

Unwrapping of DNA-protein complexes under external stretching

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A DNA-protein complex modeled by a semiflexible chain and an attractive spherical core is studied in the situation when an external stretching force is acting on one end monomer of the chain while the other end monomer is kept fixed in space. Without a stretching force, the chain is wrapped around the core. By applying an external stretching force, unwrapping of the complex is induced. We study the statics and dynamics of the unwrapping process by computer simulations and simple phenomenological theory. We find two different scenarios depending on the chain stiffness: For a flexible chain, the extension of the complex scales linearly with the external force applied. The sphere-chain complex is disordered; i.e., there is no clear winding of the chain around the sphere. For a stiff chain, on the other hand, the complex structure is ordered, which is reminiscent of nucleosome. There is a clear winding number, and the unwrapping process under external stretching is discontinuous with jumps of the distance-force curve. This is associated with discrete unwinding processes of the complex. Our predictions are of relevance for experiments, which measure force-extension curves of DNA-protein complexes, such as nucleosome, using optical tweezers.

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I. INTRODUCTION

Complexations between chainlike molecules and spherical host particles are frequent in nature. Key examples can be found in living organisms, where various DNA-protein complexes play important roles in fundamental life processes [1]. This complex formation is also important for potential applications in gene delivery, where negatively charged DNA is complexed with various cationic substances to be an efficient gene carrier. One of the prominent examples is the nucleosome, which is constituted by cationic proteins, called a histone octamer, and DNA wrapping around them. The formation of the nucleosome is the first step for a dramatic compaction of long DNA chains from the order of cm down to a nucleus size of $\sim \mu\text{m}$ [2–4]. Since the tight wrapping of DNA around the histone should limit the accessibility of transcriptional factors, the nucleosome structure in genetically active states is expected to be loosened or, at least, partially unwrapped. Therefore, the stability and dynamical properties of the nucleosome are crucial factors for the gene activity in eukaryotic cells [5,6].

In a real nucleosome, there are 14 binding regions on the histone surface, which define the helical wrapping path of the DNA. However, from the side of physics, the first task is to figure out the basic and principal mechanisms, which are free from the molecular specificity. Along this line, simple systems with a spherical or cylindrical particle and a polymer chain have been adopted in the hope of capturing the essential features of nucleosomes [6–17]. The sphere-chain complexation behavior is controlled by several factors, such as the nature of interaction between them, the sphere size, and the chain stiffness. It is an interesting question to study the

response of the complex with respect to an external force acting on the chain [13,18]. A dramatic change of the complex structure is expected for large external forces. In fact, it is known that the wrapping behavior of nucleosomes in the cell is influenced by the tension generated by molecular motors [19,20].

In the present article, we study the complexation behavior of a simple DNA-protein model system by means of computer simulations and a phenomenological theory. Currently, the only experimental example relevant to our study is the nucleosome—i.e., the stretching of chromatin by optical or magnetic tweezers [20–23]. However, we remark that potential applications to other relevant experimental studies such as colloid-polyelectrolyte complexes under tension are expected, which should be interesting in the context of nanotechnology as well as biological science. Thus, we do not restrict ourselves to the nucleosomelike structure only, but aim to get a full picture of the properties inherent in the sphere-chain complex under tension. In particular, we investigate the effect of chain stiffness on the structure of a sphere-chain complex and its consequent characteristics in response to external tension acting on the end monomers of the chain. We find two different scenarios, which depend crucially on the chain stiffness: For a flexible chain, the extension of the complex scales linearly with the external force applied. The sphere-chain complex is disordered; i.e., there is no clear winding of the chain around the sphere. In the opposite limit of a stiff chain, however, the complex takes a nucleosomelike ordered structure and there is a clear winding number. The unwrapping process under external tension is discontinuous, exhibiting jumps in the distance-force curve. This can be traced back to discrete unwinding processes of the complex. Our predictions are of relevance for experiments, which measure force-extension curves of DNA-protein complexes, such as the nucleosome, using optical tweezers [20–23].

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Our paper is organized as follows: In Sec. II, we introduce a monomer-resolved model of DNA-protein complexes which is studied by simulations. Simulation results are presented in Sec. III. A further discussion based on a simple theory is contained in Sec. IV. Finally we conclude in Sec. V.

II. SIMULATION MODEL

The model we adopted is almost the same as that studied previously in Ref. [15]. First, a polymer chain is represented by $N=50$ spherical monomers at positions \mathbf{r}_i . In what follows, we rescale all lengths and energies by the size of the monomer diameter $b \equiv 1$ (which sets the molecular thickness of the chain) and thermal energy $k_B T \equiv 1$, respectively. Neighboring monomers are connected via harmonic bonds in order to ensure connectivity along the chain; the bond energy between neighbors reads as $U_{bond} = (\kappa_{bond}/2)(|\mathbf{r}_i - \mathbf{r}_{i+1}| - 1)^2$. We set the spring constant $\kappa_{bond} = 400$, which gives an almost constant bond length ~ 1 . The chain stiffness is implemented by a bending potential of the form $U_{bend} = \kappa \{1 - (\mathbf{r}_{i-1} - \mathbf{r}_i)(\mathbf{r}_i - \mathbf{r}_{i+1})\}$, which favors stretched configurations. The bending modulus κ is connected with the chain persistence length λ_p via $\lambda_p \approx \kappa - 0.5$ (for $\kappa > 2$) [15]. The excluded volume of monomers is modeled by the repulsive part of a Morse potential, $U_{M,rep}(\mathbf{r}_{i,j}) = \epsilon_m \exp\{-\alpha_m(r_{i,j} - 1)\}$, where $\epsilon_m = 1.0$, $\alpha_m = 24$, and $r_{i,j}$ is the distance between monomers.

Next, we introduce a spherical particle. The interaction between each monomer and the spherical particle is modeled through the full Morse potential $U_M = \epsilon[\exp\{-2\alpha(r_i - \sigma)\} - 2\exp\{-\alpha(r_i - \sigma)\}]$, where r_i denotes the distance between the i th monomer and the spherical core. We set $\alpha = 6$ and $\sigma = 1.9$ (corresponding to a sphere diameter of about 2.6), so that the volume ratio between the spherical core and polymer chain mimics a real nucleosome [15]. The strength of attraction is fixed to be $\epsilon = 8$, which ensures a tight wrapping or adsorption of a polymer on the spherical core in the absence of stretching force. It should be noticed that such a model with only short-range interactions would be readily accepted for the charged system, too, in the salty environment (including the physiological condition), where long-range electrostatic interactions become local due to screening.

Even though a tightly wrapped complex is formed, the spherical core slides along the chain and prefers positioning at the chain end [15]. We would like to put the complex now under external tension. In order to eliminate possible end effects of the chain and to get a clear-cut configuration, we fix simultaneously one end monomer *and* the center of the sphere: the spherical core is fixed at the origin and the end monomer at $\mathbf{r}_1 = (-8, 0, 0)$. Then, a stretching force is applied to the other end monomer with position \mathbf{r}_N along the x axis (see Fig. 1). We realize this by either applying a constant force f or stretching the monomer at a constant velocity v . In the former case, we obtain the average extension in the x direction, $r \equiv \langle r_{N,x} \rangle$, while in the latter, we monitor the resistant force during the possibly nonequilibrium, unwrapping process.

The monomers obey the stochastic dynamics described by an underdamped Langevin equation

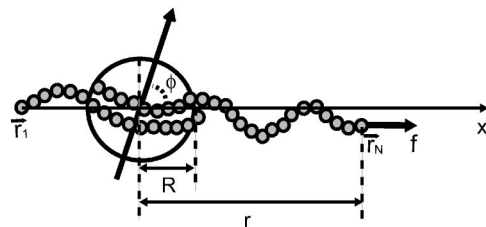


FIG. 1. Schematic sketch of the complex under external stretching. The first end monomer is fixed at \mathbf{r}_1 , the protein sphere with radius R is fixed at the origin, and the other end monomer is pulled by the force f along the x axis. The chain extension r and the tilt angle ϕ , which can be defined for the ordered complex, are also shown.

$$m \frac{d^2 \mathbf{r}_i}{dt^2} = -\gamma \frac{d\mathbf{r}_i}{dt} + \mathbf{R}_i(t) - \frac{\partial U}{\partial \mathbf{r}_i}. \quad (1)$$

The role of the solvent is incorporated by the friction (γ is the friction constant) and the random kicks acting on the particles. This random force is represented by a Gaussian δ -correlated noise whose variance is related to the friction constant through the fluctuation-dissipation theorem: $\langle \mathbf{R}_i(t) \mathbf{R}_j(t') \rangle = 6\gamma \delta_{ij} \delta(t-t')$. Here m is the monomer mass and the total internal energy U splits naturally into $U = U_{bond} + U_{bend} + U_{M,rep} + U_M$. We integrate the discretized equation of motion using a leapfrog algorithm with time step of $\Delta t = 0.0025\tau$, where $\tau (= \gamma b^2 / k_B T)$ is a typical time scale of monomer diffusion. In the following, the time is represented with a rescaled unit with τ . Let us remark that the monomers are, in fact, in an overdamped situation. However, by putting a fictitious inertial term in the equation of motion, it is possible to take a rather long-time step, which results in a significant reduction of the calculation time. This inertial term only affects the velocity relaxation of monomers, but does not affect events happening on the large time scale of our interest. It does not affect at all equilibrium quantities. We further remark that hydrodynamic interactions as induced by the solvent flow are neglected in our approach, but again these are irrelevant if equilibrium quantities are calculated.

III. RESULTS

We first study the response of the complex to applied constant tension. We carried out sufficiently long simulations, typically $\sim 4 \times 10^8$ time steps, to extract equilibrium properties of the ensemble. We carefully checked that our simulations accomplish the equilibrium sampling in the configurational space and do not suffer from a possible kinetic trap due to the energy barrier. In Fig. 2, we show the force-extension relation for the cases with different three chain stiffnesses $\kappa = 2, 5$, and 10 . In all cases, when the applied tension is weak, the extension increases rather rapidly with the tension. However, the response under moderate or high tension crucially depends on the chain stiffness. The extension of the complex with a flexible chain ($\kappa = 2$) gradually increases with the applied tension with almost *linear* dependence. On the other hand, if the chain is stiff enough ($\kappa = 10$), the extension is almost constant; in other words, the

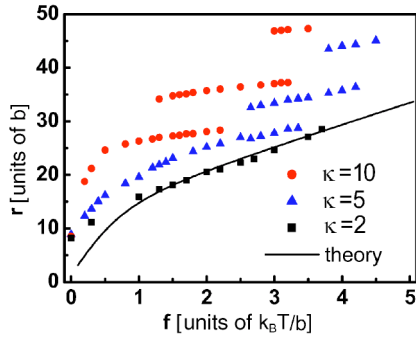


FIG. 2. (Dots) Force-extension relation of the sphere-chain complex obtained by computer simulations for different chain stiffnesses $\kappa=2, 5$, and 10 . In the case of a bimodal distribution of r , we plot both peak positions. (Line) Theoretical force-extension relation of the disordered sphere-chain complex. The parameters are estimated from the corresponding system in the simulation with $\kappa=2$: $a_1=-7$, $a_2=0.12$, $L_0=44$, and $\lambda_p=1.5$.

susceptibility is very low until an abrupt discrete change occurs around some critical tension. It can be shown that this distinction comes from the structural property of the complex.

To see this, we introduce the parameter [15]

$$\eta \equiv \frac{|\sum_{\langle i \rangle} \mathbf{r}_{i,i+1} \times \mathbf{r}_{i+1,i+2}|}{N_p}, \quad (2)$$

where the summation in η is taken only over the monomers in the vicinity of the particle's surface ($r_i < 2.9$) and N_p is the number of such monomers. This quantity measures a degree of "wrapping ordering" of the complex. If the chain wraps orderly and traces the helical path on the sphere surface, η takes a high value of $\eta \gtrsim 0.4$. Otherwise, the complex is regarded as a random adsorption of the chain on the sphere, which results in a small value of $\eta \lesssim 0.2$. Figure 3 shows the probability distribution of η for complexes of different chain stiffnesses. The ordered and disordered complexes are formed from the stiff ($\kappa=10$) and flexible ($\kappa=2$) chains, respectively, and the bimodal distribution between these two states is observed in the case of intermediate chain stiffness ($\kappa=5$). Figure 4 shows typical simulation snapshots of the complex corresponding to ordered and disordered states. Note that η for the complex with one turn (the number of

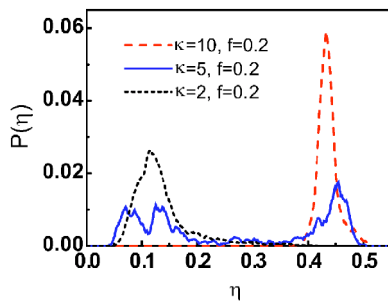


FIG. 3. Probability distribution of the order parameter η for complexes made from chains with different stiffnesses $\kappa=2, 5$, and 10 under a stretching force $f=0.2$.

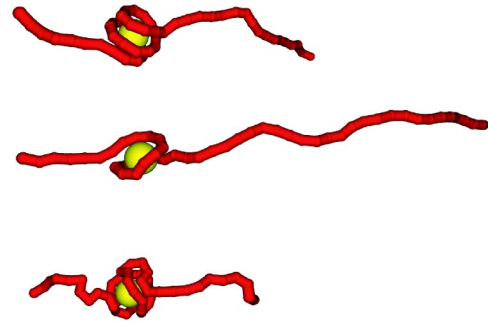


FIG. 4. Typical simulation snapshots of the sphere-chain complex. Top: an ordered wrapping with wrapping number $w=2$ for $\kappa=10$, $f=1$. Middle: an ordered wrapping with $w=1$ for $\kappa=10$, $f=2.5$. Bottom: a disordered state for $\kappa=2$, $f=1$.

helical turns around a core or wrapping number $w=1$) is about $\eta \approx 0.33$, which is slightly smaller than that for a complex with $w=2$ ($\eta \gtrsim 0.4$).

Figure 5 shows the specific heat C_f for various chain stiffnesses as a function of the applied stretching force f . In the constant-force ensemble, it is the temperature derivative of the enthalpy, which is calculated as $C_f = \langle U^2 \rangle - \langle U \rangle^2 - f(\langle r_{N,x} U \rangle - r \langle U \rangle)$. For a flexible chain ($\kappa=2$), C_f just slightly increases with f in a monotonic way, while for stiffer chains, it shows sharp peaks around $f=1.6, 3.2$ for $\kappa=10$, and $f=2.8, 4$ for $\kappa=5$. In general, a peak in the specific heat indicates a transition between two different states. In fact, these peaks exactly correspond to the points, where the force-extension relation reveals abrupt jumps, and indicate a transition from wrapping number $w=2-1$ and $w=1-0$. In the remanent values of an applied tension f , C_f is very small and r is almost constant. In contrast to the lax response of the disordered complex from a flexible chain, the response of the ordered complex is characterized by a "switching behavior": it is very stable against tension, but reveals a sudden switching to a different state by an unwrapping transition at some critical tension. This trend becomes more evident for the complex with the stiffer chain.

In Fig. 6, we show the probability distribution of the chain extension r around the critical force of the transition from $w=2$ to 1 for $\kappa=10$. Clear bimodal distributions are seen, where the relative probability changes with the increase in f , whereas the peak positions remain unchanged. The free en-

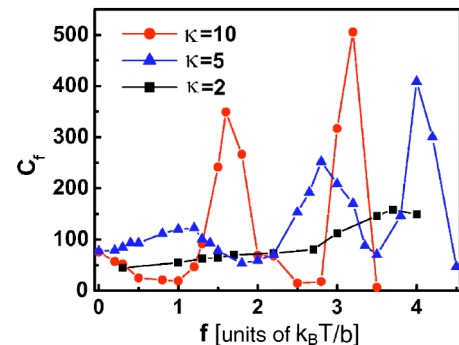


FIG. 5. Specific heat as a function of the stretching force for different chain stiffnesses $\kappa=2, 5$, and 10 .

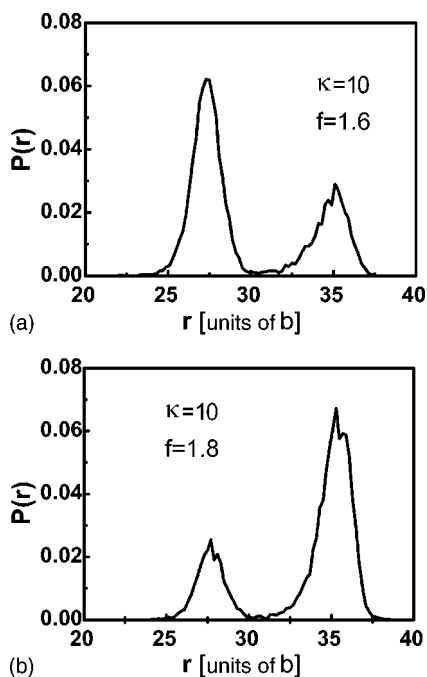


FIG. 6. Probability distribution of the chain extension r (a) below ($f=1.6$) and (b) above ($f=1.8$) the critical stretching force to induce the unwrapping transition from $w=2$ to 1 for a chain stiffness of $\kappa=10$.

ergy barrier between these two states is deduced to be $\Delta G \approx 4-5$.

For the chain with $\kappa=5$, an additional, somewhat broad peak in C_f is seen around $f \approx 1.2$, where the jump in the extension is hardly recognized. Instead, the complex changes its preferred structure around this point. The analysis within the distribution of η indicates that this is a signal for a tension-induced ordering transition. As Fig. 3 shows, the complex with intermediate stiffness ($\kappa=5$) reveals the bimodal distribution of η under the weak tension. This equilibrium between disordered and ordered states shifts to an ordered one with an increase in f . At $f \approx 1.5$, the distribution of η becomes similar to that of an ordered complex. Under stronger tension, the complex behaviors are almost identical to those of an ordered one.

IV. DISCUSSIONS

A. Force-extension relation in a disordered complex

Now, we present a phenomenological theory to describe the properties of the sphere-chain complex in a disordered state under the stretching force. We consider a polymer chain (length L_0 , thickness $b=1$), one part of which (its length is L) is adsorbed on the spherical core of radius R .

The remaining part of the chain (length $L'=L_0-L$) is free and unbound by the core particle. It takes a stretched conformation due to the stretching tension applied to the chain end, whose end-to-end distance (distance from the core surface to the stretched chain end) is denoted as r' .

In the disordered state, there are substantial freedoms for the adsorbed segment distribution on the core surface. To

describe this situation, we adopt a Flory-type mean-field argument. A conditional free energy of the disordered state characterized by an adsorbed length L , under the action of a stretching force f , is written as

$$G_d(L) = F_d(L) + F_u(L'), \quad (3)$$

where F_d and F_u represent the free energy of the disordered segments on the core surface and that of unbound segments under tension.

$F_d(L)$ is composed of the contributions

$$F_d(L) = F_{ad} + F_{conf} + F_{ss}. \quad (4)$$

The first term is the energetic gain due to the segment adsorption on the core: $F_{ad} = \epsilon L$, where $\epsilon < 0$ is the adsorption energy per length. The second term is the conformational entropy of the chain on the core, which is evaluated from the random walk on the core (proportional to the segment number L/λ_p) plus its deviation from ideal chain statistics: $F_{conf} \approx -L/\lambda_p + R^2/L\lambda_p + L\lambda_p/R^2$ [24]. The last term in Eq. (4) describes the segment-segment interaction, which can be taken into account through a virial expansion up to second order: $F_{ss} \approx Bn^2R^2$, where B is the second virial coefficient $B \sim b\lambda_p$ and n stands for the segment density on the core, $n \sim L/R^2\lambda_p$.

We describe an unbound chain under tension by a freely jointed chain with segment length $2\lambda_p$, which writes the free energy F_u as [24]

$$F_u(L') = -\frac{L'}{2\lambda_p} \ln\left(\frac{4\pi \sinh y}{y}\right), \quad (5)$$

where $y \equiv 2\lambda_p f$. The end-to-end distance r' is associated with the contour length of unbound part L' as

$$r' = L' \left(\coth y - \frac{1}{y} \right). \quad (6)$$

By putting Eq. (4) and Eq. (5) in order, we obtain

$$G_d(L) = a_1 L + a_2 L^2 + a_3 L^{-1} - \frac{L_0 - L}{2\lambda_p} \ln\left(\frac{4\pi \sinh y}{y}\right), \quad (7)$$

where $a_1 \approx \epsilon + \lambda_p/R^2$, $a_2 \approx b/\lambda_p R^2$, and $a_3 \approx R^2/\lambda_p$. The third term is shown to be always negligible compared to the second term in the case of our interest; thus, we can safely neglect it. And note that $L=L_0-L'$ is a function of r' [see Eq. (6)].

The most probable length for the adsorbed chain part is determined through the minimization of the free energy, $\partial G_d / \partial r' = (\partial G_d / \partial L)(\partial L / \partial r') = 0$ (this is equivalent to the equality of the chemical potentials of adsorbed and unbound segments):

$$\langle L \rangle = -\frac{a_1}{2a_2} - \frac{1}{4a_2\lambda_p} \ln\left(\frac{4\pi \sinh y}{y}\right). \quad (8)$$

To compare with the result from simulations, it is convenient to rewrite this relation in terms of r using $r=r'+R$:

$$r = \left[L_0 + \frac{a_1}{2a_2} + \frac{1}{4a_2\lambda_p} \ln \left(\frac{4\pi \sinh y}{y} \right) \right] \left[\coth y - \frac{1}{y} \right] + R. \quad (9)$$

This function is depicted in Fig. 2. All of the coefficients in Eq. (9) can be estimated once the system is specified. Therefore there is, in principle, no space for adjustable parameters. The theoretical prediction shows a good agreement with the simulation result, especially for large forces.

Let us consider the two limiting cases: (i) the small force regime ($y \ll 1$) and (ii) large force regime ($y \gg 1$). By taking asymptotic limits in Eq. (9), we obtain

$$r = \begin{cases} b_1 + b_2 f & (y \ll 1), \\ b_3 + b_4 f & (y \gg 1), \end{cases} \quad (10)$$

where $b_1 = R$, $b_2 = \lambda_p(L_0 + a_1/2a_2 + \ln(4\pi)/4a_2\lambda_p)$, $b_3 = a_1/2a_2 + L_0 + R$, and $b_4 = 1/2a_2$.

In the first limiting case ($y \ll 1$), the unbound chain section is coiled in space, where the chain extension is linear as expected (linear response to the weak external field). In the freely jointed chain model, the response coefficient of the chain with contour length L and segment length l is easily calculated from Eq. (6) as $Ll/2$. However, in the sphere-chain complex, the contour length of the unbound chain section is not fixed but dependent on the conditions. Our theory claims that the response of the disordered sphere-chain complex to the weak stretching force is dictated by the entropic elasticity of the unbound chain, whose contour length is determined by the balance between the energetic gain due to adsorption (and other terms proportional to L) and intersegment repulsion on the core. It should be noted that the theory underestimates the chain extension for very low stretching force. This deviation probably comes from the steric repulsion between the core particle and unbound chain segments, which is not taken into account in our theory.

The second limit ($y \gg 1$) corresponds to the situation where the unbound chain section is completely stretched. Such a situation should be realized if the attractive interaction between segments and the core particle (ϵ) is sufficiently strong. Equation (10) indicates that, in this limit, too, the chain extension under large stretching force is a *linear* function with applied tension with a slope b_4 . However, the origin of the linearity stems from the different physics from that in the weak-stretching-force regime. In this limit of the complete stretching of unbound chain, the chain extension is linearly related to the length of the adsorbed chain section. In the disordered complex, the length of the adsorbed chain section is determined by the balance between energetic gain due to adsorption (and other terms proportional to L) and intersegment repulsion on the core. When the external tension is applied, the system responds by shifting this balance, where the response coefficient is given by b_4 .

It is also intriguing to consider the situation in which attractive interactions work between segments. In this case, the second virial coefficient B of the segment-segment interaction is expected to decrease and to change its sign with an increase of the segment-segment attraction. At that “ θ point,” the third virial coefficient C , instead of B , becomes the rel-

evant term in Eq. (4), and as a consequence, we have a term proportional to L^3 , instead of L^2 , in the conditional free energy $G_d(L)$ [Eq. (7)]. As a result, a *nonlinear* response to the stretching force is expected at “ θ conditions.”

B. Unwrapping transition in an ordered complex

Contrary to the disordered structure made from a random adsorption of a flexible chain, a stiff chain forms an ordered complex with a core, where the segment fluctuations around the optimal configuration are negligible. In this case, a theoretical argument based on a ground-state analysis indicates the all-or-nothing unwrapping transition [7]. Consider a stiff chain wrapping around a cylindrical core particle. The free energy of this cylinder-wrapped chain complex can be written as a sum of the adsorption and bending energy terms:

$$F_0(L) = F_{ad} + F_{bend}, \quad (11)$$

where $F_{ad} = \epsilon L$ and $F_{bend} = \kappa L/2R_0^2$. Here L and R_0 denote the chain length and radius of curvature, respectively, of the wrapped part. Both terms are linear in the wrapped chain length L . This indicates that, by changing either the adsorption energy density ϵ ($\epsilon < 0$) or chain rigidity κ , one expects the following two situations: a complete wrapping (the chain wraps around the cylindrical core as much as possible until the adsorption space is exhausted) or a complete unwrapping (the chain takes a stretched configuration due to the chain rigidity). The boundary between these two regimes is given as $\epsilon = -\kappa/2R_0^2$.

In our system, too, the ground-state analysis is expected to be a good approximation for the ordered complex. When the tension is weak, the entropic elasticity of the unbound part plays an important role as is discussed in Sec. IV A. In this regime, the chain extension increases rather rapidly with the tension. We note that this regime of weak stretching force becomes narrower with an increase in the chain stiffness, since the relevant parameter is $y \equiv 2\lambda_p f$ [see Eq. (10)], which is indeed confirmed by the simulation (Fig. 2).

Here we consider another limiting case, where the unbound chain part is completely stretched by a strong tension. Under such circumstances, the free energy of the ordered complex with the applied tension f is written as

$$G_0(L) = F_0(L) - f(L_0 - L). \quad (12)$$

Since the added term due to the stretching force is also linear in L , the all-or-nothing unwrapping transition is expected in this case, too. However, the following differences should be noted: (i) the presence of stretching force acting on the chain and (ii) the possibility of multiple wrapping of the chain around a spherical core. As for the first point, the stretching force strongly restricts the chain segment around the boundaries between adsorbed and free segments—i.e., entry and exit points. This results in the discrete unwrapping transition between states with different wrapping numbers separated by an energy barrier, which is discussed below. And the second point leads to the stepwise, but not all-or-nothing (predicted for a cylindrical core), unwrapping transition. The stepwise unwrapping is a consequence of the spherical geometry of a core particle, in which the bending energy contribution de-

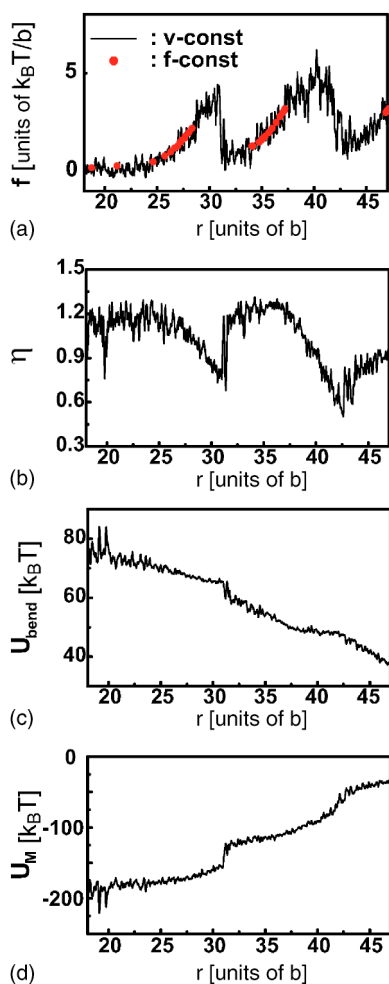


FIG. 7. Unwrapping process by stretching an end monomer by a constant speed for the chain stiffness parameter $\kappa=10$. (a) Force-extension relation. The result from the force constant ensemble is also plotted by circles for comparison. (b) Tilting angle-extension relation. (c) Bending energy-extension relation. (d) Adsorption energy-extension relation.

depends on the wrapping number due to the curvature of the core and hard-core volume of the chain.

To elucidate the first point—i.e., the effect of the stretching force on the energy barrier—we study the dynamical process of the unwrapping transition by stretching the end monomer slowly by constant speed v . We adopt $v\Delta t=0.0002$, which is, in fact, very slow compared to the diffusion.

Figure 7(a) shows the force-extension curve for the case with stiff chain of $\kappa=10$, where the characteristic sawtooth pattern is observed. For comparison, the correspondence with the result from the constant force ensemble (Fig. 2) is also included. This clearly demonstrates the energy barrier during the unwrapping transition and that quite a large force is required to unwrap the chain. To see the behavior of the complex during the unwrapping process by the stretching force, we monitor the tilting angle of the ordered complex ϕ , which is defined by the angle between the axis of the helical pathway of the chain on the sphere and the direction of the force (x axis), as is depicted in Fig. 1. The helical axis is

calculated by a sum of cross products of bond vectors in the vicinity of the core particle's surface [see also the definition of the order parameter η given in Eq. (2)]. Figure 7(b) shows the tilting angle and extension relation. Because of the finite thickness of the chain, the vector connecting the monomers at entry and exit points of the complex is not parallel to the force direction, which produces a torque working on the complex. Owing to this torque, the complex maintains almost constant tilting angle, which slightly deviates from the perpendicular angle: $\phi \approx 1.1-1.2$ up to $r \approx 27$. By further stretching the chain beyond $r \approx 27$, the tilting angle shows a sudden decrease. This point exactly corresponds to the region where the resistant force sharply increases. These observations indicate the unique feature of unwrapping process of the ordered sphere-chain complex by the stretching force. It is not a gradual peeling of the chain around the core, but a chain unfolding accompanied by the complex tilting. Comparing Figs. 7(a) and 7(b), the complex in the large tilting angle is not in the global minimum of the free energy, but in the metastable state, if the stretching force does not exceed the threshold of the limit of stability. However, this metastable state is blocked by an energy barrier, which should be overcome by a further tilting to reach the globally stable state. Therefore, even if a stretching force larger than a critical strength for the unwrapping transition is applied, the sphere-chain complex stays in a kinetically stabilized state during a finite lifetime.

Figures 7(c) and 7(d) show the bending energy U_{bend} and adsorption energy U_M versus extension relations, respectively. In the region of large tilting, $r \approx 27-31$ and $r \approx 37-43$, these quantities behave differently from the other regions. The change in U_{bend} becomes small, or even almost constant, while the change in U_M becomes sharper. According to these observations, in the tilted state, the number of monomers adsorbed on the core is diminished, thus energetically less favored, and nevertheless, the cost in the bending energy is not changed, indicating this state is unstable in terms of bending, too [18].

In the experiments of chromatin stretching by optical tweezers, similar sawtooth patterns in force-extension curves have been reported [20–23]. The measured force peaks are attributed to the unwrapping of the nucleosomes, and the strength of the force peaks was found to be ≈ 20 pN, which is almost 10 times larger than the estimated value from the equilibrium theory [6,13,25]. To understand these observations, the inevitability of the nucleosome tilting under the stretching force has been suggested [21], and the corresponding energy barrier has also been calculated [18]. Although this feature is expected to be enhanced in the system with specific site-site interactions as in the case of nucleosome, our results confirm that it is a general one inherent in unwrapping process of an ordered core-chain complex under tension.

C. Tension-induced ordering for intermediate chain stiffness

In this subsection, we investigate the possibility of tension-induced ordering, which is observed in the simulation with an intermediate chain stiffness $\kappa=5$. It is expected

that the ordering by the stretching force is induced by a rather strong force ($y \gg 1$), as is indeed the case in the simulation. In the regime of strong forces, the free energy of the disordered state under the stretching force f [Eq. (7)] is transformed into the following simple form:

$$G_d(L) = (a'_1 + f)L + a_2L^2 + \text{const}, \quad (13)$$

where $a'_1 \equiv a_1 + \Delta a_1$. Here Δa_1 denotes the bending energy associated with the disordered segment distribution, which should be taken into account, since the chain under consideration has some stiffness. It is approximated as $\Delta a_1 \sim \kappa/R'^2$. Here R' is the effective mean radius of curvature of the chain segments on the core and should be determined self-consistently for a quantitative discussion. However, on a qualitative level, it is enough to notice that Δa_1 is small for a flexible chain and becomes substantially large for a stiff chain. After representing the system by the most probable state, which is derived by $\partial G_d(L)/\partial L = 0$ (mean-field approximation), we obtain the optimum free energy for the disordered complex:

$$G_d^* = -\frac{(a'_1 - f)^2}{4a_2} + \text{const}. \quad (14)$$

It is noticeable that this is a *quadratic* with respect to f .

On the other hand, the free energy of the ordered state under stretching force is given by Eq. (12), which is a *linear* function of f .

The position and form of these free energies as functions of f depend on the chain stiffness and size of the core particle. For a flexible chain and a large core, $G_d^* < G_0$ independent of the value of f , while $G_d^* > G_0$ for a chain with sufficient stiffness and a small core. However, the crossover from the one state to another is expected for the intermediate chain stiffness at a critical force, where $G_d^* = G_0$ holds. This is a consequence of the dependencies of free energies on f [Eqs. (14) and (12)] and indeed corresponds to the tension induced disorder-order transition.

V. CONCLUSIONS

In conclusion, we have investigated a simple model for a complex formed by a globular protein which attracts a DNA chain. Depending on the model chain stiffness, the complex is either disordered on the spherical surface or exhibits an order—i.e., a clear winding around the spherical core. We have studied by computer simulations and simple phenom-

enological theory the unwrapping of this complex under an external stretching force which acts on one end monomer of the chain, while the sphere and other end monomer are kept fixed. For a disordered complex, we observe a linear scaling between the force applied and amount of stretching achieved. This linear force-distance law is quantitatively confirmed by a simple phenomenological approach in the case where the forces are relatively high. On the other hand, for large chain stiffness when there is a clear winding, there are abrupt unwrapping transitions which are connected to a change of the winding number of the chain around the sphere. If a constant velocity to one end monomer is applied, there is a large energetic barrier in unspooling the complex. Moreover, the unwinding is accompanied by a tilt of the spooled complex relative to the pulling direction. Finally we have observed the effect of tension-induced ordering for intermediate chain stiffness: If a disordered complex is stretched, the external stretching force induces ordering—i.e., winding around the sphere. It is noted that the geometrical shape of the core, which is spherical in the present case, may affect some of our results.

Our model is in principle to be realized in chromatin stretching experiments [20–23] where the protein and end monomers are guided by optical tweezers. Other realizations of our model on a larger length scale are complexes of polyelectrolytes and spherical charged colloidal particles [26,27], where the persistence length of the chain can be tuned via the salt concentration in the solution [28].

Meanwhile, we have to note that many real complexes, especially biomolecular complexes, are equipped with complicated structural details, such as inhomogeneity of charge distribution, specific interaction sites, etc. Although some general properties of such complexes could be understood in the framework of our simple model, there should be other aspects, which are strongly affected by their specificities. Therefore, further more specific studies based on microscopic details are also important to bridge the gap between real complexes and our phenomenological model.

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[1] R. Saecker and M. Record, *Curr. Opin. Struct. Biol.* **12**, 311 (2002).
 [2] K. van Holde, *Chromatin* (Springer, New York, 1988).
 [3] R. Kornberg and Y. Lorch, *Cell* **98**, 285 (1999).
 [4] A. Wolffe, *Chromatin Structure and Function* (Academic, London, 1998).
 [5] J. Workman and R. Kingston, *Annu. Rev. Biochem.* **67**, 545 (1998).

[6] H. Schiessel, *J. Phys.: Condens. Matter* **15**, R699 (2003).
 [7] N. Marky and G. Manning, *Biopolymers* **31**, 1543 (1991).
 [8] T. Wallin and P. Linse, *Langmuir* **12**, 305 (1996).
 [9] H. Zhang, P. Dubin, J. Ray, G. Manning, C. Moorefield, and G. Newkome, *J. Phys. Chem. B* **103**, 2347 (1999).
 [10] E. Mateescu, C. Jeppesen, and P. Pincus, *Europhys. Lett.* **46**, 493 (1999).
 [11] R. Netz and J.-F. Joanny, *Macromolecules* **32**, 9026 (1999).

- [12] K.-K. Kunze and R. Netz, *Phys. Rev. Lett.* **85**, 4389 (2000).
- [13] K.-K. Kunze and R. Netz, *Phys. Rev. E* **66**, 011918 (2002).
- [14] H. Schiessel, J. Rudnick, R. Bruinsma, and W. Gelbart, *Europhys. Lett.* **51**, 237 (2000).
- [15] T. Sakaue, K. Yoshikawa, S. H. Yoshimura, and K. Takeyasu, *Phys. Rev. Lett.* **87**, 078105 (2001).
- [16] M. Jonsson and P. Linse, *J. Chem. Phys.* **115**, 3406 (2001).
- [17] A. Akinchina and P. Linse, *Macromolecules* **35**, 5183 (2002).
- [18] I. Kulić and H. Schiessel, *Phys. Rev. Lett.* **92**, 228101 (2004).
- [19] P. Cook, *Science* **284**, 1790 (1999).
- [20] S. Leuba, M. Karymov, M. Tomschik, R. Ramjit, P. Smith, and J. Zlatanova, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 495 (2003).
- [21] Y. Cui and C. Bustamante, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 127 (2000).
- [22] M. Bennink, S. Leuba, G. Leno, J. Zlatanova, B. de Grooth, and J. Greve, *Nat. Struct. Biol.* **8**, 606 (2001).
- [23] B. Brower-Toland, C. Smith, R. Yeh, J. Lis, C. Peterson, and M. Wang, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 1960 (2002).
- [24] A. Grosberg and A. Khokhlov, *Statistical Physics of Macromolecules* (American Institute of Physics, New York, 1994).
- [25] J. Marko and E. Siggia, *Biophys. J.* **73**, 2173 (1997).
- [26] J. Dzubiella, A. Moreira, and P. Pincus, *Macromolecules* **36**, 1741 (2003).
- [27] H. Löwen, E. Allahyarov, C. N. Likos, R. Blaak, J. Dzubiella, A. Jusufi, N. Hoffmann, and H. M. Harreis, *J. Phys. A* **36**, 5827 (2003).
- [28] J.-L. Barrat and J.-F. Joanny, *Adv. Chem. Phys.* **94**, 1 (1996).