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Calculating potential of mean force between like-charged nanoparticles: A comprehensive study on salt effects

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A B S T R A C T

Ions are critical to the structure and stability of polyelectrolytes such as nucleic acids. In this work, we systematically calculated the potentials of mean force between two like-charged nanoparticles in salt solutions by Monte Carlo simulations. The pseudo-spring method is employed to calculate the potential of mean force and compared systematically with the inversed-Boltzmann method. An effective attraction is predicted between two like-charged nanoparticles in divalent/trivalent salt solution and such attraction becomes weakened at very high salt concentration. Our analysis reveals that for the system, the configuration of ion-bridging nanoparticles is responsible for the attraction, and the invasion of anions into the inter-nanoparticles region at high salt concentration would induce attraction weakening rather than the charge inversion effect. The present method would be useful for calculating effective interactions during nucleic acid folding.

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1. Introduction

Ions play critical roles in the thermodynamic and kinetic properties of charged systems, such as nucleic acids and other polyelectrolytes [1–8]. For example, the folding of nucleic acids into compact native structures would bring the build up of negative charges and requires cations to neutralize the negative backbone charges, and for other polyelectrolytes, ionic condition is also essential for their structure and stability [9–17].

Extensive experiments, theories and simulations have been employed, attempting to obtain a fundamental understanding on the important and complex roles of ions in polyelectrolyte system [18–26]. A typical paradigm is the system of two like-charged polyelectrolytes immersed in ion solution, which has attracted considerable interests in recent years, since ions can switch the like-charge repulsion into attraction at some ionic conditions [27–30]. For DNA and RNA, the addition of multivalent salt ions can condense DNA/RNA from extended state to compact state [31–38]. For (spherical) polyelectrolytes, the multivalent ions could induce the dispersed distribution to form compact clusters [39–43]. Although many efforts have been made and much progress has been achieved on understanding the ion roles in modulating like-charge interaction [44–46], there is still lacking of the comprehensive understanding on how ions influence the effective interactions, including the effects of ion concentration, valence, size and charge density, especially at very high salt and charge density on polyelectrolytes.

However, to quantify the ion effects in the systems of highly charged polyelectrolytes still remains a challenge, especially for multivalent ions, not only because the ion-modulated interaction is not strong ($\sim k_B T$), but also polyelectrolytes could induce (strong) correlations between (multivalent) ions in the vicinity of molecular surface. Up to now, there have been two classic theories for treating ion–polyelectrolyte interaction: the counterion condensation (CC) theory [47] and the Poisson–Boltzmann (PB) theory [48–55]. The two theories are rather successful in predicting electrostatic properties of polyelectrolyte in monovalent/aqueous solutions. Nevertheless, the CC theory is based on the line-charge structural model and is developed for dilute salt solution and linear polyelectrolytes of infinite length. Thus it is inapplicable for shaped polyelectrolytes in salt solutions. The PB theory is based on the Poisson equation with a Boltzmann weighted mean distribution for diffusive ions, where ions are modeled as continuous fluid-like particles moving independently in a mean electrostatic field. Thus, the PB theory ignores discrete ion properties such as ion correlation and ion fluctuation, and always predicts like-charge repulsion even in multivalent ion solutions. For spherical polyelectrolytes, the Derjaguin–Landau–Verwey–Overbeek (DLVO) theory has been developed to describe the effective interactions [56–58]. The electrostatic contribution of the DLVO interactions comes from the linearization of nonlinear term in PB equation at weak electric potential approximation, and has the form of Debye–Hückel-type potential for two spherical polyelectrolytes. In analogy to PB,

the DLVO theory always predicts a (screened) like-charge repulsion.

To account for the effects of ion correlation and ion-binding fluctuation, some advanced theories have been proposed, such as the dressed ion theory/strong coupling theory for charged colloids [59–61], integral equation theory for polyelectrolyte [62,63], and tightly bound ion theory for nucleic acids [64–67]. These advanced theories have successfully predicted a variety of thermodynamic properties for polyelectrolytes and nucleic acids in ionic solutions, while they are either developed for the salt-free solutions in strong coupling limit or for specified polyelectrolytes (e.g., nucleic acids). To deal with the electrostatic properties of biomolecule system, some other approaches have been developed, such as variational multiscale models and density-functional theory [68,69]. As a needful bridge between theories and experiments, computer simulations have become a powerful tool for the multi-body statistical systems and has made many valuable predictions for charged systems [70–73]. Especially in recent years, along with the great development of computation facility, all-atom MD simulations have been used to predict the interaction between biological molecules. Recently, Luan et al. predicted the interaction between two short DNA helices in monovalent and divalent electrolytes by the all-atom MD simulation, as well as the end-to-end interaction between DNAs and DNA–DNA interaction in tight supercoils [74–77]. The "ion bridge" has been proposed to be responsible for the effective attraction between two like-charge DNAs.

In this Letter, we will employ Monte Carlo (MC) simulations to systematically calculate the ion-modulated potential of mean force (PMF) between two like-charged nanoparticles. The pseudo-spring method is employed to calculate the PMF, and compared systematically with the inversed-Boltzmann method. Beyond the previous studies, *we emphasize the method for calculating the PMF, and physical mechanism for the ion-modulated like-charge interactions at extensive ionic conditions, especially at very high salt concentration.* Such methods would be helpful for probing the effective interaction during nucleic acid folding.

2. Model and methods

In this work, for simplicity, we use charged macro-spheres to represent nanoparticles [78,79], and the ion solution is considered to be an ensemble of small spheres of different charges and sizes, different kinds of ions are represented by the corresponding charge and size, and all of them are dispersed in a continuum dielectric medium whose permittivity corresponds to that of the solvent.

The interaction defining the system is composed of two contributions: the electrostatic interaction U_{el}, and the excluded volume interaction U_{ex}. The electrostatic interaction U_{el} between charges i and j (ions and nanoparticles) is given by

$$U_{el} = \frac{q_i q_j}{4\pi\epsilon\epsilon_0 r}, \tag{1}$$

where q_i and q_j are charges on spheres i and j, and r is the center-to-center distance between the two spheres. ϵ is the dielectric constant of solvent ($\epsilon = 78$ at room temperature), and ϵ_0 is the permittivity of vacuum. The excluded volume interaction U_{ex} between spheres i and j is accounted for by a repulsive Lennard-Jones potential

$$U_{ex} = \begin{cases} 4U_0\left(\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6\right) & \text{for } r < \sigma; \\ 0 & \text{for } r \geqslant \sigma, \end{cases} \tag{2}$$

where σ is the sum of the radii of the two spheres, and U_0 is the volume exclusion strength. In this study, we take $U_0 = 100$. Our control test shows that our results are not sensitive to the value of U_0 around 100.

The simulation cell is a rectangular cell where periodic boundary condition is applied. To diminish the boundary effect, we always keep the cell size larger than two nanoparticles by six times of the Debye length, and the calculation results are stable as tested against different cell sizes. In the simulations, the radii of nanoparticles and ions are taken as 10 Å and 2 Å, respectively. The charges Z on nanoparticles are taken as $-21e$, ensuring the surface charge density is close to that of phosphate groups in nucleic acid [80]. Also, the additional calculations are performed for other ion radii (3 Å, 4 Å) to study the ion size effect, and for other nanoparticle charge Z ($= -12e, -24e, -36e$) to study the charge density effect. In the calculations of potential of mean force $\Delta G(x) = G(x) - G(x_{ref})$, for simplicity, the outer-reference distance x_{ref} is taken as 40 Å for all ion conditions.

We used the Metropolis Monte Carlo algorithm for all simulations in our work, which is a computational approach for generating a set of N configurations of the system by the relative probability proportional to the Boltzmann factor: $p(N_i) \propto e^{-E(N_i)/k_B T}$, and the transition probability $p_{i \to j}$ from configuration i to configuration j is given by $p_{i \to j} = e^{-(E_j - E_i)/k_B T}$. Starting from an initial configuration with the two nanoparticles in the center and the ions randomly distributed in the simulation box, every particle randomly moves to a trial position and we calculate the energy change ΔE due to the move. If a random number R ($\in [0, 1]$) $< p = e^{-\Delta E/k_B T}$, the trial move is accepted. Repeat the trial move until the system reaches the equilibrium. Figs. S1 and S2 (in the supplementary material) show that the statistical results of our simulations can quickly reach the convergence.

Based on the MC simulations with the above described system and energy functions, we calculate the potential of mean force for two nanoparticles with the pseudo-spring method, as well as the inversed-Boltzmann method.

2.1. Pseudo-spring method

To calculate the PMF between two nanoparticles, we add a pseudo-spring with spring constant k to link the centers of the two nanoparticles as shown in Fig. 1(a). The effective force between the two nanoparticles can be given by

$$F = k\Delta x, \tag{3}$$

where Δx is the deviation of the spring length away from the original length x_0 at equilibrium. Then the PMF between the two nanoparticles can be calculated by the integration

$$\Delta G(x) = G(x) - G(x_{ref}) = \int_{x_{ref}}^{x} F(x')\, dx'. \tag{4}$$

Eq. (4) shows that we need to calculate $F(x)$'s at a series of x in order to obtain $\Delta G(x)$.

Figs. 1(a)–(c) illustrate the process of calculating PMF between the two nanoparticles using the pseudo-spring method. Firstly, we employed MC simulation for the system of pseudo-spring linked nanoparticles in salt solution. The statistical analysis on the fluctuation of x versus MC steps at equilibrium (shown in Fig. 1(b)) gives the distribution probability $p(x)$ of separation x, which can be used to estimate Δx. In practice, we fit the distribution probability to the Gaussian function $g(x) \propto e^{-(x-b)^2/(2c^2)}$ to obtain the deviation in spring length Δx ($= b - x_0$). The negative and positive Δx's correspond to the attractive and repulsive effective force, respectively. Consequently, the force $F(x)$ and PMF $\Delta G(x)$ between the two nanoparticles can be calculated based on Δx's and the above described formulas (Eqs. (3) and (4)).