

Extended-gate MOSFET Biosensor Array LSIs

Kazuo Nakazato, Mitsuo Ohura, Kiyomasa Sugimoto, Junichi Tsukada, and Shigeyasu Uno

Department of Electrical and Computer Science, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

E-mail: nakazato@nuee.nagoya-u.ac.jp

Field effect transistor (FET) type microbiosensor has recently attracted considerable attention because of its many advantages in miniaturization, standardization, mass-production and suitable configuration for smart sensor in which both sensor and measurement circuit are integrated.

This paper describes bioCMOS LSIs with the matrix array of biosensor cells. A cell consists of an extended gate MOSFET and a voltage follower circuit. Single-stranded (ss) DNA molecules with known sequence (probe DNA) are immobilized on the Au extended gate, and the ss DNA molecules with unknown sequence (target DNA) are injected into the solution. If the sequence of the target DNA matches to that of the probe DNA, double-stranded (ds) DNA can be formed. If the sequences do not match, the interaction between them is weak and the target DNA will be washed out. Since a nucleotide has negative charge $-e$ on the phosphate group, variation of electronic charge due to ss DNA and ds DNA after hybridization results in the variation of the gate voltage of MOSFET. To perform the detection simultaneously, probe DNA molecules with various sequences are formed on a matrix array of biosensor cells.

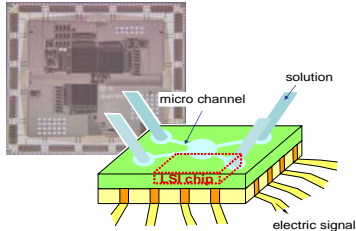
Accurate detection requires the method to reduce the effects of variation of transistor characteristics and temperature across a chip. The local detection of gate voltage within a cell should be performed independently of transistor parameters and local temperature. A compact and low power voltage follower circuit was proposed in which the sense transistor operates at a fixed point of V_{GS} and V_{GD} with small internal electric field, so the stable operation is maintained and the degradation of gate oxide can be avoided. Accuracy of the output voltage to the sense voltage is within 10mV between 20 °C and 100 °C. The circuit can operate in subthreshold region, the drain current of 5nA, where the response time is estimated to be 10 μ s when a load capacitor with capacitance 100 fF (estimated bit line capacitance) is attached to the output node. Each signal from the cell is compared to the reference signal produced by a dummy cell in the column.

Two bioCMOS LSI circuits were demonstrated. One is 1,024 x 1,024 cell array to detect all possible sequences of 10 bases of A, G, C, T. The array size and power consumption are 20 mm x 24.6 mm and 64 mW, respectively, using 0.35 μ m CMOS technology. The other is 16 x 16 cell array with the calibration circuit of extended gate charges and the temperature controlled self-heating circuit. Chip size including peripheral circuits of address buffer, XY decoders, multiplexer, and output buffer, is 2.3 mm x 2.2 mm using 1.2 μ m CMOS technology.

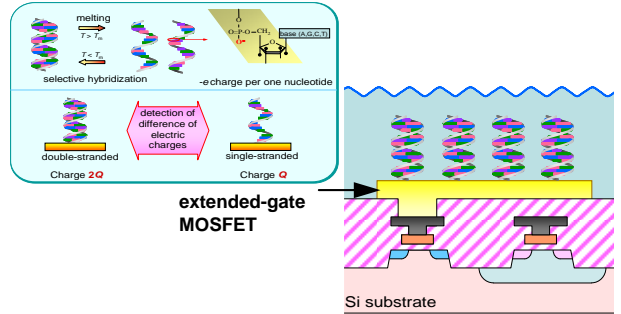
Extended-gate MOSFET Biosensor Array LSIs

Kazuo Nakazato, Mitsuo Ohura, Kiyomasa Sugimoto, Junichi Tsukada, and Shigeyasu Uno
 Department of Electrical and Computer Science, Graduate School of Engineering, Nagoya University

- label free, electrical detection
- system-on-a-chip + lab-on-a-chip



- Detection of biomolecules
- sensor device structure
 - device fabrication process
 - control circuit of sensor device
 - sensing signal processing
 - sensing methods
- Control of biomolecules
- physical movement of molecules
 - enhancement and suppression of molecular interactions
- Supply of biomolecules



Fabrication of Device and Measurement Method

- 1** fabrication of chip using standard CMOS process
 - VDEC (Rohm 0.35μm) (Motrola 1.2μm)
- 2** Formation of Extended Gate
 - Au/Ti evaporation
 - optical photolithography
 - plasma O₂
 - Au wet etching (AURUM-301)
 - Ti wet etching (WLC-T)
 - Removal of resist
 - UV ozone
- 3** immobilization of probe DNA
 - thiol modified oligonucleotide
- 4** hybridization of target DNA
 - measurement

1M(10⁶) cell array

technology	0.35μm CMOS
array size	20mm×24.6mm
power consumption	64mW

target: Genomic Analysis of 10 bases (4¹⁰) simultaneously

M Ohura, S Uno, and K Nakazato, "An Analog BioCMOS Circuit for the Electrical Detection of Biomolecular Charges with Extended Gate MOSFET Cells," 2006 IEEE International Analog VLSI Workshop, November 16-18, 2006, Hangzhou, China

Cell Circuit

Conventional
(discrete transistor+external control circuit)

source/drain follower circuit
maintain transistor at a fixed bias point
 $V_{GS}, V_{GD} = \text{constant}$

Proposed
(integrated circuit)

	conventional	proposed
area	10000 μm ²	500 μm ²
power consumption	10 μW	0.2 μW
transistor operation	S/D follower	S/D follower
influence of transistor variations	100 mV	10 mV
influence of temperature (27-100°C)	250 mV	7 mV

Measured Characteristics

Measured Characteristics. Current of 3nA (power consumption 15nW) with 10mV accuracy between $V_{GS} = 0.5\text{--}3\text{V}$

Measured characteristics with a parameter V_{th} which determines the current. $f_{SD} = 100\text{pA--}100\text{mA}$.

Control of Extended-gate Charges

Origin of Variations of Extended-gate Charges

- Variations of the double layer in solution
- Charging of extended-gate
- Variation of the number of probe molecules

Control of Extended-gate Charges

OFF current of control transistor determines the amplitude of signal.

$I_{OFF} = 1\text{nA}$, $I_{OFF} = 1\text{pA}$, floating

vertical: output voltage [50mV/div] horizontal: time [100ns/div]

DNA chip with control of extended-gate charges

Reference

Cell

Initialization of extended-gate charge
 Suppression of leakage current of control transistor ($V_D - V_G$)

optical photograph of fabricated chip

Control of Biomolecules

- physical movement of molecules
 - applying bias voltages on extended gates
- enhancement and suppression of molecular interactions
 - self-heating (27-90°C)
 - precise control of surface temperature

Assembling

Initial experimental setup

LSI chip

package

chip packaging

Wiring using laser direct-write lithography

Formation of micro channel