Grand-canonical simulation of DNA condensation with two salts, effect of divalent counterion size

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The problem of DNA–DNA interaction mediated by divalent counterions is studied using a generalized Grand-canonical Monte-Carlo simulation for a system of two salts. The effect of the divalent counterion size on the condensation behavior of the DNA bundle is investigated. Experimentally, it is known that multivalent counterions have strong effect on the DNA condensation phenomenon. While tri- and tetra-valent counterions are shown to easily condense free DNA molecules in solution into toroidal bundles, the situation with divalent counterions are not as clear cut. Some divalent counterions like Mg\textsuperscript{2+} are not able to condense free DNA molecules in solution, while some like Mn\textsuperscript{2+} can condense them into disorder bundles. Similarly, strong electrostatic effect is also observed for DNA condensation in a restricted environment such as inside a viral capsid. By varying the salinity of solution, one can vary the amount of DNA ejected from viruses. Interestingly, monovalent counterions such as Na\textsuperscript{+} have negligible effect on the DNA ejection process \cite{6}. In contrast, multivalent counterions (Z–ions for short) such as Mg\textsuperscript{2+}, CoHex\textsuperscript{3+}, Spd\textsuperscript{+4} or Spm\textsuperscript{+4} exert strong and non-monotonic effects \cite{7}. There is an optimal counterion concentration, $c_{Z,0}$, where the least DNA genome is ejected from the phages. For counterion concentration, $c_{Z}$, higher or lower than this optimal concentration, more DNA is ejected from phages. The case of divalent counterions is more marginal. The non-monotonicity is observed for MgSO\textsubscript{4} salt but not for MgCl\textsubscript{2} salt up to the concentration of 100mM. Such ion specificity for the case of divalent salts also present in condensation of DNA in free solution \cite{2}.

The non-monotonic 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 in the presence of counterions of tri-, tetra- and higher valence \cite{8–12}. Although, divalent counterions are known to condense DNA only partially in free solution \cite{2–3}, 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/tetra-valent counterions. Indeed, 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 [13]. For virus systems, theoretical fitting suggests that the DNA is neutralized at $c_{Z,0} \approx 75$ mM for divalent counterions, and the short-range DNA attraction at this concentration is $-0.006 k_BT$ per nucleotide base [14, 15].

In this paper, we study the problem of DNA condensation in the presence of divalent counterions using computer simulations. The simulation method developed by our groups in Ref. 15 and 16 is used, expanded and the influence of the ion size on the strength of DNA–DNA interaction mediated by divalent counterions is investigated [17]. The Grand Canonical Monte Carlo simulation for a system of two salts is presented in detail. The electrostatic contribution to the free energy of packaging DNA into bundles is calculated from simulation. It is shown that, if only the non-specific electrostatic contribution is included, divalent counterions can indeed induce DNA reentrant condensation like those observed for higher counterion valences. However, correlations among divalent counterions are not strong enough to decondense DNA bundles. As already mentioned, experimental results also show that there is a ion specific effect. As a first step taken to study this ion specific effect, the DNA–DNA effective interaction is calculated from simulation for three different counterion sizes. It is shown that varying counterion sizes can have significant impact on DNA condensation pictures, which can explained some variations among DNA condensation experiments with Mg2+, or Mn2+ counterions.

The paper is organized as follows. In Sec. II the Grand-canonical Monte-Carlo is formulated to simulate a system of two salts (a divalent salts and a fixed monovalent salt from buffer solution). In Sec. III the model of our system and various physical parameters used in the simulation are presented in details. In Sec. IV the results are presented and their relevance to available experimental data is discussed. We conclude in Sec. V.

II. GRAND CANONICAL MONTE–CARLO SIMULATION FOR MIXTURE OF TWO SALTS

In practical situation, the DNA bundle is in equilibrium with a water solution containing free mobile ions at given concentrations. Therefore we simulate the system using Grand Canonical Monte-Carlo (GCMC) simulation. 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. Another factor that complicates the simulation of DNA condensation phenomenon arises from the fact that there are both monovalent and divalent salts in solution in experiments. At very low concentration of divalent counterions, $c_Z$, DNA is screened mostly by monovalent counterions. To properly simulate the DNA bundle at this low $c_Z$ limit, and to properly capture the screening of electrostatic interactions among divalent counterions by monovalent ones, both salts are included in the simulations.

To simulate two different salts present in our system, the standard GCMC method for ionic solution [18] is generalized to simulate of a system containing a mixture of both multivalent and monovalent salts. For simplicity, we assume both salts have the same coion (for example, Cl−). Thus, a state $i$ of the system is characterized by the locations of $N_{iZ}$ multivalent counterions, $N_{i+}$ monovalent counterions and $N_{i-}$ coions. In the grand canonical ensemble of unlabeled particles, the probability of such state is given by

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

(1)

Here, $Z$ is the grand canonical partition function, $\beta = 1/k_BT$, $\Lambda_{Z,+,-} = h/\sqrt{2\pi m_{Z,+,-} k_BT}$, $U_i$ is the interaction energy of the state $i$, and $\mu_Z$, $\mu_+$, $\mu_-$ are the chemical potentials of the multivalent counterions, of the monovalent counterions and of the coions respectively.

In a Monte Carlo simulation, a Markov chain of system states $i$ is generated with a limiting probability distribution proportional to $\pi_i$. This chain is defined by a probability $p_{ij}$ of transitions from state $i$ to state $j$. A sufficient condition for the Markov chain to have the correct limiting distribution is:

$$\frac{p_{ij}}{p_{ji}} = \frac{\pi_j}{\pi_i}$$

(2)

As usual, at each step of the chain, a “trial” move to change the system from state $i$ to state $j$ is attempted with probability $q_{ij}$ and is accepted with probability $f_{ij}$. Clearly,

$$p_{ij} = q_{ij} f_{ij}$$

(3)

It is convenient to regard the simulation box as consisting of $V$ discrete sites ($V$ is very large). Then for a trial move where $\nu_\alpha$ particles of species $\alpha$ are added to the system:

$$q_{ij} = \frac{1}{V^{\nu_\alpha}}$$

(4)

Conversely, if $\nu_\alpha$ particles of species $\alpha$ are removed from the system:

$$q_{ij} = \frac{(N_\alpha - \nu_\alpha)!}{N_\alpha! \nu_\alpha!}$$

(5)

Putting everything together, equations (1)–(5) give us a recipe to calculate the Metropolis acceptance probability of a particle insertion/deletion move in GCMC simulation. For example, if in a transition from state $i$ to
state \( j \), a multivalent salt molecule (one \( Z^- \)ion and \( Z \) coions) is added to the system, the Metropolis probability of acceptance of such move can be chosen as:

\[
f_M = \min\{1, \frac{f_{ij}}{f_{ji}}\} \tag{6}
\]

where

\[
\frac{f_{ij}}{f_{ji}} = \frac{B_z}{(N_{iz}+1)(N_{i-}+1)\ldots(N_{i-}+Z)} \exp[\beta(U_i - U_j)], \tag{7}
\]

with

\[
B_z = \exp[\beta\mu_{Z,\text{salt}}] \frac{V^{Z+1}}{\Lambda_+^Z \Lambda_-^Z}, \tag{8}
\]

and

\[
\mu_{Z,\text{salt}} = \mu_z + Z\mu_- \tag{9}
\]

is the combined chemical potential of a multivalent salt molecule.

On the other hand, if a multivalent salt molecule (one \( Z^- \)ion and \( Z \) coions) is removed from the system,

\[
\frac{f_{ij}}{f_{ji}} = \frac{B_1}{(N_{iz}+1)(N_{i-}+1)\ldots(N_{i-}+Z)} \exp[\beta(U_i - U_j)], \tag{10}
\]

Similarly, for addition a monovalent salt molecule (one monovalent counterion and one coion) in transition from state \( i \) to state \( j \),

\[
\frac{f_{ij}}{f_{ji}} = \frac{B_1}{(N_{iz}+1)(N_{i-}+1)\ldots(N_{i-}+Z)} \exp[\beta(U_i - U_j)], \tag{11}
\]

with

\[
B_1 = \exp[\beta\mu_{1,\text{salt}}] \frac{V^2}{\Lambda_+^3 \Lambda_-^3}, \tag{12}
\]

and

\[
\mu_{1,\text{salt}} = \mu_+ + \mu_- \tag{13}
\]

is the combined chemical potential of a monovalent salt molecule. For a “trial” move where a monovalent salt molecule is removed from the system,

\[
\frac{f_{ij}}{f_{ji}} = \frac{N_{i+}N_{i-}B_1}{(N_{iz}+1)(N_{i-}+1)\ldots(N_{i-}+Z)} \exp[\beta(U_i - U_j)], \tag{14}
\]

Because we are trying to simulate a mixture of salts, to improve the system relaxation and to improve the sampling of the system’s phase space, one can also make a “trial” move where one \( Z^- \)ion is added to the system and \( Z \) monovalent counterions are removed the system. For such move, it is easy to show that

\[
\frac{f_{ij}}{f_{ji}} = \frac{B_z^Z N_{i+}\ldots(N_{i+}+Z+1)}{B_z(N_{iz}+1)} \exp[\beta(U_i - U_j)], \tag{15}
\]

Vice versa, for a “trial” move where one \( Z^- \)ion is removed from the system and \( Z \) monovalent counterions are added to the system,

\[
\frac{f_{ij}}{f_{ji}} = \frac{B_z N_{iZ}}{B_z^Z(N_{i+}+1)\ldots(N_{i+}+Z)} \exp[\beta(U_i - U_j)]. \tag{16}
\]

Note that because the system maintains charge neutrality in all particle addition/deletion moves, instead of using 3 different chemical potentials, \( \mu_{Z,+,+} \), to simulate the system, only two combined chemical potentials, \( \mu_{Z,\text{salt}} \) and \( \mu_{1,\text{salt}} \), are actually needed. In our actual implementation, the dimensionless parameters \( B_z \) and \( B_1 \), Eqs. (12) and (8), are used instead of the chemical potentials themselves to simulate the DNA system. The values of these parameters for different mixtures of divalent and monovalent salts are listed in Sec. III Table I.

Lastly, beside particle addition/deletion moves, one also try standard particle translation moves. They are carried out exactly like in the case of a canonical Monte-Carlo simulation. In a “trial” move from state \( i \) to state \( j \), an ion is chosen at random and is moved to a random position in a volume element surrounding its original position. The standard Metropolis probability is used for the acceptance of such “trial” move:

\[
f_M = \min\{1, \exp[\beta(U_i - U_j)]\}. \tag{17}
\]

### III. THE SIMULATION MODEL

We model the DNA bundle in hexagonal packing as a number of DNA molecules arranged in parallel along the \( Z \)-axis. In the horizontal plane, the DNA molecules form a two dimensional hexagonal lattice with lattice constant \( d \) (the DNA–DNA interaxial distance) (Fig. 1). Individual DNA molecule is modeled as an impenetrable cylinder with negative charges glued on it. The charges are positioned 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 1\( \text{nm} \). The solvent water is treated as a dielectric medium with dielectric constant \( \varepsilon = 78 \) and temperature \( T = 300^\circ\text{K} \). 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). The coions have radius of \( \sigma_- = 2\AA \) and charge \(-e\). The divalent counterions have radius of \( \sigma_+ = 2.0, 2.5, \) or 3.0\( \AA \) and charge \(+2e\). The interaction between two ions \( \alpha \) and \( \beta \) with radii \( \sigma_{\alpha,\beta} \) and charges \( Q_{\alpha,\beta} \) is given by

\[
U = \begin{cases} 
Q_{\alpha}Q_{\beta}/\varepsilon r_{\alpha\beta} & \text{if } r_{\alpha\beta} > \sigma_{\alpha} + \sigma_{\beta} \\
\infty & \text{if } r_{\alpha\beta} < \sigma_{\alpha} + \sigma_{\beta} 
\end{cases} \tag{18}
\]
where \( r_{\alpha\beta} = |\mathbf{r}_\alpha - \mathbf{r}_\beta| \) is the distance between the ions.

The simulation is carried out using the periodic boundary condition. Unless explicitly stated, 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. The dimensions of the box are \( L_x = 3d\), \( L_y = 2\sqrt{3}d\) and \( L_z = 102\AA\). This gives, for the volume of the simulation box,

\[
V_{cell} = 612\sqrt{3} \, d^2 \, \text{Å}^3
\]  

(19)

The long-range electrostatic interactions between charges in neighboring cells are treated using the Ewald summation method. In Ref. [13, 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. Test runs with 1, 4, 7 and 12 DNA molecules are carried out to verify that this is indeed the case.

As mentioned above, the DNA bundle is simulated in equilibrium with a bulk solution containing two salt concentrations: a varying bulk multivalent counterion concentrations \( c_Z \) and a fixed bulk concentration of monovalent salt, \( c_1 = 50\text{mM} \). The detail implementation of the GCMC method for this case is described in section II. In simulation, the chemical potential of each salt is set by fixing the parameters \( B_{1,Z} \) given by Eq. [8] [12]. In Table II various values for the parameters \( B_{2,Z} \) and \( B_{1}^* \) that are used in this work for divalent counterion size of 2Å are shown. These values are listed for a reference volume \( V_{cell}^* \) that is chosen to have the same dimensions as that of a DNA bundle system with \( d = 50\AA \), so \( V_{cell}^* \approx 2.65 \times 10^6 \, \text{Å}^3 \). For a simulation system where \( d \) is different from 50Å, the parameters \( B_Z \) and \( B_1 \) are scaled correspondingly:

\[
B_Z(d) = B_Z^* \left( \frac{d}{50\AA} \right)^{2Z+2} \quad B_1(d) = B_1^* \left( \frac{d}{50\AA} \right)^4.
\]  

(20)

| \( B_Z^2 \) | \( B_1^* \) | \( c_Z \) (mM) | \( c_1 \) (mM) | \( P_b \) (atm) |
|---|---|---|---|---|
| 0.744 \times 10^5 | 0.612 \times 10^4 | 13.9 \pm 3.0 | 50.0 \pm 5.6 | 3.183 \pm 0.001 |
| 2.568 \times 10^5 | 0.808 \times 10^4 | 29.9 \pm 3.4 | 50.2 \pm 4.9 | 4.17 \pm 0.01 |
| 14.48 \times 10^5 | 1.306 \times 10^4 | 74.6 \pm 6.2 | 50.1 \pm 5.3 | 6.874 \pm 0.006 |
| 26.43 \times 10^5 | 1.580 \times 10^4 | 99.8 \pm 5.7 | 50.3 \pm 5.4 | 8.391 \pm 0.006 |
| 56.67 \times 10^5 | 2.128 \times 10^4 | 150.2 \pm 8.4 | 50.6 \pm 6.7 | 11.42 \pm 0.02 |
| 323.82 \times 10^5 | 3.715 \times 10^4 | 299.6 \pm 11.2 | 49.4 \pm 6.8 | 20.81 \pm 0.04 |
| 1302.73 \times 10^5 | 6.601 \times 10^4 | 507.1 \pm 13.6 | 50.3 \pm 6.9 | 35.0 \pm 0.1 |

TABLE I: The parameters, \( B_Z^2 \) and \( B_1^* \), of the salts used in the simulation for the reference volume \( V_{cell}^* \approx 2.65 \times 10^6 \, \text{Å}^3 \) (see text for detail). Columns 3 and 4 show the corresponding salt concentrations of the simulated DNA–free bulk solution. Column 5 shows the total pressure of the bulk solutions obtained from simulation.
\( \Delta \Omega \), we can calculate the total pressure of the system:

\[
P(T, V, \{\mu_c\}) = -\frac{\partial \Omega(T, V, \{\mu_c\})}{\partial V} \bigg|_{T, \{\mu_c\}} \simeq -\frac{\Delta \Omega}{\Delta V} \tag{21}
\]

Here \( \{\mu_c\} = \{\mu_Z, \mu_1, \mu_{-1}\} \) are the set of chemical potentials of different ion species. The osmotic pressure of the DNA bundle is then obtained by subtracting the total pressure of the bulk DNA–free solution, \( P_b(T, V, \{\mu_c\}) \), from the total pressure of the DNA system:

\[
P_{\text{osm}}(T, V, \{\mu_c\}) = P(T, V, \{\mu_c\}) - P_b(T, V, \{\mu_c\}) \tag{22}
\]

The total pressure of the bulk solution, \( P_b(T, V, \{\mu_c\}) \), needs to be calculated only once for each set of salt concentrations, \( c_Z \) and \( c_1 \). For reference purpose, their values are listed in column 5 of Table I.

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.

IV. RESULT AND DISCUSSION

A. Counterion mediated DNA–DNA interactions and the DNA packing free energy

In Fig. 2 the osmotic pressure of DNA bundle at different \( c_Z \) is plotted as a function of the interaxial DNA distance, \( d \) for the case the counterion size is 2 Å. Because this osmotic pressure is directly related to the “effective” force between DNA molecules at that interaxial distance [19, 20], this figure also serves as a plot of DNA–DNA interaction. As one can see, when \( c_Z \) is greater than a value around 20mM, there is a short-range attraction between two DNA molecules as they approach each other. This is the well-known phenomenon of like-charge attraction between macroions [11, 12, 21]. It is the result of the electrostatic correlations between counterions condensed on the surface of each DNA molecule. The attraction appears when the distance between these surfaces is of the order of the lateral separation between counterions (about 14 Å for divalent counterions). The maximal attraction occurs at the distance \( d \approx 27 \) Å, in good agreement with various theoretical and experimental results [2, 22]. For smaller \( d \), the DNA-DNA interaction experiences sharp increase. This can be understood as the result of the hard-core repulsion between the counterions.

From the P-V curve, we can also calculate the free energy, \( \mu_{\text{DNA}} \) of packaging DNA into bundles. This free energy is nothing but the difference between the free energy of a DNA molecule in a bundle and that of an individual DNA molecule in the bulk solution (\( d = \infty \)). It can be calculated by integrating the pressure with the volume of the bundle. Per DNA nucleotide base, the packaging free energy is given by:

\[
\mu_{\text{DNA}}(d) = \frac{l}{L_z N_{\text{DNA}}} \int_0^d P_{\text{osm}}(d')dV = \frac{l}{N_{\text{DNA}}} \int_0^d P_{\text{osm}}(d') \frac{2L_z L_w}{d'} dd' \tag{23}
\]

Here \( l = 1.7 \) Å 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 \( c_Z \). Due to the limitation of computer simulations, the numerical integration is performed up to the distance \( d = 50 \) Å only. However, this will not change the conclusion of this paper because the omitted integration from \( d = 50 \) Å to \( d = \infty \) only gives an almost constant shift to \( \mu_{\text{DNA}} \). As evident from Fig. 3 the non-monotonic dependence of the electrostatic contribution to DNA packaging free energy is clearly shown. There is an optimal concentration, \( c_{Z,0} \), 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 [8, 21, 23] and the experiment results on ejecting DNA from bacteriophage under varying counterion concentrations [2]. However, it must be stated, unlike the condensation with counterions of higher valence [2, 8, 24], the divalent counterions in our simulation are not able to decondense the DNA bundle within the range of concentration considered. The free energy does not become positive beyond \( c_{Z,0} \). This is in line with experimental results [2].
FIG. 3: (Color online) The free energy of packaging DNA molecules into hexagonal bundles as a function of the divalent counterion concentrations. The points are results of numerical integration of $P_{osm}$ from Fig. 3.

Figure 3 gives the short-range attraction among DNA molecules to be $-0.04k_BT$/base. This is larger than the fitted value obtained from the viral DNA ejection experiments [14]. There are many factors that lead to this quantitative discrepancy. Our main approximation is that in the simulation, the position of the DNA cylinders are straight with infinite bending rigidity. Inside viruses, DNA are bent, and the configuration entropy of the DNA are not necessary zero, and there is not a perfect hexagonal arrangement of DNA cylinder with fixed inter-DNA distance. We also neglect the contribution from the region $d > 50\AA$ in our integration. The physical parameters of the system such as ion sizes, DNA orientations (twisting, frustrations),... [5, 25, 26] can also affect the strength of DNA–DNA short range attraction. 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.

B. Role of finite size of counterions

In all the systems simulated so far, the radius of the divalent counterion is fixed at 2.0Å. The results agree qualitatively and semi-quantitatively with some of the experimental results of DNA ejection from capsid with MgSO$_4$ salt. However, experimental results also show that there is an ion specific effect. There are some significant differences in condensations of free DNA, condensations of DNA inside viruses when different divalent salts such as MgSO$_4$, MgCl$_2$, or MnCl$_2$ are used [2, 6]. This shows that the hydration effect and the entropy of the hydrated water molecules are significant and need to be properly taken into account when one deals with the problem of DNA confinement inside viral capsids. In this section, a first step is taken to study this ion specific effect. Specifically, we study how DNA–DNA interaction is affected by changing the radius of the counterions.

In Fig. 4 and Fig. 5 the dependence of DNA-DNA "effective" interaction on the DNA-DNA separation distance are plotted for the counterion radii 2.5Å and 3Å respectively. Compare to similar plot for the case of $\sigma_Z = 2.0\AA$ (Fig. 2), we can clearly see that the main physics remains when we change the counterion size. The DNA-DNA short-range interaction remains evident. However, the depth and location of the strongest attraction change when the counterion size changes. The smallest counterions (2Å) cause the strongest attraction among DNA at smaller distance. This is easily understood, the smaller counterion cause less entropic cost of bringing DNA closer to each other. Hence the short-range attraction is enhanced.

FIG. 4: (Color online) The osmotic pressure of the DNA bundle as function of the interaxial 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 2.5 Å

The change in the equilibrium separation of DNA in the bundle is even more evident in Fig. 6a. In this figure, the osmotic pressure (which is proportional to the effective DNA–DNA interaction) of the hexagonal DNA bundle is plotted as a function of the inter DNA distance for three counterion sizes, 2Å, 2.5Å, and 3Å, respectively. The counterion concentration is chosen to be approximately 150mM in each simulation. As one can see, the first consequence of changing counterion size is obviously the equilibrium distance of the DNA bundle. The optimal inter DNA distance, $d^*$, where the short range DNA attraction is strongest increases with the counterion radius. As the counterion radius is increased from 2.0Å to 2.5Å to 3.0Å $d^*$ increases from 26Å to 27Å then 29Å respectively.

However, it is an interesting observation that not only the optimum distance $d^*$ is shifted by $2\sigma_Z$, the interaction between DNA molecules from the distance $d^*$ to $\infty$, which is dominated by electrostatics, is shifted by the same amount. This is evident as in Fig. 6b, where the
FIG. 5: (Color online) The osmotic pressure of the DNA bundle as function of the interaxial 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 $\sigma_Z = 3.0\text{Å}$.

The horizontal axis for each curve is shifted by $2\sigma_Z$. One can see that the right side of these curve from the distance $d^*$ to $\infty$ show a good degree of overlapping. This is in agreement with the “correlated liquid” nature of DNA–DNA attraction mediated by multivalent counterions [15, 21]. In this strongly correlated liquid theory of DNA–DNA interaction, the combined system of DNA+condensed counterions acts as a charged metallic cylinder. The correlations between the condensed counterions on the surface of two neighboring DNA induce a short range attraction between them. In this theory, the center of mass of condensed counterion cannot approach the DNA surface at a distance less than its radius, $\sigma_Z$. Because of this, the effective surface of the dressed metallic DNA is lifted off the bare DNA surface by a distance of

$$x = \sigma_Z + \lambda + |\xi|,$$

where $\lambda$ is the Goy-Chapman length. The length $\xi$ is half the (negative) screening length of the strongly correlated liquid of the condensed counterions on the surface of the DNA molecule.

$$\xi = \frac{\varepsilon}{4\pi(Ze)^2} \frac{d\mu}{dn}$$

with $\mu$ the chemical potential of a counterion in the liquid, and $n$ is its two-dimensional density. This screening length, $|\xi|$, depends weakly on the ratio, $\sigma_Z/r_{DNA}$. For our purpose, it can be considered to be constant. Therefore, if one considers the correlation-induced attraction between two DNA cylinders only works when the closest approach between their surfaces is greater than $2x$ (so that the two DNA’s ”effective” metallic layers donot overlapped), one immediately comes to the conclusion that the electrostatic like-charged attraction between two neighboring DNA cylinders is simply shifted by a distance of $2\sigma_Z$ when the radius of the counterion changes. This agrees with our simulation results.

In Fig. 7, the free energy of packaging DNA into an hexagonal bundle with the optimal inter–DNA distance, $d^*$, is plotted as a function of the counterion concentrations for the three different counterion radii. It can be seen clearly that, within the range of counterion concentrations studied, there is a quantitative and qualitative difference in the free energy of packaging for the three sizes of counterion consider. For $\sigma_Z = 2\text{Å}$ and $2.5\text{Å}$, the dependence of the free energy of packaging DNA in bundle on the concentration $c_Z$ is non-monotonic. However, for the larger counterion size, $\sigma_Z = 3\text{Å}$, in the range of concentration considered, DNA condense later...
but stronger into hexagonal bundle as the counterion concentration increases. This behavior is actually observed in experiments. While the non-monotonic behaviors of DNA ejection is observed clearly for MgSO4 salt, and somewhat evident for MgCl2 salt, MnCl2 are known to condense DNA in free solution without ever disintegrated. Our simulation suggests that the difference in the hydration radius of the counterions can be used to explain such differences. Our results suggests that Mn2+ counterion has larger ion radius. This is in good qualitative agreement with computational and EXAFS and X-ray studies on divalent counterions hydration shell (see Table 3 of reference 27 and the corresponding references therein). These work shown that the number of water molecules in the hydration shell of ions increases with its atomic number. Specifically, as the atomic number of the divalent counterions increases from Mg2+, Ca2+, Sr2+ to Ba2+, the coordination number increases from 6 to 9 water molecules in the hydration shell. Even though, Mn2+ hydration was not studied in these works, its atomic number is higher than that of Ca2+ and Mg2+ ions suggesting that its hydration radius is larger than that of Mg2+ counterions.

It is of importance to note that, according to our Fig. 7 although the larger counterions do not produce a reentrant non-monotonic behavior, they actually cause stronger DNA-DNA attraction energy. Based on what is observed from Fig. 4 Fig. 5 Fig. 6 and the horizontally shifted Fig. 8, this observation can be explained as the result of two effects. First, smaller counterions can condense better on DNA, causing a stronger short-range like charge attraction among DNA cylinders. However they also cause a higher degree of overcharging at larger concentrations, so it is costlier to packaging DNA. This is evident by the increase in the packaging free energy at higher concentration for $\sigma Z = 2\sigma$. Secondly, the short-range attraction between DNA is shifted to larger $d$ for larger counterions. Since one integrates $\int PdV$ to find the packaging free energy, a simple geometric argument shows that the contribution from larger $d$ would dominate this integral, therefore the larger counterions can cause lower energy minimum at large concentration.

V. CONCLUSION

In this paper, we use a Grand-Canonical Monte-Carlo simulation to study the electrostatics of DNA condensation, using a primitive model for the screen ions. Specifically, the effective electrostatic interaction between DNA molecules in a hexagonal bundle is computed in the presence of 50mM monovalent counterions and with varying concentration of divalent counterions. The entropy of DNA configures fluctuation 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, even at the level of non-specific electrostatic interaction, divalent counterions can strongly influence DNA interaction and packaging. The simulation results for divalent counterions with 2.0Å radius show that the electrostatic free energy of packaging DNA into hexagonal bundle varies non-monotonically with the counterion concentration. However, divalent counterions do not correlate strong enough with each other to drive DNA de-condensation.

The counterion specificity such as the ion hydration radius can influence strongly the qualitative and quantitative picture of DNA condensation. Three different counterion sizes are studied. They show that the non-monotonicity changes significantly and disappears as the counterion size increases. The most important results of this paper are presented in Fig. 5 and Fig. 7 where it is shown that increasing counterion radius simply raises the “metallic” surface of condensed counterions off the DNA and shift the correlation-induced attraction between two DNA cylinders by an amount of $2\sigma Z$. This interestingly is responsible for making the larger counterions to cause a deeper minimum of DNA packaging free energy. In fact, in the range of concentration considered in our simulation with counterion radius of 3Å, this free energy keeps going lower with increasing counterion concentration. Such qualitative differences are observed with DNA condensation experiments involving Mg2+ and Mn2+ counterions and suggesting that Mn2+ has bigger ion radius, in agreement with previous computational and EXAFS and X-ray experimental results.

Going beyond the scope of DNA ejection experiments, we believe the quantitative results of our paper can be used to understand many other experiments involving DNA and divalent counterions.

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