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Redox-potential sensor array based on extended-gate field-effect transistors with ω-ferrocenylalkanethiol-modified gold electrodes

Hiroo Anan[a,*], Masao Kamahori[b], Yu Ishige[b], Kazuo Nakazato[a]

[a] Department of Electrical and Computer Science, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan
[b] Central Research Laboratory, Hitachi, Ltd., 1-280 Higashi-Koigakubo, Kokubunji, Tokyo 185-8601, Japan

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ABSTRACT

A chip was developed with a 32 × 32 array of extended-gate field-effect transistor (FET)-based redox-potential sensors, each with a gold electrode modified with 11-ferrocenylundecane-1-thiol (11-FUT). The potential of the sensors was stable to within 0.5 mV/h. Overall, for the 32 × 32 sensor cells, 80% showed potentials that were within ±5 mV of the median and 92% were within ±1 mV of the median. The sensor array detected the redox reaction of hexacyanoferrate(II) and hexacyanoferrate(III) as a change in the electric potential of the 11-FUT-modified electrode with a Nernstian response, at a slope of −58.0 mV/decade at room temperature, and a dynamic range of more than five orders of magnitude. Two-dimensional and real-time visualization were made possible by imaging of the sensor array. With an enzyme-catalyzed redox reaction, the FET-based sensor array showed a slope of −59.5 mV/decade for logarithmic concentrations of glucose in the range 0.1–2 mM, and it successfully detected glucose levels from 22.5 to 360 mg/dL. The limit of detection of glucose was 50 μM. Finally, the FET-based enzyme sensor array successfully detected glucose levels in samples of human serum from 100.1 to 264.3 mg/dL.

1. Introduction

Biosensors based on field-effect transistors (FETs) have been studied intensively for use in label-free medical diagnostic systems. Because FET-based biosensors can be fabricated by the standard complementary metal oxide semiconductor (CMOS) process, they can be reduced in size, and it is possible to integrate signal-processing circuits with multimodal biosensors on a single chip.

An ion-sensitive field-effect transistor (ISFET) is capable of detecting changes in electrostatic potential at an ion-sensitive surface, which is formed on the gate insulator of a metal oxide semiconductor FET (MOSFET) by removing the gate metal. Since its introduction in 1970 for the measurement of ions in effluxes around nerves [1], the ISFET has been widely used in chemistry and biology because of its high sensitivity, rapid response, and convenience. In particular, ISFETs with silicon nitride (Si_3N_4) membranes have been used extensively in pH measurement and in the detection of DNA and proteins [2–5]. Furthermore, extended-gate FET sensors with sensing electrodes made of gold have been developed for the detection of DNA [6,7]. In these sensors, DNA probes are immobilized on the gold sensing electrodes by means of gold–thiol binding chemistry. Similarly, various biomolecules can be detected by means of self-assembled monolayers on a gold electrode [8,9]. However, conventional FET sensors are strongly affected by buffer conditions, such as pH and salt concentration, which can decrease the efficiency of detection and increase the instability of the electric potential of the electrode when the salt concentration is reduced to eliminate screening by ions [6,10,11].

Ishige et al. developed an extended-gate FET-based sensor that permits the measurement of changes in the redox potential arising from a redox reaction [12]. Whereas the sensitivity of ISFET-based enzyme sensors is strongly affected by buffer conditions, the extended-gate sensor is not affected by changes in the pH or the buffer capacity, suggesting that the enzyme-catalyzed reaction, rather than any change in pH, is responsible for changes in the potential of the extended-gate FET sensor.

Nakazato et al. reported an extended-gate FET cell array fabricated by the standard CMOS process [13]. Each cell consists of an extended-gate FET and a low-noise circuit with a low power consumption. This opens the way to two-dimensional (2D) chemical reaction imaging, which has considerable potential for massive parallel assays of test solutions, for example in DNA sequencing.

Abbreviations: 11-FUT, 11-ferrocenylundecane-1-thiol; 2D, two-dimensional; ADP, adenosine diphosphate; ATP, adenosine 5′-triphosphate; CMOS, complementary metal oxide semiconductor; CV, coefficient of variation; FET, field-effect transistor; G-6-P, glucose-6-phosphate; G-6-PDH, glucose-6-phosphate dehydrogenase; HK, hexokinase; IPA, isopropyl alcohol; ISFET, ion-sensitive field-effect transistor; LCC, leadless chip carrier; MCU, microcontroller unit; MOSFET, metal oxide semiconductor field-effect transistor; NAD, nicotinamide adenine dinucleotide; NADH, reduced form of NAD; PBS, phosphate-buffered saline; PC, personal computer; RE, reference electrode.

* Corresponding author. Tel.: +81 52 7892794; fax: +81 52 7893139.
E-mail address: h_anan@echo.nuee.nagoya-u.ac.jp (H. Anan).

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Here we report the fabrication of a CMOS chip that integrates 32 × 32 redox-potential sensors and their associated control circuitry to produce a 2D chemical reaction-imaging array.

2. Material and methods

2.1. Materials

The following chemicals and reagents were used in the experiments: phosphate-buffered saline tablets (PBS, pH 7.4), ethanol, magnesium chloride, potassium hexacyanoferrate(III), potassium hexacyanoferrate(II), adenosine 5′-triphosphate (ATP), and nicotinamide adenine dinucleotide (NAD) purchased from Sigma–Aldrich (St. Louis, MO, USA); acetone, isopropyl alcohol (IPA), sodium sulfate, and glucose purchased from Kanto Chemical Co. Inc. (Tokyo, Japan); 11-ferrocenylundecane-1-thiol (11-FUT) purchased from Dojindo Laboratories (Kumamoto, Japan); hexokinase (HK), glucose-6-phosphate dehydrogenase (G-6-PDH), diaphorase purchased from Oriental Yeast Co. Ltd. (Tokyo, Japan), and human serum (JCCRM 521-11) obtained from the Reference Material Institute for Clinical Chemistry Standards (ReCCS; Kawasaki, Japan). All solutions were prepared by using Milli-Q water.

2.2. Fabrication of the 11-ferrocenylundecane-1-thiol-modified FET-based redox-potential sensor array chip

The structure of the on-chip 32 × 32 extended-gate FET sensor array with 11-FUT-modified gold electrodes is shown in Fig. 1(a)–(c). The FET-based sensor array chip was fabricated by using a standard 1.2-μm two-metal and two-polycrystalline silicon CMOS process (ON Semiconductor). The wafer was diced and then the chip surface was cleaned sequentially with acetone, IPA, and deionized water to remove contaminants such as organic matter and oil. A 20-nm-thick layer of Ti and 100-nm-thick layer of gold were deposited. Then, Au/Ti electrodes were patterned by optical lithography and wet etching using AURUM-301 (Kanto Chemical) and WLC-T (Mitsubishi Gas). A layer of SU-8 (an epoxy-based negative resist) was applied to the chip to protect it from the solution. As a result, a series of 20 μm × 56 μm extended-gate electrodes were exposed to the solution. After the formation of electrodes, the CMOS chip was mounted on a ceramic leadless chip carrier (LCC) package and bonded by wire. A silicone rubber film was then applied to the chip and a silicone paste was flowed outside the silicone rubber film to protect the wire bonding (Fig. 1d).

To modify the gold electrodes with the alkanethiol, the FET sensor array chip was steeped in a 500-μM solution of 11-FUT in ethanol for 24 h. The chip was rinsed twice with ethanol and deionized water to remove the unreacted alkanethiol. The chip was then stored in 0.1 M aqueous sodium sulfate at room temperature until it was used.

2.3. Measurement system

The CMOS source-drain follower circuit was used to output the potential of the extended-gate electrode [14], permitting the electrode potential to be measured in real time. Fig. 2 shows the measurement setup, which consists of a solution flow cell, a DC power supply (Agilent E3631A), a DC voltage current generator (Advantest TR6142A), and a microcontroller unit (MCU). The solution flow cell, made from acrylic resin, was located on the CMOS chip. The maximum volume of the solution flow cell was 20 μL. The reference electrode (RE) was attached to a jointed microflow path, as shown in Fig. 2. The reference electrode was a Ag/AgCl electrode with 3 M aqueous NaCl (RE-3VP, BAS, Tokyo, Japan).

The MCU generates control signals and sends these signals to the chip. On receiving these signals, the address buffer in the chip transmits signals to the decoder to select an FET from which to read the output voltage. The MCU also acquires data from each FET cell through the on-chip multiplexer and the output buffer. These data are sent from the MCU to a personal computer (PC) through a USB cable. In the case of the 32 × 32 array, the time required to acquire 32 × 32 items of data is about 3 s [15]. The E3631A unit supplies the voltage to the chip, whereas the TR6142A unit supplies the reference electrode voltage. The write–read signals of the MCU and the voltage outputs of the E3631A and R6142A units are controlled by a program written in Microsoft Visual C++ running on the PC.

2.4. Measurement procedure

The stability of the interfacial potential of the FET-based redox potential-sensor array was examined by the following procedure.

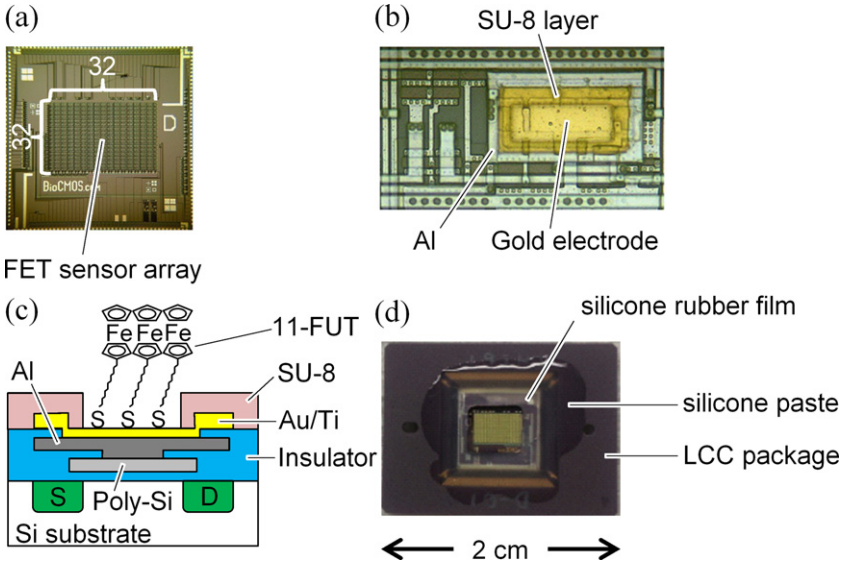

Fig. 1. Photographs of (a) the sensor array and (b) the sensor unit. (c) Schematic showing a cross section of the structure of the sensor and (d) the leadless chip carrier (LCC)-packaged CMOS chip. After the formation of electrodes on the CMOS chip, it is mounted on a ceramic LCC package and bonded by wire. A silicone rubber film is then placed on the chip. Silicone paste is flowed outside the silicone rubber film to protect the wire bonding.

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