Molecular Dynamics Investigations on Base Sequence Specificity of Counterion Binding to DNA

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DNA is a highly charged polyanion, whose structure, flexibility and biological functionality are strongly influenced by the interactions with solvent and counterions. In recent years it has been shown that the monovalent cations, as the physiological counterions Na+ and K+ can bind directly to DNA, partially losing their hydration water. These studies have revised the common view of monovalent cations binding to the DNA double helix in a delocalized manner, without dehydration and irrespective of the base sequence.

However, obtaining detailed information at the atomistic level on the binding of highly mobile ions like Na+ or K+ is tricky [1,2], and often the experimental data leaves space to several interpretations. Detailed information on counterion/DNA interaction can be obtained by Molecular Dynamics simulations. Its validity has always to be carefully checked.

We present here a Molecular Dynamics investigation of interactions between DNA and its counterions discussing the sequence specific interactions with alkali ions. Studied DNA sequences. Red: Adenine, Blue: Thymine; Green: Guanine, Yellow: Cytosine.


Improved Parametrization of Ion-DNA Interactions for MD Simulations of Dense DNA Systems

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Nucleic acids - highly charged polyanions - are often densely packed in biological systems. Counterions play an essential role in the biological processes involving densely packed DNA, such as chromosome remodeling and RNA folding. However, experimental measurements of the ion atmosphere around the nucleic acids remain elusive. All-atom molecular dynamics (MD) simulations can be used to characterize the ion atmosphere in great detail; however, the usefulness of such simulations depends on the accuracy of the underlying computational model. Here, we test the accuracy of the current all-atom force field by carrying out an MD simulation of 64 parallel DNA duplexes (DNA array). Undesirably, we find both DNA array pressure and DNA distributions derived from these simulations to be inconsistent with the X-ray diffraction and osmotic pressure measurements. We find that at constant concentration of PEG monomer, increasing PEG size increases the excluded volume effect but decreases the chemical interaction effect, because in a large PEG coil a smaller fraction of the monomers are accessible to the DNA. Volume exclusion by PEG has a much larger effect on intermolecular duplex formation than on intramolecular hairpin formation.

The Effect of Formation Pathway on the Structure and Stability of PEGylated Lipoplexes at Physiological Conditions: Implications for Gene Delivery

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Cationic liposome - DNA (CL-DNA) complexes (or lipoplexes) are among the most promising materials for delivery of genes into mammalian cells for gene therapy applications. These complexes are found to remain stable in monovalent salt solutions until ca. 500 mM. Long term circulation in blood requires a repulsive polymer coat to prevent removal by the immune system. A viable way of obtaining coated CL-DNA particles is incorporation of polyelectrolyte glycol lipids (PEG-lipids) before mixing with DNA (Ewert et al. Topics Curr. Chem. 2010, 296, 191-226). Here, we show that pegylated complex stability in salt depends on the preparation method of the particles. CL-DNA particles with 5 mol% of PEG 2000 form stable complexes with well defined lamellar peaks in water. The structure remains stable after addition of a 150 mM NaCl or DMEM medium (both with ionic strength near physiological conditions). Conversely, if complexes are initially formed in salt or DMEM medium, the structure is less stable with small-angle X-ray scattering (SAXS) showing the coexistence of narrow and broad lamellar peaks. If the PEG amount in the bilayers is increased to 10%, the particles formed in water continue to be well defined, but the ones formed in salt and DMEM exhibit small domain sizes as revealed in SAXS experiments. Cryo-TEM images also show onion-like structures with very few layers. Since pegylated CL-DNAAs are widely used in gene therapy applications, these results are of significance since it is reasonable to expect that the degree of compactness of these particles (which depends on the preparation method) will strongly affect complex stability and transfection efficiency.

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