Brownian dynamics simulation of directional sliding of histone octamers caused by DNA bending

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Chromatin-remodeling complexes such as SWI/SNF and RSC of yeast can perturb the structure of nucleosomes in an ATP-dependent manner. Experimental results prove that this chromatin remodeling process involves DNA bending. We simulate the effect of DNA bending, caused by chromatin-remodeling complexes, on directional sliding of histone octamers by Brownian dynamics simulation. The simulation results show that, after a DNA loop being generated at the side of a nucleosome, the histone octamer slides towards this DNA loop until the loop disappears. The DNA loop size is an important factor affecting the process of directional sliding of the histone octamer.

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I. INTRODUCTION

Nucleosome is the basic unit of chromatin and much has been known about its crystal structure [1,2]. It consist s of one histone octamer and 146 bp DNA which wraps around the histone octamer in about two turns [3]. With the development of single molecule manipulation methods, many experiments have been done to disclose the mechanical behavior of nucleosomes [4–8]. The structure and location of a nucleosome are always changing in the biological processes of gene expression, cell division, and so on. However, our knowledge to the remodeling dynamics of the nucleosome is far from complete. The position distribution of histone core particle along DNA was observed with atomic force microscopy and calculated with Brownian dynamics simulation [9]. It is known that chromatin-remodeling complexes such as SWI/SNF and RSC of yeast play important roles in the relocation of histones along DNA. They perturb the structure of nucleosome in an ATP-dependent manner [10,11]. Experimental results show that this dynamical process is transient and a nucleosome can be converted to the altered state in less than 1 s [12]. More and more experimental results proved that DNA bending helps histone octamer to slide to a new location [12–16]. And DNA twisting is not required for chromatin remodeling but can enhance its efficiency [17–19]. For directional sliding of a histone octamer along DNA, a bulge-diffusion model was suggested by Schiessel *et al.* in Ref. [20] where the authors theoretically proposed that the repositioning of nucleosomes may be explained through the diffusional motion of intranucleosomal loops. In this paper, we performed, based on our previous works [21,22], Brownian dynamics simulations for the effect of DNA bending, caused by chromatin-remodeling complexes at the side of the nucleosome, on directional sliding of histone octamers and show some detailed dynamical behaviors of this process. There is no intranucleosomal DNA bulge in our model. Therefore, it is different from the previous models [15,20].

II. MODEL

Our system consists of one DNA chain, one histone octamer and one chromatin-remodeling complex. As in our previous work [21], the DNA chain is modeled as a semiflexible homopolymer chain which consists of N spheres connected by bonds. Each sphere corresponds to 7 bp DNA. The diameter of the sphere is equal to the width of the DNA molecule. This DNA chain is described with three potential functions: One is a bonding potential to connect the N spheres. The second is a self-avoiding potential to avoid its tight folding. The third is a bending potential to describe the stiffness of the chain. The histone octamer is modeled as a spherical particle with a diameter which is equal to the size of the octamer. The interaction between the DNA chain and the histone octamer is described with the Morse potential. The random force which obeys the fluctuation-dissipation theorem is included for the Brownian motion. The Langevin equation with the aforecited potential and the random force is used to describe the whole system. By numerically solving the Langevin equation with the parameters given in Ref. [21], we obtained the stable nucleosome structure. The DNA bending induced by the chromatin-remodeling complex is introduced by programming after the stable nucleosome structure is obtained.

The self-avoiding effect of DNA chain is considered by using the repulsive part of the Morse potential

$$U_{m,\mathrm{rep}} = \varepsilon_m k_B T \sum \exp[-\alpha_m(r_{i,j} - \sigma_m)], \qquad (1)$$

where $\varepsilon_m = 0.2$ and $\alpha_m = 2.4$. We set the Boltzmann constant k_B to unity and choose 298 K for temperature T. $r_{i,j}$ is the distance between the ith and jth spheres of the

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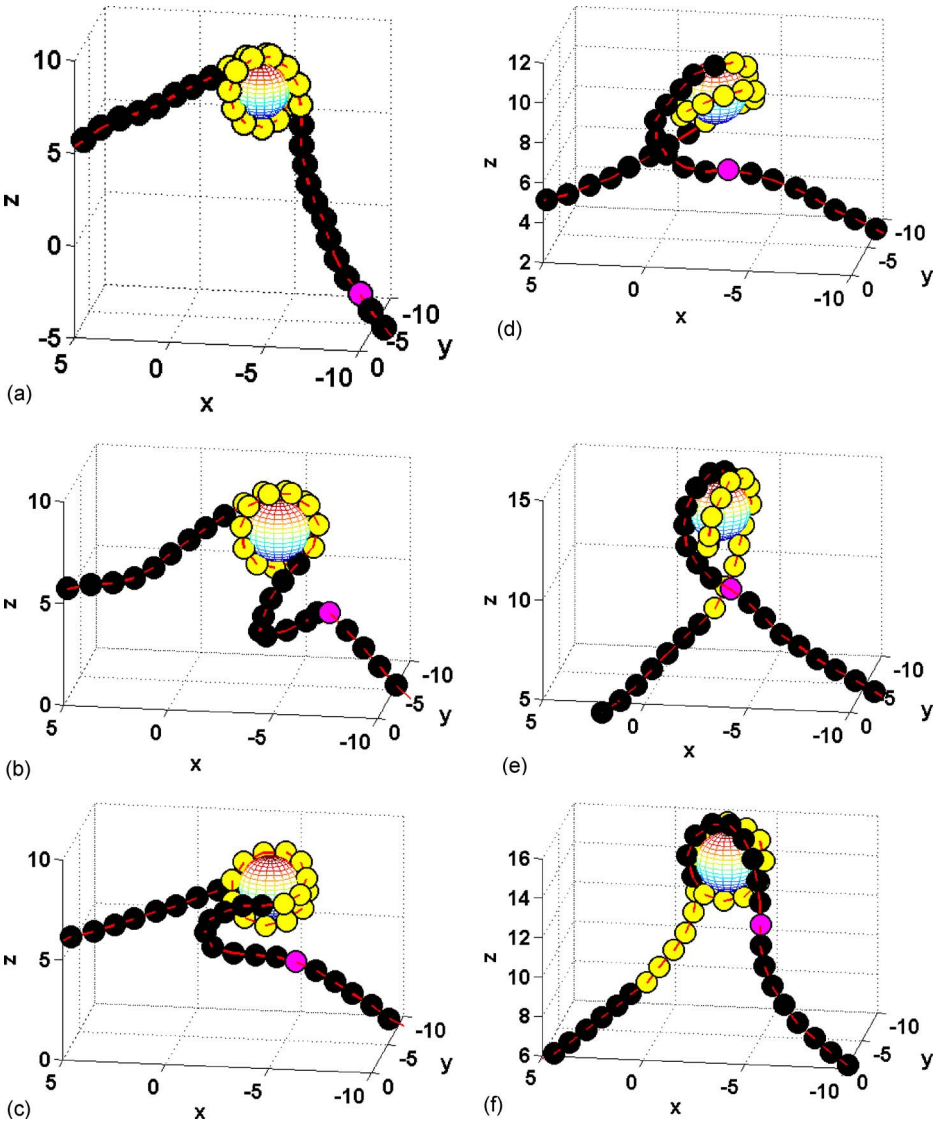

FIG. 1. (Color online) After getting a stable nucleosome structure (a), a DNA bending with contour length of $9\sigma_m$ is introduced at the left side of the nucleosome (b). The histone octamer slides towards this DNA loop. The length unit for all the axes is σ_m (i.e., 2.3 nm). (The same length unit is used in all the following similar figures.) The time corresponding to each snapshot is: (a) 0; (b) 0.009; (c) 0.046; (d) 0.114; (e) 0.2; and (f) 0.858 s. The yellow spheres represent the DNA part that initially wrap around the histone octamer. The pink DNA sphere represents the location where the bending starts.

DNA chain. σ_m is the width of DNA and is also the equilibrium distance between two neighboring sphere centers of the DNA chain. We use σ_m as the length unit in the simulation.

The bonds between neighboring spheres of the DNA chain are considered through harmonic bonding potential

$$U_{\text{bond}} = \frac{kk_BT}{2\sigma_m^2} \sum (|\vec{r}_i - \vec{r}_{i+1}| - \sigma_m)^2, \tag{2}$$

where $k=400$, $\vec{r}_i$ and $\vec{r}_{i+1}$ are the location vectors of the ith and $(i+1)$th spheres of the DNA chain. We model the chain stiffness by using the bending potential

$$U_{\text{bend}} = \kappa k_BT \sum \left\{ 1 - \frac{(\vec{r}_{i-1} - \vec{r}_i)(\vec{r}_i - \vec{r}_{i+1})}{\sigma_m^2} \right\}, \tag{3}$$

where we choose $\kappa=15$.

The interaction between the DNA chain and a histone octamer is simulated with the Morse potential

$$U_M = \varepsilon k_BT \sum \{\exp[-2\alpha(r_i - \sigma)] - 2\exp[-\alpha(r_i - \sigma)]\}, \tag{4}$$

where $\varepsilon=6$, $\alpha=6$, and $\sigma=1.9\sigma_m$. So, the radius of the histone octamer is $1.4\sigma_m$ (i.e., $1.9\sigma_m-0.5\sigma_m=1.4\sigma_m$). r_i is the distance between the histone octamer and the ith sphere of the DNA chain, i.e., $r_i=|\vec{R}-\vec{r}_i|$, where $\vec{R}$ is the location vector of the histone octamer. We choose these parameters for DNA and histone octamer so that the relative sizes of DNA and histone octamer fit the actual ones: In nature, the width of DNA is about 2.3 nm and the diameter of a histone octamer is about 6.4 nm. Therefore, the length unit σ_m corresponds to 2.3 nm.

In our model, the chromatin-remodeling complex is assumed to have strong interaction with both DNA and the

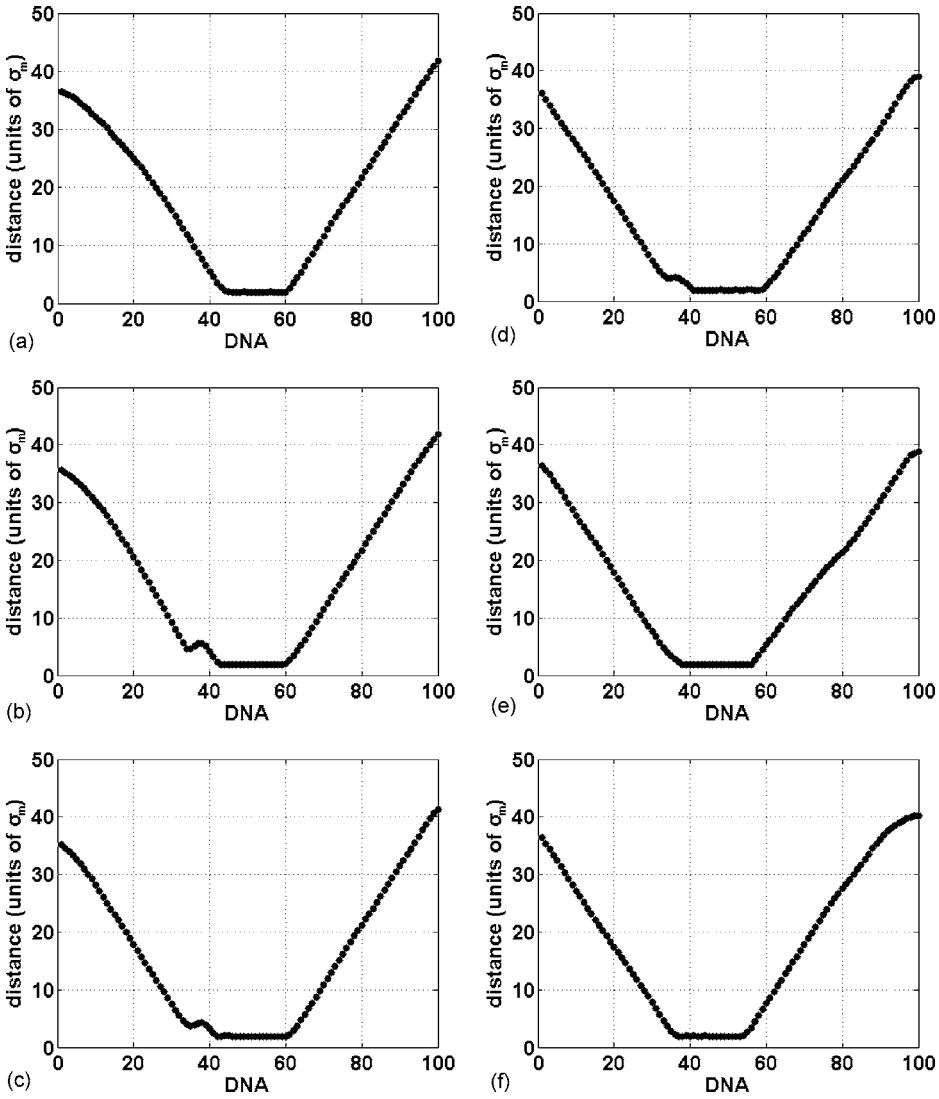

FIG. 2. The distance between the histone octamer and every DNA sphere. These curves correspond to the snapshots in Fig. 1. The time is: (a) 0; (b) 0.009; (c) 0.046; (d) 0.114; (e) 0.2; and (f) 0.858 s. The horizontal axes correspond to the serial numbers of the DNA spheres. The vertical axes correspond to the center distances between the histone octamer and the DNA spheres.

histone octamer. The complex produces one DNA bending when ATP is added and maintains this bending until the nucleosome remodeling finishes. In the simulation, we simply introduce this bending by programming. The time duration in which the bending is maintained is also controlled by programming.

The overdamped Langevin equations are used to describe the motion of each DNA sphere and the histone octamer

$$-\gamma_m \frac{d\vec{r}_i}{dt} + \vec{R}_{m,i}(t) - \frac{\partial U}{\partial \vec{r}_i} = 0, \tag{5a}$$

$$-\gamma_M \frac{d\vec{R}}{dt} + \vec{R}_M(t) - \frac{\partial U}{\partial \vec{R}} = 0, \tag{5b}$$

where γ_m and γ_M are the friction constants of the DNA sphere and the histone octamer, respectively. They are calculated according to Stokes law. $\vec{R}_{m,i}$ and $\vec{R}_M$ are the Gaussian white noises which obey the fluctuation-dissipation theorem. The total internal energy U consists of four terms: $U = U_{m,\mathrm{rep}} + U_{\mathrm{bond}} + U_{\mathrm{bend}} + U_M$.

We perform the dynamics of this system using a stochastic Runge-Kutta algorithm (white noise) [23]. k_BT is chosen as the unit energy, and $\gamma_m \sigma_m / \sqrt{T}$ as the unit time which corresponds to 0.0143 s.

III. SIMULATION RESULTS

As in Ref. [21], we first simulate the interaction between the DNA chain and a histone octamer with Eq. (5a) and Eq. (5b). The DNA chain and the histone octamer first come close to each other, then DNA wraps around the octamer gradually to about two turns, forming a stable nucleosome structure as shown in Fig. 1(a). After the stable nucleosome structure being formed (this takes about 1.2 s of time), a DNA bending with a certain contour length is introduced at one side of the nucleosome by programming. The histone octamer slides to this DNA loop until it disappears. A typical sliding process is shown in Fig. 1.

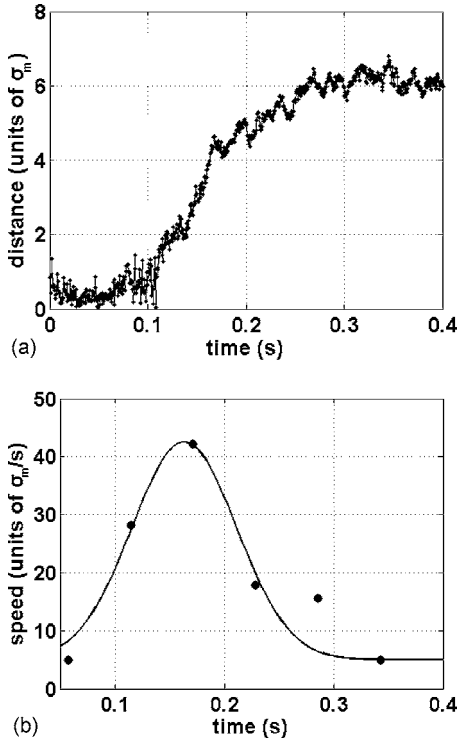

FIG. 3. (a) The sliding distance and (b) the sliding speed of the histone octamer as a function of time. The solid curve in (b) is a polynomial fit of the dots for guiding the eyes.

It can be seen that, in the process of the histone octamer's directional sliding, the DNA loop located at the left side of the nucleosome gradually shrinks and finally disappears. This process can also be seen in Fig. 2 where the distance between the histone octamer and every DNA sphere is shown. The histone octamer slides continuously towards the DNA loop and stops at the location where the DNA bending starts.

The temporal evolution of the sliding distance and speed of the histone octamer is shown in Fig. 3. From these results we can see that the histone octamer passes the most sliding distance in a short time. The sliding speed is small both at the beginning and at the end of sliding. A maximum speed is reached in the middle of the sliding process. This phenomenon is understandable because at the beginning the histone octamer needs time to accelerate and when approaching to the end the DNA loop disappears gradually.

In the simulations above, we have shown the process of histone octamer's directional sliding caused by only one DNA loop. For continually generated DNA loops, in order to simulate a multiple-step sliding process, we choose a nucleosome located at the left end of DNA as shown in Fig. 4(a) and successively introduce three DNA loops, as an example, at the right side of the nucleosome. Each loop is kept for a period of 2.574 s. We can see that the histone octamer slides continually as shown in Fig. 4.

In Fig. 5, we record the sliding distance of the histone octamer corresponding to the three-loop case. Three steps of the histone octamer's sliding can be distinguished clearly. The system's energy is shown in Fig. 6 where three peaks can be seen at the moments when the three loops were introduced.

IV. DISCUSSION

The DNA loop size is an important factor to affect the histone octamer's directional sliding. If the contour length of the DNA loop is larger than the persistence length of DNA, we anticipate that the histone octamer will not be affected by the bending because over the persistence length the DNA molecule can be considered as flexible. This phenomenon can be seen in Fig. 7 where the loop size is close to the DNA persistence length and the histone octamer no more slides toward the loop.

We make simulations with different DNA loop size and find that the DNA loop size has an influence on the histone octamer's average sliding speed as shown in Fig. 8(a) from which we can see that the smaller the DNA loop size, the faster the histone octamer slides. Accordingly, the sliding time of the histone octamer increases with the DNA loop size as shown in Fig. 8(b).

We fit the simulation data points in Fig. 8(a) with a linear function $y=a-bx$, obtaining $a=55.3$, $b=2.808$. Linear extrapolation of y-axis to zero average speed yields the maximum DNA loop size $19.69\sigma_m$. This means that the upper limit of the DNA loop size is about $19.69\sigma_m$, above which the histone octamer sliding will not occur. We note that this size $(19.69q_m)$ is not far from the persistence length of the DNA ($\sim$50 nm or $21.7\sigma_m$).

We fit the simulation data points in Fig. 8(b) with a function of $y=\alpha/(\beta-x)^2$, obtaining $\alpha=27.78$ and $\beta=19.74$. It means that when the DNA loop size approaches to $19.74\sigma_m$, the time needed for the histone octamer to finish its sliding will be infinity. This is a critical slowing down phenomenon with a critical exponent of 2. We can see that both the fitted relations give almost exactly the same maximum DNA loop size.

Considering the fact that a nucleic acid binding protein may has probability of detachment, one may ask what will happen if the chromatin-remodeling complex detaches from the nucleosome during the process of the histone octamer directional sliding? This corresponds to a situation of DNA loop release in our simulation. In this case, the simulation results show that the histone octamer will stop its directional sliding (see Fig. 9). Different lasting time of the DNA loop induces different sliding distance of the histone octamer as shown in Fig. 10 where the percentage of the sliding distance relative to the loop size is plotted versus the DNA bending time.

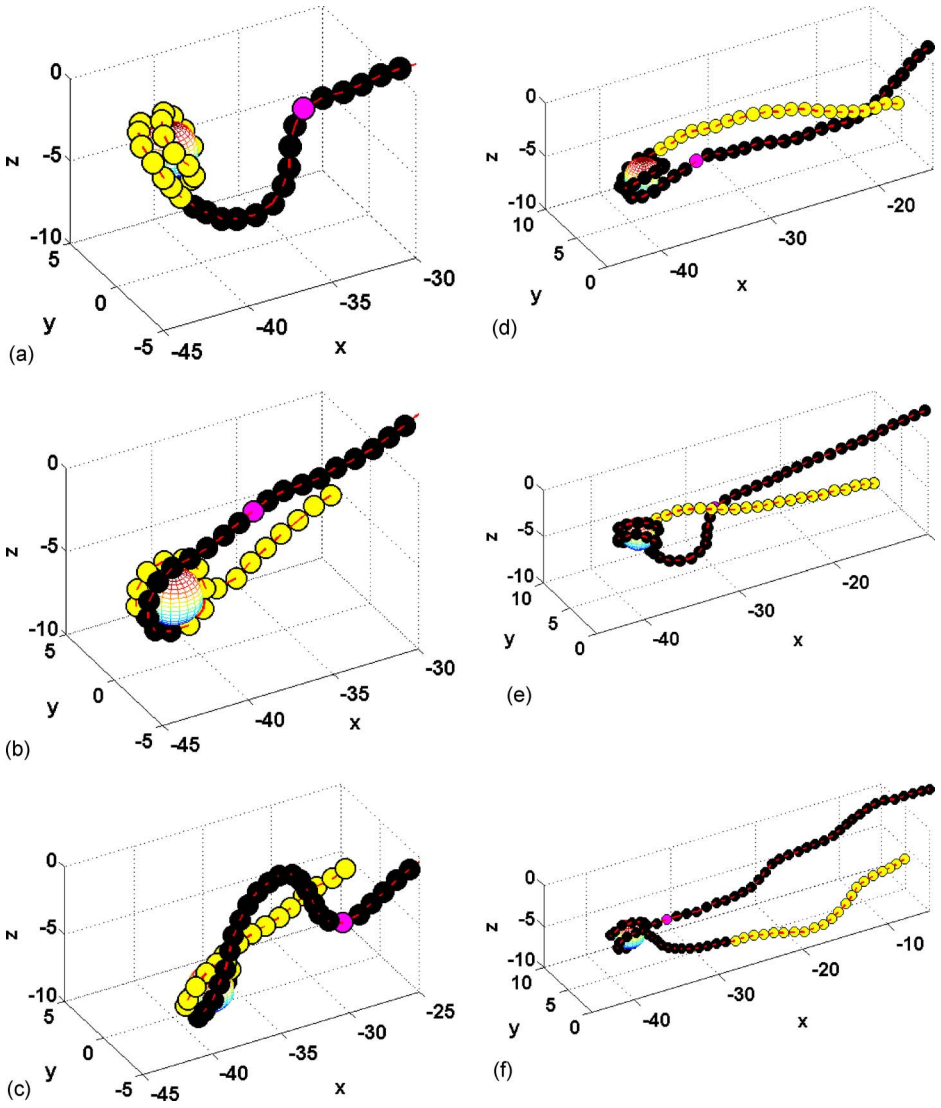

FIG. 4. (Color online) When three DNA loops are introduced successively, the histone octamer slides continually. The time corresponding to every snapshot is: (a) 0.0681; (b) 2.4701; (c) 2.6074; (d) 5.1462; (e) 5.2148; and (f) 7.7193 s. The contour length of each DNA loop is $14\sigma_m$.

Based on the simulation results and taking into considerations of previous models for the chromatin-remodeling complex [15,20], we propose a similar but different model for the dynamics of the interaction between the nucleosome and the chromatin-remodeling complex to interpret directional sliding of histone octamers caused by DNA bending as shown in Fig. 11. First, the chromatin-remodeling complex produces a DNA loop at the side of the nucleosome. Then the histone octamer slides towards the DNA loop. This results from the strain-driven sliding of DNA over the surface of the histone octamer. During the process of the sliding of the histone octamer, the DNA loop diminishes. After the loop disappears completely, the histone octamer stops sliding. Our model is different from the previous ones [15,20] in the sense that there is no intranucleosomal DNA bulge in our model.

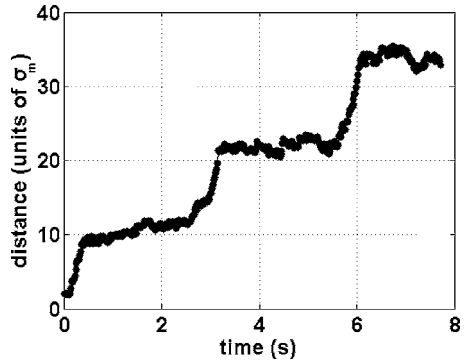

FIG. 5. The sliding distance of the histone octamer as a function of time.

V. SUMMARY

In the biological processes of gene expression or cell division, the structure of nucleosome is always altered. The chromatin-remodeling complex plays an important role in these processes. We simulate directional sliding of histone octamers caused by DNA bending. We find that when a DNA bending is produced at the side of the nucleosome, the histone octamer slides towards the DNA loop. There exists a maximum size of the DNA loop that can cause directional

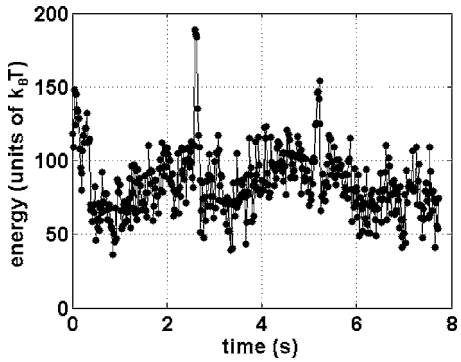

FIG. 6. The energy of the system in the process of histone octamer's sliding.

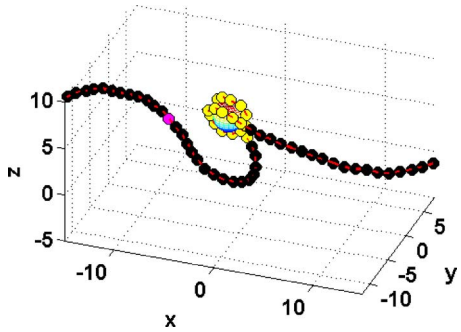

FIG. 7. (Color online) When the contour length of the DNA loop is increased to $20\sigma_m$, the histone octamer does not slide. The snapshot is taken at 0.586 s after the bending is introduced.

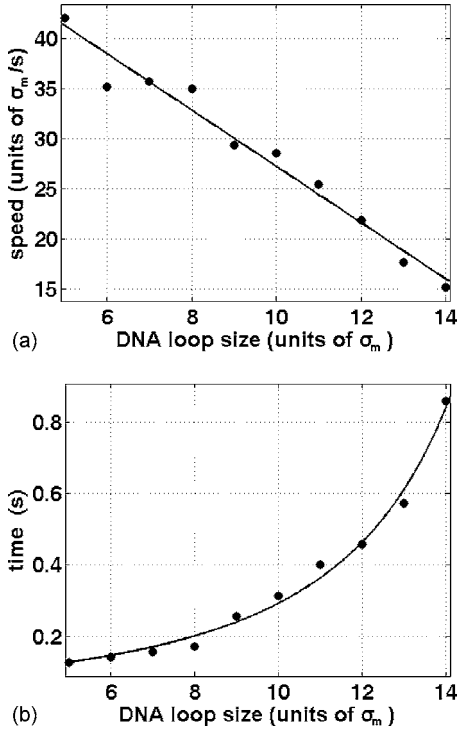

FIG. 8. (a) The histone octamer's average sliding speed as a function of DNA loop size. (b) The time for the histone octamer to slide 90% of the DNA loop size. Dots are the results of simulation. Solid curves are the fits (see text).

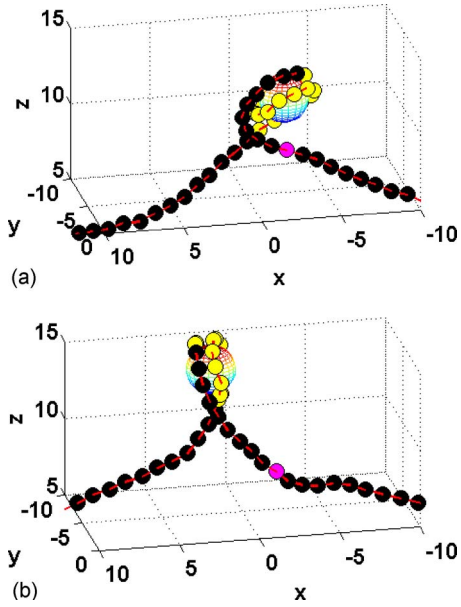

FIG. 9. (Color online) The histone octamer stops directional sliding when the DNA loop is released. The DNA loop size is $9\sigma_m$. (a) The histone octamer slides a distance of $4.8\sigma_m$ towards the DNA loop in 0.245 s. (b) Snapshot taken at 0.858 s after the DNA loop is released at the time of 0.245 s.

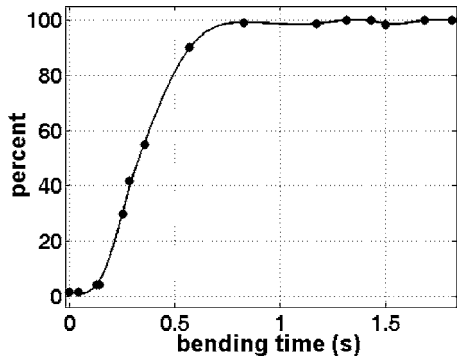

FIG. 10. Relation between the bending time and the percent of sliding distance relative to the contour length of the DNA loop. The DNA loop size is $14\sigma_m$.

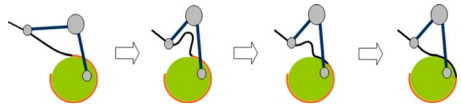

FIG. 11. (Color online) Model for the interaction between a nucleosome and a chromatin-remodeling complex. In the model, the histone octamer (the large green sphere) slides after a DNA bending is produced by the chromatin-remodeling complex (gray balls connected with blue bars) at one side of the nucleosome. In the process of the histone octamer's sliding, the DNA loop is shrinking. At last, the DNA loop disappears and the histone octamer stops sliding.

sliding of histone octamers. This size is close to the persistence length of the DNA molecule. The histone octamer will stop sliding if the DNA loop is released. A model is suggested to interpret directional sliding of histone octamers induced by chromatin-remodeling complexes.

ACKNOWLEDGMENTS

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