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A study of DNA tethered to a surface by an all-atom molecular dynamics simulation

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Abstract. In order to understand the structure of DNAs and their interactions when on microarray surfaces, we performed the first all-atom molecular dynamics simulation of DNA tethered to a surface. On the surface, the binding of the DNA was enhanced, and its average equilibrium conformation was the *B* form. The DNA duplex spontaneously tilted towards its nearest neighbor and settled in a leaning position with a interaxial distance of 2.2 nm. This close packing of the DNAs, which affects both in situ synthesis and deposition of probes on microarray surfaces, can thus be explained by salted-induced colloidlike DNA–DNA attractions.

DNA microarrays, devices made of oligonucleotides tethered to surfaces, have recently had an explosion of interest [1]. Fueled by advanced fabrication and signal detection techniques, their applications have reached diverse areas, such as genetic screening/sequencing [2], drug discovery [3], and DNA computing [4]. However, very little is known about the structure and physical behavior of DNAs and their interactions when on microarray surfaces. This information would be important not only in designing and optimizing new DNA microarrays but also in exploring other potential applications. We have performed the first all-atom molecular dynamics simulation of DNA tethered to a surface. Here we report that the overall conformational equilibrium of DNA on the surface is on average the B form [5] even with a high G-C content in a high salt. In the simulation, the hydrophobic amine linker which tethered the DNA to the surface remained mostly in an extended set of conformations. The DNA duplex tilted towards its nearest neighbor and settled in a leaning position with an interaxial distance of 2.2 nm. This close packing of the DNAs can be explained by salted-induced colloidlike DNA–DNA attractions.

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To study the conformations and interactions of DNAs on a surface, we performed an all-atom molecular dynamics simulation. The model consists of a glass surface coated with an epoxide monolayer, a 12-base-pair B-DNA duplex tethered to one of the surface epoxides through its 5′-amine linker, and a surrounding solution of 0.8 M NaCl. With the two-dimensional periodicity parallel to the surface, this setup is relevant to a DNA-coated interface [6] with a surface density of 0.07 DNA nm^{-2}.

The simulation used a glide-plane boundary condition [7] (GBC) with a simulation box of dimension $4.1 \times 3.5 \times 7.5$ nm^3. Following Ref. [7] we modeled the glass substrate by a layer of β-cristobalite [8]. Sixty-four epoxides were grafted on the surface by bonding with the surface silicon atoms. As illustrated in Fig. 1, the terminal of one epoxide was modified and connected to the amine linker of a DNA strand d(CGTGTCCCTCTC) hybridized with its complement. The force field parameters of the silica layer were adopted from the CVFF force field [9] and Ref. [10]; the parameters of the epoxides, the amine linker, and the DNA were from the all-atom CHARMM22 proteins [11] and CHARMM27 nucleic acids [12] force fields. The DNA duplex was started in the canonical B form and pointed towards the positive *z* direction. The empty space of the simulation box was filled with water molecules [12, 13, 14], of which 97 were randomly chosen and replaced by 60 sodium and 37 chloride ions [15]. Using the molecular dynamics program ESP [16] with the GBC implementation, we performed the simulation in the microcanonical (NVE) ensemble [17]. The electrostatic interactions were treated with an Ewald sum [18]. The equations of motion were solved by the velocity Verlet [19] integrator with a time step of 2 fs and the RATTLE algorithm [20].

The initial conformation of the DNA was the canonical B form [5]. During the simulation, the DNA relaxed from the canonical conformation and then fluctuated between the A and B forms; however, its overall average conformation resembled the B form. The fluctuations are consistent with recent DNA simulations [21] using the latest all-atom CHARMM27 nucleic acids

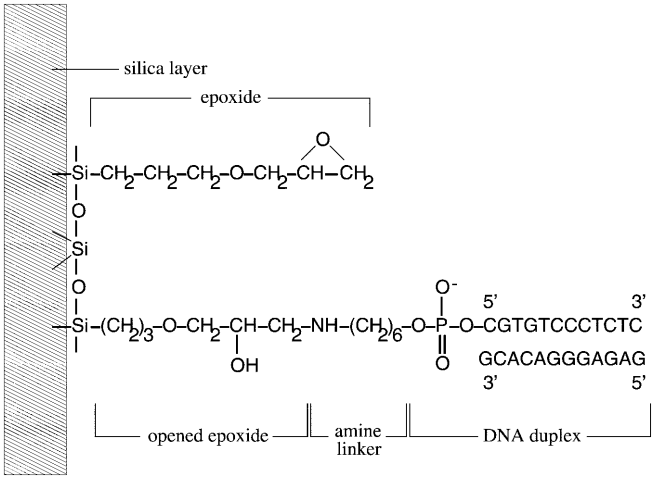

Fig. 1. The chemical structure of the unreacted epoxides on the silica surface, the opened epoxide which bonds with the amine linker, and the DNA duplex

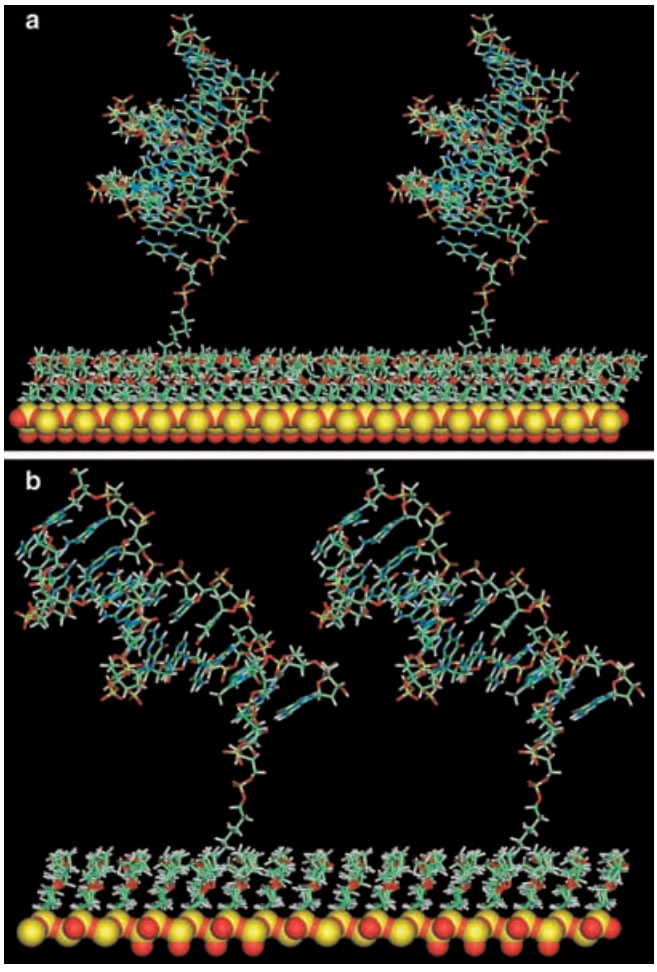

Fig. 2a, b. Snapshot of the simulation at 6.3 ns. **a** and **b** are the views from two perpendicular directions. Each figure displays two DNA duplexes. **a** In this view, the DNAs are pointing out of the page. **b** This view shows the DNA tilted towards its periodic image. Note the narrow space between the DNAs

force field [12]. In simulations of DNAs in bulk solutions, the base pairs at the ends of the DNA duplex open up frequently [22]; however, this was not observed here. This absence of fraying of the edge base pairs in this case suggests that the surface effectively modifies the dielectric environment and enhances the binding of the complementary DNA strands over that in bulk solution, where fraying is often seen in simulations.

In our simulation, the DNA and its amine linker were in an upright position initially. Considering that the amine linker is hydrophobic, it might have been expected to coil up or collapse onto the surface, pulling the DNA duplex towards the surface [23]. Nevertheless, for the entire 7-ns simulation, the amine linker remained mostly in an extended conformation with an average length of about 0.9 nm. This is considerably longer than the time for rotational transitions in the linker torsions. The average angle between the linker and the surface normal was approximately 40°, which indicates that the linker did not collapse onto the epoxide surface.

During the simulation, the DNA duplex, initially in an upright position, also reoriented itself. After swinging in random directions for about 1 ns, the DNA started to tilt. The tilting progressed and after another nanosecond, it settled in a tilting position. In that configuration it can be seen from Fig. 2 that it moved to tilt towards a periodic image forming a solvent-layered complex with a periodic neighbor. We determined the global helix axis of the duplex using the program FREEHELIX [24]. At the beginning of the simulation, the helix axis was perpendicular to the surface, and the interaxial distance between the DNA and its nearest neighbor was 3.5 nm. When the DNA was in the leaning position the average angle between the helix axis and the surface normal was 55°. The average interaxial distance in the titled configuration is estimated to be 2.2–2.4 nm. A snapshot of the simulation at 6.3 ns is shown in Fig. 2. One may attempt to explain the tilt of the DNA as the result of attractive DNA surface forces; however, if this was the case, the DNA would have leaned towards the open, diagonal lattice direction with the amine linker collapsed onto the surface in order to lie directly on the surface. Therefore, the tilt seen is not the result of attractive DNA surface interactions but of a colloidal state [25] induced by the surface-induced solvent activity changes and the geometry of linking. These colloidal structures may form before DNA probe–strand attachment to the surface in fabrication. This colloidlike behavior is therefore responsible for the even coverage found within a given multimicron spot of probes [25]. This effect has obvious implications for the optimal experimental conditions for either attachment of presynthesized oligonucleotides or in situ synthesis of the probes.

Carrying net negative charge, the DNA might be expected to stay nearly perpendicular to the surface in order to minimize the electrostatic repulsion with its periodic images. Therefore, it was unanticipated that it assumed a leaning position with an interaxial distance of only 2.2 nm, which implies that only one or two layers of solvent (or ions) intervene. This observation can be accounted for by effective attractive DNA–DNA interac-

tions. According to Manning's counterion condensation theory [26], 76% of the negative charges on the DNAs are neutralized by the sodium counterions located within 0.7 nm of the helix surfaces. As a result, electrostatic repulsions between the DNAs are substantially reduced, and with the induced surface ordering, colloidal attractive forces may become dominant [27], especially in concentrated salt solutions [25]. This can lead to DNA aggregations in salt solutions, which have been confirmed by various theoretical [28, 29] and experimental [30, 31] studies, particularly in the presence of multivalent salts [32]. Therefore, we conclude that the observed tilt of the DNA is apparently a manifestation of geometry and salt-induced DNA–DNA attractions, likely modified by the surface.

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