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A Non-Watson–Crick Motif of Base-pairing on Surfaces for Untethered Oligonucleotides

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A structural view of DNA association/hybridization to a target oligonucleotide molecule near a surface has been developed. Recent experiments have showed a kinetically rapid hybridization between large target DNA fragments and oligonucleotides electrostatically immobilized (untethered) to a surface. Theory and computer simulations have been used to investigate the nature of the specificity and affinity in such a system. Simulations were performed for a modified silicon dioxide surface with positively charged groups at neutral pH. The dosing of a surface with unattached oligonucleotide was simulated. The oligonucleotide was found to associate with the surface in salt water in a way that some of the bases remained stacked, and most of the bases near the surface on average pointed preferentially toward the solution, away from the surface. Use of an analytic solution to the linear Poisson–Boltzmann (PB) theory of the electric double layer interaction between DNA and a hard surface predicts tight binding in this system. The simulation thus gives a mechanism for specificity and the theory a mechanism for affinity. The geometry is such that only non-helical base pairs would be accommodated with an irregular backbone.

Keywords: Poisson–Boltzmann theory; Thermodynamics; Oligonucleotide; Non-Watson–Crick motif

INTRODUCTION

Nucleic acid oligomers behave differently near surfaces than free in solution. In viruses, recent electron microscopy images have demonstrated that nucleic acids can have specific structures near the interior capsid protein surface [1]. Research on DNA chips and their growing applications in medical diagnostics, genetics and drug development have

been presented in recent reviews [2]. In biochip assays, both affinities and specificities or association are different from those observed in homogeneous solution. Often times the probes are covalently linked to the surface with tether molecules of various, specific lengths [3]. Thus, there is some restriction in orientation, which can be even more severe for crowded surfaces [4]. In such cases, apart from the orientational restrictions, the difference in binding comes from changes in the solvent activity and electrostatic fields induced by the surfaces presence [5]. The hybrid structure and resultant pairing, however, is apparently of the standard Watson and Crick sort.

Surfaces order the solvent and salts in solution, sometimes strongly. Differences in solvent and salt activity are well known to induce structural changes in nucleic acids [6]. Understanding the relationship of a nucleotide's structure and thermodynamics with its solution environment is important for probing the fundamental relation of conformation with biological or chemical activity [7]. Understanding the properties of DNA near surfaces requires delving into the interplay between the solvent structure and DNA structures and equilibrium thermodynamics.

Recent experiments [8–11] have shown specific, high affinity hybridization binding near surfaces for systems where the DNA probe molecules are associated with but not tethered to the surface. In particular, positively charged amino-silanized glass surface demonstrated high promise for biochip applications [8–11] and thus is studied here theoretically, including molecular dynamics simulations and interface electrostatic analytical models.

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Using Streptavidin charge tunable surfaces for pH conditions where the surface was expected to be positively charged, oligonucleotide probes were allowed to bind without tethering [8–11]. The system then showed specific, high affinity binding of large targets with relatively rapid kinetics.

A central question arising from this work was the structural nature of the duplex formed with non-tethered, surface associated probes. Given that the single stranded oligonucleotides would be expected to adsorb to the surface in a variety of conformational states, what would the resulting duplexes look like? The experiments done on preformed and so presumably standard Watson–Crick helical duplexes showed very different characteristics from the hybridization experiments described above [8–11]. In fact, the intact duplexes could only be removed (under relatively extreme conditions) as a whole; no washing conditions resulted in melted DNA with a strand remaining preferentially attached to the surface.

To explain these observations we have undertaken a theoretical study in this paper to consider the nature and geometry of the binding of single stranded oligonucleotides to a charged surface and their subsequent ability to make specific double strand associations. We use computer simulations to obtain hypothetical geometries. Our recently published analytical theory for the binding thermodynamics is then used to consider the affinity and specificity in the system.

The paper is organized as follows. The next section contains a brief description of the methods used followed by a presentation of the results obtained. We finish with a discussion of the results in the context of recent experiments.

METHODS

Simulations

To study the conformations and interactions of the single strand DNA near the surface, we performed two all-atom molecular dynamics simulations. In both simulations, the model consists of a glass surface coated with an ammonium monolayer, a 12-base B-DNA single strand in helical B-form and a surrounding solution of 0.8 M NaCl with explicit water molecules. The simulations, denoted by **I** and **II**, differ in the initial positions of the oligonucleotides. Considering two-dimensional periodicity parallel to the surface, this setup is relevant to a DNA coated interface with a surface density of 0.04 DNA nm^{-2} , approximately half the density of an adsorbed monolayer.

To achieve a constant volume for the closed system, the simulations used our recently developed glide-plane boundary condition (GBC) [12] with a simulation

box of dimension $5.1 \times 5.3 \times 4.9 \text{ nm}^3$. As done previously [12], we modeled the glass substrate by a layer of β -cristobalite [13]. One hundred and twenty propyl ammoniums were grafted on the surface by bonding with surface silicon atoms.

The single DNA probe strands had the following composition: CGTGTCCCTCTC. This sequence has been used before in this laboratory for tethered duplex simulations and so forms a good system for comparisons [4]. The force field parameters of the silica layer were adopted from the modified CVFF force field [14,15], and the ammoniums were from the all-atom CHARMM22 proteins parameters [16] and CHARMM27 was used for the nucleic acid [17] force field.

The DNA single strands were started in canonical B-form [18] with the helical axes parallel to and about 12 and 22 Å above the surface in simulations **I** and **II**, respectively. The empty space of the simulation boxes was filled with water molecules [17,19], of which 215 were randomly chosen and replaced by 53 sodium and 162 chloride ions [20]. Final numbers of water molecules in the simulations were 3461 and 3452, respectively. Figure 1 shows the initial configurations of the simulations. The oligonucleotides were oriented such that the phosphates of G(2), T(11), and C(12) were closest to the surface while phosphates of C(6) and C(7) were the furthest away. Using the molecular dynamics program ESP [21] with the GBC implementation, we performed the simulations in the microcanonical (NVE) ensemble [22]. Coordinates of the silica atoms were fixed during the simulations, and electrostatic interactions were treated with Ewald sums [23] optimized for GBC's. The equations of motion were solved by the velocity Verlet [24] integrator with a time step of 2 fs and the RATTLE algorithm [25].

The simulations were performed with nearly identical protocols. Initial configurations of the systems were relaxed by minimizing the potential energy with 50 steps of steepest descents minimization. This was followed by about 25 ps of molecular dynamics simulation with periodic velocity re-assignment at 300 K and the DNA atoms fixed. The above procedure allowed the ions to partially move towards the distribution expected for a solution near a charged wall which retained sufficient positive surface charges to attract the oligonucleotides to move towards the surface within the nanoseconds time scale of the simulations. Each simulation was run for a total of roughly 10 ns, and coordinates and velocities of the atoms were saved every 0.1 ps for analysis.

Theory

Here, we give a brief account of our theory of binding near surfaces. A more complete account has

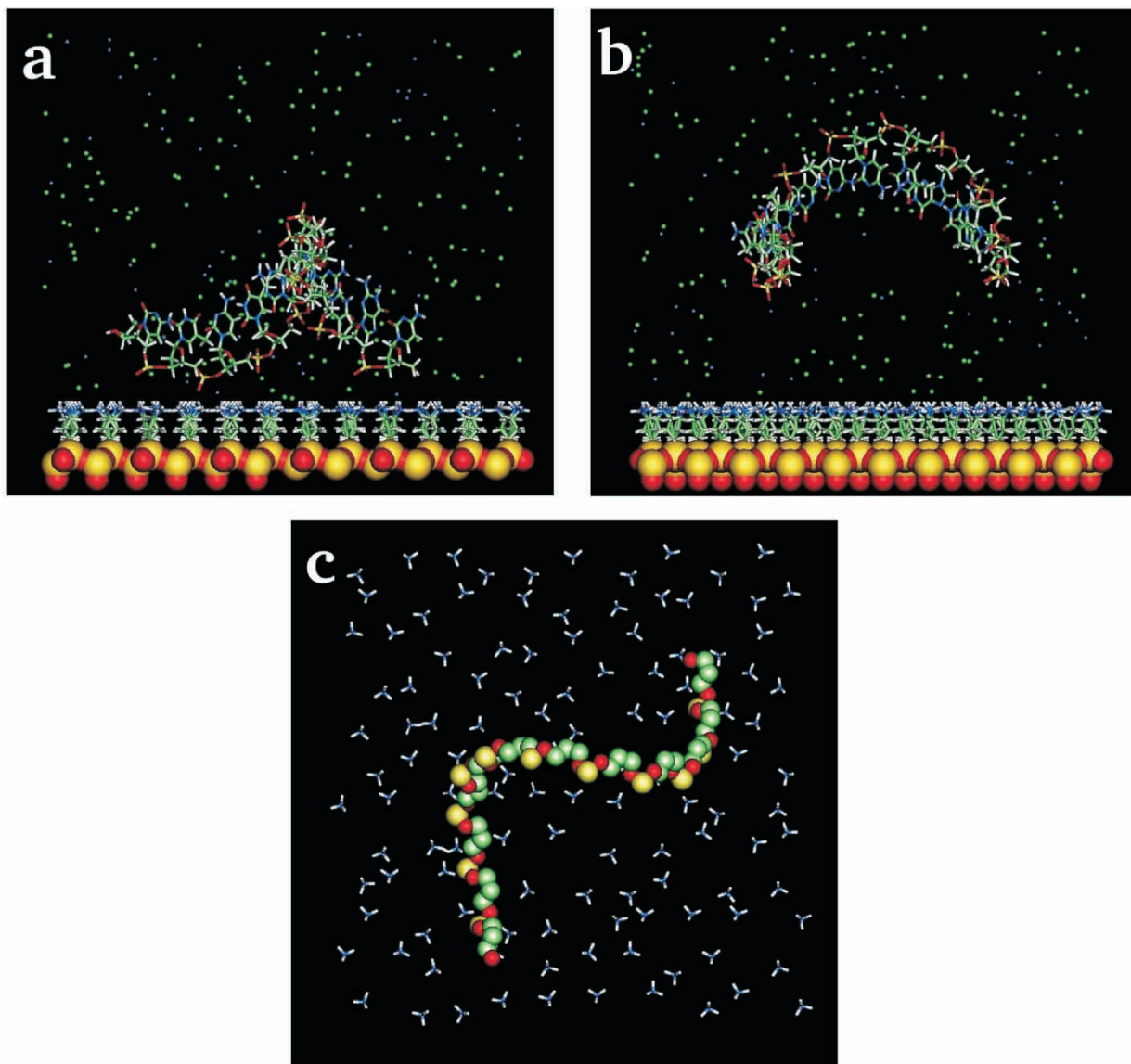


FIGURE 1 Initial structure of the oligonucleotide near the surface before steepest descent minimization (a) and (b) are the side views of I and II, respectively. The views are from two perpendicular directions, with silica atoms rendered in van der Waals model, propyl ammoniums and DNA atoms in liquorice model, sodium ions in blue balls, and chloride ions in green balls. Note the larger distance between the DNA and the surface in (b) compared to (a), (c) is the view from the top, which is identical for simulation I and II. For clarity, only the ammoniums atoms and oligonucleotide backbone atoms (P, O5', C5', C4', C3', and O3') are displayed.

recently been published [5]. We wish to calculate the difference between duplex formation in homogeneous solution and near a surface. In a notion used previously, we use the Gibbs free energies of formation (f) for the reaction/association between the probe (p) and target (t) giving rise to the formation of complex (c) in solution

$$G = G^f_c - G^f_p - G^f_t \quad (1)$$

and for the same reaction immobilized (i) near the surface

$$G_i = G^f_{ci} - G^f_{pi} - G^f_t. \quad (2)$$

From Eqs. (1) and (2) we get that the probe immobilization shifts the Gibbs free energy of

binding by

$$\Delta G = G_i - G = (G^f_{ci} - G^f_c) - (G^f_{pi} - G^f_p). \quad (3)$$

The two terms on the right side correspond to interaction with the surface of the immobilized complex, V_c , and immobilized probe, V_p ,

$$V_c = G^f_{ci} - G^f_c, \quad (4)$$

$$V_p = G^f_{pi} - G^f_p. \quad (5)$$

Thus in terms of the Gibbs interaction energies of the immobilized complex-surface and probe-surface

$$\Delta G = V_c - V_p \quad (6)$$

giving the difference in free energy for the complex in solution and bound to the surface. The DNA

oligomer is a polyanion and thus the electric interaction is attractive ($V < 0$) for positive surface potential ϕ_o . Assuming $V_p = q\phi_o$ for a probe and for duplex $V_c = 2q\phi_o$, where q is the charge of the single DNA strand ($q < 0$) we get $\Delta G = q\phi_o < 0$ for the attractive potential. This implies the binding affinity for the duplex becomes stronger for a positive surface charge.

Our simulations and many types of DNA chips use solution conditions with high salt (~ 1 M NaCl) concentrations [3,26,27]. In a previous publication we showed, given an exponential Debye screening, that $\Delta G = 0.7$ kcal/mol for a duplex 8-mer placed at 0.3 nm distance from the surface at 300 K.

We considered charged DNA-surface free energy of by interaction in electrolyte using linear [28] or non-linear [29,30] Poisson–Boltzmann (PB) theory. An analytical solution exists in the linearized case [31] for the relevant case of an ion-penetrable [32] sphere. We have showed the electrolyte penetrable particle to be a reasonable model for both a DNA single strand and a double helix where the solution and ions penetrate inside due to the hydrophilic groups and deep grooves [32].

Given the surface potential of the non-interacting plate φ_{po} with constant surface charge density σ in electrolyte

$$\varphi_{po} = \sigma / \epsilon \epsilon_o \kappa \quad (7)$$

and the surface potential, φ_{so} , for the sphere immersed in electrolyte

$$\varphi_{so} = (q/4\pi\epsilon\epsilon_o a) [\exp(-\kappa a) \sinh(\kappa a) / \kappa a] \quad (8)$$

for a spherical particle of radius a , separated by a distance h with the surface where ϵ is the relative dielectric constant of the solution, ϵ_o is the permittivity of vacuum and $1/\kappa$ is the Debye screening length for the concentration c_o of added NaCl salt, we can calculate the Gibbs free energy difference with respect to the distance from the plane for a low dielectric constant surface,

$$V(h) = V_1(h) + V_2(h) \quad (9)$$

where $V_1(h)$ is the interaction between a charged particle and surface charge given by

$$V_1(h) = 4\pi\epsilon\epsilon_o a \varphi_{po} \varphi_{so} \exp(-\kappa h), \quad (10)$$

whereas $V_2(h)$ is the interaction between a charged particle and electrostatically induced charge on an initially uncharged surface. As is well known, $V_2(h)$ can be expressed by the charge-image charge

pair interaction with the distance $2h$

$$V_2(h) = \pi\epsilon\epsilon_o a^2 \varphi_{so} \exp(-2\kappa h) / (a + h). \quad (11)$$

With this simple mean field picture we have previously shown that the qualitative features of these systems are faithfully reproduced [5]. Quantitatively, the theory gives surprisingly good results for measured properties in a variety of thermodynamic properties in several cases [5,33–35].

RESULTS

Simulation

Only two simulations with different initial configurations of a non-equilibrium system were run. Therefore, we do not assume to have a complete sampling of configuration or a kinetic description from the dynamic trajectories. Nevertheless, these two simulations yielded consistent structures. This gives a plausible, experimentally testable hypothesis for the structure of duplex formation which is consistent with the observed binding characteristics as interpreted by the statistical thermodynamic theory described in the previous section.

As described in the methods section, a single stranded oligonucleotide of 12 bases in length was released in a partially equilibrated box of sodium chloride and moved towards the positively charged surface. In **I**, when the DNA approached the surface, adsorption layers of the chloride ions above the ammoniums were only partially formed. The phosphate of T(11), which was closest to the surface, bound tightly to the surface ammoniums. Only chloride ions and almost no water molecules were found between them. The portion of the oligonucleotide, from C(7) to C(12), formed a curve segment and stayed close to the surface. The remaining part of the oligonucleotide bended upwards. Figure 2 is a snapshot at 9.0 ns. It shows a triangular shape that is well represented in the equilibrated conformations of the DNA. In simulation **II**, a substantial surface double layer was formed involving the surface ammonium ions and the free chlorides. Again, the strand of DNA rapidly formed a salt bridge with phosphates of C(10) and T(11), which were closest to surface ammoniums. This created a complicated layered structure of ions and water molecules between the phosphates and surface ammoniums. The remaining of the oligonucleotide curved upwards into the solution. In this run, the DNA strongly populated an S shape conformation. A snapshot at 9.0 ns is shown in Fig. 3. This feature remained for the rest of the simulation. Because of the non-equilibrium dynamics of the water and ions redistribution and DNA conformational

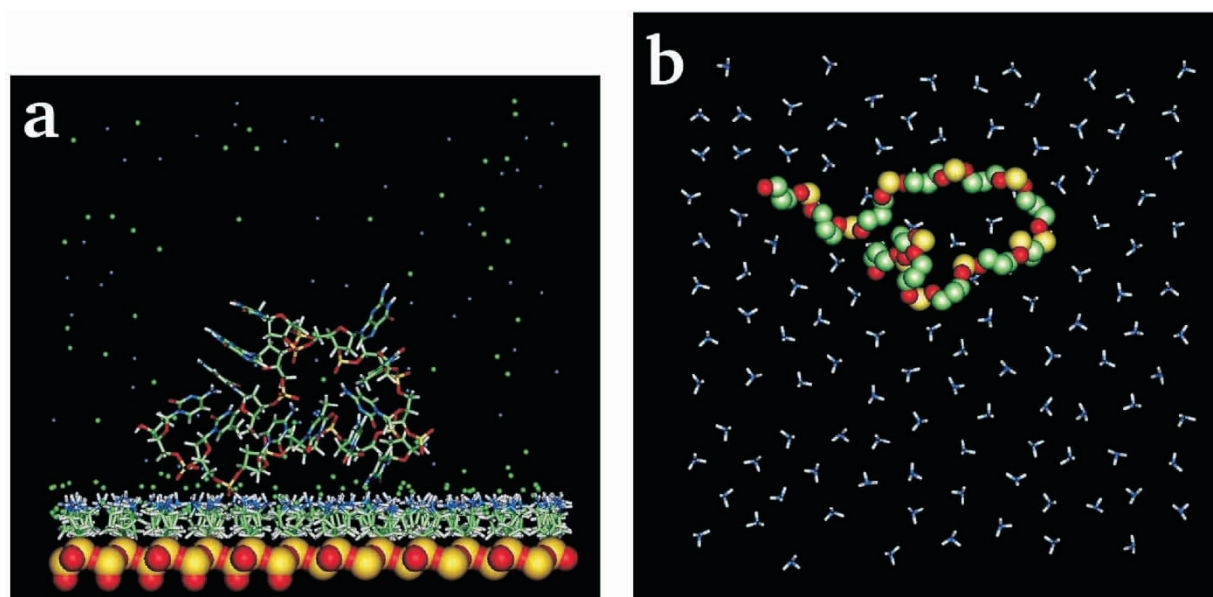


FIGURE 2 A snapshot of simulation I at 9 ns, (a) is the side view, which is identical to the view in 1(a), (b) is the top view. Note the phosphate of T(11) was tightly bound to a surface ammonium, and the bases were predominantly stacked.

changes during the first several nanoseconds of both simulations, we focus our analysis of the trajectories on the well equilibrated portions between 8.0 and 9.0 ns.

Due to the highly positive charge density on the surface, spatial distributions of water molecules and ions near the surface are expected to be very different from the bulk. This leads to a distinct screening environment and modifies the kinetics and thermodynamics of DNA hybridization near the surface compared to homogeneous bulk solution. Figure 4 presents the density of water, sodium ions, chloride ions, and phosphates in the simulations as a function

of z , which is the distance measured from the edge of the simulation box. For simplicity, we used the coordinates of the water oxygen to calculate the water density, and the phosphorus for the phosphate density. As a reference, the surface ammoniums located at about $z = 0.76$ nm. As shown in Fig. 4, for simulation I, chloride ions were strongly adsorbed on the positive charged surface and formed two ion layers at 0.70 and 0.92 nm, sandwiching the surface ammoniums. The density of phosphates near the surface peaks at 0.96, 1.14, 1.30, and 1.53 nm. The first three peaks correspond to the phosphates of T(11), C(12), and C(10), respectively, and the last peak

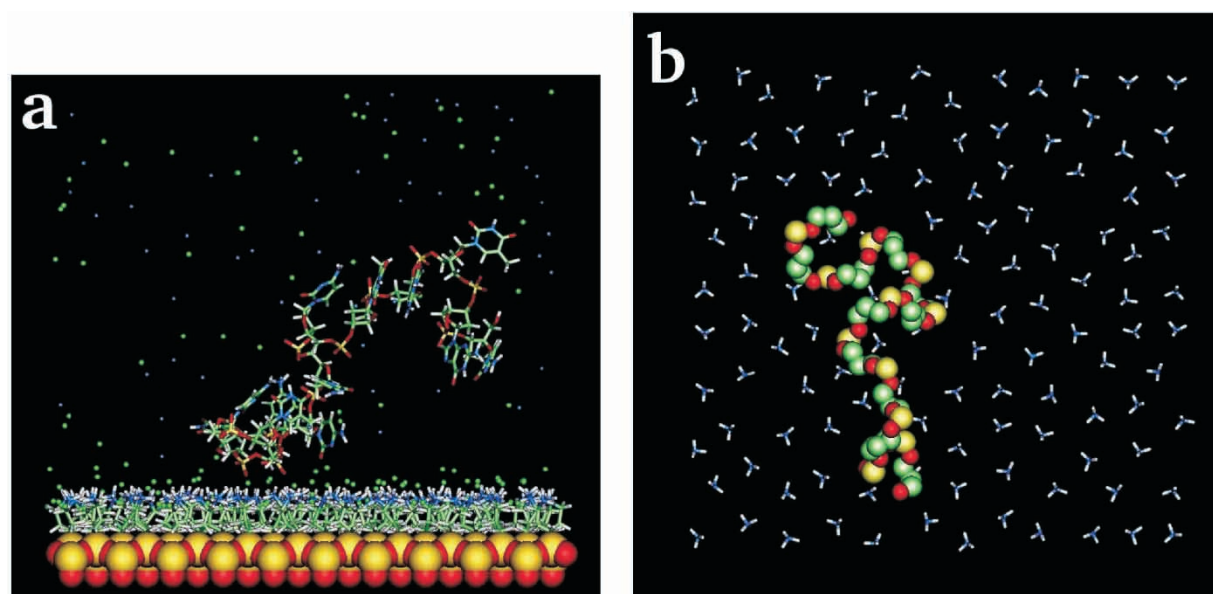


FIGURE 3 A snapshot of simulation II at 9 ns, (a) is the side view, which is identical to the view in 1(b), (b) is the top view. Note the bigger gap between surface ammoniums and the nearest phosphates compared to I. The other end of the DNA reached further into the solution.

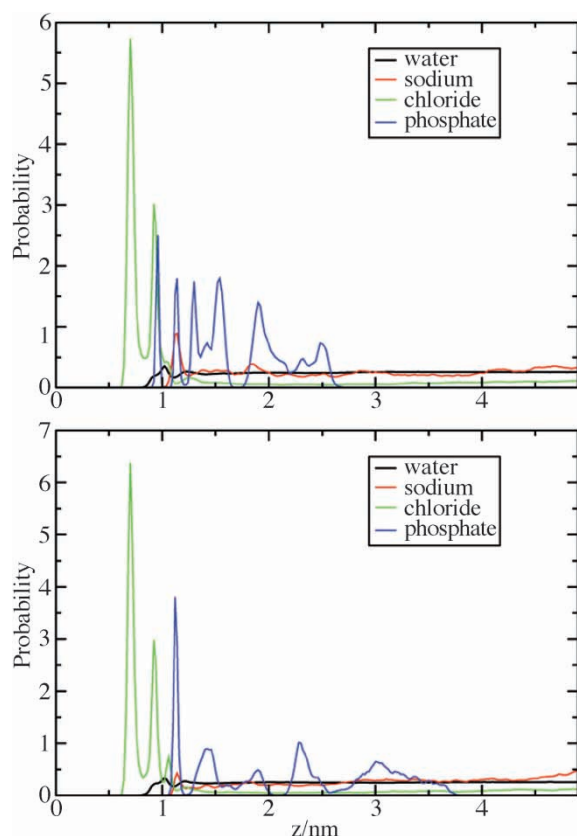


FIGURE 4 Probability distributions of sodium ions, chloride ions, water oxygens, and phosphates as a function of z in simulation I (top) and II (bottom).

corresponds to C(8) and T(9). The water and sodium densities exhibit less fluctuations near the surface. They, respectively, peak at 1.02 and 1.13 nm. The apparent variation of sodium ion density in the bulk region originates from poor statistics, an expected result of the low ion concentration. A similar plot for II is illustrated in Fig. 4. The water, sodium, and chloride densities show similar behavior as in I, except that the chloride density has an additional, small peak at 1.06 nm, and the sodium density peak is lower in II. However, the phosphate density in II is significantly different from that in I. Since the oligonucleotide in II was initially further away from the surface, it formed a structure with the resulting free ions and surface charges that was less tightly bound and stayed further on average from the surface in II than in I. The first phosphate peak in II, originating from C(10) and T(11), is located at 1.12 nm compared to 0.96 nm in I. The free portion of the DNA also manifested higher mobility in II and reached 3.7 nm into the solution compared to only 2.6 nm in I.

The DNA in both simulations remained stacked on average with several backbone transitions occurring. Along the trajectories the oligonucleotides moved towards the surface in the first several nanoseconds and eventually settled into

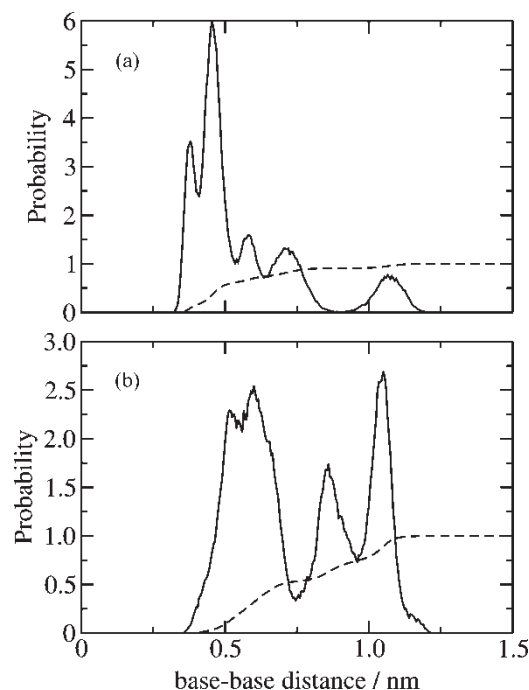


FIGURE 5 Probability distributions of the base-base distance in simulation I (top) and II (bottom). Solid line is the probability and dashed line is the integrating line.

configurations which were remarkably different from the starting configuration. In order to estimate the fraction of bases that is stacked, we calculated the distances between the pair of bases in each base step,

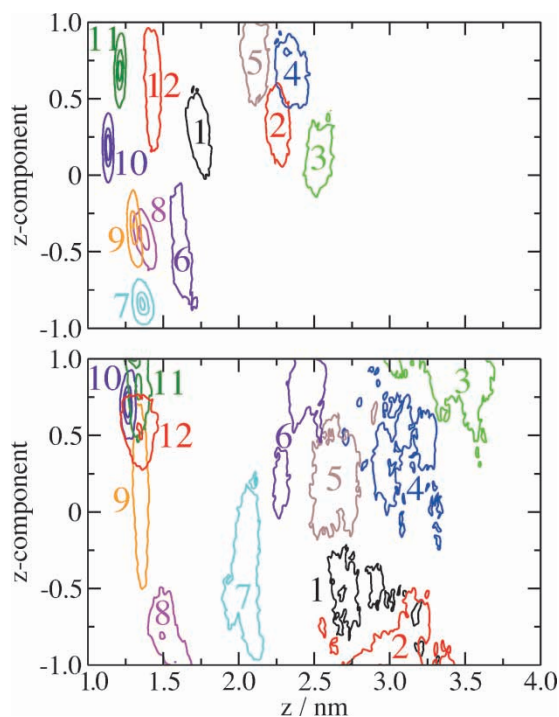


FIGURE 6 Contour maps of the probability distribution of the z -component of the hydrogen bond vector as a function of the average z coordinates of C3 and C4 in simulation I (top) and II (bottom). Contour levels shown are 5, 40, and 75 in I, and 2, 32, and 62 in II.

which can be defined as the distance between the glycosidic nitrogen atoms (N1 in pyrimidine and N9 in purine) in the consecutive bases [35]. Probability distributions of the base–base distance for **I** and **II** are then plotted in Fig. 5. The bases are considered stacked when the base–base distance is less than 0.6 nm. As demonstrated in the figure, the bases remained stacked 70% of the time in **I** and 32% in **II**. The larger extent of base stacking in **I** can partially account for the reduced mobility of the oligonucleotide observed.

A segment of the DNA was adsorbed on the surface with the phosphates bound to surface ammoniums in both simulations. Those surface-bound phosphates exhibited significantly reduced mobility compared to those far from the surface. Most of the bases in the surface-bound portion pointed away from the surface, with the hydrogen bond donors and acceptors available for base pairing. On the other hand, the part of the DNA far from the surface maintained its mobility and adapted various conformations during the simulations, especially in **II**, in which the DNA displays larger mobility. Here, we study the orientations of hydrogen bond donors and acceptors of the bases at different distances from the surface. To describe the orientations of the base, we designated a unit vector pointing from C6 to N3 in cytosine and thymine, and from C4 to N1 in adenine and guanine. We call it the hydrogen bond vector since it indicates the direction of hydrogen bond donors and acceptors in the bases. The distance of the residue from the surface is estimated by averaging the *z*-coordinates of C3 and C4 of the sugar ring. Since C3 and C4 are on the DNA backbone and are equally closest to the base, their averaged *z*-coordinates change very little when the orientation of the base fluctuates. For each base, we calculated the *z*-component of the hydrogen bond vector and the distance of the residue from the surface. A hydrogen bond vector with a positive *z*-component means the hydrogen bond donors and acceptors point upwards towards the solution and are available for hybridization, and vice versa. Figure 6 represents contour maps of the probability distribution. As shown in the figure, for simulation **I**, the nucleotides C(7), C(8), T(9), C(10), and T(11) were strongly bound to the surface and had little fluctuation in their orientations and positions. C(7) interacted strong with the surface ammoniums and pointed downwards, while C(8), T(9), C(10), and T(11) had their hydrogen bond donors and acceptors pointed away from the surface and were available for hybridization with a complementary strand. Their phosphates were attracted by the surface ammoniums and pointed downward. The other bases of the oligonucleotide were further away from the surface and retained greater mobility in term of orientation and position. Compared to **I**,

bases in **II** generally demonstrated a greater mobility. The bases T(9), C(10), T(11), and C(12) were more strongly adsorbed on the surface than other bases, and their upward orientation enable them to hybridize with complementary strands. Other bases were further away from the surface and had greater mobility to re-orient themselves in order to hybridize with a potential complementary strand.

As a whole, some of the bases remained in a stacked formation, with the surface-bound ones pointing away from the surface on average. Thus most of the bases would be available for recognition. However, the DNA has no obvious way to form a helix with a target strand because part of it is geometrically restrained by the surface and loses its flexibility to adapt helix conformations.

The final apparently stable structures of the DNA can be viewed from a vantage normal to the surface as well. In Figs. 2(b) and 3(b) we see the single stranded probe oligonucleotide formed a curved structure on the surface. During the non-equilibrium settling of the oligonucleotide onto the surface, the natural twist in the DNA oligonucleotide was essentially converted into curvature on the surface. In our simulations, the curvatures seen are substantial. Considerable variation (fluctuation) in these angles might be expected given the flexibility (number of single bond torsions) of an oligonucleotide.

Given the size of the electrostatic forces in the system, we view our findings as a general result. While only two of such computer experiments were performed we would extrapolate that a variety of individual strand structures are possible but that the overall topology would predominantly have the phosphates staying close to the surface, bases generally stacked and pointing upwards with a backbone that had converted helical twist into curvature of the oligonucleotide on the surface. This suggests only a non-Watson–Crick like structure with a target strand would be possible. This has been suggested previously to form a ladder like structure for the recognition [8–11]. Here, we suggest that the ladder would have significant curvature along the surface, and its actual conformation greatly depends on the conformation of the probe adsorbed on the surface.

Thermodynamics

In the experimental work done on a similar system, several characteristics of the thermodynamics found were unusual. First the rate of hybridization was very rapid compared to normal, tethered systems. In addition the affinity or free energy of binding was substantially more negative compared to a tethered oligo-probe system.

For a probe non-covalently immobilized near the surface between 3 and 10 Å we predict an increase of

10–20 kcal/mol in binding for 0.01 M NaCl and a concomitant change of the melting temperature. This is in good qualitative agreement with experiments made on oligonucleotides with a charge (pH) tunable surface. In those experiments [8–11], reasonably good specificity or discrimination was found. Using our theory for a standard duplex we would have expected better specificity under the same conditions for a duplex tethered at the appropriate distance.

The slight loss of specificity could be accounted for by an additional penalty to forming the hybrid. In our interpretation this penalty would come from the non-Watson–Crick pairing imposed on the system by the geometry of the probes on the surface. The structures formed in the simulation (above) were not strained and stacking persisted. Thus, we expect that the free energy penalty comes from both the lack of a normal twisted duplex and the presence of some defects as seen in the structures above.

CONCLUSIONS

We have developed a picture of hybridization of oligonucleotides electrostatically immobilized (untethered) to a surface. Theory and computer simulations have been used to investigate the nature of the specificity and affinity in such a system. Recent experiments indicated an increase in the kinetics and affinity of hybridization in systems with positively charged surfaces. Simulations were performed for a modified silicon dioxide surface with positively charged groups at neutral pH. The oligonucleotide was found to associate with the surface in salt water with the stacked bases pointed preferentially toward solution, away from the surface. Some significant curvature was found in the oligonucleotide which had essentially untwisted upon settling on the surface. Using an analytic solution to the linear PB theory of the electric double layer interaction between DNA and a hard surface we showed that tight binding high affinity is expected in this system, due to the surface field effects.

The simulations provided hypothetical structures which suggest a mechanism for specificity and, in combination with the theoretical interpretation of the thermodynamics, a mechanism for the change in affinity. The geometry found is such that only non-helical base pairs would be accommodated. A previous proposal included the characteristics of a duplex untwisted and stretched linearly along the surface forming a ladder like complex. The structure proposed for hybridization on such a surface here is non-helical and while well stacked [36] is somewhat irregular and curved in comparison. Thus we propose a ladder like structure with significant bends, many of which may be random. The change

in specificity is proposed to come from the penalty from forming such a bent ladder like duplex along with the possibility of defects in the ladder due to incomplete conversion of the twist to curvature, resulting in an occasional base not being pointed optimally for recognition by a target strand.

Work in our laboratories continues to probe the consequences of this system. It should be possible to check a variety of lengths of hybrids and check the end-to-end distances with energy transfer probes. This would result in information about the nature of the curvature on the surface. Work is in progress to consider the case of other electrochemically induced potentials.

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