

Grand–canonical Monte–Carlo simulation of DNA condensation in equilibrium with a salt mixture containing 2:2 salt

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Abstract. The Grand–canonical Monte–Carlo simulation method is used to simulate DNA hexagonal condensate in the presence of a mixture of 1:1, 2:1, 2:2 salts using the primitive ion model. Previous results show that DNA can be condensed by divalent counterions in restricted environment, such as inside viruses. In this work, we study the effects of divalent co-ions on condensation of DNA by divalent counterions. It is shown that divalent co-ions lead to weaker DNA condensation free energy and DNA de–condensation at smaller counterions concentration.

1. Introduction

The problem of DNA condensation in the presence of multivalent counterions has seen a strong revival of interest in recent years. This is because of the promising development of DNA-based nanotechnology that can be controlled exquisitely at nanoscale into precise 2D and 3D shapes. This has the potential to enable the fabrication of precise nanoscale devices that have already shown great potential for biomedical applications such as: drug delivery, biosensing, and synthetic nanopore formation [1, 2]. Furthermore, DNA study enables us to find effective ways of gene delivery for the rapidly growing field of genetic therapy. DNA viruses such as bacteriophages provide excellent study candidates for this purpose. One can package genomic DNA into viruses, then deliver and release the molecule into targeted individual cells. Recently there is a large biophysics literature dedicated to the problem of DNA condensation (packaging and ejection) inside bacteriophages [3].

Because DNA is a strongly charged molecule in aqueous solution, electrostatics and the screening condition of the solution play an important role in the structure and functions of DNA systems. Specifically, the condensation of DNA molecules is strongly influenced by the counterion valence [4, 5, 6, 7, 8, 9]. The strong influence of multivalent counterions on DNA ejection from viruses is expected to have the same physical origin as the phenomenon of reentrant DNA condensation in free solution [10, 11, 12, 13, 14]. The marginal case of divalent counterions can be also understood. While divalent counterions are able to condense DNA only partially in free solution [4, 5], DNA virus provides a unique experimental setup. The constraint of the viral



capsid strongly eliminates configurational entropic cost of packaging DNA. This allows divalent counterions to influence DNA condensation similar to that of trivalent/tetravalent counterions. DNA condensation by divalent counterions has also been observed in another environment where DNA configuration is constrained, namely the condensation of DNA in two dimensional systems [15].

In this paper, we study the problem of DNA condensation in the presence of divalent counterions using Grand canonical Monte Carlo computer simulations within primitive ion model, expanding upon previous works from our groups [16, 17, 18]. We study numerically the osmotic pressure of DNA hexagonal bundle in equilibrium with a bulk solution of salt mixture of monovalent and divalent counterions. We give some preliminary result on the effect of divalent co-ions. The paper is organized as follows. In Sec.2, the model of our system and various physical parameters used in the simulation are presented in details. In Sec.3, the results are presented and their relevance to available experimental data is discussed. We conclude in Sec.4.

2. The simulation model and method

We assume the DNA molecules in the bundle to arrange in a two dimensional hexagonal lattice with lattice constant d (see Fig. 1). The DNA axis is parallel to the Z -axis. Individual DNA

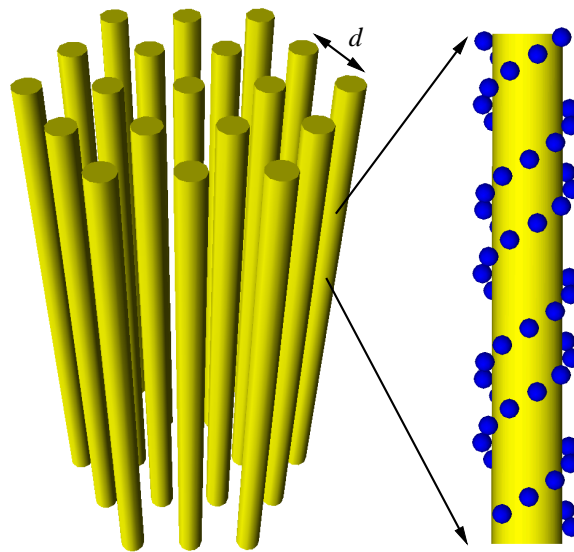


Figure 1. A DNA bundle is modeled as a hexagonal lattice with lattice constant d . Individual DNA molecule is modeled as a hard-core cylinder with negative charges glued on it according to the positions of nucleotides of a B-DNA structure.

molecule is modeled as an impenetrable cylinder with negative charges glued on it in accordance with the locations of nucleotide groups along the double-helix structure of a B-DNA. The hardcore cylinder has radius of 7\AA . The negative charges are hard spheres of radius 2\AA , charge $-e$ and lie at a distance of 9\AA from the DNA axis. This gives an averaged DNA radius, r_{DNA} , of 1nm . The solvent water is treated as a dielectric medium with dielectric constant $\epsilon = 78$ and temperature $T = 300^\circ K$. The positions of DNA molecules are fixed in space. This mimics the constraint on DNA configurational entropy inside viruses and other experiments of DNA condensation using divalent counterions in restricted environment. The mobile ions in solution are modeled as hard spheres with unscreened Coulomb interaction (the primitive ion model). For simplicity, all ions have radius of $\sigma_x = 2\text{\AA}$.

The simulation is carried out using the periodic boundary condition. A periodic simulation cell with $N_{DNA} = 12$ DNA molecules in the horizontal (x, y) plane and 3 full helix periods in the z direction is used. In Ref. [19, 20], it is shown that the macroscopic limit is reached when $N_{DNA} \geq 7$. Our simulation cell contains 12 DNA helices, hence it has enough DNA molecules to eliminate the finite size effect.

The simulation is carried out using the Grand canonical ensemble where the number of ions is not constant during the simulation. Instead their chemical potentials are fixed. These chemical potentials are chosen in advance by simulating a DNA-free salt solution and adjusting them so that the solution has the correct ion concentrations. If a state i of the system that is characterized by the locations of N_{iZ+} multivalent counterions, N_{i+} monovalent counterions, N_{iZ-} multivalent counterions, N_{i-} coions ($Z = 2$ for divalent ions), in the grand canonical ensemble of unlabeled particles, the probability of such state is given by

$$\pi_i = \frac{1}{\mathcal{Z}} \frac{1}{\Lambda_{Z+}^{3N_{iZ+}} \Lambda_{+}^{3N_{i+}} \Lambda_{Z-}^{3N_{iZ-}} \Lambda_{-}^{3N_{i-}}} \exp[\beta(\mu_{Z+}N_{iZ+} + \mu_{+}N_{i+} + \mu_{-}N_{i-} + \mu_{Z-}N_{iZ-} - U_i)] \quad (1)$$

Here, \mathcal{Z} is the grand canonical partition function, $\beta = 1/k_B T$, $\Lambda_x \equiv h/\sqrt{2\pi m_x k_B T}$ are the thermal wavelength of the corresponding ion type (here x are either $Z+$, $Z-$, $-$ or $+$), U_i is the interaction energy of the state i , and μ_x are the corresponding chemical potential of the ions. This formula is the basis for Grand canonical Monte-Carlo simulation. More details on this method can be found from previous works[18, 17, 21]. Unless explicitly stated otherwise, through this work, we simulate the hexagonal DNA condensate in equilibrium with a bulk solution contains 50mM NaCl, 10mM MgCl₂ and varying MgSO₄. Fugacities of each ion species used in our simulation can be found somewhere else [22]. In this way, one can study the influence of divalent coions on DNA condensation.

For each simulation run, about 500 million MC moves are carried out depending on the average number of ions in the system. To ensure thermalization, about 50 million initial moves are discarded before doing statistical analysis of the result of the simulation. All simulations are done using the physics simulation library SimEngine develop by one of the author (TTN). This library use OpenCL and OpenMP extensions of the C programming language to distribute computational workloads on multi-core CPU and GPGPU to speed up the simulation time. Both molecular dynamics and Monte-Carlo simulation methods are supported. In this paper the Monte-Carlo module of the library is used.

3. Result and Discussion

In Fig. 2 the osmotic pressure of DNA bundle at different counterion concentrations, c_{2+} is plotted as a function of the inter-axial DNA distance. Because this osmotic pressure is directly related to the “effective” force between DNA molecules at that inter-axial distance [19, 20], this figure also serves as a plot of DNA-DNA interaction. As one can see, there is a short-range attraction between two DNA molecules as they approach each other. The minimum osmotic pressure reaches as low as -5atm at high divalent counterion concentration. This is the well-known phenomenon of like-charge attraction between macroions [13, 14, 23] mediated by multivalent counterions (divalent counterion in this study). The maximum attraction occurs at the distance $d \simeq 26 - 27\text{\AA}$, in good agreement with various theoretical and experimental results [4, 24]. For smaller d , the DNA-DNA interaction experiences sharp increase due to the hardcore repulsion between the counterions.

From the P-V curve, we can also calculate the free energy, μ_{DNA} , of packaging DNA into bundles by integrating the pressure with the volume of the bundle. Per DNA nucleotide

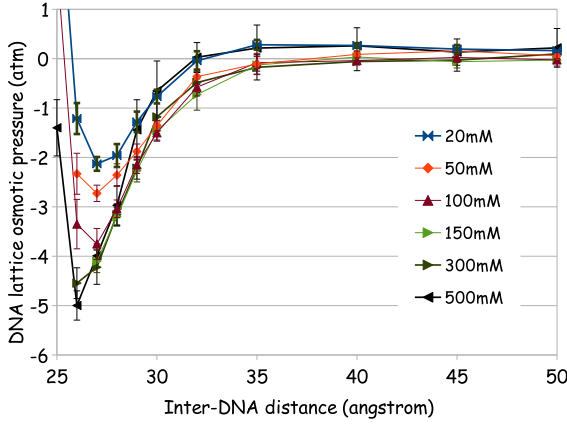


Figure 2. The osmotic pressure of the DNA bundle as function of the inter-axial DNA distance d for different divalent counterion concentration c_Z shown in the inset. The solid lines are guides to the eye. The counterion radius is 2.0 \AA

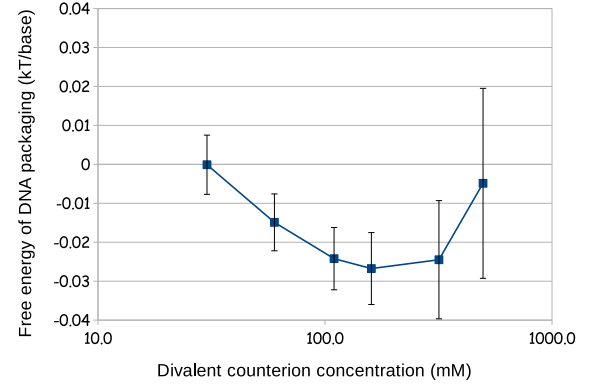


Figure 3. The free energy of packaging DNA molecule into hexagonal bundles as a function of the divalent counterion concentrations (Mg^{2+}) in the presence of divalent coions (SO_4^{2-}). The points are results of numerical integration of P_{osm} from Fig. 3.

base, the packaging free energy is given by:

$$\mu_{\text{DNA}}(d) = \frac{l}{L_z N_{\text{DNA}}} \int_{\infty}^d P_{osm}(d') dV = \frac{l}{N_{\text{DNA}}} \int_{\infty}^d P_{osm}(d') \frac{2L_x L_y}{d'} dd' \quad (2)$$

here $l = 1.7 \text{ \AA}$ is the distance between DNA nucleotides along the axis of the DNA. The numerical result for $\mu_{\text{DNA}}(d^*)$ at the optimal bundle lattice constant d^* is plotted in Fig. 3 as function of the divalent counterion concentration c_{2+} . Fig. 3 shows a non-monotonic dependence of the electrostatic contribution to DNA packaging free energy. There is an optimal concentration, c^* , where the free energy cost of packaging DNA is lowest. It is negative indicating the tendency of the divalent counterions to condense the DNA. At smaller or larger concentrations of the counterions, the free energy cost of DNA packaging is higher. These results are consistent with the correlation theory of DNA reentrant condensation by multivalent counterions [25, 23, 10] and the experiment results on ejecting DNA from bacteriophage under varying counterion concentrations [9].

In Fig. 3, the error bar of free energy is large at high counterion concentration. This is due to the Grand Canonical Monte Carlo simulation method that we use in our work. There is a limitation of application of this method at high particle density. In this limit, the Metropolis acceptance probability of adding or removing a salt molecule is very small. This leads to the requirement of long simulation and large sampling time to obtain good statistical result. Nevertheless, the non-monotonic dependence of free energy of DNA packaging on Mg^{2+} counterion concentration has been demonstrated in experiment [9] and matches qualitatively with the average values of free energy in our simulation. We believe that the large error bar due to finite simulation time do not change this qualitative result.

Fig. 3 gives the short-range attraction among DNA molecules to be $-0.025 k_B T/\text{base}$. This is larger than the fitted value obtained from the viral DNA ejection experiments [26]. There are many factors that lead to this quantitative discrepancy such as DNA flexibility, ion sizes, DNA orientations (twisting, frustrations),... [27, 28, 7] All these factors are expected to reduce

the attraction between the DNA compared to our idealized simulation. Nevertheless, the non-monotonic electrostatic influence of divalent counterions on DNA-DNA “effective” interaction is clearly demonstrated in our idealized simulation. More importantly, compare to the case of no divalent coions [18], our result for NaCl + MgCl₂ + MgSO₄ mixture shows that divalent coions reduce of depth of DNA–DNA interaction by about 25% and make DNA decondensation happen sooner. This match qualitatively with experiment result of MgCl₂ and MgSO₄ solution [8, 9].

4. Conclusion

In this paper, we presented a study of the DNA condensation problem using the Grand canonical Monte–Carlo simulation using a primitive model for the mobile ions. is suppressed in simulation by fixing the position of the DNA cylinders in the bundle. Such study can be applied directly to the experimental problem of DNA ejection from bacteriophages where DNA condensed in a strongly confined environment. It is shown that divalent counterions strongly influence DNA interaction and packaging. The simulation results for divalent counterions with 2.0 Å radius show that the electrostatic free energy of packaging DNA into hexagonal bundle varies non-monotonically with the counterion concentration. We study DNA condensation with different divalent co-ion concentration. It is show that divalent co-ions reduce DNA condensation free energy and make DNA de-codensation happens earlier. This can explain experimentally observed quantitative differences of DNA condensation inside viruses in the presences of MgCl₂ salt mixture and in the presence of MgSO₄ salt mixture.

5. Acknowledgments

We would like to thank Drs. A. Lyubartsev, B. Shklovskii, A. Evilevich, L. T. Fang, W. Gelbart, T. X. Hoang, Paolo Carloni for valuable discussions. TTN acknowledges the financial support of the Vietnam National Foundation for Science and Technology NAFOSTED Contract 103.02-2012.75 and the USA National Science Foundation grant NSF CBET-1134398. The authors are indebted to Dr A. Lyubartsev for providing us with the Fortran source code of their Expanded Ensemble Method.

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