Nucleosome Dynamics between Tension-Induced States

Laleh Mollazadeh-Beidokhti,[†‡*] Farshid Mohammad-Rafiee,[†‡] and Helmut Schiessel[§]
[†]Department of Biological Sciences and [‡]Department of Physics, Institute for Advanced Studies in Basic Sciences, Zanjan, Iran; and
[§]Instituut-Lorentz, Universiteit Leiden, Leiden, The Netherlands

ABSTRACT We studied the dynamical behavior of a mononucleosome under tension using a theoretical model that takes into account the nucleosomal geometry, DNA elasticity, nonspecific DNA-protein binding, and effective repulsion between the two DNA turns. Using a dynamical Monte-Carlo simulation algorithm, we demonstrate that this model shows a behavior that for an appropriate set of parameters is in quantitative agreement with data from micromanipulation experiments on individual nucleosomes. All of the parameters of the model follow from the data obtained from two types of pulling experiments, namely, constant force and constant loading rate ensembles.

INTRODUCTION

The accessibility of a cell to its genes is of vital importance to many essential life processes, such as transcription, replication, and DNA repair. However, eukaryotic DNA is tightly packaged into chromatin, a DNA-protein complex. Stretches of 147 basepairs (bp) of DNA are wrapped in 1 (3/4) turns around octamers of histone proteins along left-handed superhelical wrapping paths. The resulting DNA spools are called nucleosomes (1). Crystallographic studies (2,3) reveal that the histone-DNA interactions are localized at 14 binding sites with a 10 bp spacing. The nonspecific attraction between the DNA and the histones competes with the bending cost for wrapping DNA into a nucleosome that results in an effective adsorption energy per binding site just of the order of 1 k_BT (4). This allows thermal fluctuations to cause spontaneous partial unwrapping of the nucleosomal DNA from the histone core. Through this breathing mechanism, nucleosomes give temporary access to their DNA (5). In addition, various active motors, such as transcribing RNA polymerases (6) and chromatin remodelers (7), apply forces to nucleosomes. Such external forces are expected to have an effect on the nucleosome dynamics.

Single-molecule experiments have shed some light on the mechanisms of such dynamic structures (8). In a series of optical trap experiments, investigators studied the behavior of strings of nucleosomes under external forces (9–12). More recently, it has become even possible to follow the dynamics of a single nucleosome under tension (13,14). Such experiments provide a wealth of quantitative information about the dynamic behavior of such a nucleosome: The nucleosomal DNA unravels in two abrupt stages, each corresponding to the opening of half of the wrapped portion. The first turn of the nucleosomal DNA is opened in a reversible manner, whereas the second turn is opened irreversibly on the experimental timescales. The force needed to open the first turn is distributed around 3 pN, and the second turn opens at forces more broadly distributed around ~8−9 pN. In a constant-force experiment, the system hops between two different states at a range of forces of ~2−3.5 pN and the difference in length of the free DNA between the two states is ~18−20 nm, corresponding to the opening of six to seven binding sites. These findings show an all-or-none opening of the nucleosomal DNA, in agreement with previous studies (11,12).

Investigators have proposed three main explanations for the observed behavior. The first explanation attributes the different forces needed to open the two turns and the jumpwise opening of the nucleosomal DNA to differences in the energies of the binding sites between the DNA and the histone octamer (11,15). The second explanation is based on the model of Kulić and Schiessel (16), which showed that force-induced unwrapping of the last DNA turn proceeds via a high-energy transition state in which the DNA close to the entry-exit points is substantially bent. To achieve consistency with earlier breathing experiments (5), it was suggested that the outer DNA turn is effectively adsorbed more weakly than the inner turn as the result of the electrostatic repulsion between the two turns. Third, in a recent study, Sudhanshu et al. (17) refined the model of Kulić and Schiessel (16) and showed that different conformations of the free DNA arms can explain the discrepancy seen in the opening of the two turns, even in the absence of an effective turn-turn repulsion. Although all of these studies managed to reproduce many experimental features, they did not provide predictions for the full unwrapping and rewrapping dynamics of the nucleosome, e.g., individual time traces of the force in a constant rate of pulling experiment.

MATERIALS AND METHODS

We introduce here a dynamical model based on that of Kulić and Schiessel (16) to describe the dynamics of the unwrapping and rewrapping of a nucleosome under force at a microscopic level using the energy of the system,

Submitted November 30, 2011, and accepted for publication April 10, 2012.

*Correspondence: laleh@iasbs.ac.ir

Editor: Laura Finzi.

0006-3495/12/05/2235/6 $2.00

doi: 10.1016/j.bpj.2012.04.012

kinetic modeling, and Monte Carlo simulation. We consider a nucleosome on a long DNA chain under tension by applying at its ends a force F in the y direction, as schematically shown in Fig. 1. If it is strong enough, the force unwinds some portion of the nucleosomal DNA from the histone octamer. The spool then responds by changing its orientation Ω such that the torques on both sides of the nucleosome equilibrate.

We refer to the system as being in a state n, when n of the binding sites between the octamer and the DNA are open and thus $14-n$ are closed. The opening of each binding site releases a length of DNA equal to $a = 10$ bp from the nucleosome. The cost of breaking the binding site is partially compensated for by the reduction of the bending energy of that stretch. The two contributions can be combined into an effective adsorption energy per binding site, $\varepsilon_{\rm ads}$, that may depend on the specific site (11,13,15) and the external force (18). One of our goals in this study was to show that identical binding sites are enough to reproduce experimental observations. Therefore, we assume constant energies per binding site. However, we allow for an effective electrostatic repulsion between the two DNA turns (16) that, as we shall see, cannot be neglected. Denoting that DNA-DNA repulsion energy per length by $\varepsilon_{\rm es}$, the energy of the nucleosome at state n reads $E_{\rm nucl}(n) = an(\varepsilon_{\rm ads} + \varepsilon_{\rm es}\Theta(n-7))$. Here $\Theta(x)$ is the θ-function that is zero for $x < 0$ and one otherwise. The full adsorption, $\varepsilon_{\rm ads} + \varepsilon_{\rm es}$, is only felt when there is less than one turn left, $n \geq 7$.

To derive the total energy of system, we also need to account for the effect of the external force on the free DNA portions. This energy, $E_{\rm DNA}(n, F, \Omega)$, is the sum of two terms: one for the force-induced DNA bending and one for the energy gained through the release of bound DNA. This results in $E_{\rm DNA}(n, F, \Omega) = 8\sqrt{AF}(1 - \cos(\varphi_0/2)) - F(a\,n - \Delta y)$, as derived by Kulić and Schiessel (16). Here $A = 40$ nm $k_{\rm B}T$ stands for the DNA bending rigidity (13,19), where $k_{\rm B}T$ is the thermal energy, φ_0 is the angle between the DNA and the y axis at the exit point from the spool, and $an - \Delta y$ denotes the changes of the y coordinate of this exit point relative to the initial $n = 0$ case at each F. φ_0 and Δy depend on the spool orientation Ω (see Kulić and Schiessel (16) for explicit details). In conclusion, the total energy of the system at state n is given by

$$E_{\rm tot}(n, F, \Omega) = a\,n(\varepsilon_{\rm ads} + \varepsilon_{\rm es}\Theta(n-7) - F) + F\,\Delta y + 8\sqrt{A\,F}\left(1 - \cos\frac{\varphi_0}{2}\right). \quad (1)$$

In the following, we do not consider fluctuations in the DNA arms and correspondingly in the spool orientation. These effects (17) become important for forces that are smaller than the typical forces of ≥ 2 pN that were studied here and in the corresponding experiments. Therefore, we will study the dynamics of the system in a pure energy landscape and neglect the much smaller entropic effects.

Assuming a one-by-one mechanism for the opening and closing of the binding sites results in a kinetic equation for the system at state n as $n \rightleftharpoons n+1$, where the forward step (unwrapping of the nucleosomal DNA) and the backward step (rewrapping) occur with rates k_{uw} and k_{rw}, respectively, and n can change between 0 (the fully wrapped nucleosome) and 14 (the completely unwrapped case). After each step, the nucleosome is assumed to instantly adopt its new equilibrium orientation, $\Omega_{\rm eq}(n, F)$, in which its total energy (Eq. 1) is minimized with respect to the spool orientation Ω. We define $\Delta E^*(n, F) = E_{\rm min}(n, F) - E_{\rm min}(n, 0)$ with $E_{\rm min}(n, F) = E_{\rm tot}(n, F, \Omega_{\rm eq}(n, F))$. The unwrapping and rewrapping rates are then given by

$$k_{\rm uw}(F) = k^0_{\rm uw}\, e^{-\lambda_F[\Delta E^*(n+1,F) - \Delta E^*(n,F)]/k_{\rm B}T}, \quad (2)$$

$$k_{\rm rw}(F) = k^0_{\rm rw}\, e^{(1-\lambda_F)[\Delta E^*(n+1,F) - \Delta E^*(n,F)]/k_{\rm B}T}, \quad (3)$$

where λ_F is a load distribution factor that acts as a fitting parameter of the model (20), and $k^0_{\rm uw}$ and $k^0_{\rm rw}$ are the unwrapping and rewrapping rates, respectively, of the binding sites at zero force and are estimated by the detailed balance equation (21):

$$\frac{k^0_{\rm uw}}{k^0_{\rm rw}} = e^{-[E_{\rm min}(n+1,0) - E_{\rm min}(n,0)]/k_{\rm B}T}. \quad (4)$$

With these transition rates between different states of the system, we simulate its kinetics, employing the Gillespie algorithm, a dynamic Monte Carlo method (22). Note that for any $n > 0$ there is more than one state for the nucleosome, namely, all states with $i \leq n$ binding sites open from the left end, and those with $n - i$ open from the right end. Because all of these states have the same energy, we lump them together in the above notation; however, in the simulation we explicitly keep track of the individual states.

RESULTS

Fig. 2 shows $E_{\rm min}(n, F)$, the energy of the system (Eq. 1) minimized with respect to the spool orientation Ω, as a function of n for different applied forces. It can be seen in this figure that even in the absence of high-affinity histone-DNA sections, two barriers start to grow at $n \approx 3$ and $n \approx 10$ as the force increases. These barriers reflect n-values where the spool orientation forces the free DNA

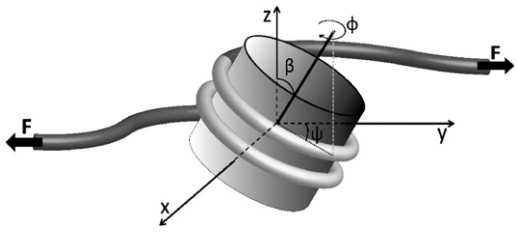

FIGURE 1 Nucleosome under an external force F applied to the DNA ends. The angles β, ψ, ϕ define the spool orientation Ω.

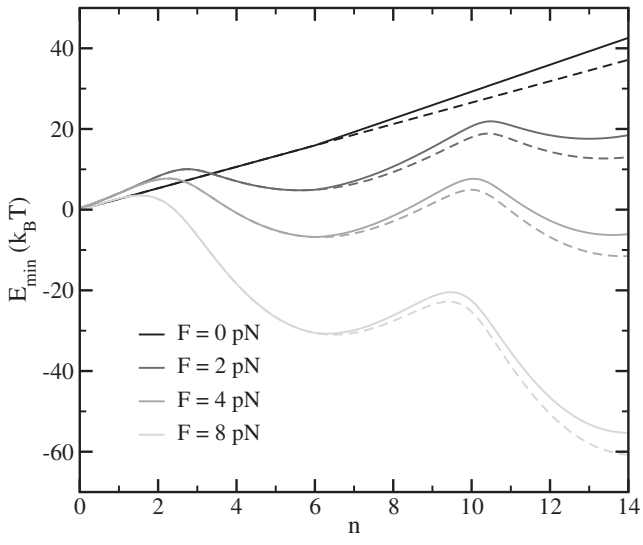

FIGURE 2 The minimum energy of the system versus the number of opened binding sites for four different forces. We set here $\varepsilon_{\rm ads} = 0.78\,k_{\rm B}T/$nm and $\varepsilon_{es} = 0.2\,k_{\rm B}T/$nm. The dashed curves indicate the case $\varepsilon_{\rm es} = 0$.

to bend strongly at the entrance to the nucleosome (16,17). The bending energy of these bent portions creates two barriers, leading to a three-state system. This is the origin of the jumpwise opening of the nucleosome under force.

Here we simulate two different situations reflecting experimental setups (13): 1), a constant-loading-rate ensemble; and 2), a constant-force ensemble. In ensemble 1, the force on the DNA ends is increased at a constant rate and the nucleosome unwrapping is observed by measuring the end-to-end distance of the DNA. In ensemble 2, the ends of the nucleosomal DNA are held at a constant force and the instantaneous dynamics of the system is monitored via the extension.

Constant-loading-rate ensemble

First we present simulations in which the end-to-end distance of the DNA increases with a constant loading rate r. Fig. 3 shows individual force-extension curves for this simulation with the rate of pulling fixed to the value $r = 2.4$ pN/s, the value used by Mihardja et al. (13). As in the experiment (13), we find two abrupt steps during the opening of the nucleosome (*black curves*) and one step during the rewrapping (*gray curves*). The length of released DNA at both forward transitions equals ~70 *bp*, reflecting the opening of seven binding sites. The force at which the first transition occurs depends on the values of ε_{ads} and k^0_{rw}. Various examples that all lead to the experimentally observed rupture force of $\sim 2.9 - 3$ pN (13) are presented in Table 1. In the following, we use $\varepsilon_{\text{ads}} = 0.78\ k_BT/\text{nm}$ and $k^0_{rw} = 10^4 s^{-1}$. For this set of values, our model also agrees well with the constant-force measurements discussed below.

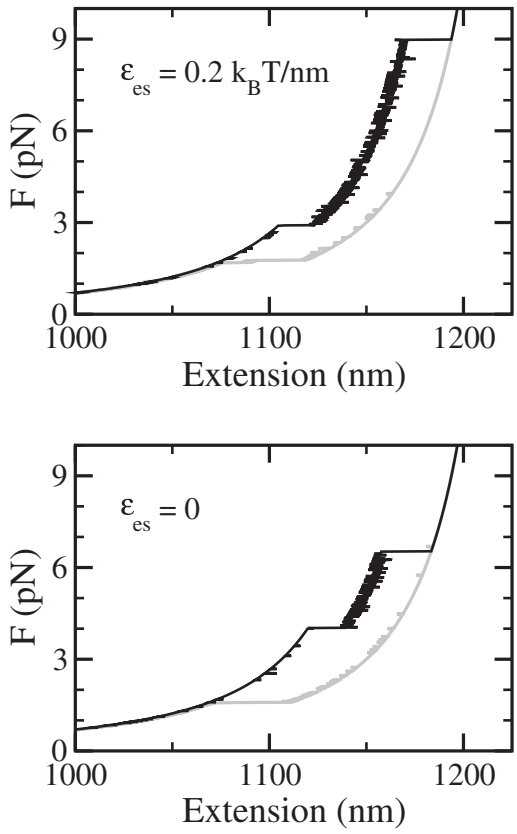

FIGURE 3 Sample force-extension curves of the DNA containing one nucleosome for $\varepsilon_{\text{es}} = 0$ (*lower plot*) and $\varepsilon_{\text{es}} = 0.2\ k_BT/\text{nm}$ (*upper plot*), both for a constant rate $r = 2.4$ pN/s. The black curves show the extension of the DNA when it is being pulled, and the gray lines show its behavior when it is released with rate r. The adsorption energy is fixed equal to $\varepsilon_{\text{ads}} = 0.78\ k_BT/\text{nm}$.

Fig. 4 shows the rates for hopping from the closed to the half-open state (*lower curve*) and back (*upper curve*) as a function of force. The data points are from Mihardja et al. (13), and the continuous curves are from the model using the load distribution factor as the fitting parameter, leading to $\lambda_F = 0.6$. In Fig. 5, a comparison of the probability of the first wrap being unraveled as a function of force is presented. It is produced by the cumulative histogram of forces at which the first transition happens. Both the experimental points (13) and the model show the typical behavior of a two-state system.

To have the second transition at $F_2 \sim 8 - 9\ pN$ for the chosen set of parameters, the value of ε_{es} must equal $0.2\ k_BT/\text{nm}$. In Fig. 6 histograms of forces for both transitions are shown (lower plot for $\varepsilon_{\text{es}} = 0$ and upper one for $\varepsilon_{\text{es}} = 0.2\ k_BT/\text{nm}$). Note that even for $\varepsilon_{\text{es}} = 0$ the second transition occurs at a higher force than the first transition, as previously noted (17). One can achieve $F_2 \sim 8 - 9\ pN$ also for $\varepsilon_{\text{es}} = 0$ by choosing a higher value of ε_{ads}, but then our model does not reproduce other experimental data.

We next study the distribution of tensions for rewrapping. In Fig. 7, the histogram of the rewrapping forces is depicted. As can be seen from this histogram, the rewrapping forces are distributed around $F_{rw} \simeq 2.8 \pm 1$ pN for $\varepsilon_{\text{es}} = 0.2\ k_BT/\text{nm}$, and $F_{rw} \simeq 2.2 \pm 0.5$pN for $\varepsilon_{es} = 0$. The electrostatic repulsion leads a larger rewrapping force and a wider distribution. According to our model, the experimentally determined rewrapping value, 3.6 ± 2.8 pN, points to the existence of DNA-DNA repulsion, but the statistics are not good enough for us to draw a definite conclusion.

Constant-force ensemble

The energy plots in Fig. 2 show three local energy minima that occur in the system as a force is exerted on it. This suggests the possibility of a hopping dynamics between these minima in a constant-force ensemble. This hopping

TABLE 1 Different sets of ε_{ads} and k^0_{rw} that result in a mean rupture force for the first turn equal to 2.9 – 3 *pN*

$k^0_{rw}(s^{-1})$	300	10^3	3×10^3	10^4	10^5	10^6	10^7
$\varepsilon_{\text{ads}}(k_BT/\text{nm})$	0.46	0.58	0.71	0.78	0.90	0.97	1.0

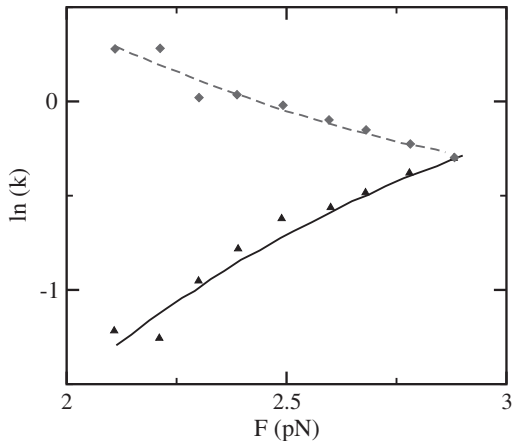

FIGURE 4 Transition rates from the wrapped to the half-open state (*lower curve*) and back (*upper curve*). The model (*lines*) is fitted to the experimental points from Mihardja et al. (13), leading to $\lambda_F = 0.6$.

was indeed observed between the fully wrapped and the half-open states (13,14), because these two states are divided by a barrier that is small enough to results in rates compatible with experimental timescales. The force at which the system spends approximately equal amounts of time in both states equals $F = 2.6$ pN (see Fig. 2 *a* in Mihardja et al. (13)). In Fig. 8 we present time traces predicted by our model for different values of ε_{ads}. The value of k^0_{rw} is chosen according to Table 1. We find hopping behavior in the experimental range of applied forces only when we choose the set $\varepsilon_{\text{ads}} = 0.78\ k_{\text{B}}T/\text{nm}$ and $k^0_{rw} = 10^4 s^{-1}$.

In Fig. 9 the probability of the nucleosome to be in the half-open state, $n \sim 7$, is shown as a function of F and ε_{ads} in two cases, $\varepsilon_{\text{es}} = 0$ and $\varepsilon_{\text{es}} = 0.2 k_{\text{B}}T/\text{nm}$. As can be seen, without turn-turn repulsion the system spends hardly any time in the half-open state. An increase in ε_{es} results in an increasing population of that state, so the model

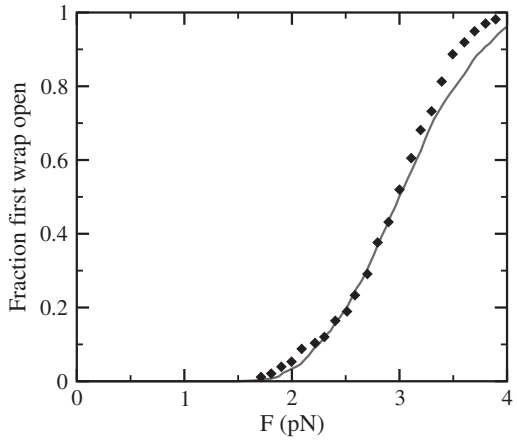

FIGURE 5 Probability of the first wrap opening as a function of force. The line corresponds to the simulation results for $\varepsilon_{\text{ads}} = 0.78\ k_{\text{B}}T/\text{nm}$ and $\varepsilon_{es} = 0.2\ k_{\text{B}}T/\text{nm}$, and the points correspond to the experimental data from Mihardja et al. (13).

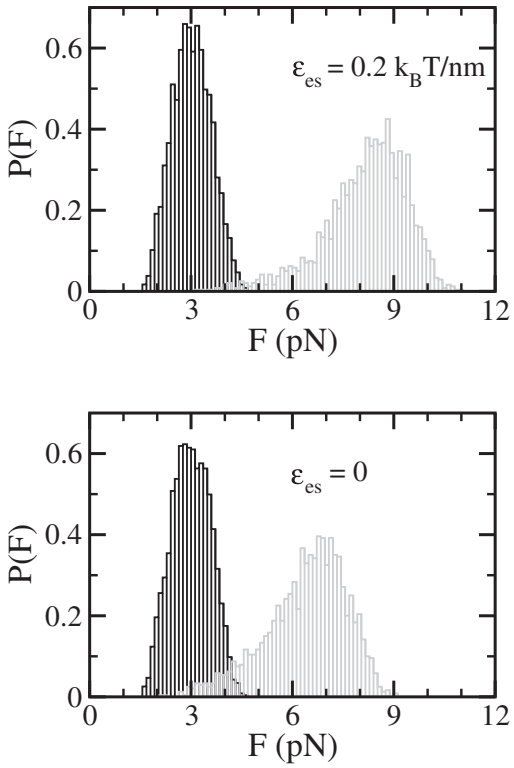

FIGURE 6 Histograms of forces for the two transitions for $\varepsilon_{es} = 0$ (*down*) and $\varepsilon_{es} = 0.2\ k_{\text{B}}T/\text{nm}$ (*up*). The black and gray histograms show the distribution of forces for the first and second transitions, respectively.

behaves as seen in the experiment (13,14). Time traces of the free DNA extension in these two cases at $F = 2.1$ pN and $F = 2.9$ pN are shown in Fig. 10. Assuming $\varepsilon_{es} = 0.2\ k_{\text{B}}T/\text{nm}$, the results are in good agreement with the experimental data (see Fig. 2 *a* in Mihardja et al. (13)). Ignoring turn-turn repulsion causes the system to jump immediately from the half-open state to the unwrapped state, which does not agree with experimental observations.

DISCUSSION AND CONCLUSIONS

In conclusion, we have introduced a kinetic model that describes the dynamics of DNA wrapping and unwrapping for a single nucleosome under force in excellent agreement with micromanipulation experiments. Our results suggest that to achieve this agreement, one only has to account for the DNA conformational energy, the nonspecific DNA-protein interaction, and an effective repulsion between the two DNA turns.

From a biological point of view, the two-turn spool design of the nucleosome with an effective repulsion between the two turns may be advantageous for two reasons: 1) All of the nucleosomal DNA can be accessed through the spontaneous nucleosome unwrapping from either end of the wrapped portion, but unwrapping of the last turn is difficult

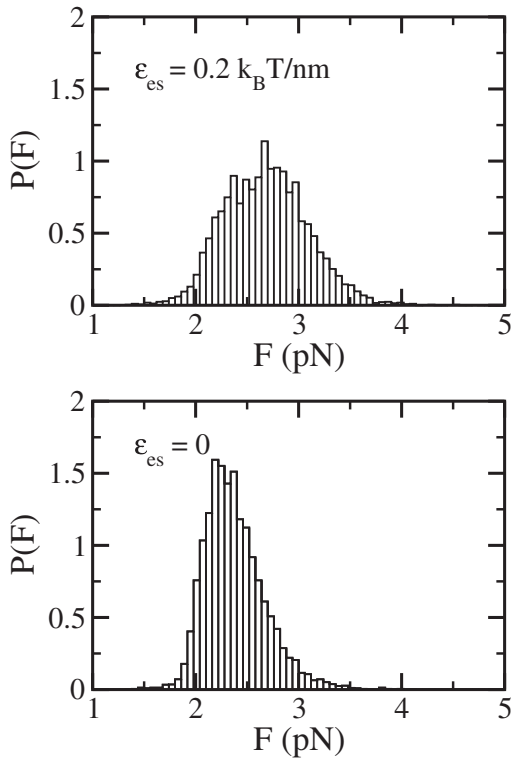

FIGURE 7 Histograms of forces for the reverse transition when DNA is released in the force-extension experiment for $\varepsilon_{es} = 0$ (*down*) and $\varepsilon_{es} = 0.2\ k_BT/\text{nm}$ (*up*).

because the effective turn-turn repulsion ceases to act. 2) The nucleosome is kinetically protected against transient forces because the spool structure leads to the formation of two kinetic barriers against unwrapping (see Fig. 2).

It is worthwhile to discuss the values of DNA-DNA repulsion energy per unit length, ε_{es}, that we used in this work. We have shown that assuming $\varepsilon_{es} = 0.2\ k_BT/\text{nm}$ gives results that are in good agreement with the experimental data. We note that our estimate is smaller than the value suggested by Kulić and Schiessel (16). Those authors deduced a large DNA-DNA repulsion from a comparison of the experiments of Polach and Widom (5) and Brower-Toland et al. (11); however, their finding may to some extent reflect differences between the experiments in question. The new data on single-nucleosome stretching (13) are much more reliable because they are based on a single experimental setup. They hint at a much smaller DNA-DNA repulsion.

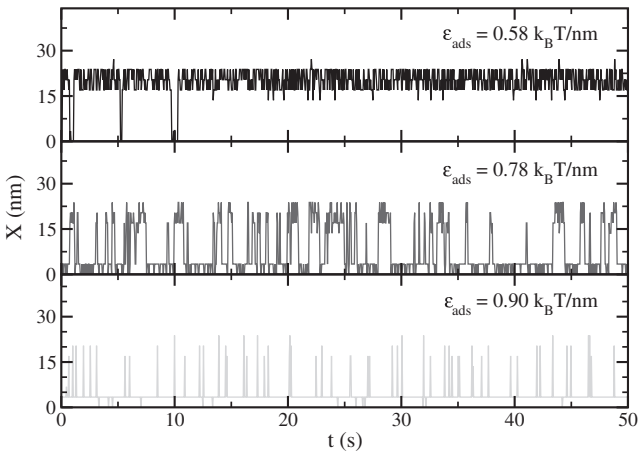

FIGURE 8 Time traces at constant force $F = 2.6$ pN for three different values of ε_{ads}. The value of k^0_{rw} is chosen in each plot according to Table 1.

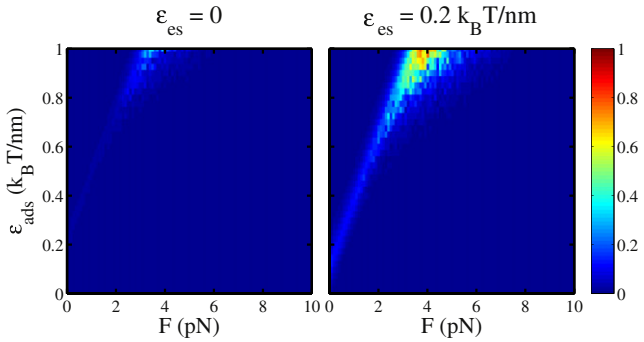

FIGURE 9 Probability of being in the half-open state as a function of external force F and binding strength ε_{ads} for two values of turn-turn repulsion, $\varepsilon_{es} = 0$ and $\varepsilon_{es} = 0.2\ k_BT/\text{nm}$.

We have neglected the effect of twist in our model. When the nucleosome unwraps one turn, the DNA has to take up one turn. The twist energy has relaxed to about $1\ k_BT$ when the twist has been distributed over a length as $L \simeq 2\pi^2 C$, where C denotes the DNA twist rigidity. The rotational diffusion time of a cylinder of length L and radius $r = 1$ nm around its helical axis follows from the rotational drag coefficient of a cylinder around its axis $\gamma_a = 4\pi\eta r^2 L$, where η is the viscosity of the solvent (23). Therefore, the required rotational diffusion time of the cylinder is given by $t_{rot} \simeq \gamma_a / k_BT = 4\pi\eta r^2 L / k_BT \simeq 8\pi^3 \eta C r^2 / k_BT$. With $k_BT \simeq 4.1$ pNnm, $C \simeq 100$ nm, $\eta \simeq 10^{-3}$ Pa.s, and $r \simeq 1$ nm, the rotational timescale is found to be $t_{rot} \simeq 10^{-7}$s. One can see that this is a very small timescale—so small that

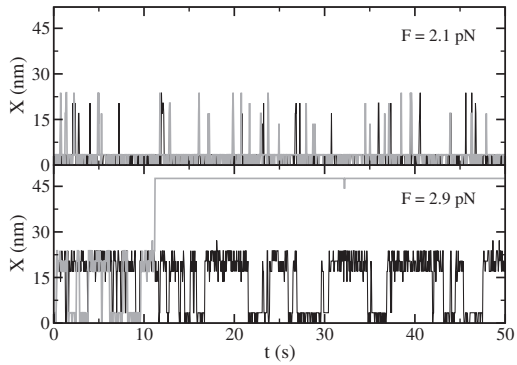

FIGURE 10 Time traces of the length of free DNA. Here $\varepsilon_{\text{ads}} = 0.78\ k_BT/\text{nm}$ and $\varepsilon_{es} = 0$ (*gray*) and $\varepsilon_{es} = 0.2\ k_BT/\text{nm}$ (*black*).

the increase in force in the pulling experiment during that time is negligible.

Even though several parameters entered our model, we have shown how one can deduce those parameters from micromanipulation data obtained from the constant loading rate and constant-force measurements for fixed experimental conditions. Obviously, when conditions change (e.g., through a change in the ionic conditions), many of the parameters are expected to change as well. A systematic set of experimental measurements for various conditions would allow one to determine the range of conditions in which nucleosomes are able to combine the above-mentioned requirements of accessibility and stability. We speculate that physiological conditions lie within that range.

We thank S. Mohammadi-nezhad and M. Charsooghi for valuable discussions.

This work was supported by the Research Council of the Institute for Advanced Studies in Basic Sciences (grant G2010IASBS105 to L.M.-B. and F.M.-R.).

REFERENCES

1. Schiessel, H. 2003. The physics of chromatin. *J. Phys. Condens. Matter.* 15:R699–R774.
2. Luger, K., A. W. Mäder, …, T. J. Richmond. 1997. Crystal structure of the nucleosome core particle at 2.8 A resolution. *Nature.* 389:251–260.
3. Richmond, T. J., and C. A. Davey. 2003. The structure of DNA in the nucleosome core. *Nature.* 423:145–150.
4. Prinsen, P., and H. Schiessel. 2010. Nucleosome stability and accessibility of its DNA to proteins. *Biochimie.* 92:1722–1728.
5. Polach, K. J., and J. Widom. 1995. Mechanism of protein access to specific DNA sequences in chromatin: a dynamic equilibrium model for gene regulation. *J. Mol. Biol.* 254:130–149.
6. Hodges, C., L. Bintu, …, C. Bustamante. 2009. Nucleosomal fluctuations govern the transcription dynamics of RNA polymerase II. *Science.* 325:626–628.
7. van Vugt, J. J. F. A., M. de Jager, …, C. Logie. 2009. Multiple aspects of ATP-dependent nucleosome translocation by RSC and Mi-2 are directed by the underlying DNA sequence. *PLoS ONE.* 4:e6345.
8. Bustamante, C., Z. Bryant, and S. B. Smith. 2003. Ten years of tension: single-molecule DNA mechanics. *Nature.* 421:423–427.
9. Cui, Y., and C. Bustamante. 2000. Pulling a single chromatin fiber reveals the forces that maintain its higher-order structure. *Proc. Natl. Acad. Sci. USA.* 97:127–132.
10. Bennink, M. L., S. H. Leuba, …, J. Greve. 2001. Unfolding individual nucleosomes by stretching single chromatin fibers with optical tweezers. *Nat. Struct. Biol.* 8:606–610.
11. Brower-Toland, B. D., C. L. Smith, …, M. D. Wang. 2002. Mechanical disruption of individual nucleosomes reveals a reversible multistage release of DNA. *Proc. Natl. Acad. Sci. USA.* 99:1960–1965.
12. Gemmen, G. J., R. Sim, …, D. E. Smith. 2005. Forced unraveling of nucleosomes assembled on heterogeneous DNA using core histones, NAP-1, and ACF. *J. Mol. Biol.* 351:89–99.
13. Mihardja, S., A. J. Spakowitz, …, C. Bustamante. 2006. Effect of force on mononucleosomal dynamics. *Proc. Natl. Acad. Sci. USA.* 103: 15871–15876.
14. Kruithof, M., and J. van Noort. 2009. Hidden Markov analysis of nucleosome unwrapping under force. *Biophys. J.* 96:3708–3715.
15. Hall, M. A., A. Shundrovsky, …, M. D. Wang. 2009. High-resolution dynamic mapping of histone-DNA interactions in a nucleosome. *Nat. Struct. Mol. Biol.* 16:124–129.
16. Kulić, I. M., and H. Schiessel. 2004. DNA spools under tension. *Phys. Rev. Lett.* 92:228101.
17. Sudhanshu, B., S. Mihardja, …, A. J. Spakowitz. 2011. Tension-dependent structural deformation alters single-molecule transition kinetics. *Proc. Natl. Acad. Sci. USA.* 108:1885–1890.
18. Wocjan, T., K. Klenin, and J. Langowski. 2009. Brownian dynamics simulation of DNA unrolling from the nucleosome. *J. Phys. Chem. B.* 113:2639–2646.
19. Bustamante, C., S. B. Smith, …, D. Smith. 2000. Single-molecule studies of DNA mechanics. *Curr. Opin. Struct. Biol.* 10:279–285.
20. Kolomeisky, A. B., and M. E. Fisher. 2000. Periodic sequential kinetic models with jumping, branching and deaths. *Physica A.* 279:1–20.
21. Hänggi, P., P. Talkner, and M. Borkovec. 1990. Reaction-rate theory: fifty years after Kramers. *Rev. Mod. Phys.* 62:251–342.
22. Gillespie, D. T. 1976. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *J. Comput. Phys.* 22:403–434.
23. Tirado, M. M., and J. G. de la Torre. 1980. Rotational dynamics of rigid, symmetric top macromolecules. Application to circular cylinders. *J. Chem. Phys.* 73:1986–1993.