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Interactions between DNA and histones– a dynamic process of nucleosome formation*

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We have studied the dynamic process of interactions between a DNA chain and a histone octamer by numerical simulations. It is found that DNA indeed may wrap around the histone octamer about two turns as in the actual situations. The simulation shows that the interaction potential between DNA and histone is a key factor for the wrapping of DNA, and the temperature is also an important parameter in the process.

Keywords: DNA, histone, nucleosome, interaction
PACC: 8715, 8715B, 8715K

In eukaryotic cells, the basic structural unit of chromatin is nucleosome which consists of 146bp of DNA and histones (H2A, H2B, H3, H4, and H1 or H5). H2A, H2B, H3 and H4, with each contributing two molecules, form a core particle − histone octamer which has a left-handed superhelix structure,[1,2] and DNA wraps around the core particle about two turns in a left-handed way. DNA has negative charges and histone octamer has positive charges, and the interaction between them is mainly electrostatic. H1 or H5 is a linker histone. The histone core particle often slips along DNA and prefers positioning at one DNA chain end in the case of short chromatin fibres (e.g. mono-, di-, and oligo-nucleosomes).[3] It is a dynamic equilibrium. This is the first level of the chromatin structure. Many nucleosomes form with DNA a "zig-zag" or "beads-on-a-string" structure.[4] This is a higher level of the chromatin structure. With the development of laser tweezers, some experiments have been done on unfolding individual nucleosomes by stretching single chromatin fibres. These experiments are very helpful for studying the interactions between DNA and histones.[5,6] Also, some numerical simulation work has been done in this field such as the folding transition of a semiflexible homopolymer chain.[7] And the results of computer simulations of pulling chromatin fibres are consistent with the experimental data.[8,9]

In this paper we study the dynamic process of the interaction of DNA and histones in the formation of nucleosome by using the model given in Ref.[3]. The aim of our present numerical simulation work is to observe the snapshots of the dynamic process of wrapping and to find the important factors in the formation of nucleosome. This would be useful for understanding the nucleosome structure better. In our work, we use the stochastic Runge–Kutta numerical method, which is more accurate and effective.[10]

As in Ref.[3], we do not consider the linker histone because we only focus on the process of DNA winding around the histone octamer, whereas the linker histone only makes the structure of nucleosome more stable. A Brownian dynamic simulation using a simple model is adopted, where the DNA chain is substituted by a stiff homopolymer chain and the histone octamer by a spherical core particle. The homopolymer chain is modelled by N spherical monomers that are connected by bonds.

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

$$U_{\mathrm{m,rep}} = \varepsilon_{\mathrm{m}} T \sum_{ij} \exp\{-\alpha_{\mathrm{m}}(r_{ij} - \sigma_{\mathrm{m}})\}, \qquad (1)$$

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where $\varepsilon_{\rm m}$=2.0 and $\alpha_{\rm m}$=2.4×10^8. Thus, the radius of the monomer is about 0.5$\sigma_{\rm m}$. In this paper, we choose 298K for T and set Boltzmann constant $k_{\rm B}$ to unity. The interaction between each monomer and the histone core particle is modelled through the Morse potential

$$U_{\rm M} = \varepsilon T \sum_i \{\exp[-2\alpha(r_i - \sigma)] - 2\exp[-\alpha(r_i - \sigma)]\}, \quad (2)$$

where ε=3.0, α=6.0×10^8 and σ=1.9$\sigma_{\rm m}$. So the radius of the core particle is about 1.3$\sigma_{\rm m}$. These radii are so chosen as to make the volume ratio between the core particle and the polymer chain be almost the same as that in the real nucleosome. Figure 1 shows the dependence of $U_{\rm M}$ on r. As will be seen later, this potential is very important in our simulation because the simulation results depend strongly on the choice of ε and α.

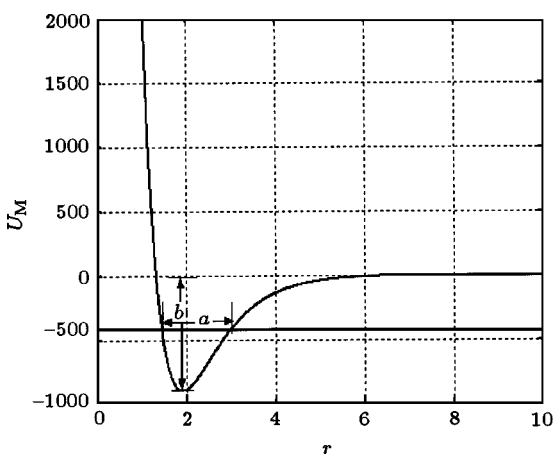


Fig.1. Morse potential for the interaction between each monomer and the histone core $U_{\rm M}$ as a function of r. b is the potential depth, a is the potential width defined at half of the depth.

The bonds between neighbouring monomers are simulated by a harmonic bonding potential

$$U_{\rm bond} = \frac{\kappa T}{2\sigma_{\rm m}^2} \sum_i (|\boldsymbol{r}_i - \boldsymbol{r}_{i+1}| - \sigma_{\rm m})^2, \quad (3)$$

where κ=400. Finally, the DNA chain stiffness is considered by choosing the following potential

$$U_{\rm bond} = KT \sum_i \left(1 - \frac{(\boldsymbol{r}_{i-1} - \boldsymbol{r}_i)\cdot(\boldsymbol{r}_i - \boldsymbol{r}_{i+1})}{\sigma_{\rm m}^2}\right), \quad (4)$$

where K=4.

The underdamped Langevin equation is used for describing the motions of each monomer and core particle

$$m\frac{{\rm d}^2\boldsymbol{r}_i}{{\rm d}t^2} = -\gamma_{\rm m}\frac{{\rm d}\boldsymbol{r}_i}{{\rm d}t} + \boldsymbol{R}_{{\rm m},i}(t) - \frac{\partial U}{\partial \boldsymbol{r}_i}, \quad (5a)$$

$$M\frac{{\rm d}^2\boldsymbol{R}}{{\rm d}t^2} = -\gamma_{\rm p}\frac{{\rm d}\boldsymbol{R}}{{\rm d}t} + \boldsymbol{R}_{\rm p}(t) - \frac{\partial U}{\partial \boldsymbol{R}}, \quad (5b)$$

where the hydrodynamic interaction is neglected. m and M are the masses of the monomer and the histone core, and $\gamma_{\rm m}$ and $\gamma_{\rm p}$ are the friction constants of the monomer and core particle, respectively. $\boldsymbol{R}_{{\rm m},i}(t)$ and $\boldsymbol{R}_{\rm p}(t)$ are Gaussian white noises which obey the fluctuation-dissipation theorem

$$< \boldsymbol{R}_{{\rm m},i}(t) > = 0,$$
$$< \boldsymbol{R}_{{\rm m},i}(t)\boldsymbol{R}_{{\rm m},j}(t') > = 6k_{\rm B}T\gamma_{\rm m}\delta_{i,j}\delta(t-t'), \quad (6a)$$

$$< \boldsymbol{R}_{\rm p}(t) > = 0,$$
$$< \boldsymbol{R}_{\rm p}(t)\boldsymbol{R}_{\rm p}(t') > = 6k_{\rm B}T\gamma_{\rm p}\delta(t-t'). \quad (6b)$$

The total internal energy U consists of four terms: $U = U_{\rm m,rep} + U_{\rm M} + U_{\rm bond} + U_{\rm bend}$. We use T as the unit energy, $\sigma_{\rm m}$ as the unit length, and $\gamma_{\rm m}\cdot\frac{\sigma_{\rm m}}{\sqrt{T}}$ as the unit time in the simulation. We choose m=1 [then $M = (1.3\sigma_{\rm m}/0.5\sigma_{\rm m})^3$=17.576] to save calculation time since the motion of interest occurs on a time scale much longer than the relaxation time of velocity and this large mass should have little effect. For numerically solving Eqs.(5a) and (5b), we use the recently developed stochastic Runge–Kutta algorithms (white noise)[10] which is an effective and accurate method. In all our simulations the time step is kept at Δt=6.0×10^{-4} unit time. If we choose a smaller time step for our simulation, we can obtain the same results. To obtain equilibrium states, we perform the multicanonical Brownian dynamics simulation with about 7.5×10^5 time steps.

We simulate the interaction between one histone core particle and a DNA chain which consists of 40 monomers. Figure 2 shows the snapshots of the dynamic process of wrapping. From Fig.2, we can see clearly that DNA wraps around the histone core about two turns, and about 24 monomers are around the core particle.

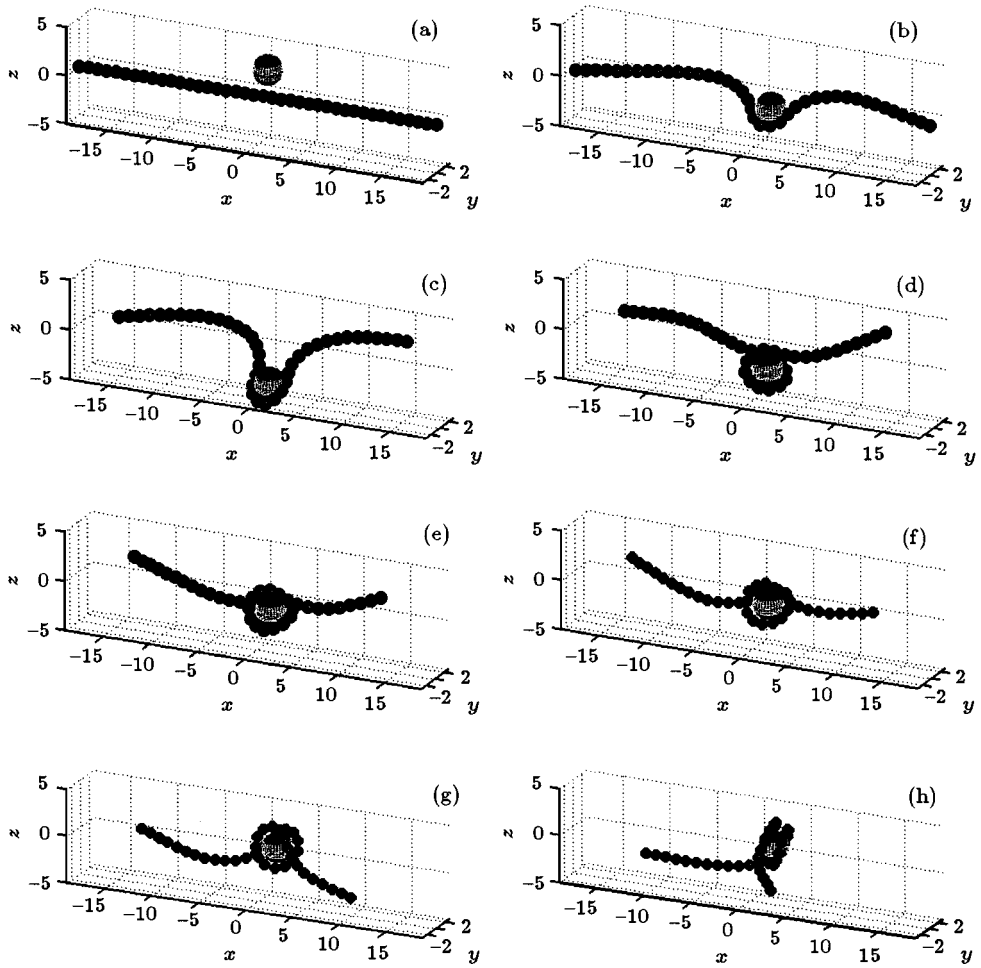


Fig.2. Snapshots of the dynamic process of DNA wrapping around the histone core at different times. (a) t=0, (b) t=60, (c) t=210, (d) t=240, (e) t=270, (f) t=300, (g) t=360, and (h) t=450.

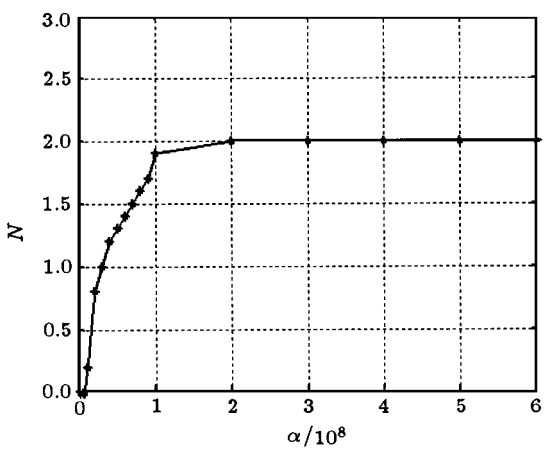


Fig.3. Number of wrapping turns N as a function of α.

In the simulation, we found that the width of the potential $U_{\rm M}$ is crucial to the results. In the potential curve as shown in Fig.1, the potential width a depends on α and the potential depth b depends on ε. By making simulations with different α, we have obtained the number of wrapping turns N as a function of α. The result is shown in Fig.3. It can be seen that when α is below $\sim 10^7$, the interaction between the DNA chain and the histone core is not strong enough to make DNA wrap around the core. When α reaches 10^8, however, DNA can wrap the core about two turns. But as shown in Fig.4, even when α is at 10^8, the interaction is still not strong enough, thus the DNA chain cannot wrap the histone core closely. When α reaches about 6.0×10^8, the DNA chain can wrap around the core closely.

We have found that the temperature T is also an important factor in the wrapping of DNA. In the above simulations, T is set to be 298K which is reasonable in vivo. When we increase the temperature, our simulation shows that the DNA chain cannot wrap on the surface of the core closely and properly. Typical results are shown in Fig.5.

We know that the nucleosome structure is left-

handed. However, in our simulation the chirality of the nucleosome has not been taken into account. After repeating the simulation many times it can be found that left-hand and right-hand structures emerge with the same probability. This is because the potential U_{M} used is non-chiral.

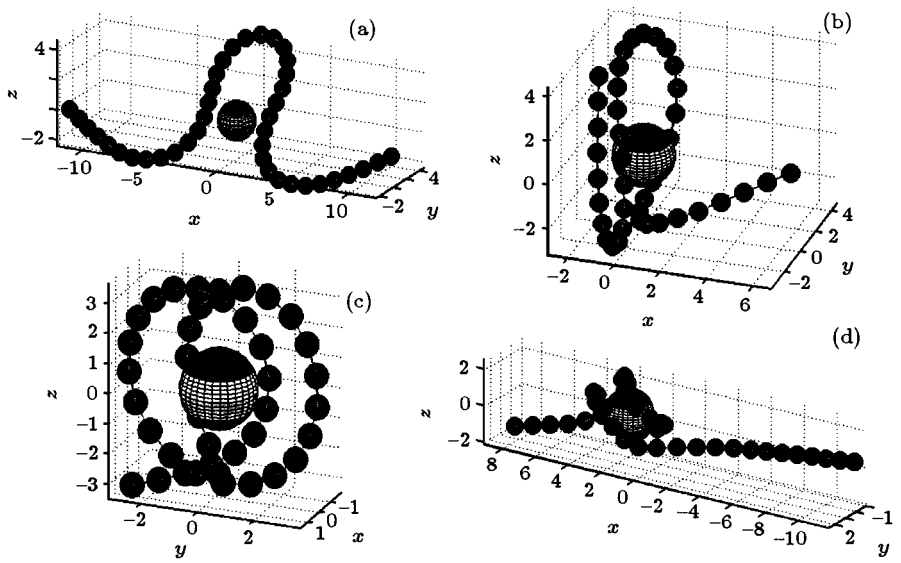


Fig.4. Wrapping patterns of DNA around the core for different α. (a) α=2.0×10^8; (b) α=3.0×10^8 (c) α=5.0×10^8; (d) α=6.0×10^8. When the value of α is large enough, the DNA chain wraps around the core properly.

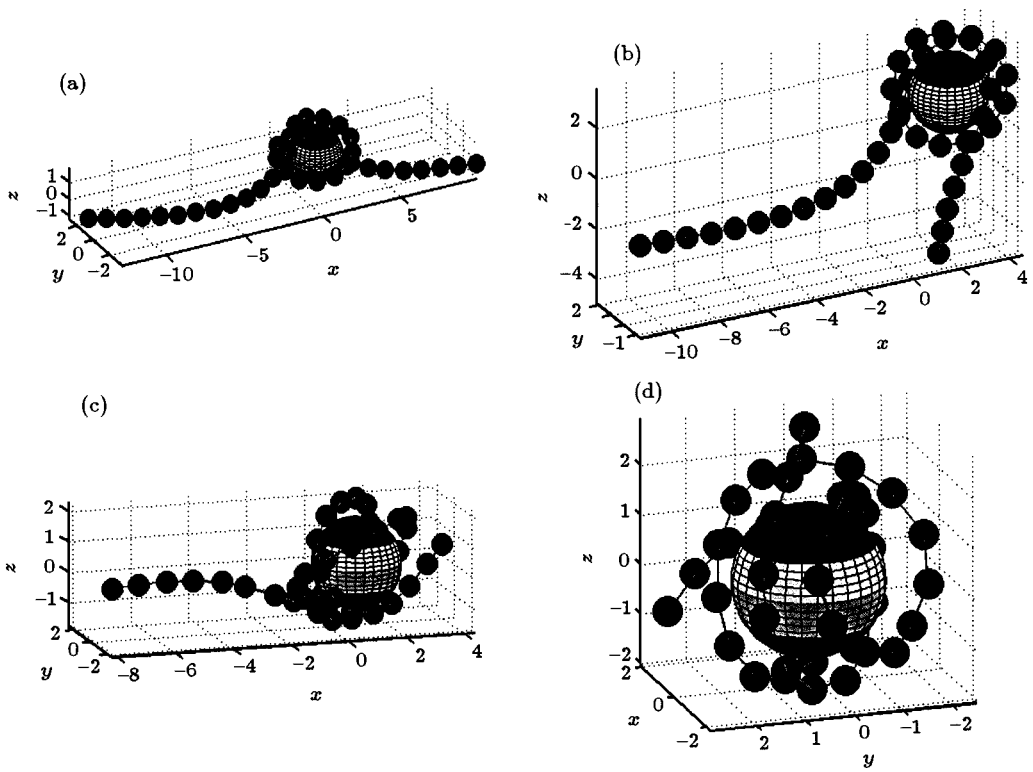


Fig.5. Wrapping patterns of DNA around the core at different temperatures. (a) T=250K; (b) T=350K; (c) T=500K; (d) T=600K. When the temperature is too high, DNA chain cannot wrap around the core closely and properly.

In summary, we have studied the dynamic process of nucleosome formation by numerical simulation. Although the situation should be more complicated for an actual nucleosome, our preliminary simulation has given the main image. From our simulation, we can also see that the histone core tends to be located at one end of the DNA chain as reported in Ref.[3]. We have not only given the dynamic process of nucleosome formation, but also demonstrated that the potential between DNA and histone, as well as the temperature, play important roles in the wrapping of a DNA chain around a histone core. This agrees with the fact that the *in vivo* physiological salt concentration and temperature are necessary for the proper folding of a DNA molecule to a chromatin with the participation of histones.

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