Communication

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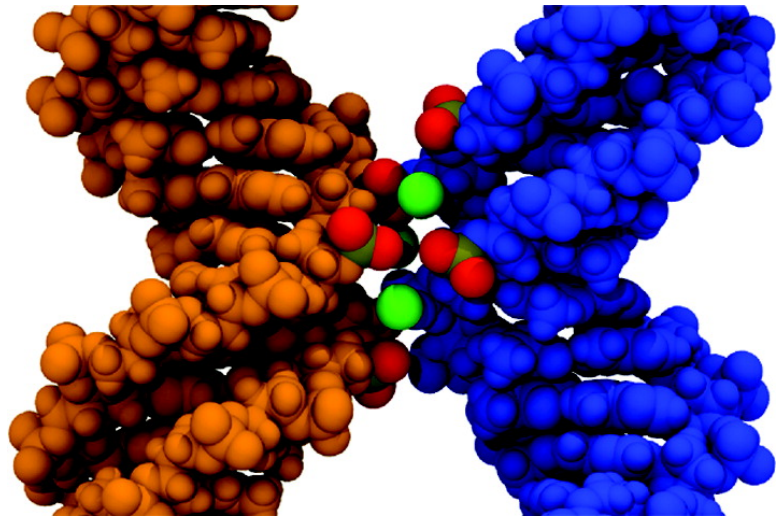

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DNA Attraction in Monovalent and Divalent Electrolytes

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It is well-known that genomic DNA is densely packed inside the cell nucleus and viral capsids. Such close packing suggests that electrostatic repulsion between negatively charged DNA in the condensed state is balanced by counterion-induced attraction.[1] Indeed, effective attraction between DNA in trivalent and quadrivalent electrolytes has been experimentally demonstrated.[2] Several theoretical models have been proposed to describe the origin of DNA attraction. Counterion correlation models,[3] which approximate DNA as a uniformly charged cylinder and neglect discreteness of the DNA charge and other structural features, predict DNA condensation in an electrolyte for ions of valence ≥ 3.[3] The electrostatic zipper model[4] accounts for the inhomogeneous charge distribution along DNA but assumes binding of counterions to the DNA grooves, which presumably renders them positively charged. In that model, effective attraction between two DNA molecules originates from interlocking positively charged grooves of one molecule with the negatively charged backbone of the other. However, common counterions found in biological cells, such as Na^+, K^+, Ca^{2+}, and Mg^{2+} (valence <3), have high affinity to the DNA backbone, not to DNA grooves.[5]

Recent small-angle X-ray scattering experiments[6] demonstrated that short DNA fragments (tens of base pairs) could attract each other in a $MgCl_2$ electrolyte. Synchrotron X-ray diffraction experiments[7] showed evidence for attraction between λ-phage DNA in divalent electrolytes when DNA was confined to a two-dimensional cationic surface. It seems that parallel alignment of DNA fragments in the presence of divalent ions facilitates DNA attraction. In contrast to previous studies employing the primitive electrolyte model,[8] here we report direct observation of DNA attraction in mono- and divalent electrolytes from all-atom MD simulations.

We consider a system containing two double-stranded DNA molecules submerged in a rectangular box of electrolyte, Figure 1. Each DNA duplex, poly(dA_{10})•poly(dT_{10}), is effectively infinite as each strand is covalently bonded to itself over the periodic boundary. Thus, we investigate interaction between parallel DNA at close distances before forming a condensate. The simulation box measured $60 \times 100 \times 32$ Å^3 and contained ~18 000 atoms. The details of the simulation procedures are provided in the Supporting Information.

First we simulate free diffusion of DNA in several electrolytes. In these simulations, each DNA molecule could move along the *x*- and *z*-axes and rotate about its axis, while translation in the *y* direction was restrained via a harmonic force. The inter-DNA distance *D*, defined as the distance between the helical axes of DNA, is plotted versus simulation time in Figure 2 for NaCl (a−c) and $MgCl_2$ (d−e) electrolytes. The shortest distance observed is approximately one DNA diameter while the longest one is a half of the system size along the *x*-axis.

As the concentration of NaCl increases, the DNA molecules are more likely to stay close to each other. At 1.0 M concentration, the two molecules formed a bound state that lasted for tens of nanoseconds but was eventually broken by thermal agitation. In a 1.0 M $MgCl_2$ electrolyte, the DNA molecules stayed close to each other (D ~24 Å) for most of the simulation trajectory. Thermal fluctuations were observed to transiently increase the inter-DNA distance but could not break the bound state. Even in the case of 0.1 M $MgCl_2$, only one complete unbinding event was observed in 150 ns. These simulations strongly suggest that DNA can pairwise attract in $MgCl_2$ and high concentration NaCl electrolytes. In experiment,[6] attraction between multiple DNA molecules was observed even at 10 mM $MgCl_2$.

To quantitatively characterize the interactions between DNA in different electrolytes, we directly measured the mean force using

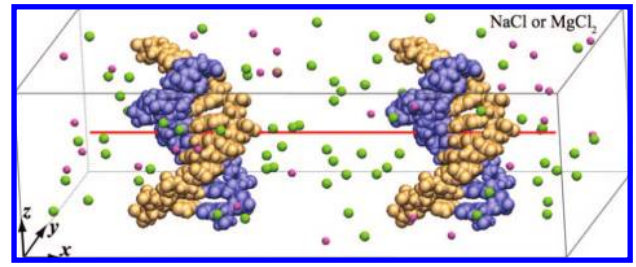

Figure 1. Simulation system. The two DNA strands are shown in blue and orange; pink and green spheres correspond to Cl^- and Na^+ ions. Water is not shown.

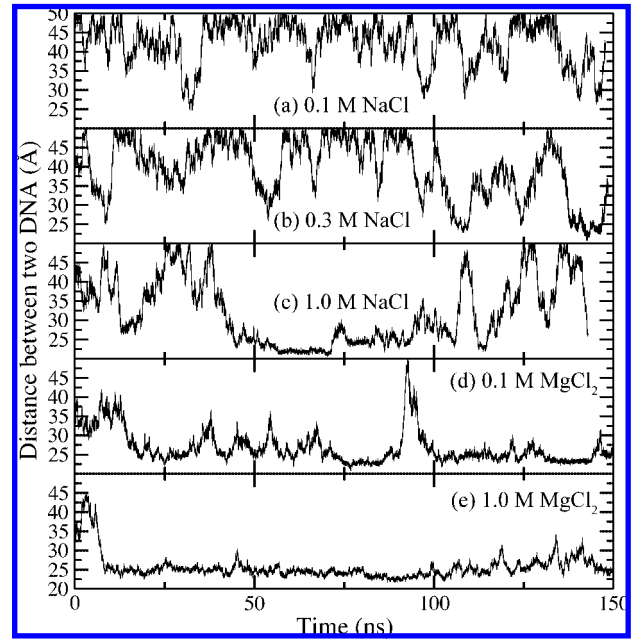

Figure 2. Distance between two DNA molecules versus time. In these simulations, DNA was allowed to freely diffuse along the *x*- and *z*-axes. The concentration and type of electrolyte are indicated in each panel.

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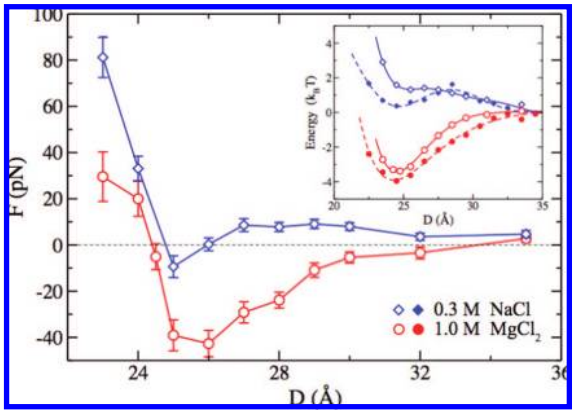

Figure 3. Effective force versus distance. Inset: Potential of mean force obtained by integrating the force-versus-distance curves (open symbols) and the Boltzmann inversion method (solid symbols).

the following procedure. A bias harmonic potential ($k_{spring} = 3$ nN/Å) was introduced to maintain the distance between DNA at a specified value. The inter-DNA distance was computed between the centers of mass of the phosphorus atoms projected on the *xy* plane. The force exerted on DNA to maintain the specified distance balanced the effective force between the two DNA molecules. For each value of the inter-DNA distance, a 160-ns MD simulation was performed to average out thermal fluctuations of the force.

Figure 3 shows the effective force F between DNA versus the inter-DNA distance D. In the 0.3 M NaCl electrolyte, the interaction force is repulsive at large and short distances. However, a weakly attractive force is observed at $D = 25$ Å. In the 1 M $MgCl_2$ electrolyte, the effective force is predominantly attractive; the maximum attractive force is ~42 pN per helical turn. In the small-angle X-ray diffraction experiment,[6] DNA attraction was observed in the presence of Mg^{2+} but not Na^+, which is in agreement with our observations.

The inset to Figure 3 shows the potential of mean force (PMF) obtained by integrating the force-versus-distance dependence. For DNA in the 1 M $MgCl_2$, the depth of the potential well is ~$3.4k_BT$ per helical turn, close to the experimental estimate.[9] It is because of this potential well DNA formed a bound state in the free diffusion simulations, Figure 2e. Although DNA can attract at short distances in the 0.3 M NaCl electrolyte, the attractive potential well in that case is too shallow (<$1k_BT$ per helical turn) to induce DNA condensation. For comparisons, we used the Boltzmann inversion (BI) procedure[10] to compute PMF from the distribution of the inter-DNA distances resulting from the free diffusion simulations (see inset to Figure 3). General features of the PMFs obtained using the two methods appear to be very similar. It is, however, conceivable that much longer simulations are required for the BI method to achieve the accuracy of the direct force measurement.

Conformational analysis of the bound state revealed the mechanism of DNA attraction. In the bound state (Figure 4a), Mg^{2+} ions reside in the negatively charged pockets formed by phosphate groups of the DNA backbone. While it is possible for a Na^+ ion to occupy such a pocket, the resulting attraction is not strong enough for the two DNA molecules to form a bound state. The presence

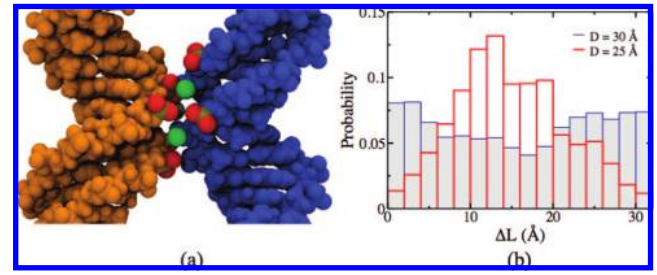

Figure 4. Mechanism of DNA attraction. (a) DNA conformation in a bound state. The two DNA molecules are shown in orange and blue; Mg^{2+} ions are shown in green; water is not shown. The phosphate groups forming the inter-DNA contacts are highlighted. (b) Histograms of ΔL at $D = 25$ and 30 Å. Each histogram corresponds to a 150-ns MD trajectory.

of multiple Na^+ ions in the same pocket has a large electrostatic penalty and was not observed.

The relative alignment of the two side-by-side DNA can be characterized by $\Delta L = \Delta L_z - L\Delta\theta/(2\pi)$, where ΔL_z is the relative displacement of the DNA along the z-axis, $\Delta\theta$ is the relative rotation of the molecules about their helical axes, and L (~32 Å) is the length of one helical turn. When the absolute value of ΔL is $L/2$, the DNA molecules align side-by-side so that their minor grooves level with each other (Figure 4a). As shown in Figure 4b, ΔL is almost evenly distributed at $D = 30$ Å. However, at $D = 25$ Å, the distribution of ΔL peaks around $L/2$, indicating that two DNA molecules align in a minor-groove-to-minor-groove conformation.

In summary, our simulations suggest a possible mechanism of DNA attraction in divalent electrolytes: bridged by Mg^{2+} ions, DNA interlocks in the minor-grove-to-minor-grove conformation. In monovalent electrolytes, DNA attraction is possible but too weak to form a stable bound state.

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Supporting Information Available: Details of the MD procedures, an illustrated definition of the alignment parameter ΔL, correlation plots of the inter-DNA distance D and ΔL, a plot of the averaged force versus time, and animations of the MD trajectories. This material is available free of charge via the Internet at http://pubs.acs.org.

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