

Novel Dielectric-Modulated Field-Effect Transistor for Label-Free DNA Detection

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Abstract

This paper describes two competing factors, a dielectric constant and a charge in a dielectric-modulated field-effect transistor (DMFET), for label-free DNA electrical detection. Essentially, the DMFET electrically detects biomolecules by monitoring a change of threshold voltage caused by a change of dielectric constant when targeted biomolecules are confined to a nanogap of the DMFET. In particular, when charged biomolecules such as DNA are introduced into the nanogap, the DMFET operation can be changed by both the dielectric constant and the strength of the charges in the gate dielectric layer.

In this work, negatively-charged DNA and neutralized DNA by sodium ion treatment are carefully compared using an n-channel DMFET in order to verify the contribution to a change of threshold voltage by the DNA charges. In the case of neutralized DNA, the threshold voltage is shifted to the negative side as previously reported. However, in the case of negatively-charged DNA, the threshold voltage is shifted to the positive side due to the negative charges of this DNA. Hence, a p-channel DMFET is clearly preferable in detections of negatively-charged DNA.

Keywords: DMFET, DNA, Charge effect, Dielectric constant effect, Label-free electrical detection, Nanogap

Introduction

Technical advancements in silicon-based microelectronics have been achieved over the past three de-

CADES, primarily through the scaling of device dimensions, in order to attain improvements in circuit speed and a reduction in size according to Moore's law. An essential aspect of this progress is miniaturization using microfabrication technologies¹⁻³. Applying silicon microfabrication technology to the detection of nucleic acid hybridization can provide direct electronic detections of biomolecular binding processes. The time and cost of the detection process can be reduced considerably due to a full compatibility with the fabrication process of the semiconductor industry. Nucleic acid hybridization is a rudimentary tool in sequence analysis, gene expression monitoring, genotyping in the fields of genomics and clinical diagnostics, pharmacology, environmental studies, the food industry, and in DNA computing. Thus, various techniques such as fluorescent⁴⁻⁶, electrochemical⁷⁻⁹, enzymatic¹⁰⁻¹¹, and magnetic¹²⁻¹³ methods have been developed to detect the hybridization of DNA. Unfortunately, these methods require labeling steps, which are unwieldy and time-consuming procedures. As a result, label-free hybridization¹⁴⁻¹⁵ technology has become attractive to researchers in this field. This study reports on a novel approach for label-free detection of DNA hybridization involving the utilization of a nanogap.

Recently, a dielectric-modulated field-effect transistor (DMFET) that had been revamped from a traditional and conventional metal oxide semiconductor field effect transistor (MOSFET) was reported¹⁶. The DMFET detects biomolecules through change in dielectric constant caused by the introduction of biomolecules in a nanogap located at the edge of the gate dielectric in the DMFET. The as-reported DMFET showed high detection sensitivity for biotin-streptavidin-specific binding, which was known to be nearly neutralized. However, in nature, there are many biomolecules that show charged behaviors; DNA is one of the most important of these biomolecules, as it is known to be the largest negatively-charged molecule¹⁷. When charged biomolecules such as DNA are introduced into the nanogap of a DMFET, its operation can be affected by this charge effect despite the known dielectric constant effect¹⁶. This study focuses primarily on analyses of these two impacts on label-free electrical DNA detections. Thus, negatively-charged DNA and neutralized DNA are detected using an n-channel DMFET and are then carefully

compared. The charge effect is then extracted. It was found that the n-channel DMFET can preferably detect neutralized or positively-charged biomolecules. In contrast, a p-channel DMFET is attractive for improvements to the detection sensitivity of negatively-charged biomolecules.

Results and Discussion

Device Structure and Fabrication Process

Figure 1(a) shows a cross-sectional view of a DMFET. The main difference between a DMFET and a conventional MOSFET involves the nanogap at the edge of the gate dielectric at which biomolecules are attached. In a conventional MOSFET, an applied gate voltage creates an electric field that can affect the channel potential in a silicon substrate through the gate dielectric material. The conventional MOSFET turns on when a channel forms on the silicon substrate by the critical gate voltage, the threshold voltage (V_T). In a DMFET, however, the same amount of gate voltage cannot create a great enough electric field that sufficiently turns on the silicon channel because the electric field becomes weakened by the nanogap as it is filled with air. In such a case, the dielectric constant of SiO_2 is 3.9, while that of air is 1. As a result, the V_T value of the DMFET is larger than that of the conventional MOSFET. However, if the nanogap is filled with biomolecules, the electric field due to the increased dielectric constant, compared to air, is strengthened again; hence, V_T is decreased. By monitoring this V_T change, the specific binding of biomolecules can be detected electrically without labeling.

Figure 1(a) shows the fabrication process flow of a DMFET. This process flow is similar to that of a conventional MOSFET. First, source and drain regions are defined by photolithography and ion implantation after a device-isolation step. Subsequently, SiO_2 , Cr, and Au are sequentially grown and deposited by thin film processes. The SiO_2 layer forms the gate dielectric of the DMFET. The Cr layer is a sacrificial layer that leaves the nanogap at the edge of the gate after selective wet etching. The Au layer is the gate electrode of the DMFET. After deposition of these three layers, they are patterned by photolithography and subsequent etching processes. The nanogap was then formed by lateral wet etching of Cr. Figure 1(b) shows a transmission electron microscopy (TEM) image of a cross-sectional view of the nanogap. The height of the nanogap, which was fitted to the size of target molecules, is 15 nm.

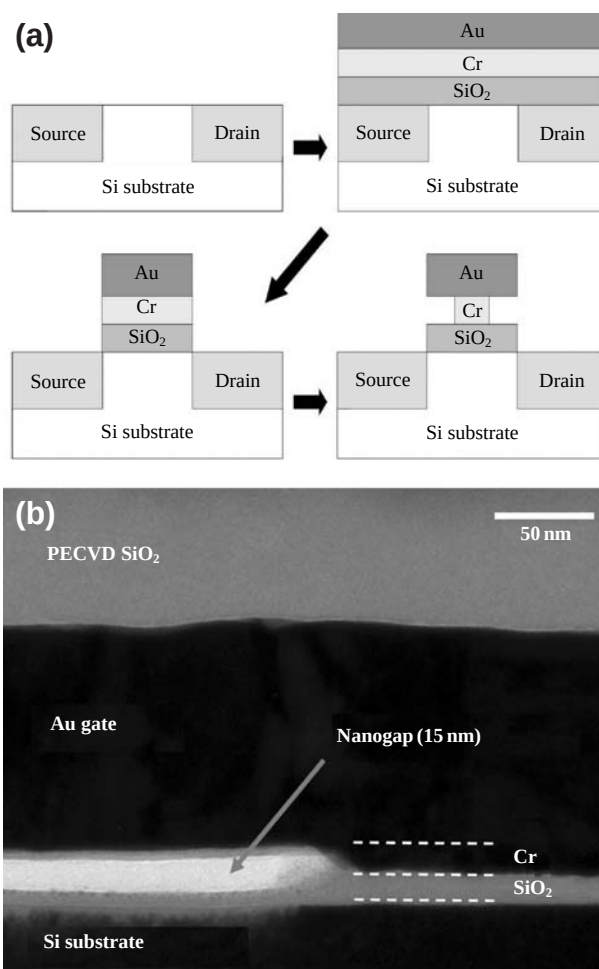


Figure 1. (a) process flow and (b) TEM image of the nanogap.

Operational Principle and Simulations

In a conventional n-channel MOSFET, V_T , which determines the on-/off-state of a device, is modeled by Eq. (1).

$$V_T = V_{FB} + 2\phi_B + \frac{Q_{dep}}{C_{ox}} - \frac{Q_{fix}}{C_{ox}}, \quad (1)$$

where V_T is the threshold voltage, V_{FB} is the flat band voltage, ϕ_B is the surface-band bending, Q_{dep} is the depletion charge density in the silicon substrate, Q_{fix} is the fixed charge density in the SiO_2 , and C_{ox} is the capacitance of the gate dielectric material (SiO_2).

By applying this equation to the structure of a DMFET, V_T in the nanogap region of the DMFET can be modified by Eqs. (2) and (3).

$$V_T = V_{FB} + 2\phi_B + \frac{Q_{dep}}{C_{DMFET}} - \frac{Q_{fix}}{C_{DMFET}} \quad \text{and} \quad (2)$$

$$\begin{aligned} \frac{1}{C_{DMFET}} &= \frac{1}{C_{mole}} + \frac{1}{C_{air}} + \frac{1}{C_{ox}} \\ &= \frac{T_{mole}}{k_{mole}\epsilon_o} + \frac{T_{air}}{\epsilon_o} + \frac{T_{ox}}{k_{ox}\epsilon_o}, \end{aligned} \quad (3)$$

where C_{DMFET} is the total capacitance of the gate dielectric materials in the DMFET, C_{mole} , C_{air} , and C_{ox} indicate the capacitances of the biomolecule, air, and silicon oxide, respectively, T_{mole} , T_{air} , and T_{ox} denote the thicknesses of the biomolecule, air, and silicon dioxide, respectively, and k_{mole} and k_{ox} are the matching dielectric constants of the biomolecule and silicon dioxide, respectively.

In Eq. (2), V_{FB} , ϕ_B , and Q_{dep} are independent of C_{DMFET} , which can be changed only by the dielectric constant of the biomolecules and charges (Q_{fix}) that the biomolecules have. Apart from the nanogap region in Figure 1(a), silicon dioxide (SiO_2 , $k_{ox}=3.9$) is the only dielectric material, and V_T is always lower in SiO_2 than in the air ($k_{air}=1$) nanogap region. Thus, V_T more sensitively responds to the changes in the diele-

tric constant in the nanogap region.

In the case of a neutralized DNA introduced in the nanogap, V_T can be estimated according to Eqs. (2) and (3), and can be changed by the hybridization of a target DNA to a probe DNA previously immobilized in the nanogap. The thickness of the biomolecule layer is fixed; its density begins to increase, which leads an increment of the dielectric constant of the biomolecule layer. Hence, the V_T shift can be estimated by Eq. (4).

$$\Delta V_T \propto \frac{1}{C_{DMFET}} \propto \frac{1}{k_{mole}} \quad (4)$$

Equation (4) indicates that V_T decreases when the target DNA attaches. This result was verified by simulation with the aid of SILVACO¹⁸. Figure 2(a) shows the simulation condition, and Figure 2(b) shows the result of the simulation and a trend that is consistent with Eq. (4).

V_T can be calculated from Eqs. (2) and (3) when the negatively charged DNA is introduced into the nano-

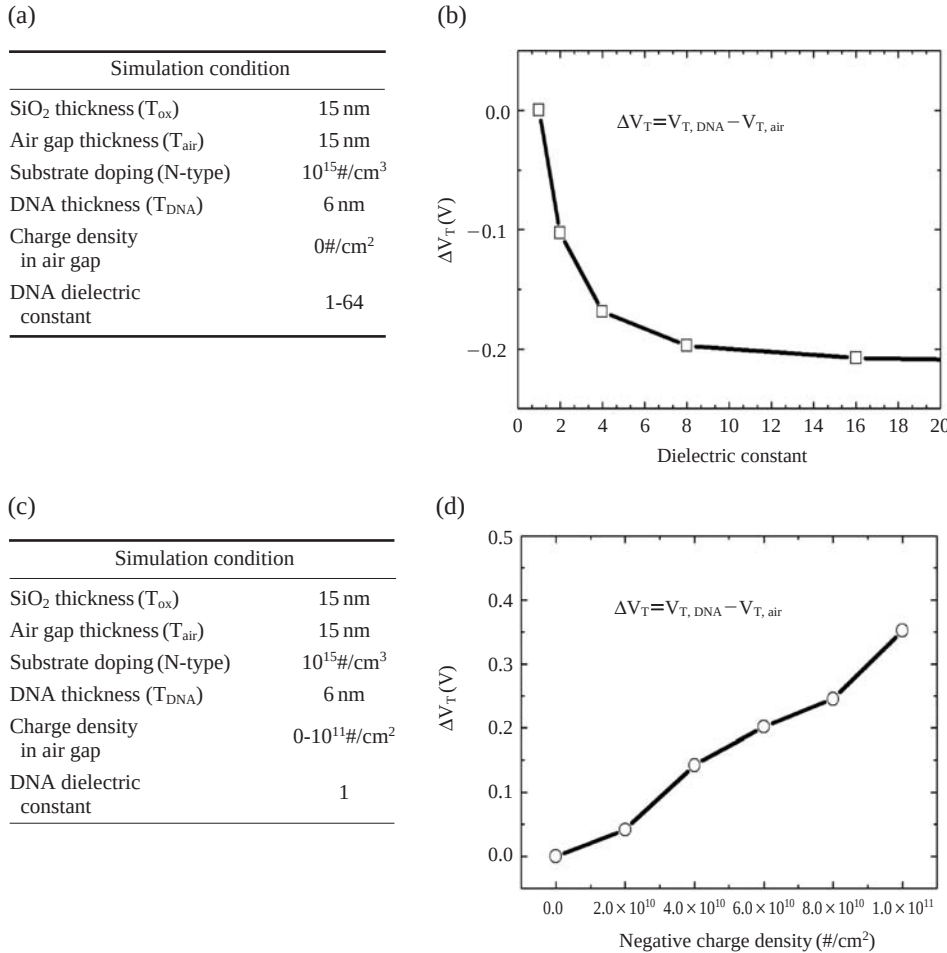


Figure 2. Simulation conditions and results: neutralized DNA (a), (b) and negatively-charged DNA (c), (d).

gap. If the dielectric constant change is assumed to be negligible for simplification, the charge density (Q_{fix}) due to the target DNA is the only factor that changes V_T . Subsequently, the V_T shift can be estimated by Eq. (5).

$$\Delta V_T \propto -Q_{fix} \quad (5)$$

Equation (5) implies that V_T increases linearly with the hybridized target DNA due to the negative charges of the DNA. This result was also verified by simulation. Figure 2(c) shows the simulation condition while Figure 2(d) shows the results of the simulation and trend that are consistent with Eq. (5).

According to the aforementioned trends of the V_T shift that were shown to depend on the dielectric constant and charge effect, these two factors can be considered to compete toward an increase or decrease in V_T . Thus, combining the two factors, a net V_T shift can be estimated by Eq. (6).

$$\Delta V_T \propto \frac{1}{k_{mole}} (Q_{dep} - Q_{fix}) \quad (6)$$

In order to investigate the trend of V_T shift for charged biomolecules, another simulation was carried out. Figure 3 shows that V_T decreases when the dielectric constant of the biomolecule layer is less than 4, whereas it increases when the dielectric constant of the biomolecule layer is larger than 4. In the first region, where V_T decreases, the dielectric constant effect is dominant. In the second region, where V_T increases, the charge effect is dominant. Figure 3 also implies that the V_T shift is not as large as we expected owing to the two competing factors for the negatively-charged DNA detections using the n-channel DMFET.

The Dielectric Constant Effect Versus the Charge Effect

The first experiment investigated the effect of the dielectric constant versus the charge. Fabricated devices were dipped for 2 hours into a proper solution containing a probe DNA with a SAM layer at one its terminals. One group of samples was then dipped into a neutralized DNA solution for an analysis of the dielectric constant effect, while another group of samples was dipped into a negatively-charged DNA solution for an examination of the charge effect. Additionally, a perfectly-mismatched DNA solution was also used as a third control group.

Figure 4 shows V_T shifts of the three groups. Figure 4(a) shows the V_T shift of the perfectly-mismatched DNA, which were not fully hybridized. As expected, there was an insignificant V_T shift between

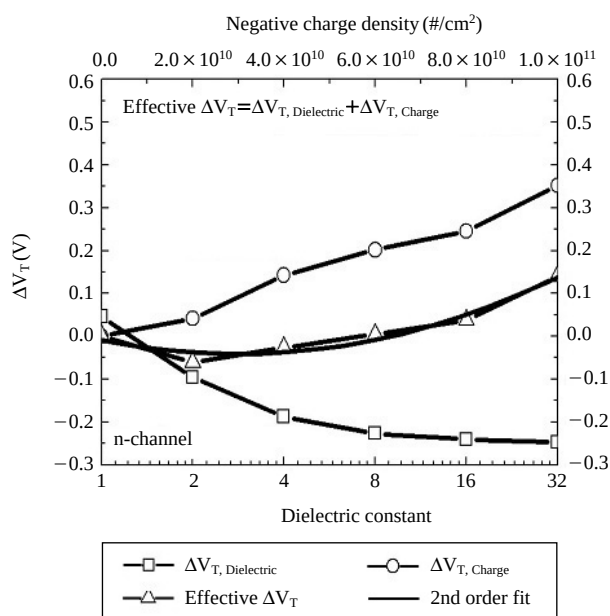


Figure 3. Simulation results of an effective threshold voltage shift for both the dielectric constant effect and charge effect.

the immobilization and the hybridization samples. Figure 4(b) shows that the V_T shift caused by the neutralized DNA that eliminates the charge effect is toward the negative side. This V_T shift originates from the increment of the dielectric constant in the nanogap due to the increased DNA density. This trend is consistent with theoretical principles, simulation data, and previously reported data¹⁶. Figure 4(c) shows the V_T shift caused by the negatively-charged DNA. In contrast, it was shifted to the positive side. In the case of the negatively-charged DNA, the dielectric constant and the charge effect are competing. It can be deduced that the charge effect is more dominant relative to the dielectric constant effect.

Figure 4(d) shows comparison data between the neutralized DNA and the negatively-charged DNA. In the neutralized DNA, the V_T was shifted to the negative side in all four devices that were measured at an average 0.07 V. In the charged DNA, the V_T was shifted to the positive side in each of the devices, and its average was 0.07 V. From these results, it can be concluded that the dielectric constant effect is dominant in the neutralized DNA and that the charged effect is dominant in the negatively-charged DNA.

True or False Test

True or false tests were performed in order to confirm that the V_T shift was caused by the target DNA

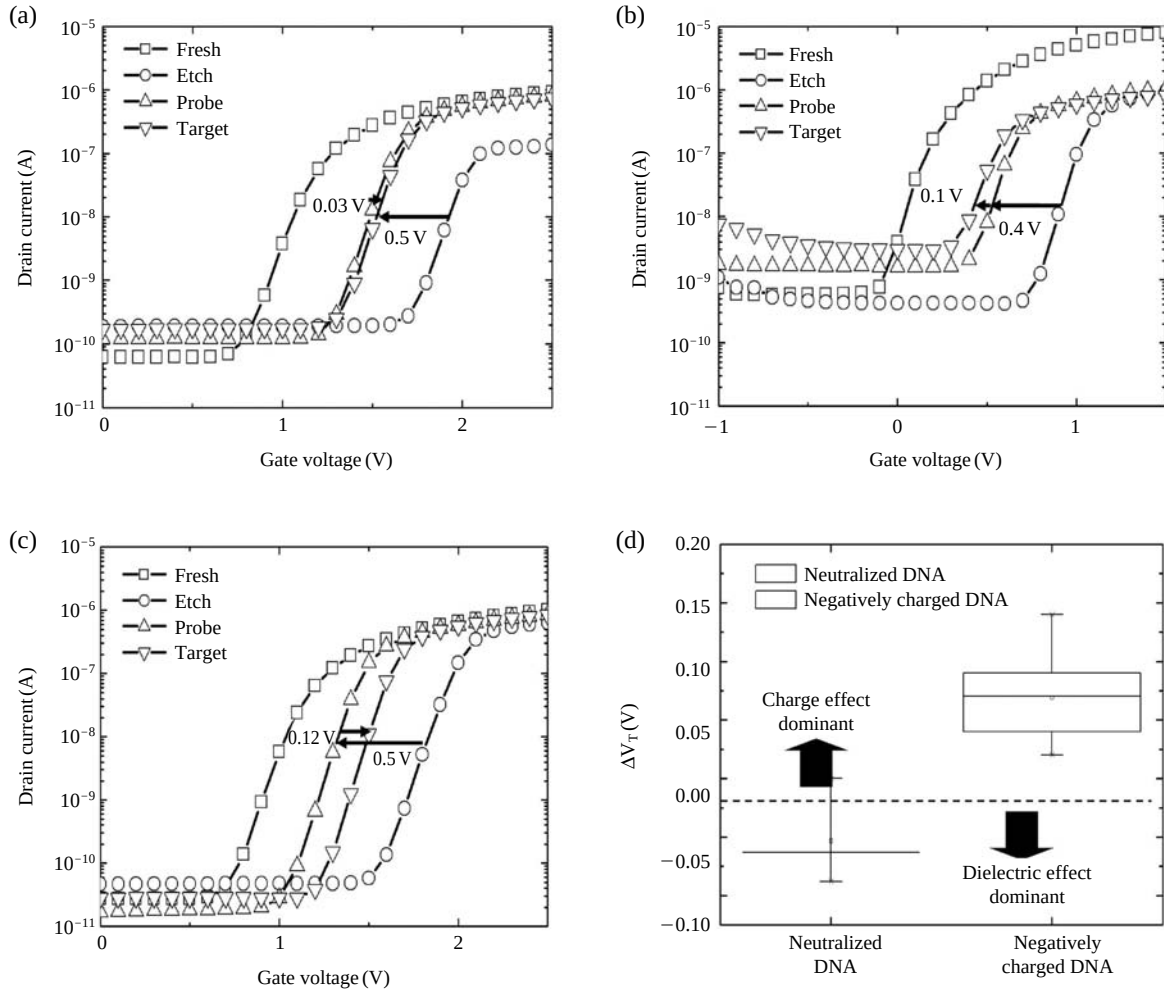


Figure 4. The threshold voltage shift by (a) perfectly mismatched DNA, (b) neutralized DNA, (c) negatively-charged DNA, and (d) a comparison of V_T shift between the neutralized DNA and negatively-charged DNA.

hybridization to the probe DNA. The first experiment compared the V_T shift between pre-hybridized DNA and sequentially-hybridized DNA. In one control group, a probe DNA was immobilized in the nanogap in a DMFET and a target DNA was then hybridized onto it. In the other control group, a pre-hybridized DNA, hybridized from a probe and a target DNA prior to the introduction to the nanogap, was directly attached to the nanogap. They were compared to the V_T of a reference sample with no DNA in the nanogap. Figure 5(a) shows that the V_T shift arises from the introduced DNA in the nanogap.

To ensure that the V_T shift results from the hybridized DNA, another experiment involving the breaking of the hydrogen bonds in the DNA was carried out. In this experiment, one group contained a probe DNA that was immobilized in the nanogap, while the other group contained a probe DNA and a target

DNA that were sequentially attached and hybridized in the nanogap. These samples were then dipped in hot DI water at 70°C for 10 min in order to break the hybridized DNA bonding between the probe DNA and the target DNA. Figure 5(b) shows that the V_T shift is approximately 0.1 V, and no significant difference can be seen between them. It can be concluded that the V_T shift was caused by the hybridization.

It is well known that a MOSFET is very sensitive to alkaline mobile ions such as sodium and potassium in sustaining reliable electrical characteristics. In a previous experiment, sodium was used for the neutralization of DNA, and the electrical characteristics of the DMFET used in the experiment were changed. In order to confirm that the V_T shift results not from the sodium ions but from the hybridization, another control experiment that measured the effect of the buffer solution was carried out. This solution was a

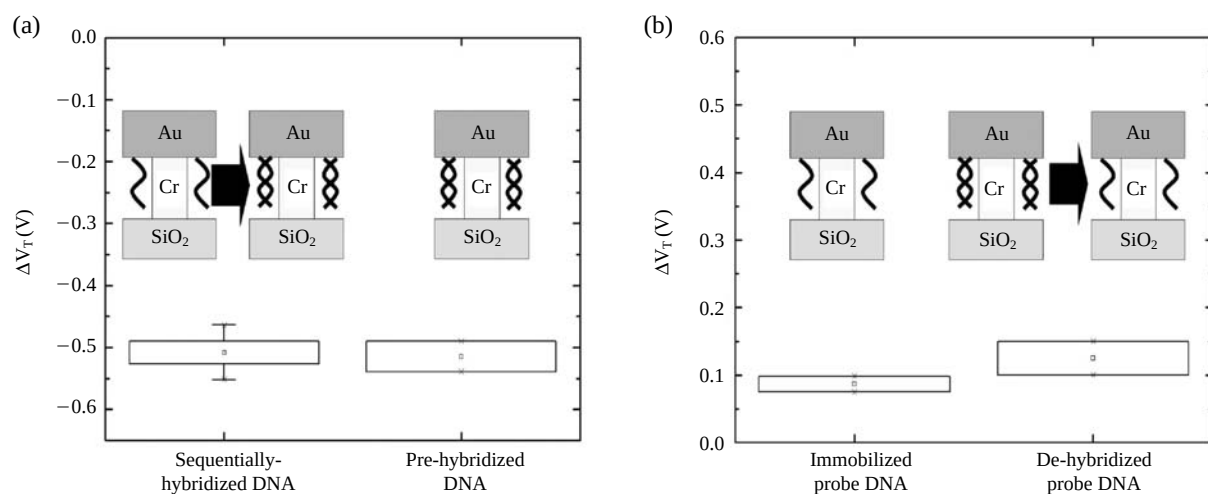


Figure 5. V_T shift of (a) sequentially-hybridized DNA versus pre-hybridized DNA, and (b) an immobilized probe DNA versus a de-hybridized probe DNA by hot DI water.

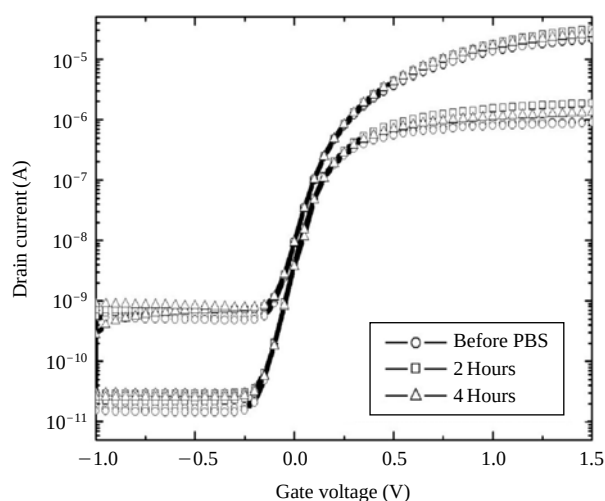


Figure 6. Comparison of transfer characteristics by dipping time in PBS.

phosphate-buffered solution (PBS) that contained many sodium and potassium ions. The DMFETs were dipped in the PBS solution, and the dip time was either 2 hours or 4 hours depending on the samples. The V_T shifts of the two groups of samples were then measured and compared. Figure 6 shows that the V_T shift was not affected by the sodium ions in the PBS.

Discussion

DNA is one of the most important biomolecules in nature, and a DMFET can be one of the most useful

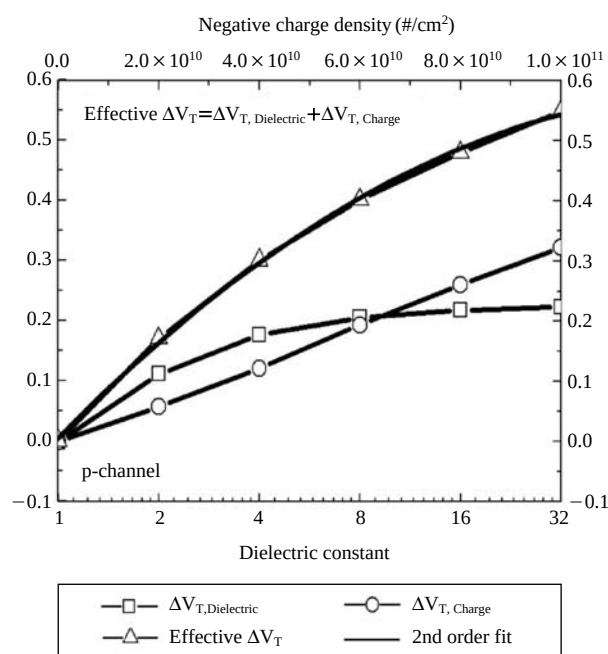


Figure 7. Simulation results of effective V_T shift for both the dielectric constant and the charge effect in a p-channel DMFET.

biosensors to achieve the typical features of biosensors, which can include miniaturization, low-cost fabrication, fast screening, and high sensitivity. Thus, it is timely to realize the feasibility of label-free electrical detections of DNA by DMFETs. It was found that a charge effect occurred in addition to a dielectric constant effect in DMFETs for DNA detection. The

dielectric constant and the charge effect can affect the degree of sensitivity, simultaneously, while acting on the V_T shift in the opposite manner. The dielectric constant effect shifts V_T to the negative side, and the charge effect shifts V_T to the positive side in an n-channel DMFET. As a result, these two effects are offset, and the sensitivity of the DMFET decreases. Although the neutralized DNA can be detected without competition between these two effects, it is less practical. Instead of an n-channel DMFET, a p-channel DMFET is proposed for the detection of negatively-charged biomolecules. Figure 7 shows the simulation results of V_T shift for a p-channel DMFET. Both the dielectric constant and the charge effect affect the V_T shift in the same direction. Therefore, the shift increases, as shown in Figure 7. This implies that the p-channel DMFET guarantees higher sensitivity than the n-channel DMFET for DNA detection. This result also applies to positively-charged biomolecules. Accordingly, with positively-charged biomolecules, the dielectric constant and the charge effect cause the V_T shift to be moved to the negative side in the n-channel DMFET. Thus, an n-channel or a p-channel DMFET can be chosen according to the charge polarity of targeted biomolecules in order to improve the degree of sensitivity.

Conclusion

This study reports that a DMFET electrically detected DNA without labeling. When the DNA is neutralized, the threshold voltage decreases due to the dielectric constant effect. In contrast, the threshold voltage increases due to the charge effect when the DNA has negative charges in an n-channel DMFET. Additionally, a p-channel DMFET was proposed so that both the dielectric constant and the charge effect can contribute to changing the threshold voltage in the same direction. This subsequently increases the detection sensitivity.

Materials and Methods

Immobilization and Hybridization of DNA

A DNA sequence composed of 23 nucleotides was extracted from *Neisseria Gonorrhoeae* DNA. The sequence of a probe DNA that attaches onto the Au surface in the nanogap to hybridize a target DNA is 5'-thiol-TCGAGCATGAACGTCAGTATTAT-3', and the sequence of the target DNA that is detected is 3'-AGCTCGTACTTGCAGTCATAATA-5'. A sequence of DNA not matched to the probe DNA perfectly was

used for a control group; its sequence is 3'-AAGCA-AGTAGTGTAAAGCGGAA-5'. In the experiment, the probe DNA was attached onto the Au surface of the nanogap, and the target DNA was then hybridized to the probe DNA. In order to attach the probe DNA onto the Au surface, a self-assembly monolayer (SAM) with a thiol- was immobilized at one terminal of the probe DNA. It is well known that the thiol- binds to an Au surface very easily¹⁹.

DNA has negative charges initially¹⁷. In order to compare the dielectric constant and the charge effect, neutralized DNA is needed. Neutralized DNA can be obtained by dipping the DNA into a sodium ion solution. In the sodium ion solution, sodium ions combine with phosphoric acid ions on the backbone of the DNA, and the DNA becomes neutralized. In order to confirm the hybridization between the probe DNA and the target DNA, a breaking procedure between them is needed. Ten minutes of dipping in deionized and distilled (DI) water at 70°C is sufficient for this, as the bonds are very weak against thermal stimuli²⁰.

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