Brownian dynamics simulation of the effect of histone modification on nucleosome structure

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Using Brownian dynamics we simulate the effect of histone modification, such as phosphorylation, acetylation, and methylation, on nucleosome structure by varying the interaction force between DNA and the histone octamer. The simulation shows that the structural stability of nucleosome is very sensitive to the interaction force, and the DNA unwrapping from the modified histone octamer usually occurs turn by turn. Furthermore, the effects of temperature and DNA break as well as the competition between modified and normal histone octamers are investigated, with the simulation results being in agreement with the experimental observation that phosphorylated nucleosomes near DNA breaks are more easily depleted. Though the simulation study may only give a coarse grained view of the DNA unwrapping process for the modified histone octamer, it may provide insight into the mechanism of DNA repair.

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I. INTRODUCTION

Nucleosome is the basic unit of chromatin and much has been known about its crystal structure [1,2]. A nucleosome consists of one histone octamer and 146-bp DNA which wraps around the histone octamer in about two turns [3]. Fifteen to 38 amino acids from each histone *N* terminus form the histone "tails", providing a platform for posttranslational modifications that modulate the biological role played by the underlying DNA [4]. Phosphorylation is one important modification of histone. The phosphorylation occurs on serine of the histone variant H2AX at the carboxy-terminal SQE motif to create a γH2AX-containing nucleosome. When a double-strand break of DNA occurs in the cell cycle, the cell division is halted and the histone variant H2AX is phosphorylated in a large region of about 50 kilobases [5–10]. After the DNA repair is finished, the phosphorylated H2AX (γH2AX) is dephosphorylated by a protein complex containing the enzyme Pph3 [11]. The phosphorylation of H2AX is very important for recruiting lots of double-strand-break-recognition and repair factors to the break site, including DNA damage checkpoint proteins, chromatin remodellers, and cohesions [12–16]. Acetylation is another important modification of histone. The acetylation of histone occurs on the free amino group of lysine [17–21]. Histone acetylation appears to be enhanced in a region containing active genes, and acetylated chromatin is more sensitive to DNAase I and micrococcal nuclease. Histone acetylation also occurs during the *S* phase, possibly associated with the incorporation of histones into nucleosomes [22,23]. The third type of histone modification is methylation. But the consequences of methylation on the lysine residues of core histones are not clear [3]. Because DNA is negatively charged and the histone octamer is positively charged, the interaction between DNA and a histone octamer is mainly electrostatic. We assume that histone modification (phosphorylation, acetylation, and methylation) weakens the interaction force between DNA and the histone octamer. As a result, the structure of nucleosome becomes unstable. Based on our previous works [24,25] on simulating the interaction between the chromatin remodeling complex and the nucleosome with Brownian dynamics, in this paper we simulate the effect of weakening of the interaction force between DNA and histone octamer on nucleosome structures. The simulation presents a coarse grained dynamical view of the DNA unwrapping process from the histone octamer when the histone octamer is modified.

II. MODEL

In our model, the DNA chain is modeled as a semiflexible homopolymer chain which consists of N spheres connected by bonds. Each sphere corresponds to about 6-bp DNA. The histone octamer is considered as a spherical core particle. The potentials of the system are considered as follows.

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

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

where $\varepsilon_m = 0.2$, $\alpha_m = 2.4$, and σ_m is the width of DNA. The Boltzmann constant k_B is set to unity and the temperature $T = 298$ K. $r_{i,j}$ is the distance between the ith and jth spheres of the DNA chain. σ_m is the equilibrium distance between two neighboring spheres of the DNA chain. We use σ_m as the length unit.

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

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

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,

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

where we choose $\kappa = 15$.

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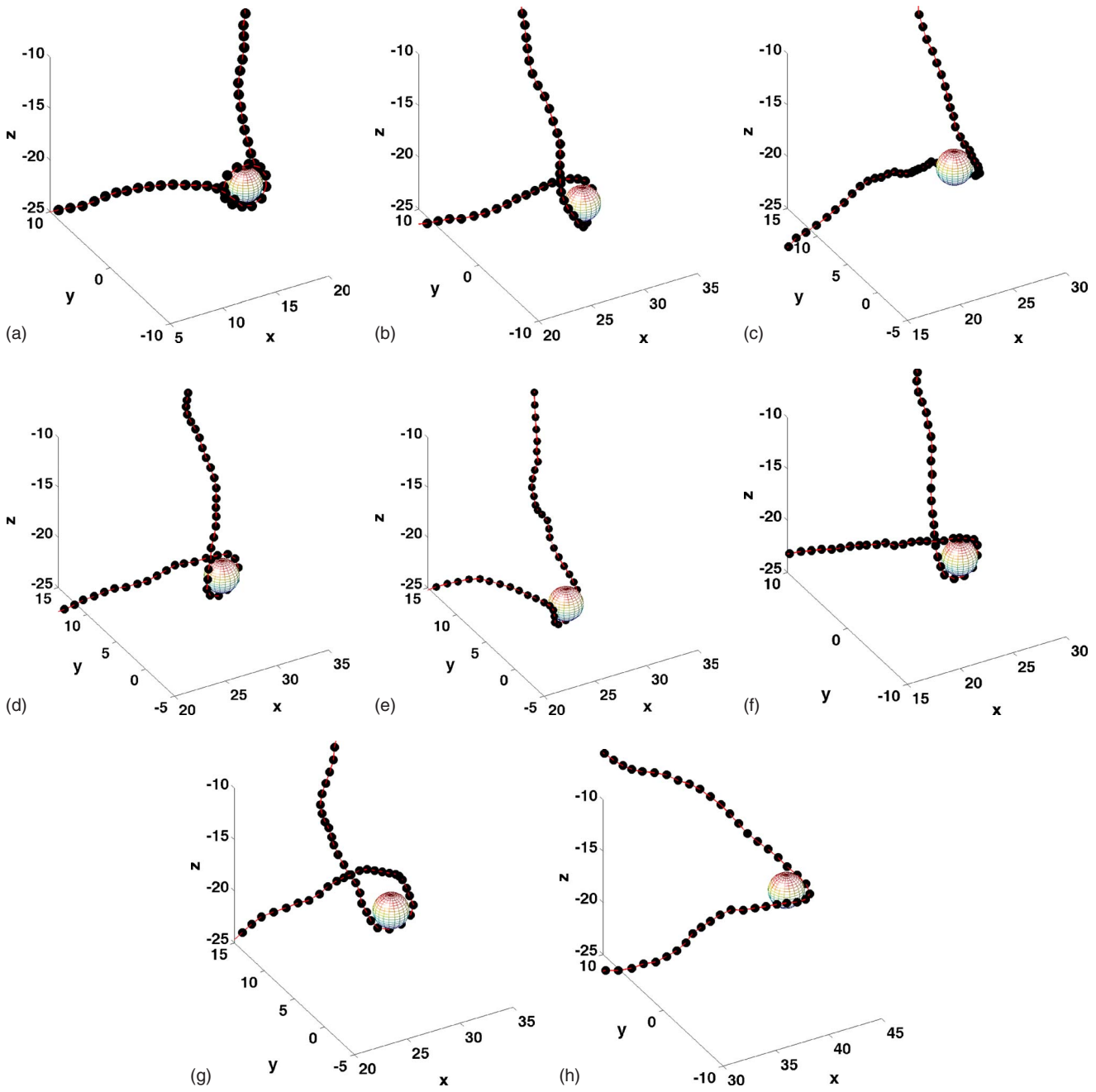

FIG. 1. (Color online) Snapshots of the simulated DNA unwrapping process from one histone octamer when the histone modification is supposed to happen at the moment of (a). Most DNA balls finally leave the histone octamer, inducing the rupture of the nucleosome structure. The time corresponding to each snapshot is (a) 0 s; (b) 1.8 s; (c) 4 s; (d) 4.57 s; (e) 5.15 s; (f) 5.66 s; (g) 7.49 s; (h) 11.44 s. Here the DNA chain consists of 100 DNA balls. ε is equal to 4.0 for the stable nucleosome structure and equal to 3.0 for the modified histone. The length unit for all the axes is σ_m.

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

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

where $\alpha=6$ and $\sigma=1.9\sigma_m$. The diameter of the histone octamer is $2.8\sigma_m$. r_i is the distance between the histone octamer and the ith sphere of the DNA chain.

We choose the diameter of the histone octamer, $2.8\sigma_m$, so that the relative sizes of DNA and the histone octamer are the same as the actual ones: In nature, the width of DNA is 2.3 nm and the diameter of a histone octamer is 6.4 nm. Therefore the length unit σ_m is 2.3 nm. Because the parameter ε determines the interaction strength between DNA and the histone octamer, we assume that the modification of histone reduces the value of ε. Therefore we choose ε as the control parameter in the simulation.

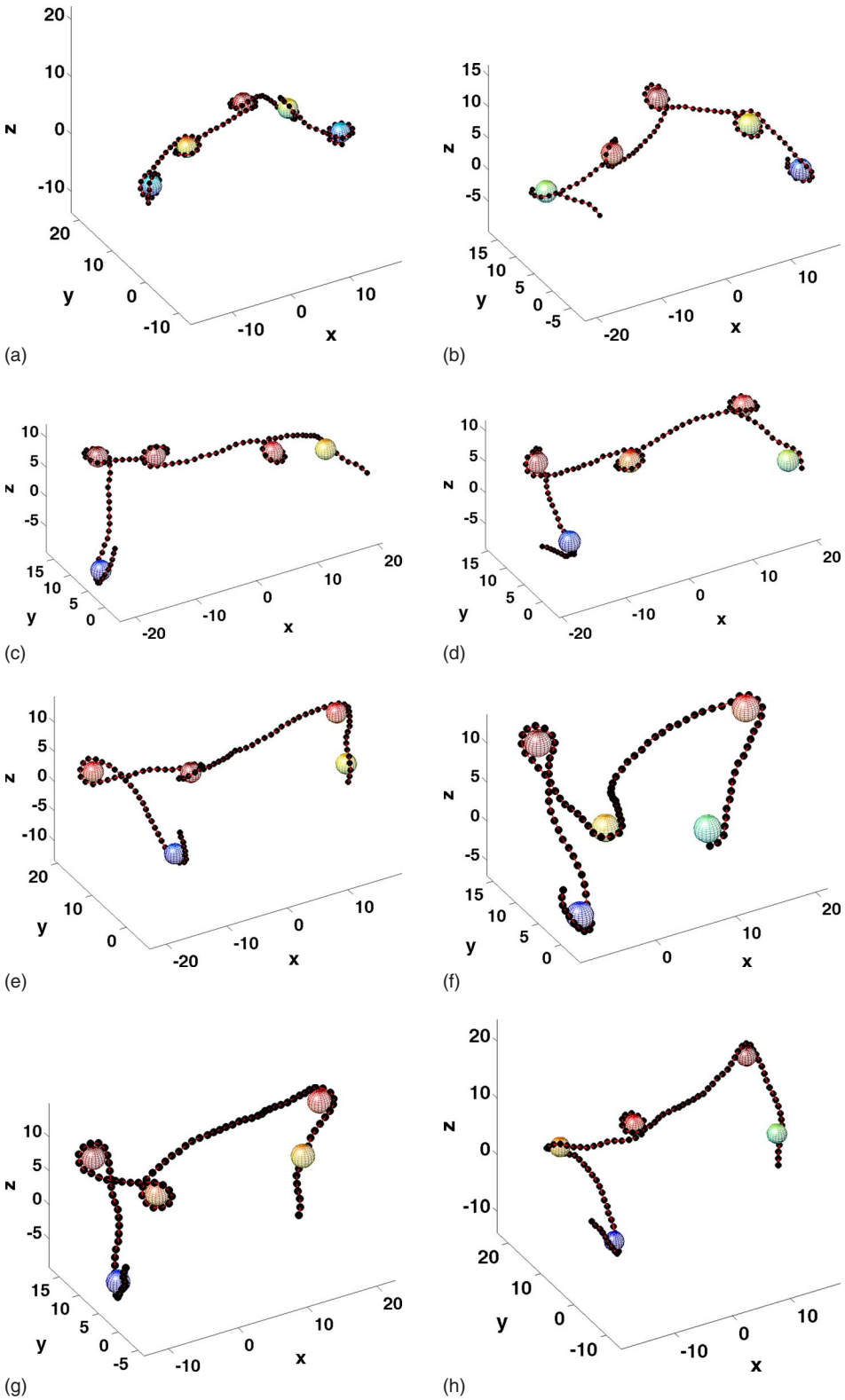

FIG. 2. (Color online) Snapshots of DNA unwrapping process when histones of the five nucleosomes are modified. The time corresponding to each snapshot is (a) 0 s; (b) 1.29 s; (c) 3.86 s; (d) 5.45 s; (e) 6.52 s; (f) 9.26 s; (g) 11.88 s; (h) 12.87 s. Here ε is equal to 4.0 for the stable nucleosome structure and equal to 3.0 for modified histones.

The repulsive potential among histone octamers is considered by using the repulsive part of the Morse potential,

$$U_{M,rep} = \varepsilon_M k_B T \sum \exp[-\alpha_M(R_{i,j} - \sigma_M)], \tag{5}$$

where $\varepsilon_M = 0.2$, $\alpha_M = 2.4$, and $\sigma_M = 8\sigma_m$.

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

$$-\gamma_m \frac{d\vec{r}_i}{dt} + \vec{R}_{m,i}(t) - \frac{\partial U}{\partial \vec{r}_i} = 0, \tag{6a}$$

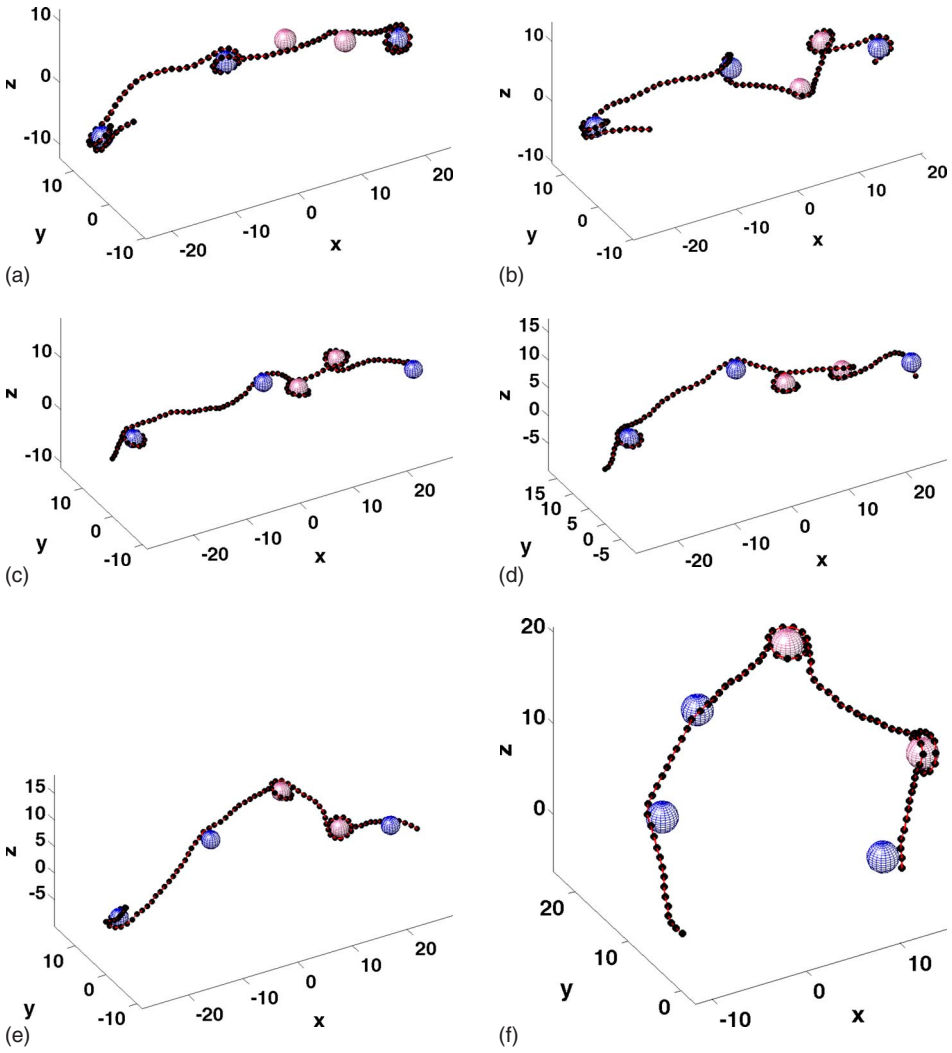

FIG. 3. (Color online) Snapshots of the process of DNA interactions with both normal ($\varepsilon=4.0$) and modified histone octamers ($\varepsilon=3.0$). At the beginning ($t=0$ s), the two normal histone octamers (pink) bind to the DNA chain on which the histone octamers (blue) of the three nucleosomes are modified. The time corresponding to each snapshot is (a) 0 s; (b) 1.22 s; (c) 2.12 s; (d) 3.22 s; (e) 5.08 s; (f) 17.11 s.

$$-\gamma_M \frac{d\vec{R}_j}{dt} + \vec{R}_{M,j}(t) - \frac{\partial U}{\partial \vec{R}_j} = 0, \tag{6b}$$

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 $\vec{R}_{M,j}$ are the Gaussian white noises which obey the fluctuation-dissipation theorem. The total internal energy U consists of five terms: $U = U_{m,rep} + U_{bond} + U_{bend} + U_M + U_{M,rep}$.

We perform the dynamics of this system using a stochastic Runge-Kutta algorithm (white noise) [26]. 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

We first simulate the interaction between the DNA chain and a histone octamer. DNA wraps around the histone octamer in about two turns and we get a stable nucleosome structure for $\varepsilon=4.0$. After a stable nucleosome structure is formed, the histone modification is supposed to happen by reducing the control parameter ε from 4.0 to 3.0. A typical dynamical process is shown in Fig. 1. From Fig. 1 we can clearly see the unwrapping process of DNA from the histone octamer and the disruption of the nucleosome structure after the interaction force between DNA and the histone octamer is reduced.

From our simulation results, we find that when the interaction force between DNA and histone octamer is reduced, the structure of the nucleosome becomes unstable in a short time and DNA begins to unwrap from the histone octamer immediately. In the process of DNA's departure from the histone octamer surface, the DNA chain falls off and then rewraps around the histone octamer several times, showing some kind of oscillation before most DNA balls finally leave the histone octamer surface.

In Ref. [11], experimental results show that histone (H2AX) phosphorylation happens not on a single nucleosome, but on nucleosomes in a region of about 50 kilobases of DNA. To simulate this situation, we assume the histone modification happens on more than one nucleosome at the same time. The dynamical process of DNA unwrapping from five histone octamers when they are modified simultaneously is shown in Fig. 2.

From Fig. 2, we find that after the histones are modified, all the nucleosome structures become unstable and DNA begins to unwrap from the histone octamers. Although the in-

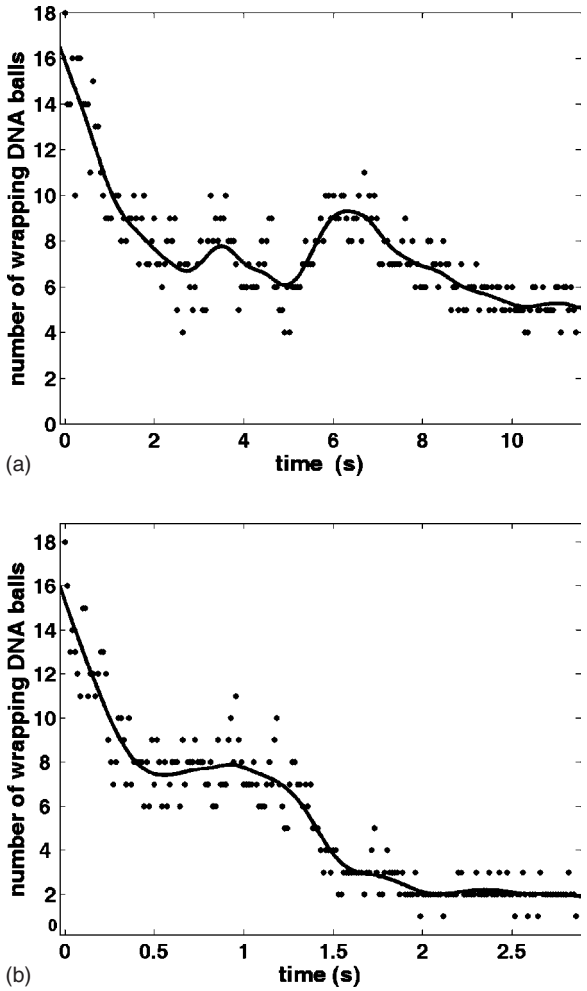

FIG. 4. The relationship between the number of wrapping DNA balls and time. Here, due to histone modification, ε is assumed to be reduced from 4.0 to (a) 3.0 and (b) 2.25.

teraction parameters between DNA and all the histone octamers are reduced to the same value, those nucleosomes located near the two free DNA ends are more unstable. In experiments [11], it was found that the nucleosomes near DNA breaks are more easily evicted. Our simulation is consistent with this experimental result.

What will happen when DNA has interactions with both normal and modified histone octamers? We simulate this situation with results shown in Fig. 3. In this case, we can see that the normal histone octamers will compete with modified histone octamers and evict the modified histone octamers from their original locations.

IV. QUANTITATIVE STUDY AND DISCUSSION

From the above simulation, we can see that the effect of histone modification, such as H2AX phosphorylation [11], on destabilizing a nucleosome structure can be well simulated by weakening the interaction force between DNA and the histone octamer. In the following, we will study in more detail the unwrapping behaviors of DNA from the modified histone octamers.

First, the number of DNA balls that remain wrapping around the octamer is recorded as a function of time in the simulation, which is shown in Fig. 4(a). It is can be seen that during the unwrapping process, at a certain instant the number of DNA balls that still stay on the histone octamer surface stopped decreasing (at about 5). Before the whole unwrapping process is completed, the DNA chain falls off and rewraps around the histone octamer several times, reflecting an oscillation behavior. In a previous theoretical work [31] addressing the effect of salt in DNA-histone complex, it was analyzed that the fully wrapped and unwrapped states could coexist at a certain salt concentration, which would dynamically lead to oscillatory behavior. In our case, we have made a systematic simulation corresponding to different values of parameter ε and found that the oscillation phenomenon only happened in a narrow range of ε value around 3.0. When the interaction between the DNA and histone octamer is more reduced this oscillation phenomenon disappears as shown in Fig. 4(b). Therefore the transient oscillation should result from the competition between unwrapping and bending, which occurs only in a small parameter range. Interestingly, as can be noticed from both figures, the histone-modification-induced DNA unwrapping from the histone octamer occurs first by one turn (the number of wrapping DNA balls decreasing from 16 to ~8), then by another turn. The oscillation phenomenon, if appearing, would occur during the DNA unwrapping of the second turn.

It is known that when histone is phosphorytated, acetylated, or methylated, the interaction between DNA and the histone octamer is reduced. But we do not know to what extent this interaction is actually reduced. Thus we simulate the process of DNA unwrapping from a histone octamer for different interaction strengths between DNA and the histone octamer. The results are presented in Fig. 5. We can notice that when the interaction between DNA and the histone octamer is reduced, the number of DNA balls that still remain in contact with the histone octamer is also reduced accordingly.

Quantitatively, in Fig. 6, we show the relation between the number of wrapping DNA balls and the parameter ε. It can be seen that when ε is around 3.5, the number of wrapping DNA balls is the most sensitive to the value of ε. If ε decreases a little, the number of wrapping DNA balls would decrease sharply. That is, there is a critical point ($\varepsilon \geqslant \sim 3.5$) for the stable nucleosome structure. This may explain why a small modification to the histone octamer, such as phosphorytation, acetylation, and methylation of histone, can make the nucleosome structure unstable. We also simulated the average unwrapping speed of DNA after the histone modification. The result is shown in Fig. 7. We can see that the unwrapping speed decreases with the increase of ε. It drops to less than one-third when ε is increased from 2 to 3.2.

It has been known that DNA sequences differ greatly in their ability to bend, and the histone octamer prefers to be positioned on specific DNA sequences [27–30]. In other words, the stiffness of the DNA chain has some effect on the nucleosome structure. Here, we alter the stiffness of the DNA chain by changing the parameter κ of the potential U_{bend} and check its effect on the nucleosome structure. As

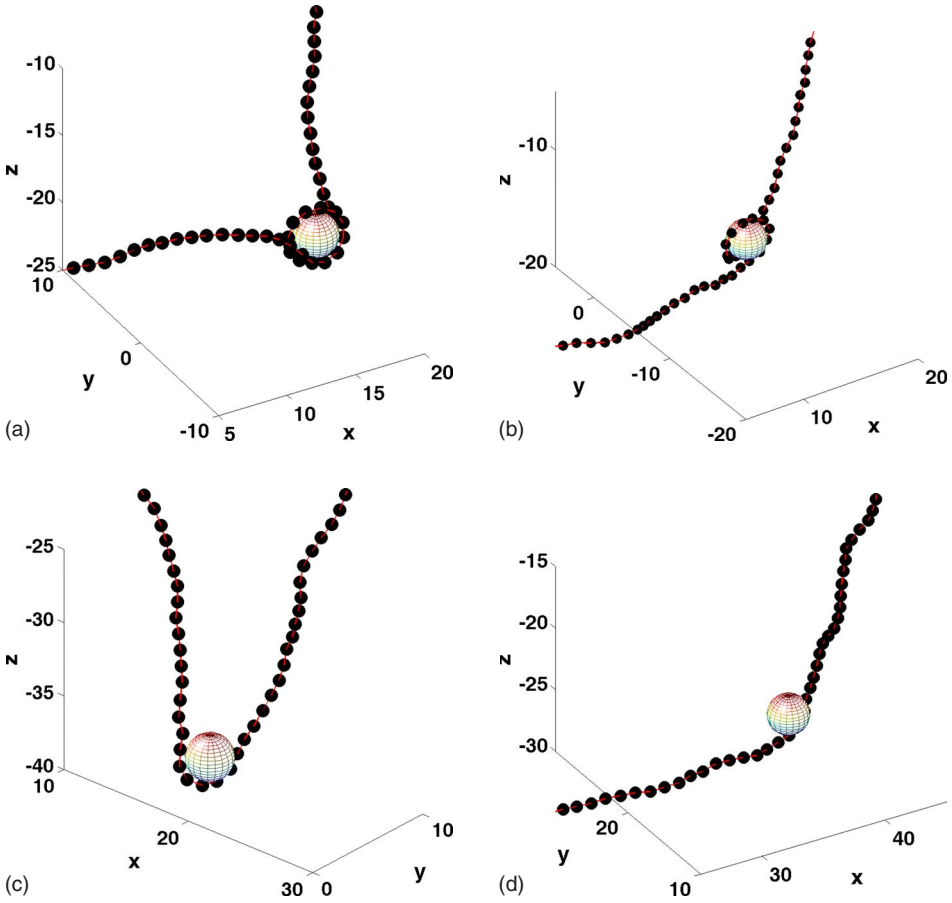

FIG. 5. (Color online) Simulated DNA unwrapping from a histone octamer with different interaction strengths as represented by the parameter ε of the potential U_M. (a) ε=4.0; (b) ε=3.5; (c) ε =3.25; (d) ε=3.0.

shown in Fig. 8, when κ is above ~16, the DNA chain can no longer wrap around the histone octamer to about two turns and thus a complete nucleosome structure cannot be formed. When κ is less than ~14, on the other hand, the DNA chain is too soft and DNA balls will pile on the surface of the histone octamer, so a normal nucleosome structure also cannot be formed. Thus for a given interaction strength between DNA and the histone octamer, the DNA stiffness also plays an important role in the formation of a normal nucleosome structure.

To see the effect of temperature on the process of DNA unwrapping after the histone modification, we simulated the relation between the DNA unwrapping speed and the temperature as shown in Fig. 9. We can see that when the temperature is increased, the speed of DNA unwrapping increases accordingly. But when the temperature is increased to about 330 K, the speed becomes almost independent on the temperature.

From Fig. 2, we can schematically see that the modified-histone-containing nucleosomes located near the free DNA ends are more unstable. To study this effect in more detail,

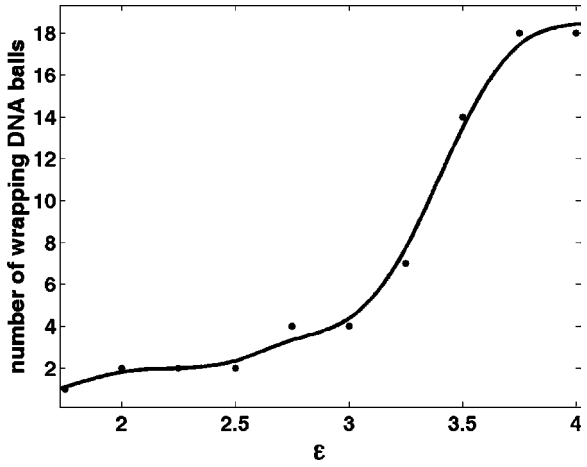

FIG. 6. The relation between the number of wrapping DNA balls and the parameter ε.

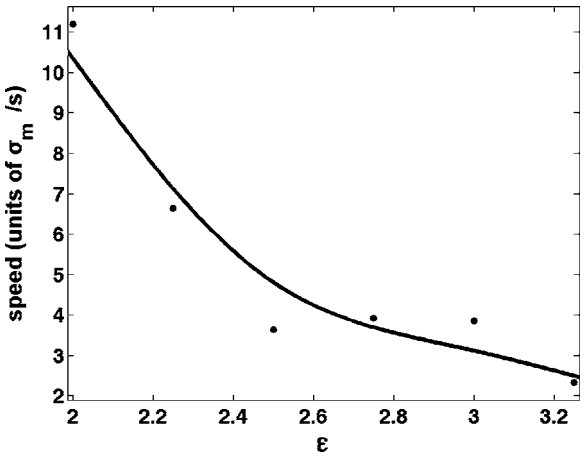

FIG. 7. The relation between DNA unwrapping speed and parameter ε.

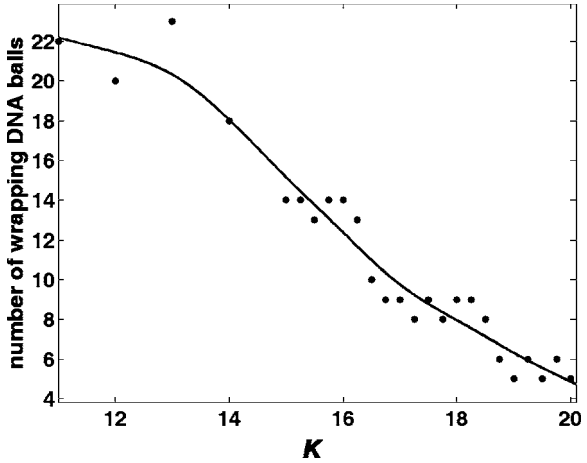

FIG. 8. The number of wrapping DNA balls as a function of the stiffness of DNA chain as represented by the parameter κ of the potential U_{bend}.

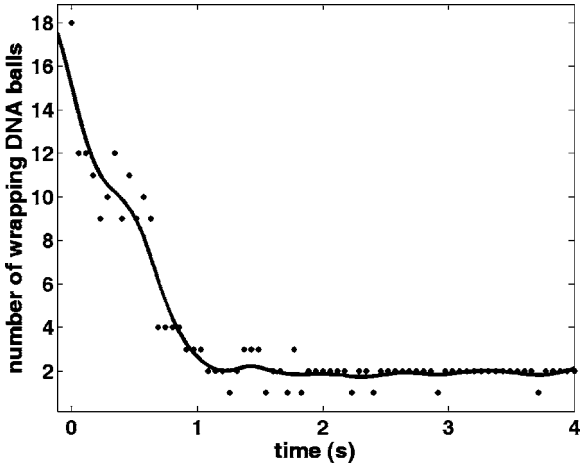

FIG. 10. The number of wrapping DNA balls as a function of time when a DNA break is generated near the modified-histone-containing nucleosome. The value of ε is 2.25.

we numerically generate a DNA break near a nucleosome and record the number of wrapping DNA balls during the process of DNA unwrapping from the histone octamer. As shown in Fig. 10, the modified-histone-containing nucleosome near the DNA break finishes unwrapping from the histone octamer in a shorter time than when there is no break [Fig. 4(b)]. In the present case, the DNA unwrapping of the first turn is followed immediately by that of the second turn.

By changing the distance between the DNA break and the modified-histone-containing nucleosome we find that the nucleosome is more unstable and unwraps more quickly when it is near the DNA break than when it is located far from the DNA break as shown in Fig. 11 where the unwrapping speed vs the distance between the DNA break and the nucleosome is plotted. This may explain why γH2AX-containing nucleosomes near DNA breaks are more easily depleted than the others as observed in the experiment [11].

In Fig. 12 we present a whole dynamical image of DNA wrapping (nucleosome formation) to normal histone octamers and DNA unwrapping from the modified histone octamers. In order to include the end effect, we take three histone octamers. At the beginning of the simulation, two histone octamers locate near the two DNA ends, respectively, and one histone octamer locates near the middle of the DNA chain. The wrapping process is shown in Figs. 12(a)–12(c). We can see that the histone octamers near the ends of the DNA chain are easier and quicker to form nucleosome structures with DNA. This may be one of the reasons that in the nucleosome reconstitution the histone octamer prefers positioning at the DNA ends [32]. After all three nucleosome structures are formed, as shown in Fig. 12(c), the interaction between DNA and the histone octamers is weakend to simulate the histone modification. The dynamical process of DNA unwrapping from the modified histone octamers is shown in Figs. 12(d)–12(f). We can see that the DNA unwrapping process at the two ends is quicker than that in the middle, showing apparent end effect.

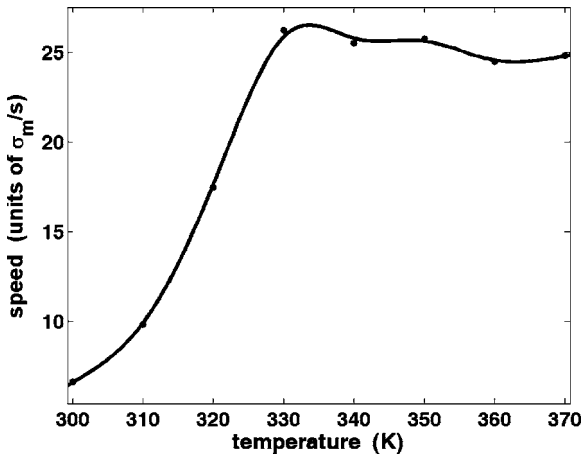

FIG. 9. The relation between DNA unwrapping speed and the temperature. The value of ε is 2.25.

V. SUMMARY

In conclusion, the process of DNA unwrapping from the modified histone octamer is numerically simulated with

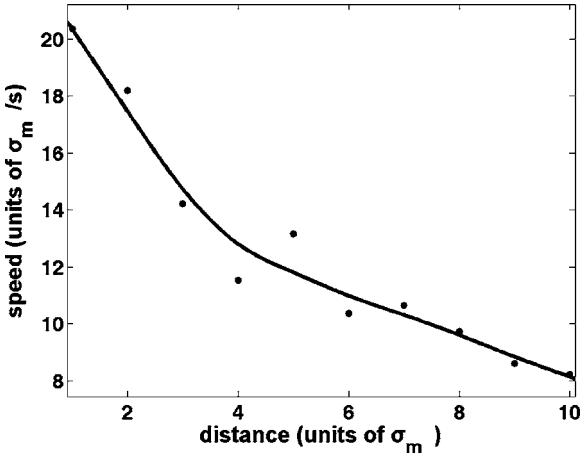

FIG. 11. The relation between the DNA unwrapping speed and the distance between the DNA break and the nucleosome. The value of ε is 2.25.

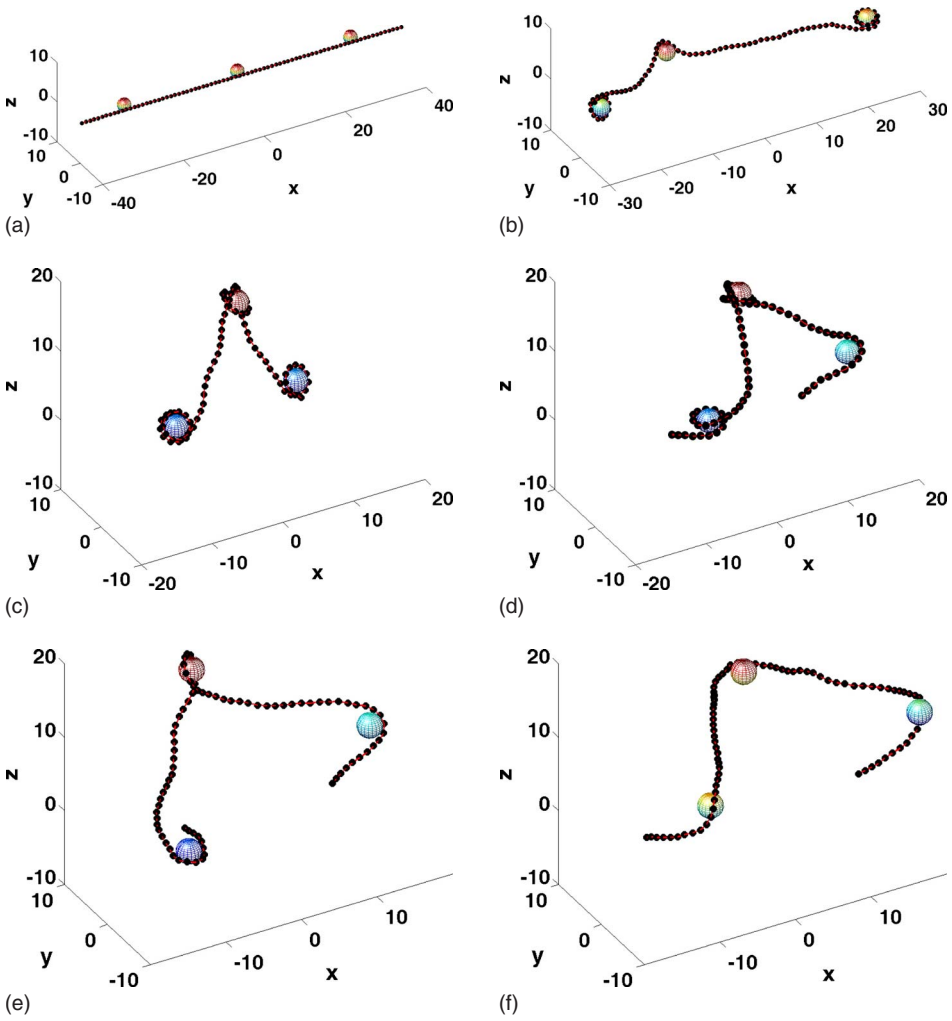

FIG. 12. (Color online) The process of interaction between DNA and three histone octamers is shown from (a) to (c). The two histone octamers near the DNA ends are easier to form nucleosome structures. After three nucleosome structures are formed, the interaction between DNA and histones is weakened and the process of DNA wrapping from histone octamers is shown from (c) to (f). The two nucleosomes located at the two ends of the DNA chain are unwrapped in a shorter time than the one located in the middle of the DNA chain. Here, the parameter ε is reduced from 4.0 to 2.0. The time corresponding to each snapshot is (a) 0 s; (b) 1.93 s; (c) 128.70 s; (d) 129.09 s; (e) 130.18 s; (f) 130.95 s.

Brownian dynamics. It is found that the stability of the nucleosome structure is very sensitive to the interaction force between DNA and the histone octamer. When the histone is modified to reduce a little the interaction force between DNA and the histone octamer, the nucleosome structure becomes unstable. From our simulation results, it is shown that in the process of DNA unwrapping, the DNA unwraps from the histone octamer turn by turn. An increase of the temperature in a certain range will help DNA to unwrap from the histone octamer. Further, we have numerically generated a DNA break near a nucleosome and found that the modified-histone-containing nucleosome near the DNA break is more unstable and DNA unwraps from this histone octamer more quickly than when it is located far from the DNA break. In addition, we have simulated the competition of modified and normal histone octamers, finding that the normal histone octamers will evict modified histone octamers from their original locations in forming new nucleosomes. Although the simulation is based on a coarse grained model and the results cannot be directly compared with previous experimental results quantitatively, this study can be helpful for qualitatively understanding the interaction dynamics between DNA and modified histone octamers, and may also provide insight into the repair mechanism of the DNA break.

ACKNOWLEDGMENTS

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