DNA Dynamics in A Water Drop

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Due to its polyionic character the DNA double helix is stable and biologically active only in salty aqueous media where its charge is compensated by solvent counterions. Monovalent metal ions are ubiquitous in DNA environment and they are usually considered as the possible driving force of sequence-dependent modulations of DNA structure that make it recognizable by proteins. In an effort to directly examine this hypothesis, MD simulations of DNA in a water drop surrounded by vacuum were carried out, which relieves the requirement of charge neutrality. Surprisingly, with zero concentration of counterions a dodecamer DNA duplex appears metastable and its structure remains similar to that observed in experiments.

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It has been long recognized that, because of the polyionic nature of DNA, solvent counterions are required for its stability, and that gross structural changes in DNA can be provoked by changing the concentration, the charge or the type of counterions [1]. More recently it has been proposed that free ions might also act as biological regulators because, by binding to DNA, they can provoke conformational deformations recognized by specific proteins [2, 3, 4, 5, 6, 7]. The most controversial is the role of the common monovalent cations Na\(^+\) and K\(^+\). They are ubiquitous in the DNA environment and can be readily available for any purpose. Until recently, they remained invisible in experimental DNA structures because it is difficult to detect them in water, and it has been suggested that they are perhaps responsible for the most widespread deformations of the double helix, namely, narrowing of the minor groove and bending. It is assumed that counterions are sequestered in the minor groove of some sequences, which breaks the symmetry of the repulsive electrostatic forces and provokes deformations. This model is general and it easily explains other puzzling effects in DNA structure.

The above hypothesis is supported by many recent studies. Penetration of monovalent cations into the minor DNA groove has been confirmed by X-ray diffraction [8, 9, 10, 11], NMR spectroscopy [12, 13], and MD simulations [14, 15, 16, 17]. However, it appears difficult to find a discriminating set-up for testing the cause and consequence relationship between the ions and the DNA structure. All available evidences have more than one interpretation making this problem highly controversial [18, 19, 20]. For example, correlations between ion positions and the local groove width observed in MD cannot answer whether the ions perturb DNA or they just bind "opportunistically" in the sites of low potential near already deformed double helix [17]. To clarify the issue of cause and effect one would have to remove solvent ions and check if the supposed counterion effects disappear with them. Unfortunately, a counterion-free DNA does not exist in nature whereas the most reliable computational procedures presently employed require that the simulation cell that holds DNA carries zero net charge. Therefore, in both simulations and experiments the counterion effects cannot be completely eliminated.

In an effort to directly address this question I have adapted the Particle Mesh Ewald algorithm [21, 22] for modeling dynamics of DNA in a water drop surrounded by vacuum. Particle-mesh calculations with vacuum boundary conditions are long known in physics [23], but, to my knowledge, they were never applied to chemical or biological systems. Free vacuum boundaries are intuitively most simple and they allow one to relieve the problems of charge neutrality and possible artifacts from interactions between periodical images. I describe here the first such "naive" all atom simulations of DNA in water, with unperturbed Coulomb electrostatics. It appears that, with zero concentration of counterions, a dodecamer DNA duplex is metastable and its structure remains similar to that observed in experiments.

The Dickerson-Drew dodecamer (CGCGAATTCGCG, [24]) in a canonical B-DNA conformation is surrounded by a spherical drop of 4000 TIP3P water molecules [25]. Initially, the drop had around 50 Å in diameter and in dynamics it remained roughly spherical. A rectangular unit cell is constructed around the drop with the minimal separation of 25 Å between the closest neighbors. A shifted Coulomb’s law is used, with \( U(r_{ij}) = z_i z_j (1/r_{ij} - 1/R_0) \) for \( r_{ij} < R_0 \) and \( U(r_{ij}) = 0 \) for longer distances, where \( R_0 = 50 \) Å, which eliminates any interactions between periodical images. Because this shifting does not affect the forces, the system behaves in dynamics as if surrounded by infinite vacuum. Within the drop the electrostatics are effectively evaluated with a cut-off of 50 Å, which is larger than the DNA size and applies only to a small fraction water molecules at oppo-
TABLE I: Some structural parameters of standard and computed DNA conformations. Sequence averaged helical parameters were computed with program Curves [27]. All distances are in angstr"oms and angles in degrees.

|                  | Xdisp | Inclin | Rise | Twist | RMSD-Aa | RMSD-Ba |
|------------------|-------|--------|------|-------|---------|---------|
| A-DNA            | -5.4  | +19.1  | 2.6  | 32.7  | 0.0     | 6.2     |
| B-DNA            | -0.7  | -6.0   | 3.4  | 36.0  | 6.2     | 0.0     |
| Tj1b             | -2.2  | +6.9   | 3.3  | 33.8  | 4.52    | 2.36    |
| Tj2c             | -2.0  | +6.5   | 3.2  | 34.1  | 4.57    | 2.18    |
| Tj3d             | -2.1  | +6.9   | 3.3  | 33.6  | 4.46    | 2.41    |

aHeavy atom root mean square deviation from the corresponding canonical DNA form.

bWater drop calculation without counterions.
cWater drop neutralized by 22 Na$^+$ ions.
dConventional PME calculation with counterions and periodical boundaries.

FIG. 1: A snapshot from the last nanosecond of the trajectory with water oxygen positions shown by dots.

The most famous feature of this DNA molecule is the middle AATT fragment. It is long known from experi-
The sequence-dependent groove-width modulations in DNA are well established experimentally and, in the recent years, they have been proposed to result from interactions with bound monovalent metal ions commonly undetectable in X-ray crystal maps. The present results evidence that it is not the case, supporting recent conclusions of different groups. They explain also why groove modulations and intrinsic DNA bending could be reproduced in MD simulations with simplified treatment of electrostatic interactions that ignored specific counterion effects.

According to the counterion condensation theory, DNA in aqueous environment should be always covered by a shell of counterions and its charge should be compensated by around 75% regardless of the bulk ion concentrations. The results presented here do not contradict this theory but they are somewhat at odds with an implicit assumption that the counterion cloud is critical for the native DNA structure. This was surprising, at least for the author, and suggests that we are still far from complete understanding of interactions that control the DNA structure. The correlations observed in earlier MD simulations apparently are due to binding of counterions in sites of low potential near an already narrowed minor groove, therefore, these interactions are structure-specific rather than sequence-specific, and they cannot be the driving force of the corresponding DNA deformations.

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