Dependence of DNA condensation on the correlation distance between condensed counterions

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Abstract Based on the ground state of counterions condensed on a DNA molecule, a model has been developed to successfully detect the process of DNA condensation. Through further investigation, the process of DNA condensation strongly depends on the correlation distance between condensed counterions on DNA molecules. Generally, there are two routes. The process of DNA condensation with the correlation distance between condensed counterions being 2 nm or 4 nm is different from the one with the correlation distance between condensed counterions being 3 nm or 5 nm. Effects of ionic strength on the diameter of toroidal condensates originate from the increase of correlation distance between condensed counterions.

Keywords DNA condensation · Monte Carlo simulation · Correlation distance between condensed counterions

1 Introduction

The DNA molecule is a semi-flexible highly charged polyelectrolyte that assumes an elongated coil conformation under “physiological” conditions (a 0.1 M solution of NaCl); conversely, in cells millimeter-to meter-long genomic DNA is usually folded into a dense and compact state to fit within 10^{-4} – 10^{-6} times smaller spaces. This remarkable compaction can be reproduced by adding a small amount of multivalent ions, such as polyamines and multivalent metal cations [1], both of which can induce the collapse of DNA into toroids [2–6]. Although much work has been done to elucidate the mechanisms of DNA condensation, until now, no consistent conclusion has been drawn.

Much attention has been paid to the mechanism of DNA condensation. Recently, the static and dynamic correlation function of segmental charge density on a rod-like poly-

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electrolyte in ionic solutions has been studied, which indicates that the charge correlation exhibits an underdamped oscillation with a wavelength comparable to the counterion size and with amplitude increasing with counterion valence [7]. At the same time, a single molecule experiment has directly demonstrated that DNA in the extended phase resembles a line of negative charge with a random sequence of positively charged patches along its backbone [8]. Based on the above facts, a ground-state model for a counterion condensed on DNA molecule has been proposed and applied to investigate the mechanism of DNA condensation (Liu et al., in preparation). Its results match the ones of other recent experimental and theoretical works.

Recent single-molecule experiments performed using transverse magnetic tweezers [9, 10] shed more light on the compaction dynamics of hexamine cobalt chloride-induced DNA compaction under tension. The compaction process is discontinuous and stepwise, more sophisticated than what the static structural model suggest. During the compaction and unraveling process with constant force, distinct jumps appear. These jumps occur because turns of DNA were wrapped regularly on the prime loop and unwrapped from the toroids, respectively. According to the experiment, one question emerged: whether all the condensation processes that involved turns of DNA were wrapped regularly on the initial nucleation loop and form toroid structures.

The results of the recently proposed ground-state model indicate that the process basically has two mechanisms, although both form toroid structures, which mechanism will be adopted in the condensation process depends strongly on the correlation distance between condensed counterions along DNA molecules.

2 Model and algorithm

2.1 Theoretical model

The model is the same as the one proposed in our recent work (Liu et al., in preparation) and will be briefly reviewed here. It simply contains two parts: elasticity energy and electrostatic energy. The total energy is given by

$$E_t = \sum_{i=1}^{N-1} E_i(\hat{t}_i, \hat{t}_{i+1}) - \tilde{N} \Delta E \quad (1)$$

where the first part gives the elasticity energy of DNA, we model the DNA molecule by a series of N straight segments of constant length $b = 1$ nm. The conformation is described by the orientations of each segment $\hat{t}_i$, i ranging from 1 to N ; in our simulation $N = 200$. The energy of every specific conformation is carried by the bending of the vertices connecting the adjacent segments E_i , which is the bending energy of the i -th vertex with unit $k_B T$. E_i depends on the two adjacent tangent vectors.

As for the elasticity energy, it is described by the energy form of a semi-flexible polymer. Thus its energy is

$$E_i(\hat{t}_i, \hat{t}_{i+1}) = \frac{\alpha}{2} (\hat{t}_{i+1} - \hat{t}_i)^2 \quad (2)$$

where α is a dimensionless quantity describing the bending rigidity of the vertex. Vertex bending rigidity α satisfies $\alpha b = A$, b is the segment length and $A = 50$ nm is the persistence length of B-form DNA, thus $\alpha = 50$.

The second part in the right-hand side of (1) is responsible for the attraction in DNA condensation. To minimize the electrostatic energy, the condensed counterions on the DNA molecule arrange themselves in a staggered configuration, called the ground state, which is sufficient for DNA condensation. As for the ground state, the DNA molecule can be represented as $\ominus \oplus \ominus \oplus \ominus \oplus \ominus \oplus$, where $\oplus$ and $\ominus$ represent the positive part and negative part, respectively. This model includes four key parameters, namely, interduplex distance D , interduplex interaction potential ΔE , interduplex distance fluctuation δ and the correlation distance between the condensed counterions η . The interduplex distance D ranges from $\lambda - \delta$ to $\lambda + \delta$. Here, λ is the sum of the diameter of the DNA molecule and the diameter of the multivalent counterion and δ . It is well accepted that the interduplex distance fluctuation is around 10% of the interduplex distance [11]. Once the interduplex distance between the positive part and the negative part (D) falls in the range $\lambda - \delta \leq D \leq \lambda + \delta$, the positive and negative parts are considered to be condensed, and at the same time, the total energy decreases by ΔE . $\tilde{N}$ is used to index the total number of positive-negative complexes. As for the correlation distance between the neighboring positive $\oplus$ along a DNA molecule η , this will be discussed at a later stage.

2.2 Algorithm

As for the algorithm, we take the Metropolis-Monte Carlo procedure [12], which is used for the statistical sampling of chain conformations. During the simulation process, two steps of perturbation moves were used, and both steps are global. For step (I), two non-neighboring vertices were randomly selected in the DNA chain, and the part between the two selected vertices rotated around the axis, which passes through the two selected vertices. The rotation angle applied for the move is uniformly distributed in the range of $[0, \phi]$, where ϕ is the upper bound determined by the acceptance ratio.

After the vertices mentioned in step (I) are selected, a rotation of the left (right) part of the chain with respect to a random axis that passes through the selected vertex is applied. The orientation of the axis is uniformly distributed in space and the rotation angle applied for the move is also uniformly distributed in the range of $[0, \phi]$, where ϕ is the upper bound determined by the acceptance ratio. The probability of accepting a trial conformation is obtained by applying the standard Metropolis rules. Namely, if the total potential energy of the trial conformation, E_{new} , is lower than that of the previous conformation, E_{old} , the trial conformation was accepted. If $E_{\text{new}} > E_{\text{old}}$ the probability of acceptance of the trial conformation is made equal to $p_{ac} = \exp[-(E_{\text{new}} - E_{\text{old}})/k_B T]$. In practice, this is accomplished by comparing a random number x (uniformly distributed in $[0, 1]$) with p_{ac} ; if $x > p_{ac}$, the new conformation is accepted, otherwise the old conformation is recounted.

3 Results and discussion

3.1 The process of DNA condensation with the correlation distance between counterions η being 3 nm

Based on our model above and a recent all-atom simulation [13], a series of parameters has been designed to investigate the condensation process. Here, a set of parameters for DNA condensation is taken as an example to illustrate our issue, namely, interduplex interaction energy $\Delta E = -6k_B T$, interduplex distance $2.3 \text{ nm} > D > 2.1 \text{ nm}$ and interduplex distance fluctuation $\delta = 0.1 \text{ nm}$, the correlation distance between condensed counterions ranging

from 2.0 nm to 5.0 nm. The dependence of the process of DNA condensation on the correlation distance is shown as follows.

While the correlation distance between condensed counterions η is 3 nm, the condensation process initiates a loop structure. But different from the arguments from single molecule experiments [14–17], the DNA molecule does not wrap regularly on the initial nucleation loop turn by turn. On the contrary, the other end of the DNA molecule folds into another loop and the loop condenses further into a parallel rod-like structure and then wraps around the initial nucleation loop regularly and forms a toroid structure.

3.2 The process of DNA condensation with the correlation distance between condensed counterions η being 2 nm

When the correlation distance between condensed counterions η is 2 nm, the condensation process also initiates a loop structure, and then DNA molecule does wrap on the initial loop turn by turn, which is same to the arguments from experiments [9, 10, 14–17].

As for the condensation process with the correlation distance between condensed counterions being $\eta = 5.0$ nm and $\eta = 4.0$ nm, with other parameters same as the example above, the corresponding simulations were also performed. The corresponding processes are similar to those in Figs. 1 and 2, respectively. Although its final conformations, as shown in Fig. 3, are all toroid structures, the condensation process strongly depends on the correlation distance between condensed counterions.

Fig. 1 The condensation process of DNA with correlation distance between condensed counterions $\eta = 3.0$ nm, interduplex distance fluctuation $\delta = 0.1$ nm, interduplex distance $2.3 \text{ nm} \geq D \geq 2.1 \text{ nm}$ and interduplex interaction energy $\Delta E = -6k_B T$

Fig. 2 The condensation process of DNA with correlation distance between condensed counterions $\eta = 2.0$ nm, interdplex distance fluctuation $\delta = 0.2$ nm, interdplex distance $2.4 \text{ nm} \geq D \geq 2.0$ nm and interdplex interaction energy $\Delta E = -6k_B T$

3.3 Effects of the correlation distance of condensed counterions on the diameter of a toroidal structure

For a long linear DNA molecule, its autocorrelation of tangent vectors [18] can be expressed as $\langle \hat{t}(s) \cdot \hat{t}(s') \rangle = \exp\left(\frac{-|s-s'|}{l_p}\right)$. Autocorrelation $\langle \hat{t}(s) \cdot \hat{t}(s') \rangle$ changes with contour distance along the DNA molecule exponentially, herein, l_p is constant, $|s-s'|$ means the length of DNA between the point s and point s' . Randomly choosing a position s on circular DNA as a reference point, with the separation between reference point s and position s'

Fig. 3 The condensed toroidal conformations with different correlation distance between condensed counterions; conformations a, b, c, d, correspond to the correlation distance between condensed counterions being 2.0 nm, 3.0 nm, 4.0 nm and 5.0 nm, respectively

increasing, the autocorrelation of tangent vectors decreases from 1 to the minimum, while $|s - s'|$ equals half of the contour length of the prime loop. With s' moving ahead along the initial nucleation loop, the $|s - s'|$ decreases from half of the contour length to zero, so that the autocorrelation of the tangent vectors increases from the minimum to 1. If the turns of the DNA molecule are wrapped on the initial nucleation loop, one can expect that the autocorrelation of tangent vectors as a function of s will oscillate periodically as shown in Fig. 4. One period represents one loop structure.

In the next step, effects of correlation distance between condensed counterions on the diameter of the toroidal structure should be detected. Just as the experiment has pointed out that the overall size of toroidal DNA condensates is decided by the size of the initial nucleation loop [19], so emphasis should be put on the effects of correlation distance between condensed counterions on the initial nucleation loop. Figure 4 shows the autocorrelation of the tangent vectors, from which, by judging how many segments are contained in the initial nucleation loop, the radius of the initial nucleation loop can be determined. For the autocorrelation in Fig. 4a and b, the initial nucleation loop contains 88 and 91 segments, respectively. For the autocorrelation in Fig. 4c and d, the initial nucleation loop contains 72 and 80 segments, respectively. Obviously, regardless of the interduple interaction potential, the radius of the initial nucleation loop increases as the correlation distance increases from 2 nm to 4 nm. This judgment can also be generalized to the condition that the correlation distance between condensed counterions η is 3 nm and 5 nm.

Effects of the correlation distance of condensed counterions on the radius of the toroidal structure are consistent with recent experimental results [16], which have reported millimolar increase in NaCl concentration in DNA toroidal samples, initially in a low-salt solution, producing significantly larger toroids upon condensation by hexamine cobalt (III). For example, 3 kbDNA toroids formed in the presence of 2.5 mM NaCl have a mean radius of 45 nm, as compared to 40 nm with no added salt. When the NaCl

Fig. 4 Autocorrelation of tangent vectors. From up to down, the correlation distance of condensed counterions for a and b are 2 nm and 4 nm, respectively, interduple distance fluctuation $\delta = 0.2$ nm, interduple distance $2.4 \text{ nm} \geq D \geq 2.0$ nm and interduple interaction energy $\Delta E = -6k_B T$; from up to down, the correlation distance between condensed counterions for c and d are 2 nm and 4 nm, respectively, interduple distance fluctuation $\delta = 0.2$ nm, interduple distance $2.3 \text{ nm} \geq D \geq 1.8$ nm and interduple interaction energy $\Delta E = -10k_B T$

concentration is increased further to 3.75 mM, the mean outer radius increases to 59 nm; the effects of a divalent cation on the radius of the DNA toroid were also studied by the addition of MgCl_2 . Toroidal condensates produced from a DNA solution with MgCl_2 at 1.75 mM are comparable in the mean outer radius to those with NaCl at 3.75 mM. These experimental results suggest that the increase of toroid radius at 3.75 mM NaCl and at 1.75 mM MgCl_2 is purely an effect of the ionic strength of co-ions and is not dependent on cation species. Another experiment reported that small co-ions with higher valency retard the compaction of DNA in the presence of a multivalent cation. This can be attributed to the formation of an ionic bound cluster structure (a dipole-like structure) between condensed counterions on DNA and co-ions [20]. Theoretical work [21] has pointed out that the interaction between the dipole-like structures decreases with increasing ionic concentration, which directly results in the increase of correlation distance between counterions.

4 Conclusions

The simulation results from the recently proposed ground-state model indicate that the condensation process strongly depends on the correlation distance between condensed counterions. When the correlation distance between condensed counterions is 2 nm or 4 nm, the condensation process initiates with a loop, and the DNA molecule regularly wraps the initial nucleation loop turn by turn, and then forms a regular toroid structure. When the correlation distance between condensed counterions is 3 nm or 5 nm, the condensation process also begins with an initial nucleation loop at one end of the DNA molecule but the other end of the DNA molecule folds into another loop and then it further condenses into a rod-like structure. The rod structure wraps the initial nucleation loop turn by turn into a toroid structure. Although the condensation processes are different, the initial and final conformations are the same, namely, both mechanisms initiate with a nucleation loop and end up with a toroid structure. The mechanism of effects of ionic strength on the diameter of toroidal condensates originates from the increasing correlation distance between condensed counterions.

Why does the DNA in the condensation experiments performed by transverse magnetic tweezers only adopt the mechanism with the correlation distance between condensed counterions being 2 nm or 4 nm? By analyzing the experiments above, one finds that both the experiments start from a large applied force or then the force is lowered gradually. Once the force reaches a critical value, the DNA molecule begins to condense but the DNA molecule is still restricted by the applied force. This makes the DNA molecule only fold turn by turn.

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