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THE MELTING MECHANISM OF DNA TETHERED TO A SURFACE

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Abstract. The details of melting of DNA immobilized on a chip or nanoparticle determines the sensitivity and operating characteristics of many analytical and synthetic biotechnological devices. Yet, little is known about the differences in how the DNA melting occurs between a homogeneous solution and that on a chip. We used molecular dynamics simulations to explore possible pathways for DNA melting on a chip. Simulation conditions were chosen to ensure that melting occurred in a submicrosecond timescale. The temperature was set to 400 K and the NaCl concentration was set to 0.1 M. We found less symmetry than in the solution case where for oligomeric double-stranded nucleic acids both ends melted with roughly equal probability. On a prepared silica surface we found melting is dominated by fraying from the end away from the surface. Strand separation was hindered by nonspecific surface adsorption at this temperature. At elevated temperatures the melted DNA was attracted to even uncharged organically coated surfaces demonstrating surface fouling. While hybridization is not the simple reverse of melting, this simulation has implications for the kinetics of hybridization.

Key Words. DNA, melting, and microarray.

1. Introduction

The recent availability of complete genomic sequences from many organisms coupled with commercial microarray platforms give ample opportunity to conduct gene expression analysis [5]. DNA microarrays are analytical devices designed to rapidly determine the composition of multicomponent solutions of nucleic acids at relatively low cost [41]. Lately, they also have become an interesting topic in nanotechnology and various biosensor technologies [29, 35]. Oligonucleotide arrays most often have the DNA tethered to surfaces with longer target DNA molecules in the solution. While the number of uses of DNA chips is impressive, the understanding of the physical chemistry of these devices, both experimental and theoretical aspects, lags behind the technological applications [19].

Recent progress has been made on developing simple analytical models that take into account several parameters common to many of the experiments. Among the required parameters are the probes' lengths, densities, spacers, and grafting procedures, as well as, the targets' lengths, preparation protocols, and the hybridization solution conditions [13, 36–40, 49]. Such theories have sufficient accuracy for many

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applications but lack atomic detail and the concomitant mechanistic insights. All-atom molecular dynamics simulations of DNA on a surface have also been performed to provide more insight into the structure of DNAs and their interactions [44,45,47]. But, little is known about the atomic details of DNA melting near surfaces.

DNA melting and hybridization are fundamental biological processes as well as crucial steps in many modern biotechnological applications. The separation of double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA) is fundamental to replication in living organisms, and to the polymerase chain reaction (PCR). At equilibrium, DNA will separate when the free energy of the separated ssDNA is lower than that of the dsDNA. In most biochemical studies of DNA separation, the strands separate upon increasing the temperature of the sample until the DNA melts (thermal separation). In living organisms, however, DNA separation is not thermally driven, rather enzymes and other proteins induce the two strands apart. Experimental investigations of dsDNA separation using *force*-induced techniques, at temperatures where the dsDNAs are stable, have recently been performed (mechanical separation) [10].

Aspects of melting of duplex DNA have been studied for decades [15]. For short DNA with fewer than 12 base pairs, melting and hybridization can often be described by a two-state thermodynamic model as an equilibrium between single- and double- stranded DNA [7]. For longer DNA, the melting curve exhibits a multi-step behavior consisting of plateaus with different sizes separated by sharp jumps [24]. A popular description for these longer molecules is the zipper model [8], which allows for partially open (intermediate) states. End effects and sequence design also control the nature of the melting transition for DNA oligomers [24].

Although many of the thermodynamic properties of melting of free DNA are known, DNA melting in a constrained space, such as on surfaces, is still poorly understood [25]. DNA confined on surfaces exhibits a behavior different from that in free solutions. Surfaces order the solvent, cosolvents and salts in solution, sometimes strongly. Differences in solvent and salt activity are well known to induce structural changes in nucleic acids [22,47,48]. Experiments on DNA arrays have revealed substantial differences in the thermodynamics of hybridization for DNA free in solution versus surface-tethered DNA. The main observations include a surface dependent change, often a decrease, in the thermodynamic stability of the DNA duplex on the surface with a concomitant suppression of the thermal denaturation temperature of the duplex into single strands, and a dramatic broadening of the thermal denaturation duplex melting curve [12]. More detailed experiments demonstrated that these effects change as the surface density of probes increases [26,31,42], which is in agreement with theory [38].

Vainrub *et al.* [36] developed a mean field model of the Coulomb effects for surface bound DNA to understand the binding isotherms and thermal denaturation characteristics of the double helix. They found that the electrostatic repulsion of the assayed nucleic acid from the array of DNA probes dominates the binding thermodynamics, and thus causes a Coulomb blockage of hybridization. The results explain, for DNA microarrays, the dramatic peak in the hybridization efficiency and the thermal denaturation curve broadening as the probe surface density increases [3, 38–40].

The system of DNA-capped gold nanoparticles exhibits unique phase transitions and represents a new class of complex fluids. The melting temperature of the DNA