

Chapter 2

Field-Effect Transistors for Detection of Biomolecular Recognition

Miyuki Tabata, Tatsuro Goda, Akira Matsumoto and Yuji Miyahara

Abstract Electrical biosensors have attracted increasing attention in such fields as point-of-care testing, drug discovery, and healthcare products. In order for next-generation biosensor platforms to become more useful in our daily lives, it will be necessary to significantly improve their sensitivity, specificity, and parallelism. A precisely designed thin layer in molecular dimension on a solid substrate is essential for biosensing. The surfaces of biosensors are designed to capture target bioanalytes. In addition, the solid/liquid interface plays an important role in realizing additional functionalities such as target manipulation, signal stabilization, and switching. A functional interface combined with a field-effect device would enable on-demand label-free biosensing in a portable format. In this chapter, we provide an overview of biomolecular recognition in the context of electrochemical sensing and biosensing. Also, we review recent progress and trends in biosensing, including our own research.

Keywords Biosensor · Biotransistor · ISFET · Sialic acid · Transporter

2.1 Introduction

Since the first ion-sensitive field-effect transistor (ISFET) was reported by Bergveld [1], various types of ISFETs and biochemical FETs have been developed, some of which have been commercialized as pH-sensors for laboratory, medical, and food applications.

Biosensors generally consist of transducers and membranes on which biologically active substances are immobilized. In the transducer, physical and chemical changes at the membrane, which occur as a result of biochemical reactions, are converted into electrical signals. These devices can record electrical, thermal, or

M. Tabata · T. Goda · A. Matsumoto · Y. Miyahara (✉)

Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University,
2-3-10 Kanda-Surugadai, Chiyoda-Ku, Tokyo 101-0062, Japan
e-mail: miyahara.bsr@tmd.ac.jp

optical outputs from biological reactions on a sensing surface. For practical applications, biosensors have been developed for detecting ions [2, 3], molecules [4], proteins [5, 6], DNA [7–9], viruses [10], etc. In general, bioassays rely on tedious labeling processes involving fluorescent dyes [2, 11], radioactive labeled probes [12, 13], or digoxigenin [14]. By contrast, label-free methods make systems simple, cost efficient, portable, and user-friendly. Several label-free methods have been proposed to date, including surface plasmon resonance (SPR) [15–17], quartz crystal microbalance (QCM) [18, 19], and electrochemical methods [20, 21]. A pH-sensitive ISFET has been used as a transducer in combination with enzymes that produce or consume hydrogen ions during enzyme–substrate reactions. As a result, a pH change is induced around the immobilized enzyme membrane, and this change is detected by the ISFET. Biochemical FETs have several advantages, including small size, low cost, and large-scale integration with other sensors and signal-processing circuits on a single chip. The type of target biomolecule to be detected and its selectivity can be determined by receptor molecules and materials coated on the surface of the gate insulator of the FET. The design and fabrication of functional interfaces on transistor gates are keys to achieving efficient molecular recognition and its transduction to electrical signals in a solid-state substrate.

With the rapid growth of knowledge in the fields of medicine and biology, the number of biomolecules to be detected and the types of information to be gathered are also increasing. Meanwhile, advanced micro- and nanotechnologies in electronics have been applied to these fields to facilitate parallel processing of information, miniaturization of analytical devices, and exploration of molecular mechanisms in biological systems. Solid-state biosensors, in which semiconductor devices are used as the transducer, are typical examples of fusion between biotechnology and microelectronics.

In this chapter, we introduce design and fabrication of functional nanointerfaces for biomolecular recognition and its transduction to electrical signals, as well as their application to field-effect transistors for biomolecular sensing. So-called “bio-FETs” have advantages over any conventional sensors in terms of miniaturization and integration due to the compatibility to established semiconductor fabrication technology. A key challenge for bio-FETs is development of sensing surfaces that can capture a wide variety of target species from ‘dirty’ real-world samples. Therefore, it is very important to create methods for designing functional interfaces.

2.2 Working Principles of FET-Based Biosensors (Bio-FETs)

2.2.1 Principles of Bio-FETs

A great deal of attention has been paid to bio-FETs in the field of bioanalytical applications. Bio-FETs detect biological events such as nucleic acid hybridization, protein–protein interactions, antigen–antibody binding, and enzyme–substrate

reactions. An FET consists of three electrodes: source, drain, and gate. The positive gate voltage attracts electrons from the bulk to the surface of the substrate. A sufficient number of electrons induced form a thin n-channel by electrically bridging the source and drain. Otherwise, when a specific molecular recognition occurs on the gate, the bio-FET detects the change of charge density at the interface by an electrostatic interaction with the electrons in the n-channel (Fig. 2.1).

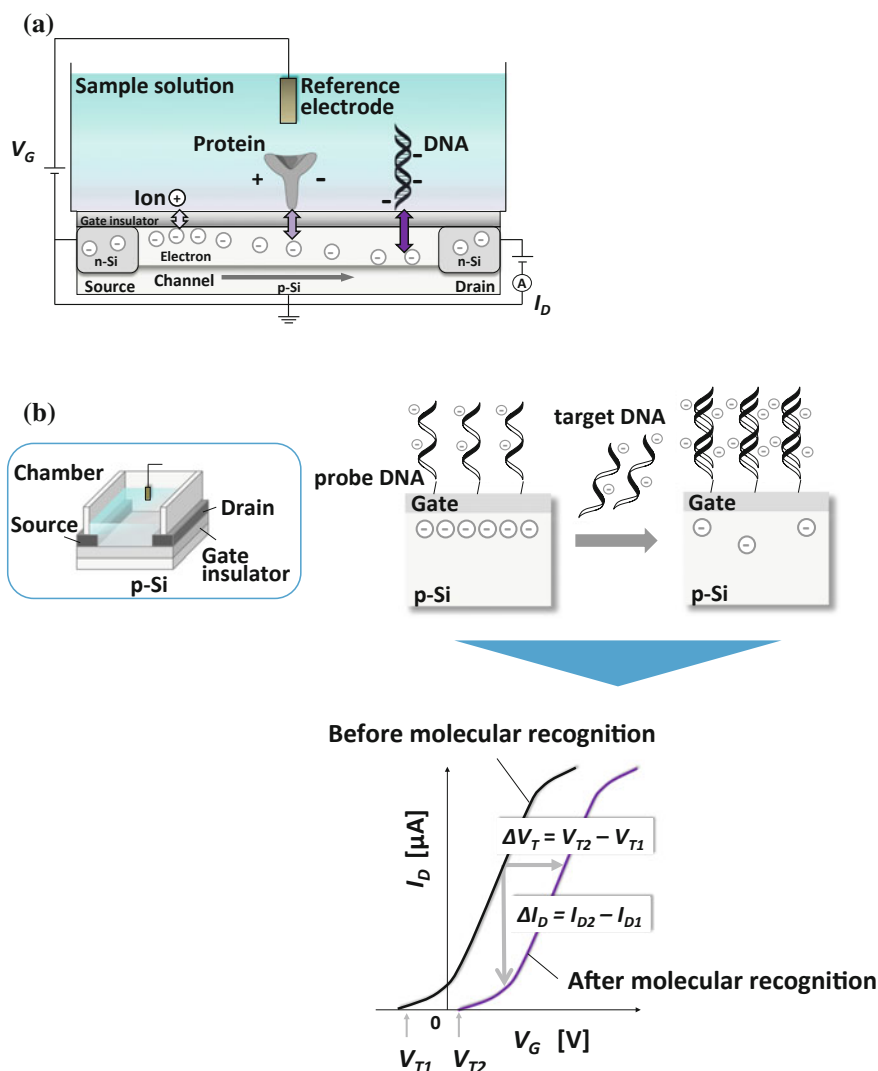


Fig. 2.1 Schematic illustrations of FET-based biosensors. **a** FET-based biosensor composed of a functional interface and signaling transducer. **b** Working principle of a device for detecting DNA hybridization. V_T - I_D characteristics of biotransistor changes before and after molecular recognition

As shown in Fig. 2.1a, the bio-FET detects the change in charge density, occurring within the electrical double layer of the gate/solution interface, as a shift in the threshold gate voltage (V_T). The Debye length, an index of the thickness of the double layer, is given by the following Eq. (2.1):

$$\delta = (\epsilon\epsilon_0 kT / 2q^2 I)^{1/2} \quad (2.1)$$

where ϵ is the relative permittivity, ϵ_0 is the permittivity of the vacuum, kT is the thermal energy, q is the electric charge, and I is the ionic strength of the solution. The change in charge density based on molecular recognition must occur within the Debye length, whereas the change in charge density induced outside the Debye length is shielded by counter ions and cannot be detected with the bio-FET. The Debye length on the gate is considered to be a few nanometers in the physiological sample solution; therefore, the design of the solid/liquid interface plays a critical role in the development of the bio-FET.

2.2.2 *Ion-Sensitive FETs (ISFETs) and Their Application to a Bio-FET*

The ion-sensitive field-effect transistor (ISFET), a pH-sensor, is the first miniaturized silicon-based chemical sensor. In general, the gate used in such pH-sensors consists of dielectric materials, such as SiO_2 , Si_3N_4 , Ta_2O_5 , and Al_2O_3 , and the selectivity and pH sensitivity of an ISFET depend on the properties of the solid/liquid interface. A nucleic acid primer-extension reaction has been detected using an ISFET [22, 23]. In this approach, single-stranded oligonucleotide probes immobilized on a gate surface were hybridized with their target DNA molecules, followed by sequential addition and washing steps with each individual deoxynucleotide triphosphate (dCTP, dATP, dGTP, or dTTP) in the presence of DNA polymerase. This process allows an unknown sequence to be determined, because extension by DNA polymerase produces additional negative charges and protons in a template-dependent manner. The increase in negative charges resulting from primer extension can be detected as a V_T shift. The reaction can be monitored at single-base resolution. Based on this fundamental mode of detection, a next-generation high-throughput DNA sequencer was commercialized by Ion Torrent (Life Technologies) in 2012 (Fig. 2.2). High-throughput reading and highly parallel analysis are achieved by integrating millions of ISFETs on a chip in a high-density array format using nanofabrication technology [24]. The sequencer employs microbeads bearing a template DNA, amplified by emulsion PCR, to perform accurate sequencing on a transistor. The extension reaction occurs on the surface of the bead mounted on each ISFET, which detects the protons released during the extension reaction. Currently, this technology is being further developed for applications in tailored medicine.

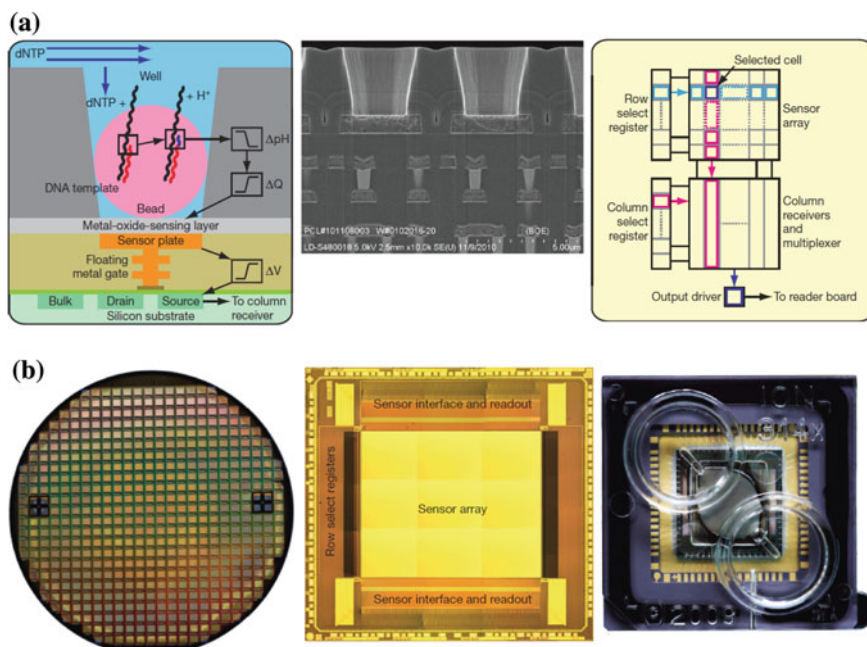


Fig. 2.2 Commercialized ISFET-based DNA sequencer. **a** Schematic illustration of sequencing mechanism and electron micrograph showing wells. **b** Ion chip on wafer, die, and chip packaging. Reprinted by permission from Macmillan Publishers Ltd: Ref. [24], copyright 2011

2.3 Sialic Acid Detection Using Phenylboronic Acid SAM Modified FETs

Bio-FETs offer great potential for addressing major medical challenges in the fields of diagnostics, therapy, and drug delivery. Fortunately, an electrical biosensor platform composed of a target-capturing element and a semiconductor device (used as a signal transducer) is compatible with high-throughput analysis via miniaturization and integration into a small chip, which can then be used for decentralized bioanalytical applications. We have successfully achieved a sialic acid (SA) detection transistor using SA–boronic acid molecular recognition.

SA is present at the ends of sugar chains on the cell surface, and its density and distribution are influenced by disease development and differentiation. Although sialylated glycoproteins are abundant on the surface of cancer cells, their levels are reduced on the erythrocytes of patients with insulin-dependent diabetes. Therefore, quantitative analysis of SA on the cell surface serves as a powerful index for diagnosis of metastatic tumors or diabetes. Phenylboronic acid (PBA) is generally used as a probe molecule for capture of various sugars due to the covalent bond that form between dissociated PBA and diols; even nondissociated PBA interacts strongly with SA [25]. We recently proposed an FET-based SA detection as a new

technique for label-free live-cell cytology [26]. To evaluate the ability of PBA to recognize SA, a self-assembled monolayer (SAM) of PBA derivative ($pK_a = 9$), which has a thiol group at the end, was formed on an extended gold electrode gate surface. Over a wide range of pH (5–9), only SA caused a significant increase of V_T (+40 mV), and no significant signal was acquired in the case of mannose or galactose. On the other hand, when similar measurements were performed at $pH \geq 9$, PBA could recognize mannose or galactose. In this configuration, the anionic charges of SA (due to carboxyl groups) bound to the electrode could be detected as positive shifts in the threshold voltage (V_T) of the FET. Consequently, it became clear that SA could be directly quantitated using PBA derivatives under physiological conditions.

This PBA-modified FET was then tested for its ability to directly capture the glycan component SA present on the cell surface [27] (Fig. 2.3). The device was capable of quantitatively analyzing SA in rabbit erythrocytes in a type I diabetes model, as well as in lungs into which mouse melanoma had been transferred as a

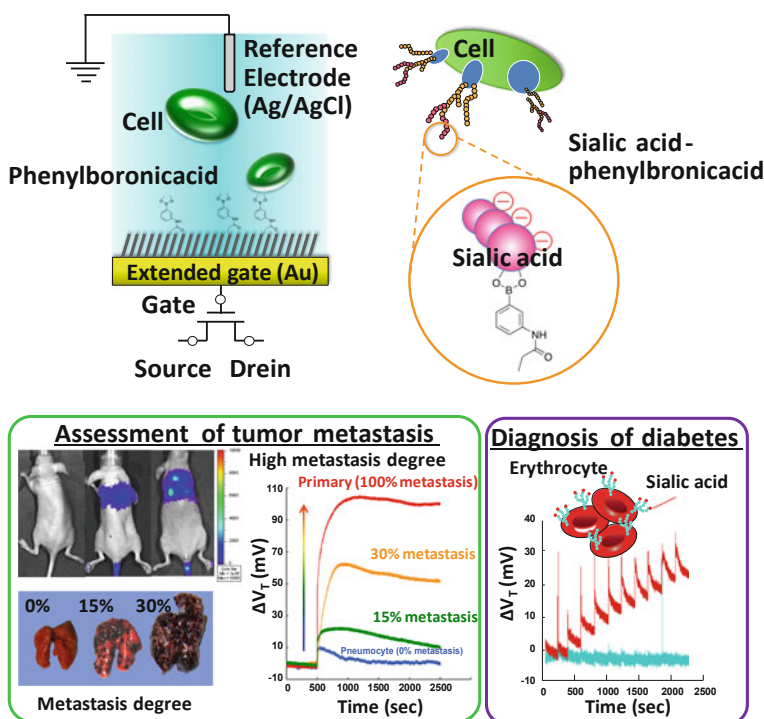


Fig. 2.3 Quantitative analysis of sialic acid using a bio-FET functionalized with phenylboronic acid. Assessment of tumor metastasis based on differentiation of the (pneumocyte) surface-expressed (Reproduced from Ref. [26] by permission of John Wiley & Francis Ltd.), and detection of sialic acid on the surface of rabbit erythrocytes as a relevant technique for the diagnosis of diabetes (Reprinted with the permission from Ref. [27]. Copyright 2009 American Chemical Society.)

model of metastatic cancer. Therefore, we predict that this approach could be applied in a simple device capable of quantitatively evaluating the degree of cancer metastasis.

2.4 Monitoring of Kinetics for Transporter–Substrate Interaction

In drug design, medical treatment, and cosmetics, it is necessary to screen for highly active compounds from among vast numbers of candidate substances, such as libraries of natural or de novo synthesized compounds. In general, various toxicity tests and in vivo pharmacokinetic studies are performed in mammals to determine the efficacy of such compounds. From the standpoint of animal protection, however, various alternatives to animal experiments have been advocated, and analytical technologies using cultured cells are becoming mainstream. Because novel compounds are often precious, it is desirable to use small amounts of such samples for analysis. Therefore, it is necessary to miniaturize the reaction field and the detection space, both of which are possible using an evaluation device combined with our transistor.

Membrane transport proteins can be regarded as gateways that connect the cytosol to the extracellular environment. They play crucial roles in metabolic processes and signal transduction that define the physiological functions in cellular systems. So, the investigation of membrane transport proteins is important not only in the field of cell biology but also in drug screening and development. *Xenopus laevis* oocytes, eggs from a clawed frog native to South Africa, have become widely used for studying membrane proteins such as ion channels and transporters. Transporter is a membrane protein or peptide allowing for passage of specific substrates such as ions and low molecular weight chemical species into or out of the cell. When heterologous expression of a membrane protein is required, RNA or cDNA encoding the target protein is injected into the oocyte. This *X. laevis* expression system is useful for electrophysiological studies of the membrane protein and drug development where a potential drug is screened against specific ion channels or transporters expressed in the membrane of *X. laevis* oocytes. Binary response, “hit-or-miss”, can be obtained to evaluate the efficacy of potential drug candidates. Membrane transport activity can be detected using electrical conductance measurement, if the transport process results in a net transfer of charge. This is usually achieved with the voltage clamp or patch clamp methods using a single cell expressing the membrane protein to be investigated. Microelectrodes and their precise manipulation are required for the electrical conductance measurements. Insertion of intracellular microelectrodes into an oocyte is an invasive process and glass microelectrodes with a very fine tip are typically used to reduce the disruption of the cell membrane. A higher degree of experience and skill is required to achieve stable and reliable measurements.

We developed an integrated microdevice for measuring proton-dependent membrane activity at the surface of *X. laevis* oocytes. By culturing an oocyte (female *X. laevis* frogs) on the surface of the ISFET gate, the kinetics of transporter–substrate interactions on the cell membrane can be monitored noninvasively. An overview of this microdevice is shown in Fig. 2.4. The output voltage of this system at varying pH buffer solutions was -58.0 mV/pH. This value is close to the ideal Nernstian slope (-59.2 mV/pH at 25 °C), demonstrating the excellent pH-sensitive material of Ta_2O_5 . To evaluate this sensing platform as a cell-based FET, we conducted transport experiments on oocytes heterologously expressing various membrane transport proteins. These heterologously expressed oocytes were prepared by injecting of mouse, flounder or human-derived cRNA according to cell engineering techniques. The protons delivered and received through the cell membrane are used as tracers, due to the much higher lateral diffusion rate of protons relative to other solutes [28].

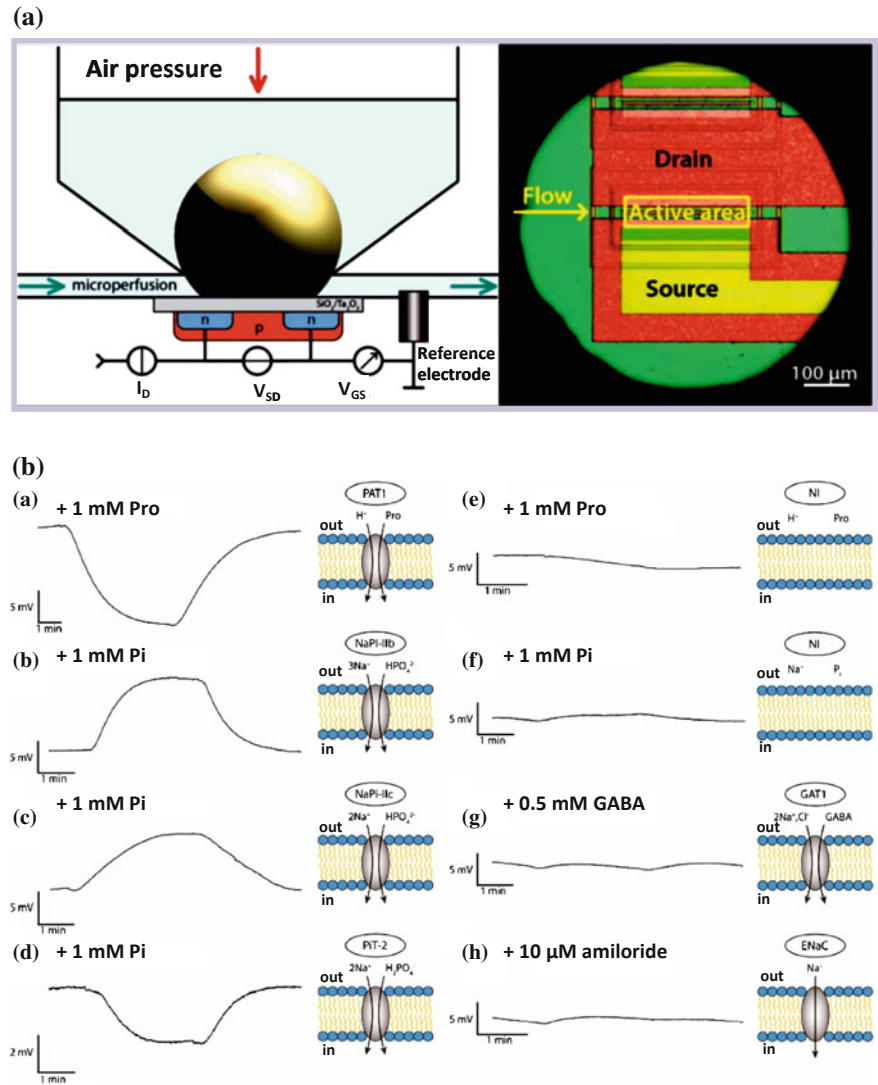
Assays on oocytes heterologously expressing the proton-driven amino acid transporter (PAT1) revealed a significant potential decrease upon exposure of the cells to a 1 mM proline solution, reflecting the local pH increase at the ISFET interface associated with intracellular inflow of a proton and proline. On the other hand, for oocytes heterologously expressing the electrogenic sodium-coupled phosphate cotransporter (NaPi-IIb), the signal deflection was reversed, indicating a decrease in the surface pH of the ISFET. This phenomenon occurred because divalent (HPO_4^{2-}) and monovalent (H_2PO_4^-) phosphate species with an assumed $\text{p}K_a = 6.8$ are held in equilibrium under physiological conditions, according to Eq. (2.2).



As a result of taking up divalent P_i (HPO_4^{2-}), the above equilibrium shifted to the left hand side and protons were newly generated due to the depletion of the divalent species. Similarly, it became clear that the transporter activity of NaPi-IIc and PiT-2 could be evaluated by proton sensing. In addition, the signal was not detected in cells expressing GAT1 and ENaC, which do not change proton concentration. Thus, electrical phenomena at the cell membrane can be monitored using an ISFET with high sensitivity ($\Delta\text{pH} = 0.01$) and high time resolution ($\Delta t = 100$ ms). The cell-based transistors are expected to contribute to high-throughput screening in pharmaceutical fields.

2.5 Nanointerfaces for Signal Transduction Using Nanotubes and Nanowires

Functional chemical modification and fabrication of nanostructures at the surface of the gates of FETs, described in the previous sections, can be applied to new types of electron devices. Nanotubes and nanowire transistors are very attractive for highly sensitive biosensing devices [29–32].



Carbon nanotubes (CNTs) possess many unique properties such as high aspect ratios, high mechanical strength, high surface areas, excellent chemical and thermal stability, and rich electronic and optical properties, all of which are potentially useful in electronics. Therefore, there has been an explosion of interest in the use of CNTs for the development of biosensors. The high surface area of single-walled CNTs (SWNTs), estimated to be $1600 \text{ m}^2 \text{ g}^{-1}$, is of particular interest, because it can provide a route to obtaining an impressively high density of biomolecules at the detection interface. Since the first appearance of the SWNT-based FETs (SWNT-FETs) [33], a large number of attempts have been made to apply the SWNT-FET to a range of biomolecular targets. To fabricate SWNT-FETs, a semiconducting-SWNT must be selectively (i.e., out of a mixture of metallic-SWNTs) manipulated to ensure it contacts and bridges between the source and the drain materials. SWNT-FETs are composed of either individual SWNTs or dispersed networks of multiple SWNTs. The chemical vapor deposition (CVD) growth method is typically employed for the fabrication of dispersed SWNT networks on the gate surface, whereas microlithography and electron beam (e-beam) lithography are common techniques for pattern source and drain contacts [29]. At the detection interface, the SWNT not only provides dense surface area for immobilization of biological receptors, but also serves as an electrical modulator of the (SWNT-bridged) source–drain channel. The main factor causing changes in the channel conductance is still controversial, and at least four possible mechanisms have been proposed so far: electrostatic gating, capacitance modulation, Schottky barrier effects, and carrier mobility change [34]. A variety of biological targets have been successfully detected based on the SWNT-FET format, including protons and small molecules such as, NH_3 and NO_2 , as well as relatively large targets such as DNA (hybridization) and proteins.

Nanowires are solid, rod-like materials with diameters in the 5–100 nm range, and are most often made from metals or semiconducting metal oxides. Silicon nanowire (SiNW)-FETs have also emerged as powerful biosensors. The sensing mechanism of SiNW-FET can be understood in terms of the change in charge density at the SiNW surface after molecular recognition, as well as typical bio-FETs. This charge sensitivity is affected by many factors, including SiNW size [35], Debye screening [36], surface chemistry [37], distance of the charge layer from the SiNW surface [38], and so on. However, SiNW-FETs can achieve highly sensitive detection of biological species by a complementary metal oxide semiconductor (CMOS)-compatible approach. The performance of SiNW-FETs has been extensively studied in regard to detection of DNA [39] and protein [40]. Since the fabrication process of SiNW-FETs is compatible with the current CMOS processing technologies, the gate region of the FET can be designed and defined precisely and reproducibly. By combining nanowire transistors with our approaches described previously (DNA or PBA-modified FET and cell-based FET), it is expected that the further miniaturized and arrayed biotransistors would be realized for functional analyses of a single molecule and a single cell, while we have to develop a method that functional modification and nanostructure can be formed selectively and separately on each gate.

2.6 Future Perspectives

This chapter described several types of FETs for biosensing, focusing on design and fabrication of functional nanointerfaces at the gate. Particularly for clinical applications, such nanointerfaces could play a crucial role in capturing a wide variety of target biomolecules with high specificity and sensitivity, without nonspecific binding, in ‘dirty’ real-world samples.

Using the FETs described in this chapter for detection of biomolecular recognition events, it should be possible to develop a small instrument for use in point-of-care testing. Indeed, a DNA sequencer employing an integrated transistor chip has already been applied to cancer genome analysis in the context of tailored medicine. These devices can be used not only in large hospitals but also in smaller medical facilities or physicians’ offices, or even in a patient’s home. In addition, we can take the small instrument out of the laboratory to detect nucleic acids of viruses or microorganisms on site for the purpose of infectious disease testing. Thus, transistor-based biosensing technology represents a useful and effective means for real-time monitoring of the biosecurity level in our environment. In advanced countries such as Japan, society is aging rapidly, and medical needs are increasing, even while the capacities of hospitals and medical doctors remain limited. We believe that one approach to improving this situation is to develop a system in which medical treatment and clinical diagnostics can be performed on patients at home. Such a system would require a simple, small, and highly sensitive detection system for point-of-care testing.

2.7 Conclusion

In this chapter, we described the fundamental principles and present the use of biotransistors with various sensing interfaces, including a discussion of our own research. Many researchers are now addressing a range of challenges in biosensing: miniaturization, parallelization for high-throughput analysis, integration, functionalization, and increasing the S/N ratio. A fusion of nanobiotechnologies will enable breakthroughs in biology and biotechnology, especially in fields such as drug design and screening, nanomedicine, and genome-based tailored medicine. We expect that biosensors with functional nanointerfaces will play important roles in developing new modes of clinical care.

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