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Label-Free DNA Biosensors Based on Functionalized Carbon Nanotube Field Effect Transistors

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ABSTRACT

A carbon nanotube transistor array was used to detect DNA hybridization. A new approach to ensure specific adsorption of DNA to the nanotubes was developed. The polymer poly (methylmethacrylate$_{0.6}$-co-poly(ethyleneglycol)methacrylate$_{0.15}$-co-N-succinimidyl methacrylate$_{0.25}$) was synthesized and bonded noncovalently to the nanotube. Aminated single-strand DNA was then attached covalently to the polymer. After hybridization, statistically significant changes were observed in key transistor parameters. Hybridized DNA traps both electrons and holes, possibly caused by the charge-trapping nature of the base pairs.

Detection of biological events is of utmost importance for medical biological and biotechnological applications. The detection of DNA hybridization in particular has been a topic of central importance for its application in diagnosis of pathogenic and genetic diseases.[1−3] The rapid detection of anomalous genes responsible for a congenital disease is highly desired, and the reading of the human genome has opened the possibility of early detection and diagnoses of congenital/terminal diseases.[4]

In addition to the most common electrical detection techniques, such as cyclic voltammetry,[5] chronoamperometry,[6] chronopotentiometry,[7] impedance spectroscopy,[8] and various field-effect transistor,[9] the combination of electrochemical sensing setups with alternative biosensor techniques is leading to an enhancement of the understanding of biointerfacial phenomena.[10] The combination of electrochemistry and surface plasmon resonance, SPR, has often been applied to optically measure reaction kinetics of biomolecules in the presence of electric fields and to monitor in situ hybridization of DNA in the presence of different electrochemical fields. Waveguide-based techniques and electrochemistry[11,12] combine evanescent-field optical sensing with the electrochemical control of surface adsorption processes, allowing direct observation of mass adsorption as a function of an applied potential. Ellipsometry and electrochemistry have been used to study protein adsorption on metal surfaces and specifically human serum albumin on gold surfaces.[13] Electrochemical quartz crystal microbalance with dissipation monitoring measures changes in the frequency and dissipation factor of an oscillating quartz crystal upon adsorption of a viscoelastic layer.[14] Likewise, the combination of electrochemistry with simultaneous scanning probe microscopy, SECM technique[15,16] and hybrid techniques, such as SECM with SPR,[17] electrochemical quartz crystal microbalance,[18] fluorescence spectroscopy,[19] near field scanning optical microscopy,[20] electrogenerated chemiluminiscence,[21] and atomic force microscopy,[22] have generated a huge increase of the biosensors related research.

The development and utilization of micro- and nanostructured materials, new semiconductor,[23] quantum dots,[24] plasmonic nanoparticles,[25] nanowires,[26] magnetic nanoparticles,[27] and CNTs[28] have promoted extensive research activity in the field of biosensing, taking advantage of the many novel phenomena that occur at nanoscale. Semiconductor technology has matured and a rapid infiltration of new technology-based approaches in the field of sensors is taking place. The

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resulting new discipline of nanobiosensing is a good example of how engineering sciences, physics, chemistry, and biology coincide at the nanometer scale. In addition, nanotechnology provides new physical phenomena that can be utilized for sensing with a potential to reach single molecule sensitivity. One dimensional nanowires,[29] superconductor materials,[30] materials with giant magnetoresistence,[31] and near-infrared fluorescent carbon nanotubes, CNTs,[32] are being used in biosensing.

The possibility of a label-free electrical detection of the DNA-hybridization utilizing semiconductor field-effect sensors offers a new approach for a new generation of DNA chips with direct electrical readout for a fast, simple and inexpensive analysis of nucleic acid samples. Poghosian[9] has evaluated the possibilities and limitations of label-free detection of DNA hybridization with field-effect-based devices. The inherent miniaturization of such devices and their compatibility with advanced microfabrication technology make them very attractive for DNA diagnostics. Therefore, in recent years several attempts have been made to detect DNA by its intrinsic molecular charge using field-effect devices, like capacitive electrolyte-insulator-semiconductor (EIS) and field-effect transistor (FET) structures.[33−44] A DNA−FET is obtained by immobilizing well-defined sequences of ssDNA onto a field-effect transducer, which could convert the specific recognition process between the two cDNA single strands into a measurable signal. In most cases, the experimentally observed sensor response is interpreted as a result of a shift of the flat-band or threshold voltage of the field-effect structure, which arises from the binding or hybridization of the immobilized ssDNA with its complementary strand. In addition to novel semiconductors, organic thin films[45] and carbon nanotubes[46] are been used for biosensing applications.

Field-effect transistors (FETs) based on semiconductor carbon nanotubes (CNTs) have attracted much interest due to their superior properties such as high conductance, high mobility, and chemical inertness, compared to ones based on conventional semiconductor materials.[47] Since the first demonstrations,[48,28] much progress has been achieved in the fabrication and performance of CNTFETs.[49] The integration of biomolecules with CNTs enables the use of such hybrid systems as electrochemical biosensors, enzyme electrodes, immunosensors or DNA sensors and active field-effect transistors.[50] Transistors with a single carbon nanotube conducting channel and devices with nanotube network conducting channels have been fabricated and their electronic characteristics examined. Current flow in a "one-dimensional" system is extremely sensitive to minor perturbations, and in nanotubes and nanowires the current flows extremely close to the surface. Biological macromolecules bound to the surface of a nanotube and undergoing a binding event with change of charge state can thus perturb the current flow in the nanotube. The research groups of Dai,[51,52] Dekker,[53] Gruner,[54,55] and Tao[56] have investigated the application of carbon nanotube devices such as electrical biosensors where biomolecules including enzymes, proteins, and oligopeptides have been immobilized.

Several biosensors based on CNT field effect transistors have been described for the electronic detection of the following interactions: biotin-streptavidin,[55] human immunoglobin (IgG), various monoclonal antibodies, and pig serum albumin.[57,58] Likewise, the utilization of networks of CNTs for the detection of DNA hybridization where the DNA is bonded noncovalently to the CNTs have been reported by Star et al.[59] and Gui et al. [60] Nevertheless, the sensing mechanism is not fully understood and possibly involves charge transfer from adsorbed species, modifications of contact work function, substrate interactions, and carrier scattering by adsorbed species.[61] Heller et al.[62] and Kauffman et al.[63] have discussed recently the possible detection mechanism. Schottky barrier modification and/or charge transfer have been identified as the dominant mechanism responsible for device response. Kong et al.[64] have proposed a mechanism for the interaction of SWNTs and DNA using first principle electronic structure calculations. These authors have also reported that nonspecifically adsorbed ssDNA molecules cannot easily bind with their complementary strand and that a more robust immobilization method is necessary to capture the DNA probes onto the surface of CNT.[64] Molecular simulations carried out by Manohar et al. have shown that DNA bases adsorbed noncovalently, unstack from the CNT and reduce the effective adhesion.[65] Besides a strong link of the DNA sequence to the device, it is necessary for the CNTFETs to detect specifically the complementary sequence and to be insensitive to proteins and other contaminants. The specificity of DNA hybridization using electronic detection methods has been hardly addressed,[66] and most of the papers concerning DNA sensing have reported control experiments showing the sensor behavior versus noncomplementary sequences[67] in clean environment. Nevertheless, this does not guarantee that proteins having amine groups could bond to CNTs, giving false positives arising from nonoligonucleotides contaminants if the devices are not completely covered with the single-strand DNA

In this paper, the label-free detection of DNA hybridization using a large array of CNTFET is reported. We present a methodology for avoiding nonspecific DNA adsorption on CNTs and providing at the same time a stable binding for DNA probes through robust amide linkages. In our method, the DNA probes are covalently bonded to a polymer that is anchored noncovalently to the CNT walls. We report and analyze the changes of the electrical CNTFET characteristics upon interaction with the chemicals used for binding the DNA and upon hybridization. The hybridization is unequivocally detected upon a statistical treatment of the electrical data from a large array of devices.

A large array of back-gated carbon nanotube devices are fabricated using conventional microfabrication techniques, using previously reported methods.[68] Palladium was used as the contact metal, and the device channel length is about 2 μm, set by the gap length between the source and drain electrode. There are a total of 896 devices laid out on an 1 cm^2 chip. The devices were characterized using the Electroglas 2001X automatic probing station in ambient condi-

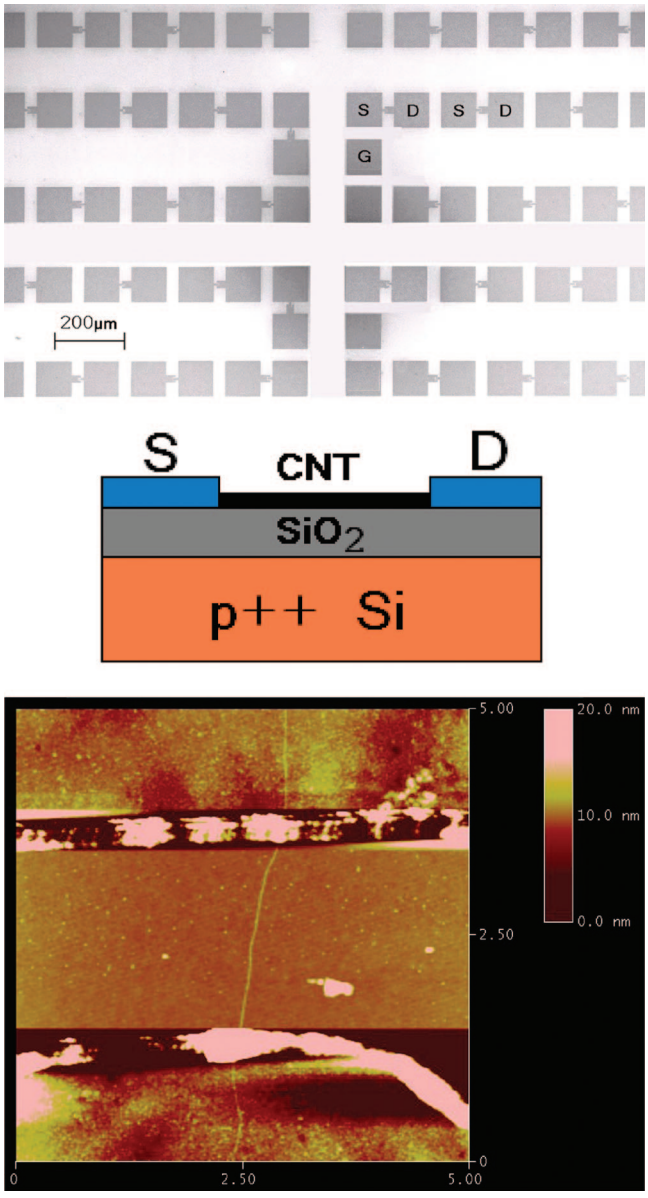

Figure 1. (Top) Scanning electron micrograph of the array of CNTFETs. S: source. D: drain. G: contact to back gate. 896 pairs of S/D electrodes are packed in 1 cm^2. (Middle) Schematic of device structure. The heavily doped p-type substrate is used as the gate. (Bottom) 5 μm × 5 μm AFM picture of a CNTFET device. Vertical scale: 20 nm.

tions. Figure 1 shows a typical device, and the design of the array.

Poly(methylmethacrylate$_{0.6}$-co-polyetyleneglycolmethylmethacrylate$_{0.15}$-co-N-succinimidyl methaccrylate$_{0.25}$) was designed to provide the bond between CNTs and DNA and simultaneously prevent any other nonspecific adsorption. This polymer (abbreviated as NO6 from here forward) is a multifunctional polymer consisting of polyethylene glycol and methacrylate groups as well as N-succinimidyl esters able to bond covalently aminated DNA sequences. The heterofunctional groups of NO6 interact electrostatically with the CNTs and provide the oxygen and heteroatoms moiety for the charge transfer as well as an aliphatic backbone that interacts hydrophobically with the CNT. Also, it has been reported that polyethylene oxide containing molecules spontaneously and irreversibly adsorb onto nanotubes from solution.[69] Polyethylene glycol methacrylate[70,71] has also been used to prevent nonspecific adsorption of proteins.

A Schlenk flask containing methyl methacrylate (0.49 g, 4.91 mmol), *N*-succinimidyl methacrylate (0.26 g, 1.40 mmol), poly(ethyleneglycol)methacrylate (0.25 g, 0.71mmol), and 2,2′-azobis(2-methylpropionitrile) (AIBN) (0.02 g, 0.12 mmol) solved in 10 mL of acetone was degassed using five freeze/pump/thaw cycles. The reaction mixture was placed in a preheated 65 °C oil bath and stirred for 24 h. The reaction mixture was then cooled to room temperature and purified by precipitation into hexane to yield the corresponding terpolymer as a white solid (0.93 g, yield: 93%). ^{1}H NMR in $CDCl_3$ (ppm) showed the following features: 4.14 (s, 2H, $-COOCH_2-$ from poly(ethyleneglycol) repeat units), 3.66 (m, 29H, CH_3O- from methyl methacrylate repeat units and $-OCH_2CH_2OH$ from poly(ethyleneglycol)repeat units), 2.83 (s, 4H, from N-succinimidyl repeat units), and 0.89−2.1 broad signal (m, aliphatic chain of the polymer). IR (neat): 3506, 3436, 2987, 2949, 1809, 1790, 1732, 1629, 1444, 1392, 1360, 1258, 1200, 1149, 1072, 1027, 982, 854, 745, 656, 489 cm^{-1}.

After polymer synthesis, a solution with a concentration of 10 mg/ml in dimethyl sulfoxide, DMSO, was prepared. The chip containing the CNTFET devices was immersed in the polymer solution for 6 h. The chip was rinsed 5 times with 5 mL of DMSO. Afterward, the chip was dried in nitrogen flow and in vacuum at room temperature for one more hour before performing the electrical characterization.

Oligonucleotide NH_2-ssDNA (5′-NH_2-hexyl-CGAGTCATTGAGTCATCGAG-3′) and its complementary C-ssDNA (5′-CTCGATGACTCAATGACTCG-3′) were prepared on 1 micromol scale using standard phosphoramidites. For the introduction of the amino group at the 5'-end, the phosphoramidite of *N*-6-monomethoxytrityl-(MMT)-6-aminohexanol (amino modifier C6, Glen Research) was used.

A solution of NH_2-ssDNA at a concentration of 0.1 mg/mL in a 20 mM phosphate buffer (pH 8) was prepared. The chip containing the CNTFET noncovalently functionalized with the polymer was covered with the DNA solution and left for 1 h at room temperature. The chip was washed five times with 5 mL of phosphate buffer, then dried in nitrogen flow and in vacuum as indicated before.

After reaction of NH_2-ssDNA with the polymer, the remaining N-succinimidyl groups of the polymer were blocked with ethanolamine ($NH_2CH_2CH_2OH$) (abbreviated EA from hereon). A 1% solution (pH 9) of EA in MilliQ water was deposited on the chip surface. After one hour, the chip was washed and dried following the procedures indicated above.

DNA hybridization was carried out with the complementary single-stranded 20mer oligonucleotide, C-ssDNA, (CTCGATGACTCAATGACTCG-3′) on the device chip where the N-succinimidyl groups remaining of the polymer were blocked. C-ssDNA were diluted in 2 × SSC buffer (300 mM NaCl;30 mM sodium citrate) at 0.1 mg/ml concentration. A

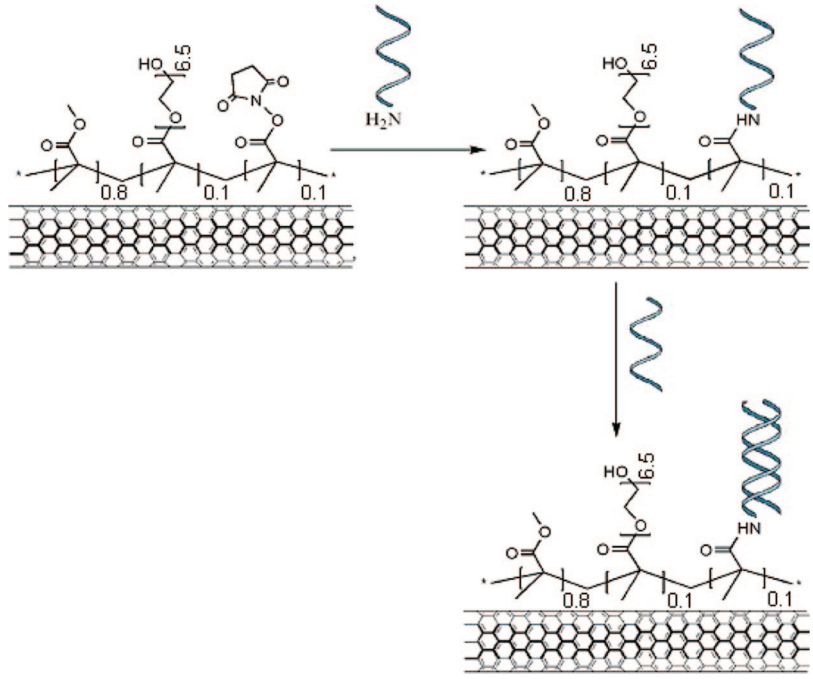

Figure 2. Schematic representation of the bonding of the polymer to SWNT (top right and left) and DNA hybridization (lower right).

few drops of solution were deposited on the chip and was incubated for two hours at 40 °C in a hybridization chamber. Later on, the chips were washed five times with 5 mL of a 0.1 × SSC solution before performing the electrical measurements. In Figure 2, a schematic representation of the NH_2-ssDNA reaction with the N-succinimidyl group of the polymer and the ssDNA hybridization is shown.

To demonstrate the importance of using the polymer NO6 to prevent nonspecific adsorption, we also perform a control experiment where NO6 was not used, and the DNA solution was deposited directly on the CNTFETs, and hybridization performed afterward. As we shall discuss later, the device response is dramatically different.

Only CNTFET devices showing transistor behavior and having and on/off ratio higher than 100 are used for the DNA hybridization sensing. This is done to reject devices that contain metallic nanotubes.[68] A device containing at least one metallic nanotube lowers the on/off ratio substantially. Since the CVD growth of nanotube yields an uncontrolled diameter and chirality, the contact resistance to these tubes, as well as the key device parameters, can vary considerably from device to device. In this work, we use data from a large set of CNTFETs. Specifically, we compile statistical distribution of key device parameters, as defined in Table 1, and observe the changes in these distributions after each step in the process. We then determine if the changes are statistically significant and postulate possible sensing mechanisms. The

Table 1.

parameter	definition
V_g	gate voltage
I_d	drain current
V_{tp}	threshold voltage
I_p	drain current at $V_g = -15$ V
I_N	drain current at $V_g = +15$ V

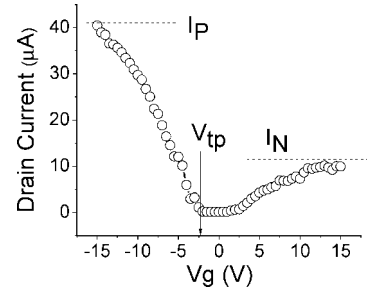

Figure 3. Definition of device parameters. I_p: drain current at $V_g = -15$ V. I_N: drain current at $V_g = +15$V. V_{tp}: threshold voltage.

definitions of these parameters are further illustrated in Figure 3.

The drain-current (I_d) versus gate voltage (V_g) characteristics of typical CNT transistors are shown in Figure 4. All the bare devices show p-type or ambipolar transistor behavior. In control samples, it was determined that neither DMSO nor the buffers used produced statistically significant changes in key device parameters, indicating that the observed electric changes are only due to the chemicals/biomolecules used and not to the solvents. Because the threshold voltage depends on the sweep direction of the back gate voltage, due to water[72] and other charge traps, a separate V_{tp} is extracted for the forward sweep (V_g from −15V to +15V) and the reverse sweep (V_g from +15V to −15V).

Figure 4 shows the change in the I_d-V_g curve as DNA is hybridized on a typical CNTFET. The device shown in Figure 4a was treated with the polymer NO6 to prevent nonspecific adsorption, and the last two steps shown here involve the blocking of excess succinidimyl groups using ethanolamine (EA) blockers, followed by hybridization. As evident from Figure 4a, there is a significant increase in the amount of hysteresis, due to the increase in the number of

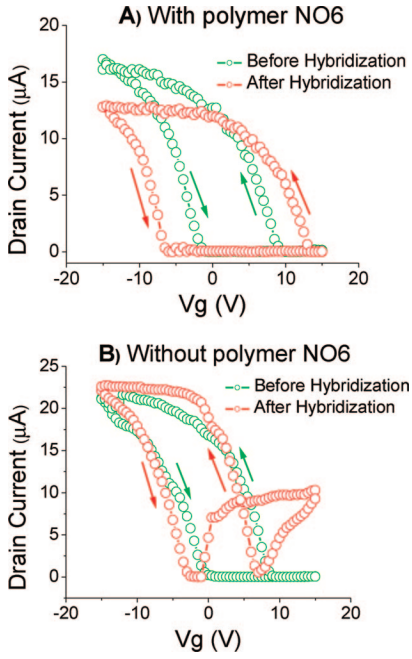

Figure 4. (A) I_d-V_g curve of a device functionalized with NO6 polymer, before and after DNA hybridization. (B) I_d-V_g curve of a device without the NO6 polymer before and after DNA hybridization.

charge traps. The simple shift in the threshold voltages in the form of increased hysteresis points to charge traps distributed along the length of the nanotube. This suggests strongly that with the utilization of the polymer NO6, the DNA molecules can be attached preferentially on the bulk of the CNT and not aggregate around the electrodes. If the charge traps are aggregated near the electrodes, a much more different electrical response than a simple shift in threshold voltages. The contact resistance would be much more different.

The device in Figure 4b was not treated with the polymer NO6, and the solution of ssDNA probes were deposited directly onto the chip with CNTFETs. Hybridization was then performed directly on the chip. As opposed to the device in Figure 4a, there is little change in the amount of hysteresis. However, the current I_N at $V_g = +15$ V is significantly increased, such that the originally p-type transistor is now ambipolar. It is well known that in normally p-type CNTFETs, there can be ambipolar conduction caused by electrons injecting from the drain electrode, via a combination of thermionic emission over the Schottky barrier and direct tunneling.[51] Since neither the temperature nor the drain voltage was changed, the increase in I_N is necessarily due to enhanced tunneling, caused perhaps by an excess accumulation of negative charges at the drain. In this case, the negatively charged DNA molecules deposited onto the chip can aggregate near the metal electrodes simply from capillary forces. Effectively, this would lead to heavy n-type doping of the nanotube near the contacts, making the tunnel barrier much thinner for the electrons, thereby increasing I_N (illustrated in figure 6). Lowering contact resistance by heavily doping the contacts is commonly used in conventional MOSFET transistors and is demonstrated for CNTFETs by using potassium dopants.[78] In general, any solid materials dispersed in a solution phase onto a surface tend to aggregate near edges or corners by capillary forces. In a structure like the CNTFET, the sidewalls of the contact electrodes present themselves as such a location. The above results imply that without the use of the polymer NO6 to anchor the DNA probes, DNA can be adsorbed nonspecifically on the sensor devices. If there were any other similarly charged biomolecules or contaminants in the buffer solution, these can also aggregate on near the electrodes via the same physical force, causing a similar sensor response. In that case, it will not be possible to distinguish DNA hybridization from other biological events.

The above observations are not limited to two isolated devices. The general behavior is reflected in the distribution of I_N and V_{tp}. The distributions of I_N (Figure S1, Supporting Information) show that I_N increases very significantly when NO6 was not used. However, I_N stays about the same when the polymer was used (Figure S2, Supporting Information). The distributions in V_{tp} also demonstrate that there is a more significant change in hysteresis when NO6 was used to anchor the DNA probes (Figure 5a), relative to the case when no polymer was used (Figure 5b). These results imply that the electrical response observed in Figure 4a,b are typical and can be reliably expected from a large number of devices.

In general, sensors are useful only when there is specificity. The sensor should only respond to a particular target molecule, and nothing else. CNTFETs, especially the contact resistance, are sensitive to a great number of things. Indeed, it was shown that CNTFET can respond very sensitively to hydrogen[51] or oxygen.[79] In the absence of a polymer such as NO6 to anchor the DNA probes on the nanotubes, it will be possible for not only the DNA molecules, but any other kind of biomolecules and contaminants to aggregate near the electrodes and cause a response in the CNTFET sensor. Therefore, a functionalized polymer such as NO6 that allows for capturing of specific target molecules (DNA in this case) is tremendously important to achieve useful sensor response.

A simple analysis of the V_{tp} distribution of devices with DNA probes anchored on NO6, shown in Figure 5a, allows for an estimation of the number of DNA molecules detectable using this statistical method. The large increase in the hysteresis in the I_d-V_g curves following DNA hybridization, as shown in Figure 5, reflects an increase in the density of charge traps. The shift of V_{tp} to more negative values for the forward sweep (V_g from -15 to $+15$ V) indicates electron traps, whereas the shift to more positive values for the reverse sweep (V_g from $+15$ to -15 V) is evidence of hole traps. It is known that both electron and hole transport can occur on a double strand DNA, with holes hopping on guanine and adenine bases, and electrons on cytosine and thymine bases.[75] The shift in V_{tp} seen here could be a manifestation of electron trapping by the guanine and adenine bases and hole trapping by the cytosine and thymine bases. In an earlier step where only ssDNA is attached, such trapping is much less likely to happen, since ssDNA assumes a different conformation and charge trapping is much less efficient, possibly due to enhanced transfer to the environment.[75,76] We can estimate

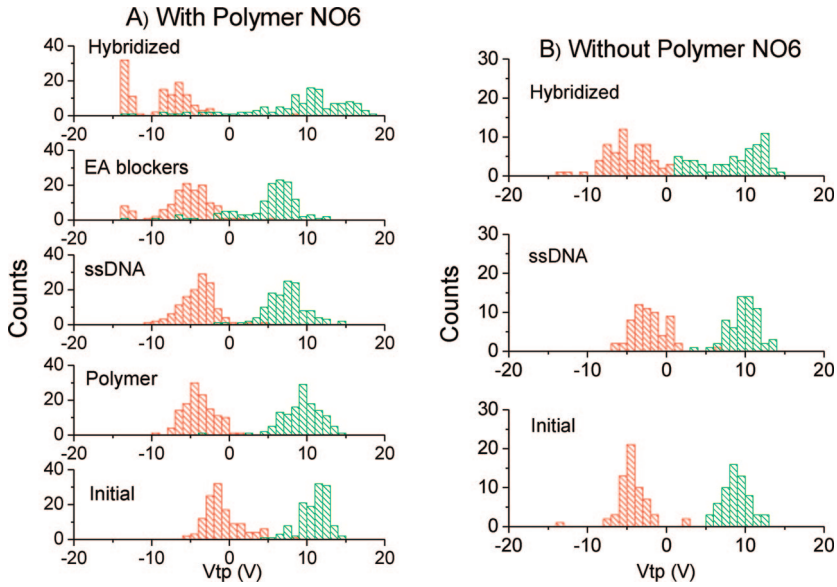

Figure 5. Distribution of V_{tp} for devices undergoing DNA hybridization. The V_{tp} distribution of initial, bare devices is at the bottom of each graph. The top of each graph corresponds to the distribution after hybridization, the last step. (A) Devices with NO6 functionalization. Red: forward sweep (−15 to +15 V). Green: reverse sweep (+15 to −15 V). Total number of devices: 128. (B) Devices without NO6 functionalization. Red: forward sweep (−15 to +15 V). Green: reverse sweep (+15 to −15 V). Total number of devices: 62.

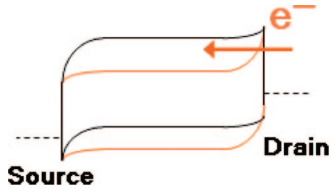

Figure 6. Schematic of electron tunneling from the drain electrodes. Orange: tunnel barrier thinning due to accumulation of negative charge near the electrodes.

roughly the trap density from the change in the average of the V_{tp} distribution. In any long-channel MOSFET, the threshold voltage is represented by eq 1, where C_g is the capacitance between gate and nanotube (about 30aF/μm in this geometry),[77] φ_M and φ_S are the workfunction of the gate and the semiconductor, respectively, φ_F is the Fermi level in the semiconductor relative to the midgap, Q_{dep} is the depletion charge inside the semiconductor at inversion, and Q_t is the interface and oxide fixed charges.

$$V_{tp} = \phi_M - \phi_S + 2\phi_F + \frac{Q_{dep}}{C_g} + \frac{Q_t}{C_g} \quad (1)$$

The CNTFETs used are not intentionally doped to control φ_F or Q_{dep}. In adding each molecule to the CNTFET, φ_M, φ_S, and C_g remain unchanged, and only Q_t is modified as a result the charge trapping behavior of the biomolecules. Thus, any observed shift in V_{tp} is a result only of the biomolecules. For a 2 μm long transistor, we can estimate a trap density ΔQ_t, using the following equation:

$$\Delta Q_t = C_g \times \Delta V_{tp} \quad (2)$$

For $\Delta V_{tp} = 2$ V, we obtain a charge of 1.2×10^{-16} coulomb or about 750 electron traps. For one electron trap per C or T base and 20 such bases for each hybridized DNA, we estimate that on average, there are about 40 hybridized strands per nanotube device. Approximating each strand to occupy an area of 1 nm in radius, each strand would occupy 3.14 nm^2. For 40 strands, this represents about 2% of the available surface (upper half-surface) of a 2 nm-diameter SWNT covered by the polymer that has 25 wt % of active esters. For the reverse sweep, the shift in the average V_{tp} is somewhat larger, although the spread in the distribution has increased significantly as well. If each G or A base were to act as a hole trap, then the shift in V_{tp} (reverse) should be the same magnitude. Improved device design with reduced initial hysteresis, or a more uniform deposition of the biomolecules across the chip may reduce the spread in the distribution and show more clearly the consequence of hole trapping.

The electronic detection of the DNA hybridization has been carried out by using a large array of CNTFETs. The method uses a synthetic polymer that is well adsorbed to the walls of CNT and carries activated succinimidyl ester groups used to fix the NH_2-ssDNA probes. This method of anchoring the probe DNA can prevent the nonspecific adsorption of DNA molecules onto the CNTFET that can occur by virtue of aggregation on the sidewalls of the contact electrodes. The mechanism of the CNTFETs' electrical response is changed significantly by the utilization of the polymer NO6. DNA hybridization produced statistically significant changes in the threshold voltages reflecting the charge trapping character of hybridized DNA. Through these observations it has been possible to detect the charge transfer inherent to the hybridization reaction.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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