Extended Abstracts of the 2008 International Conference on Solid State Devices and Materials, Tsukuba, 2008, pp. 748-749

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A BioCMOS LSI circuit with extended-gate FET sensor array

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1. Introduction

DNA chips are playing important roles in molecular biology, pharmaceutical research, and clinical applications. Most DNA chips are based on optical detection; known probe molecules are immobilized at selected locations, target molecules are labeled with fluorophors and interaction with a complementary probe is evidenced from the presence of fluorescence at the probe's location. However, this method is expensive and not suitable for portable instruments. A possible way to overcome the drawbacks is the FET type microsensors, which enable label-free electrical detection of biomolecular interactions. Fully electrical detection using CMOS LSIs has many advantages on easy-handling, miniaturization, mass-production, system integration, and standardization.

2. Sensor Cell Circuit

Biosensor array in this paper is based on standard CMOS process, followed by the formation of extended gate and molecules and/or membrane, as shown in Fig. 1. For DNA identification, gold is used for the extended gate, to which thiol modified oligonucleotides are immobilized, and the interaction with target DNA is detected by the difference of charges since a nucleotide has negative charge $-e$ on the phosphate group. Another method utilizes a silicon oxide or silicon nitride layer deposited on the extended gate and oligonucleotides are immobilized by the silane coupling method. To detect possible sequences, the biosensors are arranged in a matrix form as shown in Fig. 2.

Commonly used electronic interface circuits for FET sensor have been based on source-drain follower where FET is operated under fixed gate-source and gate-drain voltages to keep the sensing transistor always in the same operating point. In this configuration, we can obtain high sensitivity since no capacitance loads exist between the extended gate and semiconductor substrate, and long term stability in an aqueous solution since internal electric fields and carrier density in the sensing transistor are unchanged. However, conventional source-drain followers have been constructed by one, two, or four operational amplifiers per sensing transistor, which occupy a substantial area. For the applications of sensor array, for example 1,024 x 1,024 array on a single chip for DNA sequencing, low power and high density source-drain followers are required.

New source-drain follower has been designed (Fig. 3) and implemented (Fig. 4) for monolithically integrated biosensor array. [1] The circuit acts as a voltage follower, in which a sensing transistor is operated at fixed gate-source and gate-drain voltages. The sensor cell is designed for 10 mV accuracy and the cell size is 105.3 μm x 81.4 μm in 1.2 μm CMOS design rules. The chip was fabricated using standard CMOS technology, and a wide range of operation between 1 nW and 100 μW was demonstrated. The error in the output except for the threshold voltage mismatch was less than 2 mV in a range of total current between 3 nA and 10 μA and in a temperature range between 30°C and 100°C (Fig. 5). The transient step responses were measured (Fig. 6). The rise and fall times are roughly given by $C_N \Delta V/I$ and $C_L \Delta V/I$, respectively, where C_N is the capacitance on node N in Fig. 3, C_L is the output load capacitance, and I is the current through a transistor. In the measurement of single sensor cell, the transient response is influenced by external capacitance ~ 150 pF due to bonding pad, and resistance 10 MΩ of voltage probe. The effect of external capacitance and resistance can be reduced by introducing output buffer formed at the periphery of the sensor array.

3. Sensor Array LSI circuit

A BioCMOS LSI circuit with 16x16 extended-gate FET sensor array has been fabricated using ON Semiconductor 1.2 μm standard CMOS process (Fig. 7). The chip includes peripheral circuits of address buffers, XY decoders, multiplexer, and output buffers. The total power consumption is 0.5 mW. Au/Ti films were deposited and patterned as extended gates. Immobilization of 5' thiol modified oligonucleotide of 20 mer GGGAAAAAAAAAAAAAGGG, and hybridization with the complementary oligonucleotide CC CTTTTTTTTTTTTTCCC were detected in a 1 mM potassium phosphate buffer pH 7.0 (Fig. 8). Biomolecular interactions have been observed as time development of the two-dimensional distribution.

The circuit can be miniaturized by using fine process technologies. The area of a sensor cell is reduced from 105.3 μm x 81.4 μm in a 1.2 μm process to 9.22 μm x 7.56 μm in a 0.18 μm process, and DNA chip with 10^6 sensor array to detect all possible sequences of 10 bases can be constructed in a 11 mm x 10 mm chip with power consumption of 100 mW.

References

[1] K. Nakazato, M. Ohura, and S. Uno, "Source-drain follower for monolithically integrated sensor array," Electronics Letters, 43, No.23, pp. 1255-1257, 2007

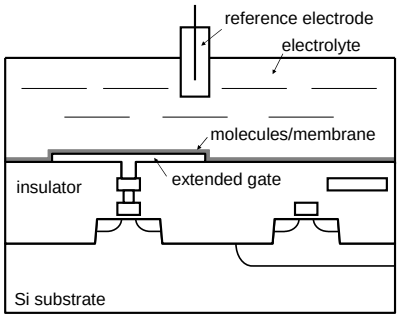

Fig. 1. Cross-sectional view of extended-gate FET sensor

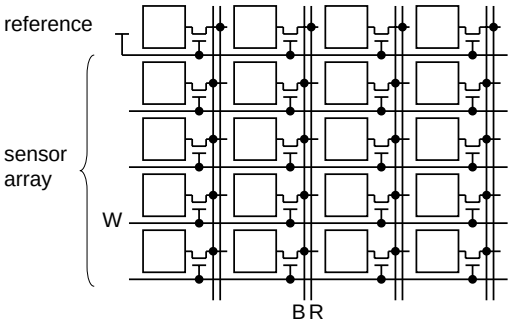

Fig. 2. Matrix array arrangement

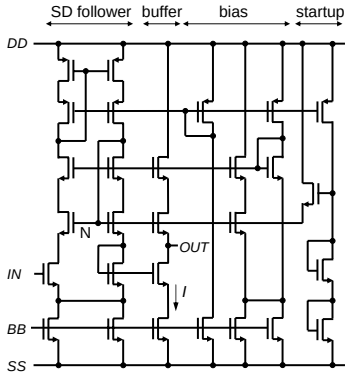

Fig. 3. Sensor cell circuit

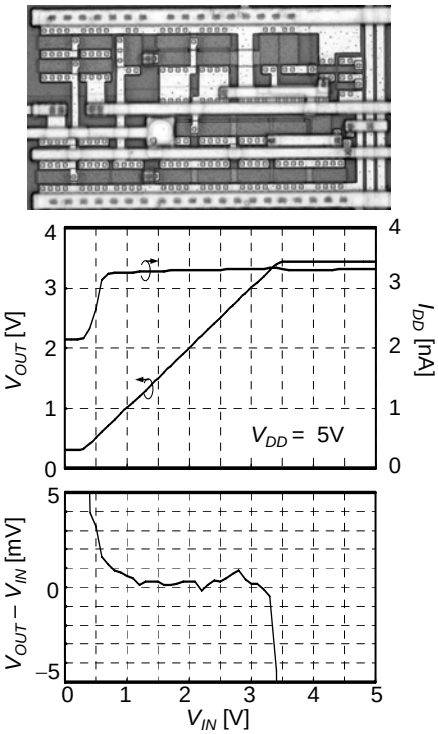

Fig. 4. Optical photograph of fabricated sensor cell and the measured output voltage, total current, and accuracy.

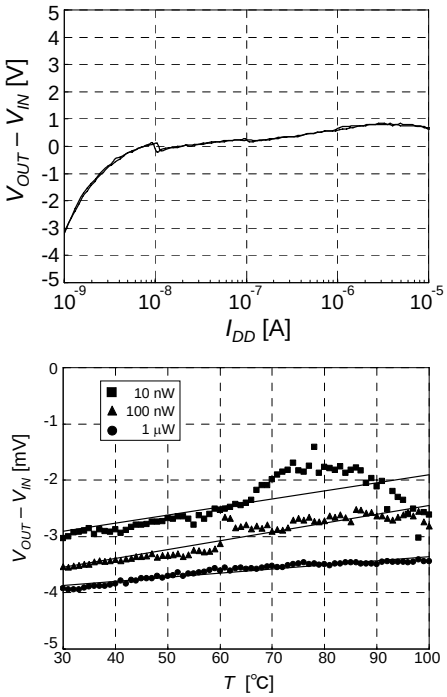

Fig. 5. Accuracy measured as a function of total current, and temperature at input voltage of 1.5 V.

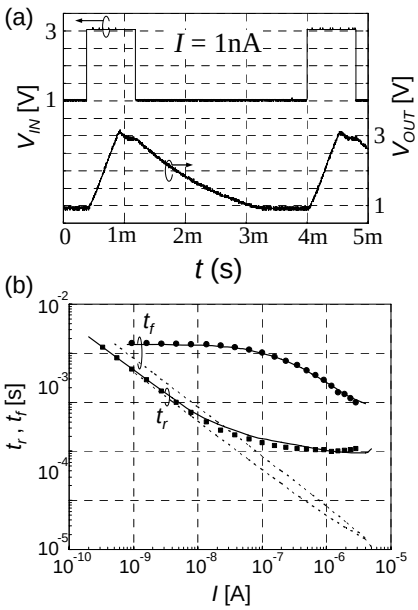

Fig. 6. Measured transient response of a sensor cell. (a) wave form, (b) rise and fall times; ●■:measured, straight lines: simulated with external capacitance and resistance, dotted lines: simulated with internal load capacitance only.

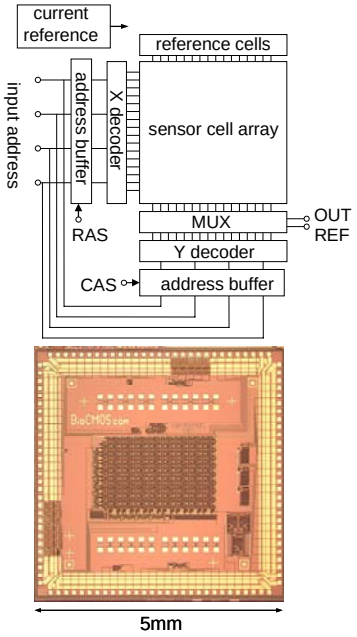

Fig. 7. Schematic circuitry and optical photograph of fabricated 16x16 biosensor array LSI circuit

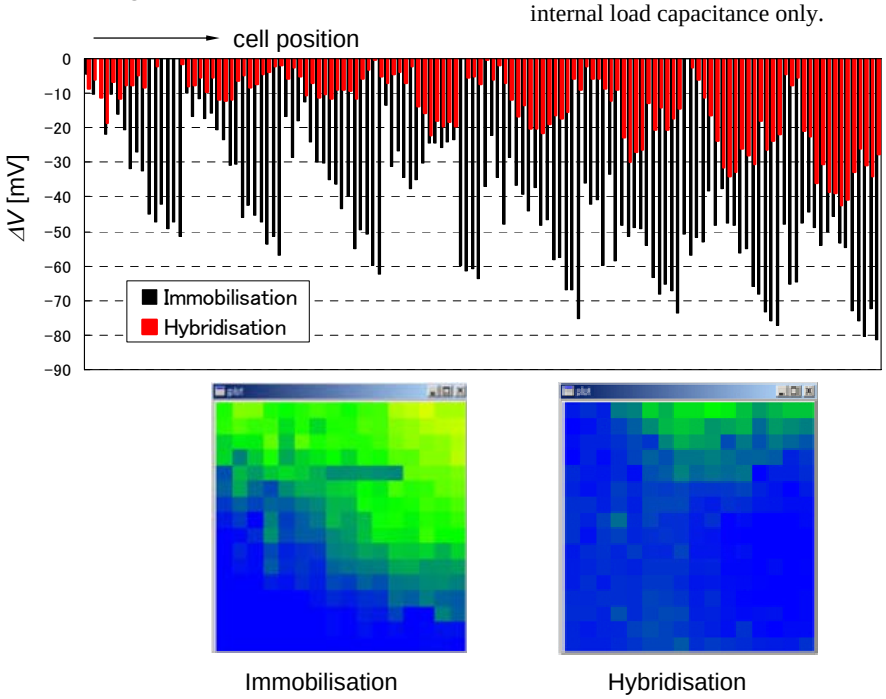

Fig. 8. Sensor signals of immobilisation and hybridisation detected by 16x16 biosensor array LSI circuit.