain and the dissipative torque of the surrounding medium.

RNAP transcribes the coding strand of DNA into mRNA. Transcription involves processive motion of RNAP. Continuous motion for thousands of bp has been observed [16]. If the polymerase is immobilized on a surface, the DNA will thread through the polymerase thereby undergoing rotation relative to the fixed transcription machinery [16]. *In vivo*, it is not known with certainity whether the DNA molecule rotates relative to the polymerase or vice versa. However, since the Stokes radius of RNAP is $\approx$10 nm, it has considerable drag in water. Moreover, the nascent mRNA and, in some cases the translation machinery attached to the mRNA, increases the molecule's effective hydrodynamic radius, thereby suggesting that, *in vivo* too, the DNA must rotate relative to the transcribing RNAP complex.

The step size for RNAP is thought to be $\approx$1 bp so that the end of the DNA molecule is rotated by a full 2π in 10.5 steps. One turn is transcribed in 0.1 s or, in other words, $\approx$100 bp are transcribed in 1 s. For every radian transcribed, 1.7 NTP's are hydrolyzed so that a torque of $\approx 10 k_B T$ per radian may well be generated (at present, only the force-generating capability of RNA polymerase is precisely known [17]). Since RNA polymerase melts DNA locally during transcription, some of the torque generated by processive transcription goes into locally opening the double helix. Recent micromechanical experiments have shown that direct application of unwinding torque $\approx 2 k_B T$ is sufficient to separate the two strands [18–21].

As the DNA threads through the polymerase [see Fig. 3(a)], base pairs near the entrance to the RNAP complex are slightly overtwisted [7]. Since the net linking number does not change during transcription (the sugar-phosphate backbone remains intact), a compensating undertwisted region develops where the DNA exits the transcribing RNAP molecule. Since the polymerase transcribes processively, it will inject a twist strain with every step along the DNA. Because the time to complete one step is $\approx$0.1 s while the characteristic time for twist strain decay is $\approx 10^{-6}$ s (see below), we

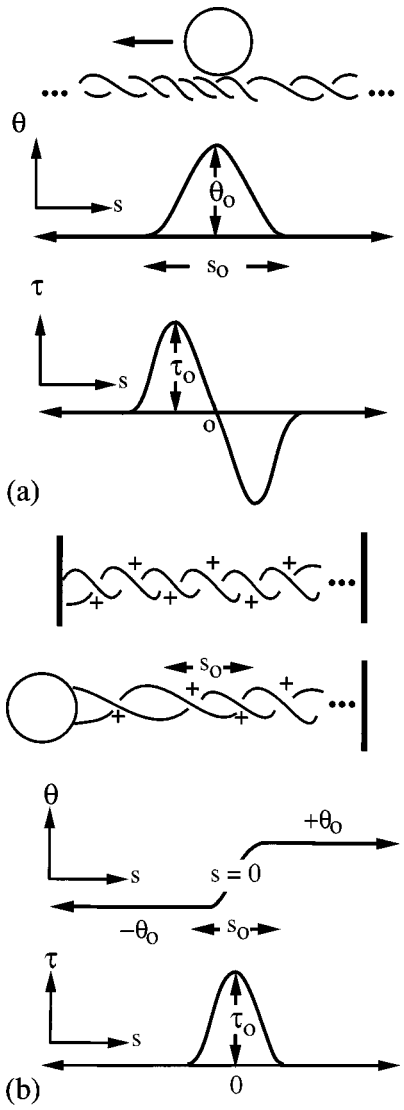

FIG. 3. Initial twist perturbations introduced by two examples of protein wrenches, in absence of DNA supercoiling. (a) RNA polymerase. Attachment of RNAP (circle) to DNA deforms DNA producing twist strain. The strain, $\theta(s,0)$, confined to s_0 bp, consists of increasing overtwist as we approach from the left, peaking at strain amplitude θ_0 and then undertwisting back to its equilibrium value: $\theta(s,0)=0$. Joint production of under twisting and overtwisting means $\Delta LK=0$, always. Since $\tau(s,t)$ is proportional to strain gradient, two domains of oppositely directed torques arise. Arrow indicates direction of motion of RNAP. (b) DNA Gyrase. In this model of gyrase, the DNA starts off with $Lk=6$ (six +'s, ignoring the rest of the molecule). When gyrase (circle) binds, two twists are taken out near the binding site (+'s more spread out near gyrase). Without the time to adjust to the new equilibrium twist for $Lk=4$, the DNA is under-rotated by $-\theta_0$ near the gyrase and over-rotated, by the same amount, close to the other end (where twist rate is still consistent with $Lk=6$). The strain switches from under-rotation to over-rotation in a region of width s_0 bp. For both RNA polymerase and DNA gyrase, our dynamics will quickly forget the exact shape of the initial condition.

can consider the evolution of each individual pulse in isolation.

2. DNA gyrase

The topoisomerase DNA gyrase uses stored energy (ATP) to change the linking number of closed dsDNA by -2 per enzyme cycle. Gyrase, found in bacterial cells, is thought to be present in order to untwist the double helix so that opening of the double helix for initiation of transcription is made energetically more favorable. The linking number change caused by a single gyrase step initially generates twist strain localized to a region a few tens of bp in length. As for the case of RNAP, the initial twist distribution will then relax to its final state. The total energy expended per cycle of gyrase is $\approx 24 k_B T$ (two ATPs are hydrolyzed), indicating that the torque imparted to the DNA molecule can be as large as $\approx 2 k_B T$.

The structural mechanism by which gyrase catalyzes the topology-changing reaction is not understood. It is thought that a sequence of DNA-gyrase binding events is needed to complete the reaction. It has been proposed [22] that after gyrase binds to the DNA, it first waits for a DNA conformational fluctuation that bends a segment of the polymer over itself in such a manner that a part of the DNA gets stuck to a temporarily open domain or gate of gyrase multimer; then a second fluctuation similarly constrains another DNA segment. This segment is then allowed to spontaneously dissociate from the gyrase followed by the closing of the gate thereby preventing thermally driven unbinding of first trapped segment. Next, gyrase introduces two nicks into the DNA to which it is bound and passes the closed trapped segment through the double-nicked DNA. This is followed by resealing of the breaks. Then the writhe introduced by gyrase gets converted into twist and propagates out through the first bent region of the DNA. The initial state that we will consider is, therefore, one where the DNA twist angle "steps" by 4π over a few tens of base pairs. Below, we assume full interconversion of writhe into twist once either of these enzymes catalyzes one reaction step.

Thus, RNA polymerase is likely able to produce large torques in DNA (i.e., more than enough to denature it), while DNA gyrase is likely generating much lower peak torques, near to the $\approx 2 k_B T$ threshold for separating DNA strands. However, gyrase expends up to twice the total stored energy as does RNA polymerase per reaction step (i.e., two ATPs vs. one ATP, respectively).

B. Spreading of twist distortions

An initially localized twist distortion in dsDNA will spread along the length of DNA and induce twisting in regions both upstream and downstream from the point where it is inserted. This spreading of a twist packet is governed by the local balance of torque produced by internal elastic strain and the dissipative torque that the medium exerts on the twisted part of DNA. Following [3], consider DNA to be an elastic cylinder so that the internal elastic torque at position s due to a given twist strain is proportional to the strain at s. If $\theta(s,t)$ is the *excess* angle, in excess of B-DNA twist, between a base pair and its nearest neighbor at position s and time t then the net torque exerted on a short segment of DNA of length Δs by internal elastic restoring forces is

$$\Delta\tau_{\text{internal}} = k_B T C \frac{\partial^2\theta}{\partial s^2}\Delta s \tag{10}$$

while the torque exerted by the drag force on the same cross section is

$$\Delta\tau_{\text{viscous}} = \zeta_R \frac{\partial\theta}{\partial t}\Delta s. \tag{11}$$

Here ζ_R is the rotational drag coefficient per length of the cylindrical dsDNA. The rotational drag coefficient per length for a cylinder of radius a is $\zeta_R = 4\pi\eta a^2$ [3], where η is the viscosity of the surrounding fluid.

In equilibrium, $\Delta\tau_{\text{internal}} = \Delta\tau_{\text{viscous}}$, which gives the equation of motion for twist:

$$\frac{\partial\theta}{\partial t} = D\frac{\partial^2\theta}{\partial s^2}. \tag{12}$$

The twist transport coefficient is $D = Ck_BT/\zeta_R$. D has the dimensions of a diffusion constant, and Eq. (12) has the form of a diffusion equation, but note that the dynamics described above are deterministic. Plugging in the DNA radius of $a = 1$ nm, the twist persistence length $C \approx 100$ nm, the viscosity of water $\eta = 10^{-3}$ Pa s, and assuming room temperature, we obtain a twist transport coefficient of $D \approx 3 \times 10^{-8}\,\text{m}^2/\text{s}$. In base pair units, this is about $2.5 \times 10^{11}\,\text{bp}^2/\text{s}$. Therefore, in a few microseconds, a twist pulse spreads about a kilobase along a double helix.

We can estimate the typical range $R_{\max}$ to which we expect the decaying twist strain to spread and produce torques τ large enough to destabilize a protein-DNA complex by $R_{\max} \sim \sqrt{k_B TC\theta_0 s_0/\tau}$, where s_0 is the length over which the disturbance is initially spread and θ_0 is the starting strain magnitude. From Sec. II, a $\tau \approx 5k_BT$ is what is needed to take apart a protein-DNA complex. If we take $\theta_0 \approx 1$ rad, $C \approx 100$ nm, $\theta_0 \approx 1$ rad and $s_0 \approx 1$ mm, we get an $R \approx 10$ nm.

We have ignored the three-dimensional shape of the DNA molecule in arriving at Eq. (12). Other authors have constructed theories including writhe dynamics [23,24], and considered effects of permanent bends in dsDNA [6]; both of these effects will play a role in the propagation of twist over long distances along DNA. Below, we analyze the dynamics of temporary twist perturbations in short (at most a few persistence lengths) DNA segments for which we can ignore the contribution of writhe (the 3D conformation) of the DNA molecule to its global topology.

C. Dynamics of twist packet with $\Delta Lk = 0$

Twist strains with net $\Delta Lk = 0$ arise during the transcription of DNA by RNA polymerase, or in general, by any DNA-binding protein that locally distorts the double helix locally, without introducing breaks in the sugar-phosphate backbone. As a model of these kinds of distortions, we consider initial conditions where $\theta = 0$ far away from the region where the twist is initially distorted. We consider the interior of a DNA sufficiently long that boundary conditions do not need to be specified.

Spreading of an angle pulse

We consider a simple case of the dissipative spreading of a twist distortion consisting of a small region of a DNA molecule that has its twisting shifted from the relaxed B-DNA structure. The base pairs can be brought back into register after the protein either unbinds from the DNA or releases the distortion into the polymer without necessarily coming off the DNA. We imagine that the starting pulse has a Gaussian shape [Fig. 3(a)]

$$\theta(s,0) = \theta_0 e^{-s^2/2s_0^2}. \tag{13}$$

This initial condition has the portion of the molecule of width s_0 centered around $s = 0$ twisted by about θ_0. DNA-binding proteins routinely apply sufficient force to the double helix to pull $s_0 \approx 10$ bp regions out of joint by ≈ 1 rad.

The elastic torque is just $k_BTC\partial\theta/\partial s$, and thus the initial condition has opposite elastic torques on opposite sides of $s = 0$. Therefore, this simple initial condition is roughly applicable to the initial twist pulse introduced by a RNAP step. The initial elastic torques have maximum amplitude $\approx \pm 0.7k_BTC\theta_0/s_0$. For one step of RNA polymerase, we consider an initial state with $s_0 = 10$ nm (30 bp) and $\theta_0 = 1$ rad, giving peak torques $\approx 10k_BT$.

Given the initial condition (13), the angle time evolution generated by Eq. (12) is just

$$\theta(s,t) = \frac{\theta_0 s_0}{\sqrt{s_0^2 + 2Dt}}\exp\{-s^2/(2[s_0^2 + 2Dt])\}. \tag{14}$$

The corresponding elastic torque in the DNA is

$$k_BTC\frac{\partial\theta}{\partial s} = \frac{k_BTC\theta_0 s_0}{[s_0^2 + 2Dt]^{3/2}}\, s\exp\{-s^2/(2[s_0^2 + 2Dt])\}. \tag{15}$$

Figure 4(a) shows a plot of Eq. (14) for different fixed times, given our proposed RNA polymerase pulse initial condition, with $s_0 = 30$ bp (10 nm), $\theta_0 = 1$ rad, $C = 100$ nm, and $D = 3 \times 10^{-8}\,\text{m}^2/\text{s}$. We note that the energy stored in the initial twist distortion is $\sqrt{\pi}k_BTC\theta_0^2/4s_0 = 4.4k_BT$, a fraction of the total energy released in an RNAP reaction step.

The width increases as $\sqrt{t}$ while the height falls off as $1/\sqrt{t}$. In Fig. 4(b) we plot the torque $\tau(s,t) = k_BTC\partial\theta/\partial s$ at fixed times. The torque drops off as the pulse spreads, on a short time scale ≈ 1 nm. In Sec. III E we will discuss how we estimate $R_{\max}$, the maximum distance to which the torque can propagate with sufficient amplitude to destabilize a bound protein, from our torque calculation.

D. Dynamics of twist packet with $(\Delta Lk \neq 0)$

Twist strains may arise from a topology-changing event, such as the action of DNA gyrase, which changes the linking number of DNA. We consider this topology change to be concentrated in DNA twisting, so that the DNA twist angle θ jumps from $-\theta_0$ to $+\theta_0$ over a contour length of about s_0:

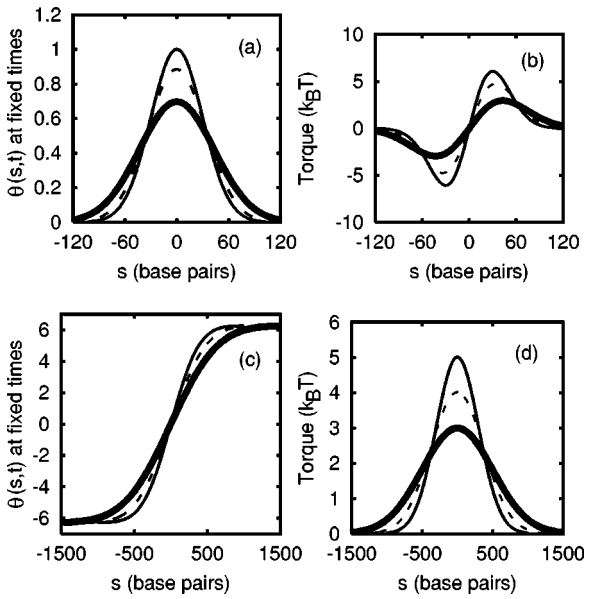

FIG. 4. Dynamical twist and torque dissipation for $\Delta Lk=0$ (a) and (b) and $\Delta Lk\neq 0$ (c) and (d), respectively. The molecule is 1000 bp long with twist persistence length $C=300$ bp. Twist transport coefficient $D=2.5\times 10^{10}$ bp^2/s. (a) Initial Gaussian angle pulse (solid-thin; $s_0=30$ bp and $\theta_0=1$ rad) decays symmetrically about the origin. By 0.5 ns (dashed), the pulse can deliver a torque of $3k_BT$ no farther than 59 bp. Beyond 1.9 ns (solid-thick), strain pulse amplitude can no longer generate $\tau=3k_BT$ anywhere on the DNA. Strain eventually decays to zero throughout the molecule. (b) Torque produced by angle pulse as a function of position along DNA (in bp) for $t=0$ ns (solid-thin), 0.5 ns (dashed), and 1.9 ns (solid-thick); τ is proportional to the strain gradient. $\tau(s,0)$ has equal amounts of undertwisting (left) and overtwisting (right) torque about $s=0$, with peak $\tau\approx\pm 6k_BT$. At $\approx$0.5 ns (dashed), the torque front has simultaneously broadened and lost amplitude, fixing the range to which $\tau=3k_BT$ can be delivered to 59 bp. By $t=1.9$ ns, torque front amplitude has everywhere slipped below $\tau=3k_BT$. (c) At $t=0$ (solid-thin), the steplike strain on DNA starts from under-rotated by $\theta_0=2\pi$ rad on the left to over-rotated by 2π on the right, in a region $s_0=300$ bp. By $t=100$ ns (dashed), the traveling strain has broadened but also lost amplitude, being able to deliver a torque of $3k_BT\approx 280$ bp away from the origin. After $\approx$300 ns (solid-thick) from the start, the strain cannot generate $\geqslant 3k_BT$ of torsion anywhere on the molecule. (d) Torque corresponding to (c) at $t=0$ (solid-thin), 100 (dashed), and 300 ns (solid-thick). Initially, the torque is Gaussian with peak of $\approx 5k_BT$ and width $\approx$300 bp. By 100 ns (dashed), the applied torque $\geqslant 3k_BT$ as far as 280 bp from the origin, in either direction. At $t=300$ ns (solid-thick), the τ amplitude is everywhere below $3k_BT$ (dashed).

$$\theta(s,0)=\theta_0\left[\left(\frac{1}{s_0\sqrt{2\pi}}\right)\int_{-\infty}^{0}dx\,\exp\{[-(s+x)^2/2s_0^2]-\exp[-(s-x)^2/2s_0^2]\}-1\right]. \tag{16}$$

This expression may be written in terms of error functions, but keeping it in this integral form makes it more clearly a solution of Eq. (12). For the case of DNA gyrase, the linking number change of -2 corresponds to $\theta_0=2\pi$. Figure 3(b) sketches this initial condition. The elastic energy of this initial state is $k_BTC\theta_0^2/\sqrt{\pi}s_0\approx 22k_BT$ (for $s_0=300$ bp, $C=300$ bp), again less than the total stored energy released in the enzyme catalytic cycle.

The initial twist state given above has a simple time evolution:

$$\theta(s,t)=\theta_0\left[\left(\frac{2}{\pi}\right)^{1/2}\frac{1}{\sqrt{s_0^2+2Dt}}\int_{-\infty}^{s}dx\,\exp\{-x^2/(2[s_0^2+2Dt])\}-1\right]. \tag{17}$$

The elastic torque is also easily computed to be

$$k_BTC\frac{\partial\theta}{\partial s}=(\sqrt{2/\pi})\frac{k_BTC\theta_0}{\sqrt{s_0^2+2Dt}}\exp\{-s^2/(2[s_0^2+2Dt])\}. \tag{18}$$

Figures 4(c) and 4(d) show $\theta(s,t)$ and $\tau(s,t)$ for the parameters $\theta_0=2\pi$ and $s_0=300$ bp, suitable to describe DNA gyrase. The initially confined twist "step" broadens $\propto\sqrt{t}$.

E. How far from a twist pulse source can a protein be removed from DNA?

To understand what biological implications of propagating twist are, we compute, in this section, the maximum distance $R_{\max}$ to which twist can spread out and still produce torque levels sufficient to dislodge bound proteins. We are interested in the distant production of torsion similar in magnitude to, for instance, the equilibrium torque needed to straighten out a looped domain in the DNA ($\approx 3k_BT$) or, perhaps, torques large enough to remove the histone core proteins from the nucleosome ($\approx 9k_BT$). We solve for $R_{\max}$ from Eq. (15) or Eq. (18) with τ set to, for instance, $3k_BT$.

It must be noted that to obtain $R_{\max}$ we compare an equilibrium torque estimate with dynamical torque (15) or (18). We, therefore, assume that the bound structure is able to equilibrate on the time scale of the pulse dwell time at $s=R_{\max}$. For tightly bound structures, it is possible that even very large transient torques at $R_{\max}$ will not be able to effect unbinding since the torque will not persist there long enough for dissociation to occur. Our $R_{\max}$ estimates are, therefore, upper bounds.

In Fig. 4(b) and 4(d), we plot the induced torque front generated by propagating twist for $\Delta Lk=0$ and $\Delta Lk=-2$, respectively. The starting $\Delta Lk=0$ and $\Delta Lk=-2$ pulses have peak torques $\approx 6.0k_BT$ and $\approx 5k_BT$. Since the twist evolution is dissipative, these torques present upper bounds to how much torsion the twist pulses can later generate. For both RNAP and gyrase, these torques are insufficient to disrupt nucleosome structure. We therefore consider $R_{\max}$ for the lower threshold $\tau^*\approx 3k_BT$, our estimate of the torque needed to open DNA loops. Since melting DNA requires torques $\approx 2k_BT$, we also consider how far propagating twist can produce sustained torques large enough to open single-

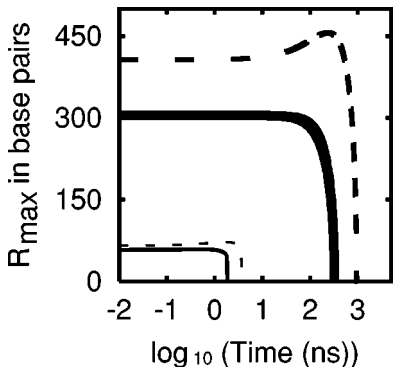

FIG. 5. R_{max} vs $\log_{10}$ (t in ns) for critical torque $\tau^*=3k_BT$ when $\Delta Lk=0$ (solid-thin) and $\Delta Lk\neq 0$ (solid-thick) and $\tau^*=2k_BT$ when $\Delta Lk=0$ (dashed-thin) and $\Delta Lk=-2$ (dashed-thick). All parameter choices as in Fig. 4. For RNAP ($\tau^*=3k_BT$), the strain ($s_0=30$ bp, $\theta_0=1$ rad) initially builds up a torque $\geqslant\tau^*$ up to 57 bp but as it spreads and loses height it cannot create such torques beyond 59 bp. The pulse needs $\approx$0.5 ms to generate torque this far. In $\approx$2 ns, torque is below τ^* at all points on the DNA so that $R_{max}=0$. When $\tau^*=2k_BT$, R_{max} at $t=0$ is 65 bp, peaking at 72.3 bp in 1.7 ns and decaying to 0 in another $\approx$2 ns. Gyrase ($\tau^*=3k_BT$, $s_0=300$ bp, $\theta_0=2\pi$ rad) at first generates torsion $\geqslant\tau^*$ up to $\approx$300 bp, asymmetrically about the origin. Bur it takes only another 200 ns for the maximum torque pulse height to slip below $\tau^*=3k_BT$, i.e., $R_{max}=0$. For $\tau^*=2k_BT$, initial R_{max} is $\approx$400 bp. With increasing pulse width R_{max} begins to rise eventually reaching a maximum of $\approx$450 bp in $\approx$300 ns. In the next 700 ns, the torque envelope becomes flatter, tending to push torque farther, but not fast enough to offset the rapid loss of pulse amplitude, the net effect being a steady decrease in R_{max}. It takes longer for $R_{max}\rightarrow 0$ when $\Delta LK=-2$ vs $\Delta Lk=0$ because of the greater starting amplitude and spread of the gyrase induced strain compared to RNA polymerase. For fixed ΔLk, the peak R_{max} is larger for $\tau^*=2k_BT$ than $3k_BT$ as expected from our scaling relation for R_{max} (see text).

stranded ''bubbles'' in the DNA. Since the binding affinity of single-stranded DNA may be lower than dsDNA for a given protein, formation of single-stranded domains in DNA may locally destabilize bound proteins.

For $\Delta Lk=-2$, the strain-induced torque profile is Gaussian [Fig. 4(d)], yielding an exact expression for R_{max} as a function of the critical torque τ^* and time:

$$R_{max}=(s_0^2+2Dt)^{1/2}\left[\ln\left(\frac{2\theta_0^2C^2}{\pi\tau^{*2}(s_0^2+2Dt)}\right)\right]^{1/2}. \quad (19)$$

We plot Eq. (19) as a function of $\log_{10}$ (time in ns) for the unlooping (Fig. 5, solid-thick) and melting torques (Fig. 5, dashed-thick). The starting Gaussian pulse can deliver $\tau^*=3k_BT\approx 300$ bp away. As the strain spreads out, the torque pulse broadens; in $\approx$100 ns R_{max} falls to 280 bp. Thereafter, in just another 200 ns, $R_{max}=0$, indicating that the torque amplitude is $<3k_BT$ at all points on the DNA. As the pulse broadens, its outer envelope becomes more horizontal, allowing larger torques to be delivered farther but, at the same time, the traveling pulse loses strength, thus tending to reduce R_{max}. For $\tau^*=3k_BT$, R_{max} steadily declines with time indicating that pulse height dissipates so fast that even with greater spread the pulse cannot deliver torques larger than $3k_BT$ any farther than at $t=0$. As a result, the torque pulse [Fig. 4(d)] produces $\tau\leqslant\tau^*$ in an ever-shrinking interval around the origin. On the other hand, when $\tau^*=2k_BT$, R_{max} is unimodal. At the start, torques $\geqslant\tau^*$ are produced up to $\approx$400 bp away. As the strain relaxes through the molecule, R_{max} increases to a maximum of $\approx$450 bp in 300 ns and then rapidly falls to 0 in another 700 ns.

For angle pulse evolution ($\Delta Lk=0$), R_{max} satisfies

$$\ln R_{max}-\left(\frac{R_{max}^2}{2(s_0^2+2Dt)}\right)=\ln\left(\frac{\tau^*(s_0^2+2Dt)^{3/2}}{C\theta_0 s_0}\right). \quad (20)$$

This is used to plot R_{max} against $\log_{10}$ (time in ns) for $\tau^*=3k_BT$ (Fig. 5, solid-thin) and $\tau^*=2k_BT$ (Fig. 5, dashed-thin). For $\tau^*=3k_BT$, R_{max} is initially $\approx$55 bp, reaching its peak of $\approx$60 bp in about 0.5 ns, thereafter decaying to 0 in another 0.5 ns. For the lower melting torque, $R_{max}=65$ bp at $t=0$, rises to $\approx$72 bp in $\approx$1.7 ns and, in another 2 ns, falls to $R_{max}=0$ bp.

Our results indicate that, with no barriers to the twist relaxation considered here, RNA polymerase will generate transient twist pulses that decay below the levels necessary to alter even loosely bound proteins over $\approx$1 ns time scales. This is probably too short for even weakly bound proteins to respond. On the other hand, we find that DNA gyrase may be able to remove weakly bound proteins with torque pulses lasting up to $\approx$100 ns, and acting up to roughly 300 bp away. This difference stems from the larger and more extended initial angle pulse, and of course the larger initial stored energy, associated with the cycle of DNA gyrase.

IV. CONCLUSION

In this paper we have considered the stability of DNA-protein complexes in the presence of torsional stress. Our equilibrium calculations have the simple result that the characteristic torque, associated with removal of a protein that allows contour length D of DNA to absorb twisting strain, is $\tau^*\approx\sqrt{k_BT\mu C/D}$, where μ is the free energy difference associated with the protein-DNA interactions holding the complex together. This formula is the torque analog of the characteristic force needed to open a protein-DNA complex, $f^*\approx\mu/D$ [12]. Strongly bound compact structures such as the nucleosome ($\mu\approx 20k_BT$, $D\approx 50$ nm) require large torques $\approx 10k_BT$ to disrupt them. On the other hand, more weakly bound structures, or DNA loops with large D values, likely will require torques in the range $2k_BT$ to $3k_BT$.

Torques in the few k_BT range may be applied by RNA polymerase and DNA gyrase, according to experimental data and rough theoretical estimates [6,23,16,17]. Thus, torques applied by RNA polymerase and gyrase to an anchored DNA segment can reach those necessary to open relatively weakly bound DNA-protein complexes. On the other hand, nucleosomes should be relatively stable to the direct effect of the torques applied by these enzymes.

These torques are close to those needed to disrupt DNA secondary structure. Double-stranded DNA is now known to be unstable against such strong torques, and converts to

''melted'' forms for left-handed (unwinding) torques larger than $2k_BT$, and for overwinding torques larger than $6k_BT$ [18,19,21,25]. This raises the interesting question of the interplay between torque-generated denaturation and protein dissociation; one can easily imagine the unbinding of a protein in response to local DNA melting. The coupling of DNA melting to protein dissociation could be described using an elaboration of the equilibrium model of the present paper.

It is important to realize that our equilibrium theory applies most strictly to equilibrium experiments, i.e., where the time scale for the experiment greatly exceeds the on and off times for the DNA-protein complex. Particularly in the case of large structures such as nucleosomes, there may be large free-energy barriers to overcome to transit between bound and unbound states [26].

We have also analyzed the dynamics of spreading of single twist pulses and steps according to the simple dynamics used to describe twist relaxation of short DNA segments in free solution [3]. The small diameter of the DNA double helix results in rapid spreading of twist pulses. In turn, this makes an initial torque pulse spread and decay rapidly. The result is that single pulses of torque injected by enzymes can affect bound proteins only at short ($<$100 bp) distances.

Our dynamical model supposes that any net linking number injected into the DNA is eventually removed, e.g., at free ends of a linear DNA. In the case where one has a small circular or otherwise topologically constrained domain, torsional stress will of course build up cumulatively with each enzyme cycle. Usually a steady state will be reached, defined in the test tube by the enzyme stall point, or *in vivo* by the action of counteracting enzymes (e.g., topoisomerase I, which allows linking number to be removed from a point along a dsDNA by generation of a transient break in one DNA strand). In the case where an appreciable steady-state torque is reached, our pulse-propagation model should not be used, and instead the ''equilibrium'' theory will be relevant.

Some enzymes may inject twist strain continuously into DNA over some time (e.g., RNAP). It is then possible that far away from the strain source, approximately steady-state torques may build up cumulatively. For instance, if the enzyme cycle time is comparable to the typical propagation time of the twist pulse then successively injected twist strains can ramp up the torque through small increments. For the simple twist propagation considered here, this is not relevant, since the RNAP/gyrase cycle times ($\approx$0.1 s) are long relative to twist propagation times on few kb scales (recall that a twist pulse spreads over 1 kb in $\approx 10^{-6}$ s). However, we note that Nelson has suggested that intrinsic bends may greatly slow the propagation of twist along long DNAs, perhaps to the point that a steady-state torque may be applied by RNA polymerase over $\approx$1000 bp distances even on linear DNA [6]. If such a steady state of torsional stress occurs, the ''equilibrium'' theory is best applied.

We have not considered the complete dynamics of linking number, including the interconversion of twist to writhe [24]. This is complicated since the subsequent relaxation of writhe must take into account hydrodynamic interactions. We have simplified the problem by considering only short ($<$1000 bp) regions of DNA for which the writhing in the dynamics can plausibly be ignored. However, on large (few kb) molecules, the twist relaxation time will become long enough for writhing to occur [23].

Enzyme-driven twist propagation has been proposed as a possible chromatin ''remodeling'' mechanism for a class of recently discovered, highly conserved, ATP-consuming proteins [27]. These enzymes facilitate *in vivo* transcription of genes, by allowing regulatory proteins to bind to DNA domains that are otherwise inaccessible because they are confined to the nucleosome. Increasing access to bound regions of the DNA could involve (a) sliding or linearly displacing the histone protein core along the DNA, (b) creating a large transient DNA loop by partially unbinding a segment of the wrapped DNA from the nucleosome, thereby exposing the looped DNA, (c) temporarily ejecting the histone from the chromatin fiber, or (d) first disassembling and later reassembling the histone octamer.

Currently, transient unbinding of a large region of nucleosome surface-bound DNA is the favored way of thinking about remodeling-enzyme facilitated gene regulation [9]. Since remodeling activity generates torque, it has been suggested that this may be used to drive twist strain through the DNA, and causing the elastic twist energy of deformed DNA to tear bound regions off the nucleosome surface. The binding energy per length of DNA bound to the nucleosome is $\approx 0.15 k_BT$/bp (assuming that 146 bp of DNA has binding enthalpy $\mu = 20 k_BT$) [14,28]. Our equilibrium estimate for the torque needed to unbind a pinned domain of DNA, $\tau^* \approx \sqrt{2k_BTC(\mu/D)}$, where $C = 100$ nm is the twist persistence length, predicts that remodeling complexes have to produce sustained torques $\approx 9k_BT$ to unbind a region of the surface-bound DNA. Since the torque depends only on the binding energy per unit length of DNA, disrupting the initial DNA-histone contacts, even in the presence of thermally induced unpinning of contacts near the DNA overhangs, requires as much torque as disrupting later contacts. Therefore, the nucleosome will be stable in the presence of gradually increased torque, until a threshold torque is reached, at which point the histones will dissociate. Of course, the large total $\mu \approx 20 k_BT$ suggests that an even larger torque barrier must be overcome for histone removal to occur.

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