Dielectrophoresis as a tool for nanoscale DNA manipulation

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Abstract: The use of the dielectrophoresis as a tool for DNA manipulation is demonstrated experimentally using both unmodified 48500 base pairs long bacteriophage lambda dsDNA (λ-DNA), $\sim$16 μm in length, and 414 base pairs long thiol-modified natural dsDNA (avDNA), $\sim$140 nm in length. We show that both dsDNA types used are effectively directed between the planar gold electrodes by the positive dielectrophoresis while applying an AC voltage at frequencies between 500 kHz and 1 MHz. With high concentrations of dsDNA in buffer the attached dsDNA molecules are shown to form bundles or clumps (both λ-DNA and avDNA). Furthermore, we demonstrate the attaching of a single avDNA molecule to an electrode via gold-thiol bonding. Also the clear orientation and straightening along the electric field is seen in this case. In addition, the electrical conductivity of dsDNA is studied by measuring the full I-V characteristics of the samples.

Keywords: Dielectrophoresis; DNA; molecule manipulation; nanoelectronics; molecule electronics; biomolecule; nanotweezers.

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1 Introduction

During the past few years DNA has gained a lot of interest also among the disciplines other than biological or genetic research. This is due to its versatile self-assembly properties and potential use as a component of the future nanoscale devices. Consequently, electrical properties of helical double-stranded DNA (dsDNA) have been studied widely. However, the experimental results obtained by several different methods seem to be controversial, ranging from insulator [1, 2] to semiconducting [3, 4] and ohmic [5, 6] behaviour. Even superconducting properties of DNA have been observed [7]. This incongruity could be explained by the charge transport along the ds-DNA being sensitive to quality of the π-stacking of base pairs [8, 9].

To further investigate properties of DNA reliably, e.g., measure its conductivity in more controllable and reproducible manner or even realise devices using DNA as a building block, one needs effective tools to manipulate DNA. Due to the polarization of counterion cloud, DNA in aquatic solution is highly polarisable [10]. Thus, for these attempts, one can use so-called dielectrophoresis (DEP), which means an electric force, induced to a polarisable particle (neutral or charged) by a non-uniformity of the applied electric field [11]. Washizu and Kurosawa were the first who successfully used DEP in trapping, stretching and orientating of dsDNA of bacteriophage lambda (λ-DNA) [12]. Since then, a lot of work has been done concerning the DEP of λ-DNA (For a review see, e.g., [13, 14]). It has been shown that dielectrophoretic force increases with the increase in the length of DNA molecule [15], which makes it more difficult to use DEP for short sequences. So far, the dielectrophoretic manipulation of shorter 368 bp (base pairs) long DNA ($\sim$125 nm) has only been demonstrated with electrodeless system, where it is possible to apply much higher voltages which makes the DEP more efficient [15]. However, in order to fabricate electrical systems out of DNA, it is essential to have conducting electrodes and proper electrical connections between them and the DNA.

In order to immobilise the DNA and to form the necessary electrical contacts, we took advantage of the widely used chemical bond formed between the thiol-group and gold surface [16, 17]. We have previously tested this bonding together with DC electric field guiding resulting in selective coating of gold surface with thiol-modified oligonucleotides [18]. Combination of dielectrophoresis and thiol-gold bonding would be an efficient tool in fabricating more complex nanodevices or experimental setups. Furthermore, these techniques could be combined to other immobilisation strategies, for example avidin-biotin technology [19].

In this paper we report our results obtained in experiments using DEP

to guide both unmodified 48.5 kbp long λ-DNA and relatively short, 414 bp long, thiol-modified biological dsDNA (avDNA) between two closely spaced gold nanoelectrodes.

2 Fabrication and methods

Fabrication of the nanoelectrodes

As a substrate we used slightly boron-doped (100)–silicon wafer with thermally grown SiO_2 at the top as a passivation layer. To apply an AC electric field needed in DEP and to attach the DNA, we used two planar gold electrodes shown in Fig. 1. These electrodes were composed of narrow ($\sim$200 nm) finger-like wires with $\sim$140 nm wide gap in between.

Electrodes were fabricated using standard electron beam lithography with *polymethylmethacrylate* (PMMA) and *co-polymer* [P(MMA-MAA)] [containing *methacrylic acid* monomers (MAA)] resists as a double layer stencil mask. After patterning by scanning electron microscope (SEM) (LEO 1430+ equipped with Raith Elphy Plus -lithography software) the upper layer of the PMMA resist was developed by immersing the sample in a mixed (1:2) solution of *methyl-iso-butylketon* (MIBK) and *isopropylic alcohol* for $\sim$2 min. After that the sample was rinsed in an isopropylic alcohol. The lower layer P(MMA-MAA) was developed in a mixture of (1:2) *methyl glycol* and *methanol* for $\sim$30 s to obtain necessary undercut needed in the shadow evaporation process, which was applied in metallisation [20]. By varying the evaporation angles, this enables fine tuning of the gap with great accuracy. Gaps even as narrow as $\sim$10 nm can be achieved using this method.

Before evaporation, the mask was cleaned using O_2 plasma in reactive ion etcher (RIE) (Oxford Plasmalab 80 Plus). The evaporation took place in an ultrahigh vacuum (UHV) chamber, pressure being of the order of 10^{-8} mbar during the evaporation. The thicknesses of the evaporated gold layers were 22 nm, under which 5 nm of titanium was used to improve the adhesion of gold.

Preparation of DNA

Chemically bonded contacts between dsDNA and electrodes were achieved by gold-thiol bonding [16, 17, 18]. Double-stranded DNA containing a thiol group, i.e., $-$SH, in both ends was obtained by using *5'-thiol-modified oligonucleotides* as primers in the polymerase chain reaction (PCR). DNA oligonucleotides were purchased from Synthegen (Houston, Texas). Oligonucleotide

5'−HS−$(CH_2)_6$−GCC AGA AAG TGC TCG CTG AC was used as a forward primer and 5'−HS−$(CH_2)_6$− TTC TCG ACA AGC TTT GCG GG as a reverse primer. Chicken avidin copy-DNA [21] in pFastBac1-plasmid (Invitrogen) was used as a template in the PCR reaction. The PCR product (414 bp) was subjected to 1 % agarose gel electrophoresis and extracted with GFX^{tm} PCR DNA and Gel Band Purification Kit (Amersham Biosciences) and finally eluted to 6.5 mM Hepes pH 7.0 buffer. The concentration of the obtained avDNA was measured spectrophotometrically and the avDNA was stored in refrigerator. Commercial 48.5 kbp (∼16 μm) long λ-DNA (MBI Fermentas) was also used in some experiments.

Dielectrophoresis of dsDNA

Before the DEP experiments the substrate and the electrodes were cleaned using RIE with oxygen plasma to remove organic contaminants from the surface. The oxygen plasma also changed the originally hydrophobic SiO_2 surface to hydrophilic. In some of the experiments a short flash with CHF_3 was introduced after the oxygen plasma to return the hydrophobicity surface.

DEP experiments were performed by incubating a few microliter drop of dsDNA solution on the surface of electrodes and keeping it in moist chamber to prevent the drop from drying out while applying the AC voltage for DEP. After this the drop was rinsed with 6.5 mM Hepes buffer and DI water and helium dried. Waveform generator (Agilent 33120A) was used to produce sinusoidal AC signals for DEP.

In the DEP experiments with 16 μm long λ-DNA we used microfabricated parallel gold electrodes (See Fig. 2) with 12 μm separation. We used frequency of 500 kHz and the field strength of the order of 10^6 V/m. Concentration of λ-DNA was 0.5 μg/ml (15.6 pM) in the buffer solution containing 20 mM Hepes and 5 mM $MgCl_2$. Divalent Mg^{+2} ions were added to fix λ-DNA onto oxide surface which has a negative surface charge [22].

Most of the experiments were carried out using 414 bp (∼140 nm [23]) long thiol-modified avDNA molecules. For DEP to function properly it must dominate over the thermal Brownian motion of the particles, and therefore the smaller the DNA molecules are the higher gradient in electric field is needed to guide them [24]. Thus, only scaling down the electrode design used in λ-DNA experiment was not sufficient for short avDNA molecules, and to further increase the gradient of the electric field we changed the design to 'finger-like' with about 100 nm separation, which is slightly less than the length of the used avDNA. Experimental setup is represented in the Fig. 1. Frequency was varied from 500 kHz to 1 MHz and electric fields from 10^6 to 10^7 V/m. Concentrations of the used avDNA solutions varied from 2

to 100 nM. Buffer solution was composed of 3−6 mM Hepes and 0−2 mM sodium borohydride ($NaBH_4$). $NaBH_4$ was used as a reducing agent to cleave disulfide bonds formed during the storage.

Imaging

Atomic force microscope (AFM) (Veeco Dimension 3100) was used in the characterisation of the immobilised DNA between the surface electrodes. The AFM was operated in tapping-mode using silicon probes (Veeco MPP-11100) with resonance frequency of 200−400 kHz and spring constant of 20−80 N/m. Different AFM imaging modes, i.e., height, amplitude and phase, were used to distinguish different features from the sample. In the case of DNA, especially the phase imaging is a powerful tool due to its suitability for mapping of different components in composite materials and differentiating regions of high and low surface adhesion or hardness. Good example of this is seen in Fig. 5.

Conductivity Measurements

Conductivity measurements were performed inside an electrically shielded room, equipped with highly filtered feedthroughs for measurement lines. Alternating DC voltage biasing and low noise current preamplifier (DL Instruments Model 1211) were used to record I-V curves. DC bias voltage was taken from battery powered digitally controlled DAC. Controlling was done through optical control lines connected to measurement computer. Data was collected to computer using data acquisition card (National Instrument DAQ-6035E) and LabVIEW user interface. Low-pass RC filter (R = 10 kΩ and C = 3.3 μF) was used to cut high frequency transients from the DC bias voltage.

3 Results

Dielectrophoresis of λ-DNA

Main results of the first DEP experiment with $\sim$16 μm long λ-DNA are represented in Fig. 2. As seen in the figure, a lot of λ-DNA bundles is laying between the gold electrodes, but there is no λ-DNA outside of them. This clearly indicates the λ-DNA undergoing positive dielectrophoresis with the parameters used. The bundling of λ-DNA is clearly seen in closer visualisation and at the lower right micrograph in Fig. 2, a lot of single λ-DNA

molecules are seen to branch out from the bundles. However, no evident orientation or stretching of λ-DNA was observed. This could be, at least partly, due to parallel design of the electrodes, which reduces the gradients of the induced electric field or to extensive bundling of the λ-DNA molecules resulting to a λ-DNA network between the electrodes, which reduces the mobility of the λ-DNA.

Since there was not any immobilisation involved in the experiment, the λ-DNA was easily removed by flushing with DI water. This indicates that adhesion between the λ-DNA and the surface (SiO_2) is not strong. Furthermore, we can deduce that the added extra divalent Mg^{+2} ions did not help to fix λ-DNA onto surface or at least their effect was not dramatic [22].

Dielectrophoresis of avDNA

For DEP of short avDNA, we tested many samples with parameters systematically varied as described in the previous chapter. The avDNA used was always of the same form but its concentration was varied. The efficiency of the DEP was found to be very sensitive to the parameters, especially to the concentrations.

To distinguish the real effect of the DEP from the random adhesion of the avDNA or other particles to the substrate, we used reference electrodes in every experiment. These reference electrodes were situated in the vicinity ($\sim$50 μm away) of the electrodes used to generate alternating field of DEP, and were identical to them, except that the guiding voltage was not applied to them. The incubated drop of avDNA solution covered both electrodes at the same time.

Results after applying DEP in one of the samples are shown in Fig. 3, where the reference electrodes are on the left and the electrodes with applied AC voltage in the middle and also on the right. The two leftmost pictures are amplitude images while the right one is a phase image, which is shown because of its better resolution for imaging soft objects like DNA. As clearly seen from the figure, the electrodes used for DEP are covered with the avDNA while the reference electrodes are clean.

It is also observed that avDNA forms bigger ropes. This is mostly due to polymerisation of short thiol-modified avDNA molecules via thiol-thiol bonding as seen in Fig. 4, which is from another experiment, where the reducing agent ($NaBH_4$) was not used. Due to resultant stronger polymerisation, the polymerised avDNA molecules are clearly visible in this figure. On the other hand, in the experiment of Fig. 3 the reducing agent was used. The forming of ropes in that case could be due to insufficient concentration of $NaBH_4$ or to regular bundling usually observed in longer DNA molecules [1, 5], e.g., in

λ-DNA. Due to the large amount of avDNA on the top of the electrodes, one cannot reliably conclude anything about the stretching or orientation of the avDNA molecules in these samples.

In another experiment, shown in figure 5, less avDNA was observed at the electrodes after the DEP. Here, the avDNA appeared as solid clumps rather than separate bundles. In the phase image shown on the left in Fig. 5 the clumps are seen as very bright objects, which indicates them being much softer than the other materials around them. This is consistent with the fact that DNA, especially a thick clump of it, is much softer than the electrodes (Au) and the substrate (SiO_2).

To see the orientation of avDNA molecules in DEP more clearly we studied samples with less avDNA at the electrodes. An example is shown on the left in Fig. 6. The avDNA molecules were mostly fixed on the edges of the electrodes, as also observed by Washizu *et al.* with λ-DNA [22]. The schematic field lines are drawn to guide the eye.

On the right in Fig. 6, we also show results from an experiment where the amount of avDNA was reduces so that a single avDNA molecule was attached from its thiol-modified end to one electrode. This about 175 nm long molecule is straightened and oriented according to electric field. The natural length of a 414 bp long avDNA molecule in B-DNA form is only about 140 nm [23] which suggests that the observed molecule may be stretched [25] or dimerised by thiol-groups.

For every DEP sample, we also determined the electrical conductivity (actually resistance) by measuring the full I-V characteristics. The I-V curves were always nearly linear with a smooth increase of the slope at high voltages ($\gtrsim$ 0.5 V). The obtained resistances are of the order of few teraohms (TΩ), to be compared to the typical resistance of empty electrodes ($10-200$ TΩ). Also in the samples with bigger avDNA clumps or bundles, the resistance was of the same order. Yet, it has been suggested that inside a bigger DNA structure, it is more likely that single molecules retain their biological conformation and thus deformation of π-stacking by surface induced forces would be prevented [26], increasing the conductivity. Experiments where the amount of the attached avDNA is systematically varied would allow to study this question.

4 Discussion

The DEP using both λ-DNA and avDNA molecules succeeded well, but, as expected, the DEP of smaller molecules was more difficult to achieve, requiring more careful tuning of the parameters and also some additional

methods to be applied, e.g., the use of $NaBH_4$ as a reduction agent and a suitable washing procedure. The applied electric field was always of the order of $10^6 - 10^7$ V/m and it cannot be increased much since too high voltage would disentangle the formed thiol-gold bonds. High voltage also enables the electrolysis in the sample, causing a finite current via the buffer, which induces a lot of heat to the gap region and therefore denaturation of the attached DNA. Nevertheless, the field strength 10^6 V/m seems to be enough even for $\sim$140 nm long avDNA molecules as perceived from the results.

When varying the frequency, we discovered that, for the small molecules, the DEP seems to work best at frequencies $700 - 800$ kHz. With frequencies lower or higher than that, the effect was decreased. This can be explained by the frequency dependence of polarisation of the dsDNA and the buffer components. If dsDNA polarises more than the buffer surrounding it, it undergoes positive DEP whose strength depends on the difference in polarisabilities. Frequency dependence of DEP has been previously demonstrated with λ-DNA in [27]. They found maximum stretching at somewhat lower frequencies than us ($300 - 500$ kHz) which can be due to the different buffer solution and the longer dsDNA used in their experiment. The perception that the shorter the dsDNA is the higher is the optimal operating frequency for DEP, has also been observed in [15]. Our results agree with this observation. Also it was seen that, as a negatively charged molecule, dsDNA is very sensitive to DC offsets of the applied AC voltage, i.e., most of the DNA easily tend to drift toward an electrode having positive DC offset voltage.

As demonstrated here, DEP is an efficient method for manipulation and attachment of dsDNA, also for rather short dsDNA molecules. This type of manipulation can be applied as a tool in building nanoelectronic devices from DNA, as well as in constructing sensors for sequence-specific detection of DNA. In certain applications, the low conductivity can be increased by M-DNA deformation [28] or oxygen hole doping [29].

5 Conclusions

We demonstrated that dsDNA (both λ-DNA and avDNA) undergoes positive dielectrophoresis at frequencies between 500 kHz and 1 MHz. However, the parameters used should be carefully tuned according to the desired application, especially when using short avDNA ($\sim$140 nm). We succeeded in attaching dsDNA bundles or clumps (both λ-DNA and avDNA) between the planar gold electrodes, as well as a single $\sim$175 nm long double stranded avDNA molecule to one electrode (straightened as well as oriented according to applied electric field). We also studied the electrical conductivity of

avDNA. So far, we found the upper limit of about 1 TΩ for the avDNA resistance.

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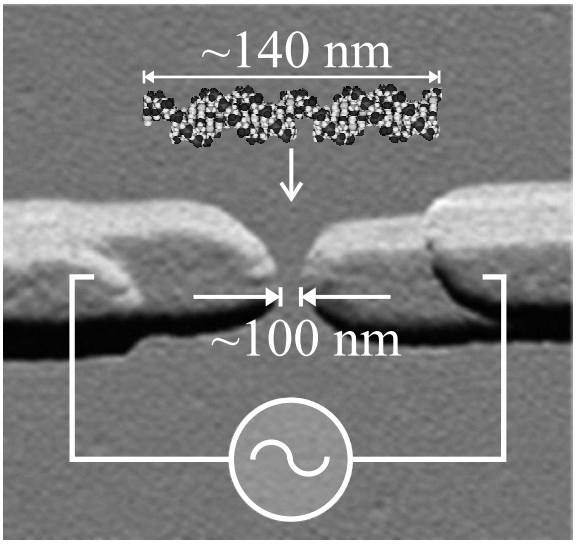

Figure 1: AFM image of the finger electrode nanostructure and experimental setup for dielectrophoresis of thiol-modified DNA helices. The drawn schematic of DNA molecule is not in scale with the AFM image.

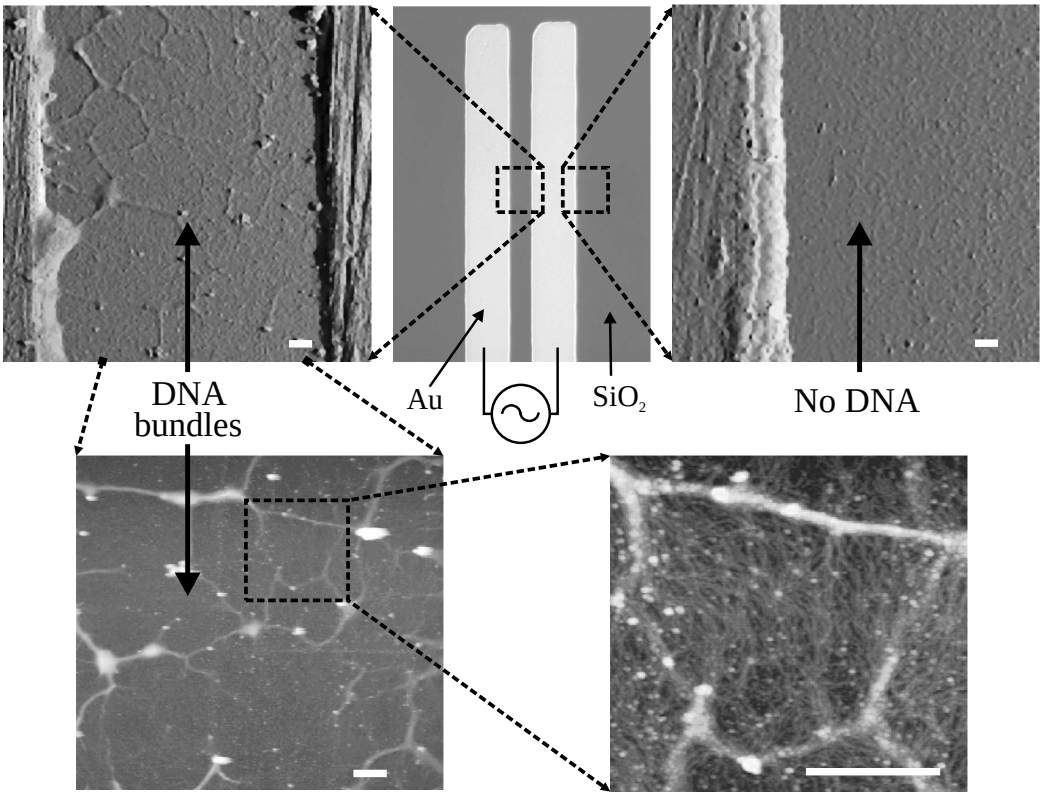

Figure 2: Images from the DEP experiment of λ-DNA. The white scale bar is 1 μm long in each picture. *Top middle*: Photomicroscope image of the parallel planar gold electrodes used in experiment. Separation between the electrodes was 12 μm. *Top edges*: AFM images of substrate between (left) and around (right) the electrodes. *Lower row*: Closer view of the λ-DNA bundles with AFM.

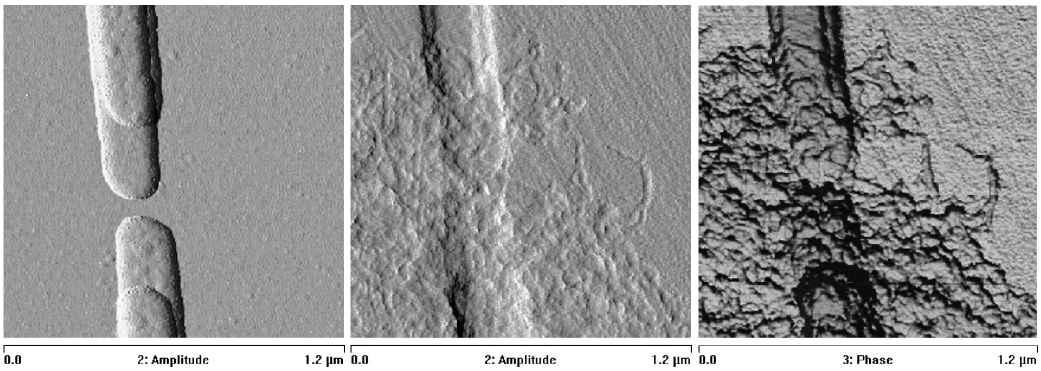

Figure 3: AFM amplitude image of the reference electrodes (left) and the electrodes used in actual DEP (middle). The DEP electrodes are also shown as a phase image (right), which visualises the fine structure of DNA better. DNA is clearly seen at the top of the DEP electrodes, but not on the reference ones.

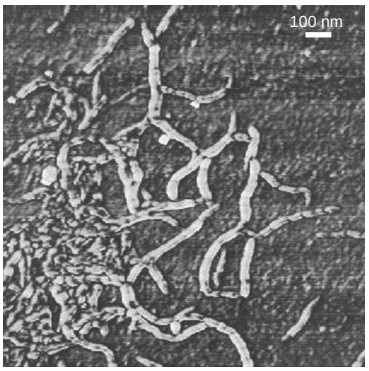

Figure 4: AFM (phase) image of avDNA molecules polymerised through the thiol-thiol bonding. In this experiment the reduction agent $NaBH_4$ was not used.

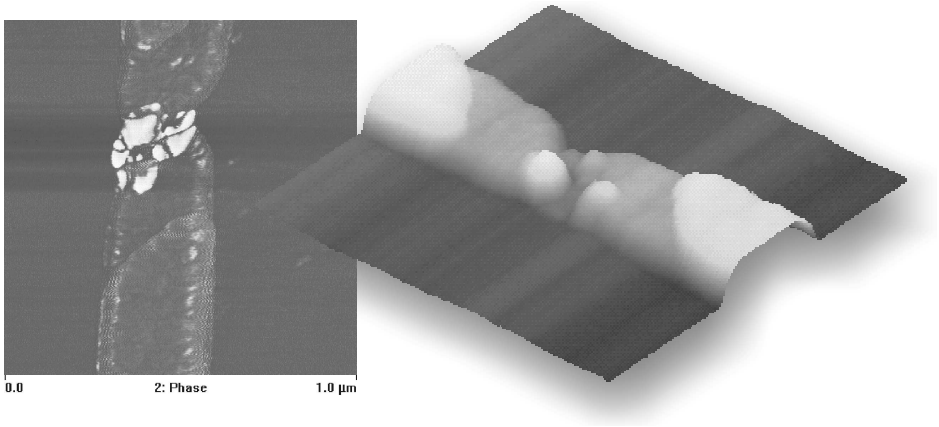

Figure 5: AFM image of small avDNA clumps localised between the electrodes in a DEP experiment. The right image is a regular 3D height image and the left one is a phase image showing soft materials as brighter areas.

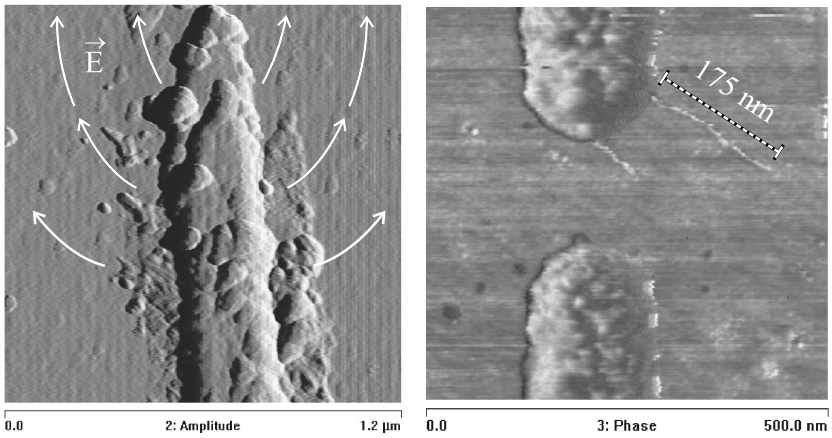

Figure 6: Orientation in electric field (left) and single avDNA attached to one electrode (right). The samples are from different experiments.