Extended Abstracts of the 2007 International Conference on Solid State Devices and Materials, Tsukuba, 2007, pp. 946-947

D-7-5

Ion-Sensitive Field Effect Transistor Based on Silicon and Zinc Oxide for DNA Sensor

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1. Introduction

Nanotechnology brings new possibilities for biosensors construction and for developing novel electrochemical bioassays. Microarray-based technology for analysis of gene expression and detection of gene mutations has become indispensable for both clinical and basic research. Recently, analysis of genomic mutations for drug-metabolizing enzymes (pharmacogenomics), including detection of single nucleotide polymorophisms (SNP), has received increasing attention for the prediction of the efficacy and side-effects of therapeutic drugs. Differences in the cytochrome P450 (CYP) superfamily are of interest because they are important mediators of in drug metabolism.

It is expected that the combination of from genomic and pharmacologic information along with improved silicon-based technology and data processing will allow generation of new highly specific, sensitive and reliable biosensors. Biosensors based on biologically modified ion-sensitive field-effect transistors (IS-FETs) are very attractive because of their small size and weight, high reliability, fast response, portability, and low cost of mass production. Basic mechanisms of potential generation for biologically modified IS-FETs include potential changes caused by (i) a catalytic reaction product; (ii) surface polarization effects or changes in the dipole moment and (iii) potential changes that are coming from living biological systems.[1] IS-FET-based enzyme-modified FET sensors are already commercially available and commonly used. [2-4] Recently, FET-based DNA sensors have received considerable attention for use in both clinical and research applications. However whether IS-FET-based biosensors will be sufficiently sensitive for detecting hybridization events has not been clear because the charge of bound nucleotides is neutralized by counter ions. In addition, only surface charge density changes within the order of the Debye length can be detected. [1,5] In a previous paper, we pointed out that the hybridization of an immobilized peptide-nucleic acid (PNA) with a complementary DNA induces a decrease in saturation current and a positive shift in threshold voltage. [6, 7] In this study, we discuss the possible utility of the PNA-modified IS-FET-based biosensor.

2. Experimental procedures

An n-channel depletion type IS-FET was fabricated by Hitachi Ultra LSI systems (Figure 1). The IS-FET consists of a p-type silicon substrate with two n-doped regions (source and drain), which are separated by a short channel covered by the gate insulator. The gate insulator is a double layer of SiO_2-Si_3N_4, and each layer is 100 nm thick. Scheme 1 shows a schematic representation of the covalent immobilization process of the probe PNA on the Si_3N_4 gate insulator. Each immobilization process was comfirmed using XPS, SPR and Zeta potential measurements.

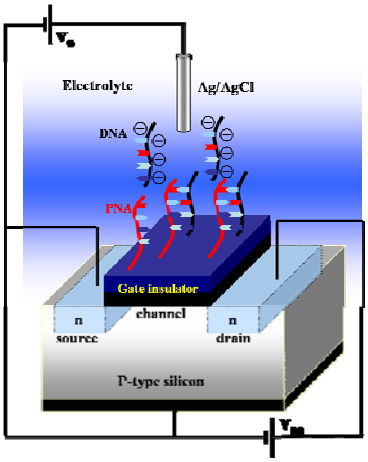
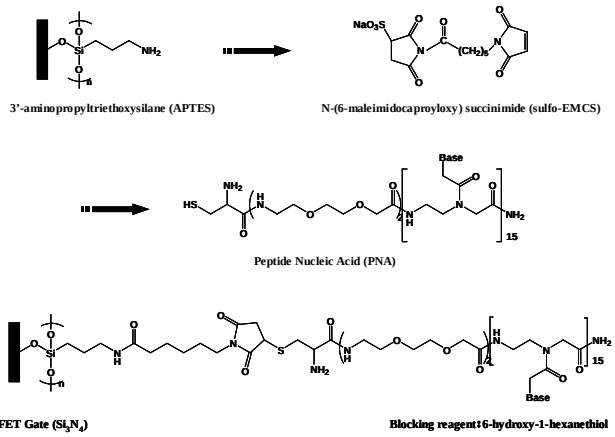


Figure 1. Schematic illustration of the hybridization of PNA-modified IS-FET



Scheme 1. Schematic representation of the process of covalently immobilizing the probe PNA on the gate insulator

Measurements of *I-V* characteristics were performed with a Keithley 4200-SCS semiconductor analyzer using a semiconductor characterization system with three terminals: source, drain, and gate. A standard Ag/AgCl electrode was used as the reference, and the electrolyte was 0.2X SSC.

3. Results and discussion

Figure 2a and c show representative results for I_D-V_D and I_D-V_G characteristics, respectively. The change in I_D before and after hybridization at a given source-drain voltage (V_D) is shown in Figure 2a. The solid line indicates the *I-V* curve of the PNA-modified IS-FET, and the dotted line indicates the *I-V* curve after DNA hybridization. As we expected, the saturated I_D decreased by 5.5 μA.

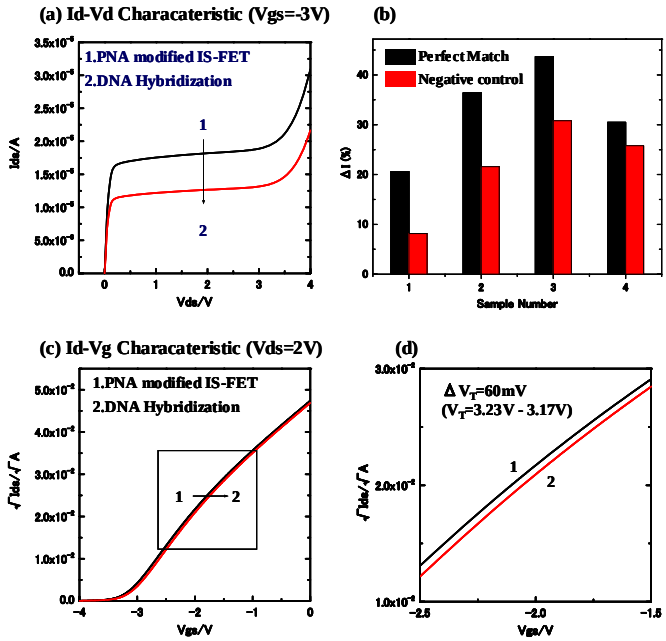


Figure 2. Measurements of *I-V* characteristics for the change in I_D before and after hybridization.

To evaluate this change in more detail, we compared the change in the I_D in the presence of complementary and noncomplementary DNA (positive and negative controls, respectively) (Figure 2b). The change ratio (ΔI) is expressed as ΔI (%) = $(I_1-I_0)/I_1\times100$, where I_1 is the saturated I_D before hybridization, and I_0 is the saturated I_D after hybridization. The values for the positive control were larger than those for the negative control, but the differences varied from 5% to 14.8%. Although these changes support the possibility of developing an IS-FET-based biosensor, it will be necessary to employ a system for measuring differential arrangement. The change in the square root of the I_D before and after hybridization at a given V_G is shown in Figure 2c, and the local area is shown in Figure 2d. A linear extrapolation of the *I-V* curve to x=0 was performed to obtain the V_T value. The solid line indicates the *I-V* curve of the PNA-modified IS-FET, and the dotted line indicates the *I-V* curve after DNA hybridization. The V_T values were −3.23 and −3.17 V, respectively. A positive shift in the V_T of 60 mV was observed after hybridization, and the negative control was also shifted in the positive direction by 20 mV (data not shown). These positive shifts are due to negatively charged DNA at the gate surface. Therefore, the changes in the I_D and the V_T upon PNA-DNA hybridization support the idea that a change in the charge density at the interface induces a change in the surface potential. Recently Macanovic and co-workers reported that an impedance-based detection of single-strand DNA sequences was possible by using PNA modified Si chips.[8] A flat-band potential shift due to hybridization of DNA was found to be -375 mV by electrochemical impedance measurements. This method provides more sensitive approach for detection of hybridization events compared to our system. However it is expected that the PNA-modified IS-FET-based biosensor would have better sensitivity compared to presented results by employing optimized gate structure and a system for measuring differential arrangement. This will be subject of further study. We have also fabricated the transparent zinc oxide (ZnO)-based IS-FET which will enable the quantitative estimation and direct microscope observation of DNA hybridization. Results will be shown in the presentation.

Acknowledgements

This work was supported by Grant-in-Aid for Core Research, Evolution Science and Technology of the Japan Science and Technology Agency.

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