

A CMOS Micro Array DNA Biosensor with an On-chip Controlled Electrolyte Electrochemical Potential Regulator

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Abstract – A 12 X 12 and 32 X 32 sensor array chip for fully electronic bio material detection is presented. The sensor principle is based on a carbon nanotube field effect transistor (CNT-FET). Each sensor cell of the array chip contains a buffer circuit which provides independent sensing signal to the common correlated double sampling type successive approximation register analog/digital converter. By using the CNT-FET's electrolyte gate characteristics, we successfully stabilized the electrochemical potential of electrolyte through voltage regulator circuits. Proper operation of the chip is demonstrated by electrochemical experiments and actual sensor realization. The chip is fabricated on the basis of a 0.35 μ m CMOS process for a 12 X 12 array and a 32 X 32 sensor array.

I. INTRODUCTION

Nano-biosensor, a convergence technology of existing biosensor technology and nano technology has been emerged to be one of the most promising candidates to overcome the barriers of current medical issues such as single molecule analysis, real time detection, low power dissipation and miniaturization to be used as in vivo applications [1]-[2]. The electrical nano-biosensors, in particular, have additional advantages in sensing speed, detection accuracy, and semiconductor device integration possibility. However, electrical sensors suffer from parasitic noise issues such as the noise from non-specific target molecules. To reduce these effects, we proposed a sensing scheme with electrolyte potential regulation, a buffer circuit for sensor isolation, and demonstrated the actual array sensor operation through statistical measurement data.

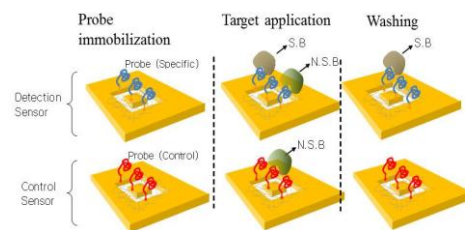
II. ELECTROLYTE CHEMICAL POTENTIAL REGULATOR

A. Biosensor System and Sensing Method

The system being measured must be at a steady state throughout the time required to detect the sensing signal. A

common cause of problems in sensing signals and their analysis is drift in the system being measured. In practice a steady state can be difficult to achieve. The solution potential can change through adsorption of solution impurities, buildup of reaction products in solution, coating degradation, and temperature changes, to list just a few factors. In this respect, the use of reference electrode using easily polarizable material, e.g. Ag/AgCl, can fix the solution potential, and this has been considered to be a de facto rule for ISFET type sensors. For CNT-FET, however, Ag/AgCl method is incomplete to reflect all these CNT-FET's variation factors because CNT-FET uses the solution dependent electrical double layer(EDL) as the gate dielectric of transistor. Moreover, the abundant surface charges which are formed at the surface of CNT are also subject to change, resulting in time dependent current decrease or increase.

Fig. 1 (a) illustrates the typical schematic of bio-sensor operation. Specific Binding(SB) means the binding to receptors of interest, and Non-Specific Binding(NSB) is the binding to other sites. The noises of biosensors usually stem from parasitic environmental factors and NSB effects. A general method to remove noises is using a control sensor and a detection sensor simultaneously and canceling the common mode signals of both sensors. Through several subsequent procedures, which are both chemical and electrical, the remaining signal component representing SB should be detected in real time. Fig. 1 (b) shows the concept of sensing method proposed by this paper which can be used for CNT-FET type sensors. The conductance modulation effect by control sensor's electrolyte gate is used to regulate the electrolyte's electrochemical potential which is commonly applied to both control sensor and detection sensor. Comparing with Ag/AgCl reference electrode method which is most popular, this method shows superior common mode noise rejection characteristics and can be implemented with negligible cost.



(a) Typical schematic of Bio-sensor operation

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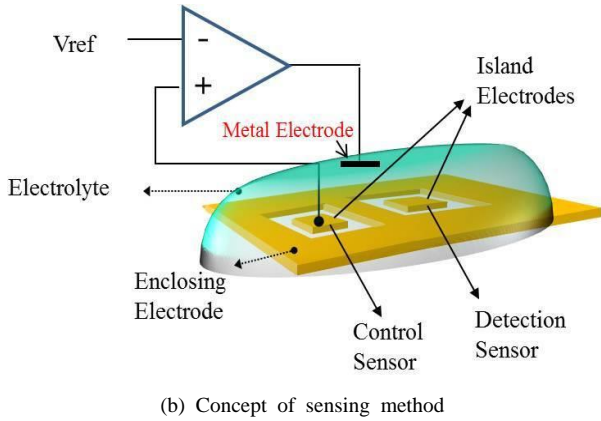


Fig. 1. Electrolyte chemical potential regulator

B. Electrochemical Regulator Theory

Fig. 2 shows the sensor configuration. As shown in Fig. 2 (b), this sensor system is composed of many individual sensors, and each sensor has a circular island electrode. The CNT-FET is made using the single walled CNT network deposited on the electrodes to form a circular electrical channel to the common enclosing electrode in a concentric fashion. Fig. 2 (a) shows the model sensor system consisting of 2 electrodes. An external metal electrode which is used to regulate the electrolyte potential is located in the upper position and the sensor system with Au electrodes is located in the bottom position. Because the size of bottom electrode is much larger than the upper electrode, the bottom electrode is assumed to be semi-infinite.

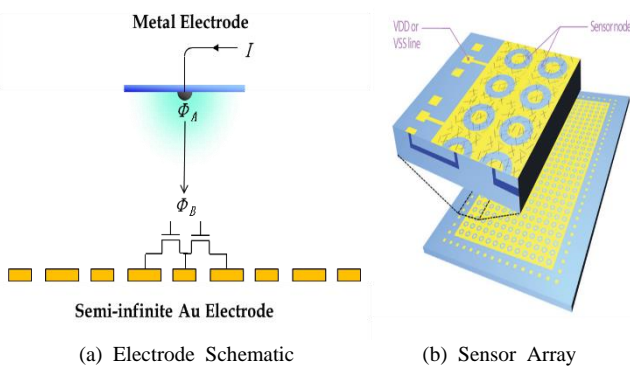


Fig. 2. Schematic and Bird's eye view of CNT-FET sensors

When a potential E is imposed between the metal electrode and Au electrode, current I flows and is carried through the solution by the migration of ions. The electric field which is necessary for ions to migrate is provided by that portion of the applied potential which is dropped across the solution between the two electrodes. The potential Φ_A , Φ_B represents the potential at the electrolyte-metal interface region of upper and bottom electrodes respectively. Because the Φ_B works as the gate voltage of CNT-FET, this potential should be controlled in such a way that the current of CNT-FET to be constant.

The theoretical model to determine the Φ_B is as follows. Charge transfer may occur at the electrode-electrolyte interface if it is thermodynamically favorable. In a metallic

electrode material (as most electrodes are) the energy level of the electrons occupies a continuum of states below the Fermi level. If this level is higher than the highest occupied molecular orbital or below the lowest unoccupied molecular orbital level of the molecules in the electrolyte then electron transfer becomes thermodynamically viable. In equilibrium these should necessarily agree with the thermodynamic equilibrium described in the Nernst Equation.

$$E = E^0 + \left(\frac{RT}{nF} \right) \sum_j v_j \ln[c_j^s] \quad (1)$$

Where

- E : Electrode potential
- E^0 : Standard electrode potential
- v_j : Stoichiometric coefficient
- c_j^s : Local concentration at the surface of the electrode
- n : Number of moles of electrons transferred
- R : Molar gas constant
- T : Absolute temperature
- F : Faraday's constant

Whenever the potential of an electrode is forced and the electrode is polarized, it can cause current to flow via electrochemical reactions that occur at the electrode surface. When there are two simple, kinetically controlled reactions occurring, the potential of the cell is related to the current by the following (known as the Butler-Volmer equation).

$$i_{net,j} = i_0_j \left[\exp \left\{ -\alpha_j \frac{n_j F}{RT} (E - E_{eq,j}) \right\} - \exp \left\{ (1 - \alpha_j) \frac{n_j F}{RT} (E - E_{eq,j}) \right\} \right] \quad (2)$$

Where

- $i_{net,j}$: net current of the redox couple j
- i_0_j : exchange current of the species j
- α : Electron transfer coefficient
- $E - E_{eq,j}$: Overpotential of a single redox couple

In the 2 electrode system consisting of upper and bottom electrodes, the bottom electrode potential Φ_B can be determined by applying the Butler-Volmer equations at both electrodes and solving the steady state current and voltage. However, solving this 2 electrode system can be very complicated if we consider the interactions between the 2 electrodes, and the IR voltage drop due to the ion transport in the solution. Moreover, depending on the ratio of exchange currents between the upper electrode and bottom electrode, a steady state condition may be never theoretically achieved. However, even though the steady condition is not achieved, the Φ_B can be controlled to be constant through the alternating control of upper electrode. (This control method is similar to the conventional potentiostat method and will be discussed in the next section.) Also, in case the exchange current of bottom electrode is very small compared to the upper electrode, the input resistance of bottom electrode can be defined to be R_i which is very large, and the Φ_B can be determined by following equation using iteration method.

$$|i_{net,or}| = \frac{|E|}{R_i} \quad (3)$$

$$E = R_i \sum_{j=1}^m i_{0j} \left[\exp \left\{ -\alpha_j \frac{n_j F}{RT} (E - E_{eqj}) \right\} - \exp \left\{ (1 - \alpha_j) \frac{n_j F}{RT} (E - E_{eqj}) \right\} \right] \quad (4)$$

Where

- E : Bottom electrode potential (Φ_B)
- Ri : Input resistance of bottom electrode

Fig. 3 shows the Au electrode case where this equation can be applied. Because Au is ideally polarized between the voltage range of -0.421V to 0.816V w.r.t. standard hydrogen electrode of pH7, the resistance at this range becomes very large.

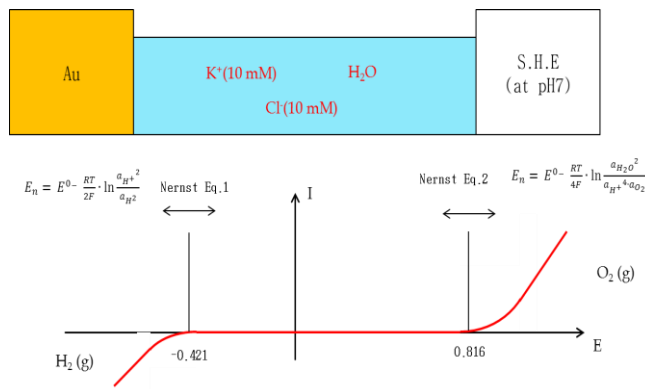


Fig. 3. H2O polarization at Au electrode

Another issue to be resolved is that the Φ_B value is also dependent on the electrical double layer(EDL) capacitance because there is no dielectric layer except EDL on CNT transistor. This layer can be modeled using a combination of concepts from electrostatics and statistical mechanics, leading to the known Poisson–Boltzmann’s equation. This diffuse layer is known as the Gouy–Chapman layer or the electrical double layer. However, it was noticed that the original theory of Gouy–Chapman overestimates the interface charge. This was remedied by Stern, who realized that ions cannot approach the electrode surface closer than their ionic radius.

Therefore, the capacitance of EDL can be modeled by 2 series capacitors which has following equation

$$C_{DL} = \frac{1}{\frac{1}{C_{Stern}} + \frac{\lambda_s}{\epsilon_s}} \quad \lambda_s = \sqrt{\frac{kT \cdot \epsilon_s}{2 \cdot c_0 \cdot z^2 \cdot q^2}}$$

Where

- λ_s : Debye length
- ϵ_s : Permittivity of solution
- z : Ionic valence
- c_0 : molar concentration of ion

This equation shows that the EDL capacitance is mainly dependent on the ion characteristics, i.e. the species and the concentration of solution ion. In case the concentration of ion changes during the sensing operation, Φ_B also changes to address this variation.

C. Analogy to 3 Electrode Potentiostat

Fig. 4 shows the analogy between 3 electrode potentiostat and this method. A modern 3 electrode potentiostat (Fig. 4 (a)) compensates for the solution resistance between the counter and reference electrodes. The main idea for this apparatus is using an operational amplifier, and the potential difference is removed through feedback mechanism. As shown in Fig. 4 (b), the op amplifier input is determined by the CNT gate voltage using a constant resistor to convert the CNT resistance to input voltage. The difference between Fig. 4 (b) and Fig. 4 (a) is that in Fig. 4 (b), the electrolyte potential at the CNT gate region is compensated by the overvoltage reaction of counter electrode(upper electrode in Fig. 2 (a)).

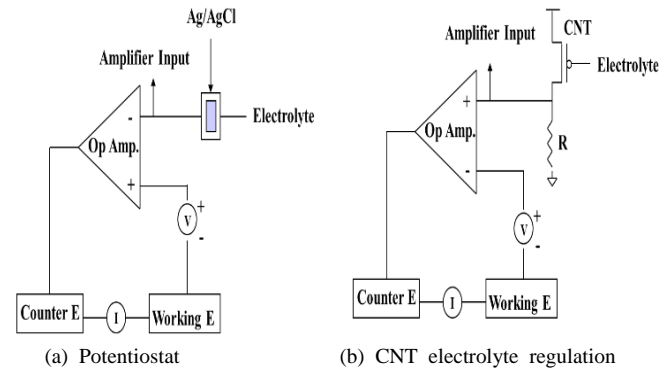


Fig. 4. Comparison of conventional potentiostat and CNT electrolyte regulation system

III. RESULTS AND DISCUSSION

A. Biosensor Circuit Design

Fig. 5 is a buffer circuit in every microarray sensor which removes the parasitic capacitance effects of other sensors. V_{bias} is the bias voltage between carbon nanotube node and common enclosing electrode. Op amplifier keeps the bias voltage through negative feedback and the upper and lower path of feedback is determined by the V_{bias} polarity denoted as V_{mode} . Current mirror circuit which is isolated from sensing part transfers the sensing result to open drain type output circuits. R_{ext} is the load resistance, and amplification factor is determined by the ratio of R_{ext} to CNT resistance. This output signal is measured by a common correlated double sampling type successive approximation register analog/digital converter which was reported by our group. [3] Measurement data can be recorded statistically to an external computer by on chip UART communication circuit.

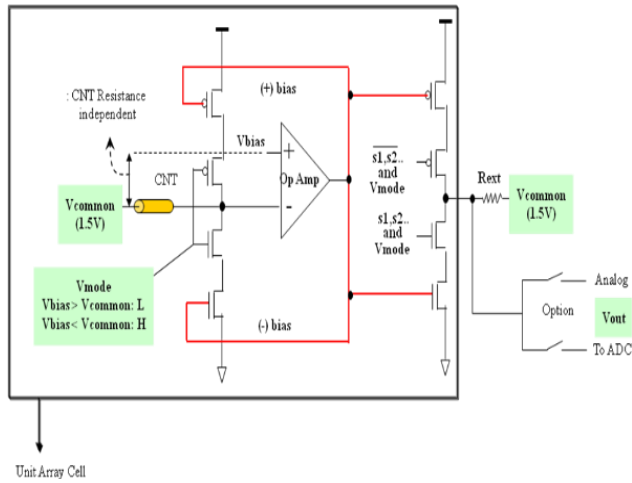


Fig. 5. A buffer circuit of each microarray sensor to remove the parasitic capacitance factors from other sensors

IV. CONCLUSIONS

B. Measurement Result

For CNT resistance sensing, CNT is deposited uniformly using dip coating method on the concentric shaped electrodes. To reduce the contact resistance between CNT and metal electrode, Au is deposited on the Al top layer using electroless plating. Fig. 6 shows the experimental DNA detection result using CMOS integrated biosensor. By functionalizing the single strand DNAs which are thiol-modified for the attachment to the Au nano particles on the CNT layer, arrayed sensor devices have been activated to detect the target DNAs(t-DNA). After about 100 seconds from the time that t-DNA was introduced, the CNT resistances of all the array sensors rapidly increased showing the t-DNA response. The concentration of t-DNA in TE buffer is 5μM. The details of experimental method are the same as the previous result of our group reported for single sensor. [3]

Without using the electrolyte voltage regulator, this sensing result shows drift and fluctuation mechanisms which diminishes the sensing sensitivity. Because these phenomena are occurring for all the sensors, this shows the mechanism is related with the electrolyte potential.

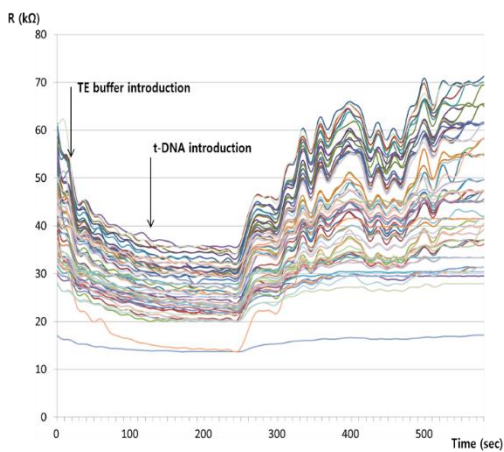


Fig. 6. DNA detection using CMOS integrated CNT biosensor

The experiment environment to demonstrate chip operation with voltage regulator is shown in Fig. 1 (b). The Vcom(1.5 V) is applied to enclosing electrode of concentric structure unit cell and the divided voltage(Vr) between carbon nanotube resistance and reference resistance(Rref = 4*Rcnt) is applied to the one of the input of operational amplifier as shown Fig. 1 (b). As a comparison experiment, the current between carbon nanotube resistance and GND is measured without voltage regulator operation (Fig. 7 (a)). The concentric structure coated by p-type CNT shows electrolyte gating effect having different drain, source electrode area ratio, and acts like a normally turned on PMOSFET. After applying step voltage to the enclosing electrode, current value of CNT is reduced as time goes by due to the delay in forming electric double layer, which plays a role in giving a gating effect. With voltage regulator, the electrolyte potential is controlled by a metal electrode connected to operational amplifier output, and uniform current is measured(Fig. 7 (b)). If Vr is larger than reference voltage(Vref = 0.8*Vcom), op-amp output goes high and Rcnt becomes smaller. Whereas, if Vr is smaller than Vref, Rcnt becomes bigger. Fig. 8 shows the simulation results using Hspice, and we confirmed that the measurement data are similar to the simulation data.

The statistical results of carbon nanotube resistance using 12 x 12 sensor array is shown in Fig. 9. Uniform resistance values are observed even though there are some arrays with abnormal resistance values by poor contact resistance between the CNT and electrode. Fig. 10 is the chip photo of 12 X 12 sensor array and 32 X 32 sensor array.

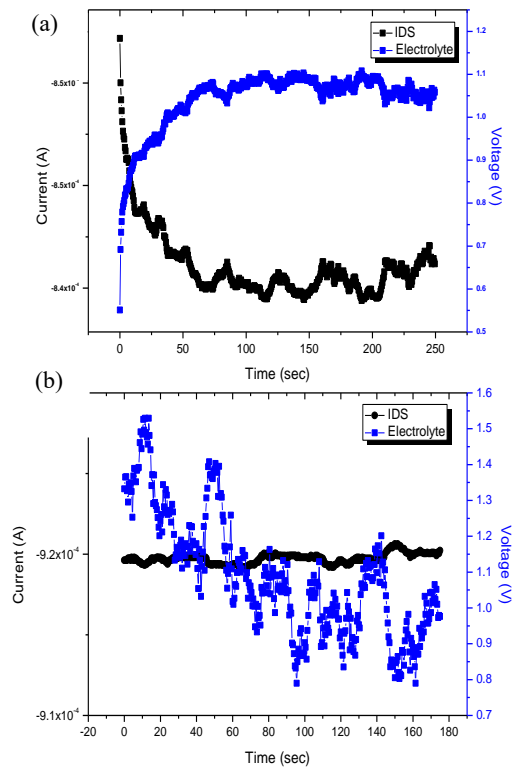


Fig. 7. Change in current value and electrolyte voltage of control sensor (a) without voltage regulator; (b) with voltage regulator

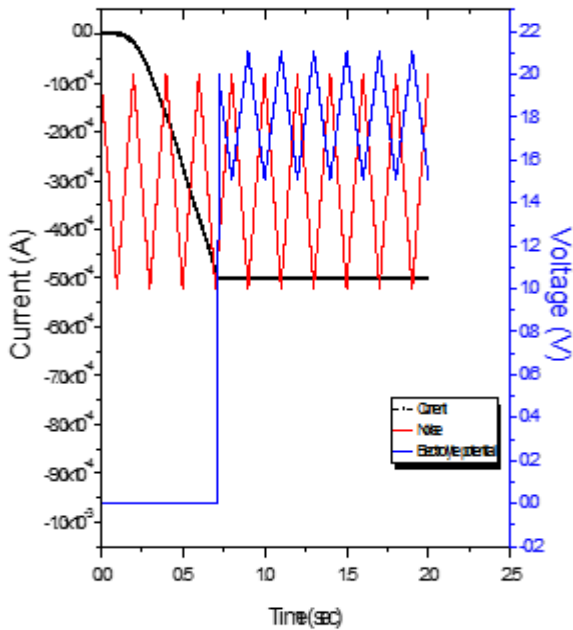


Fig. 8. Hspice simulation result

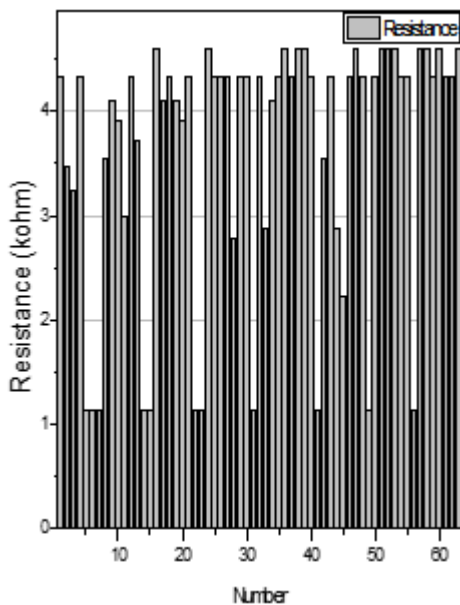


Fig. 9. The statistical results of 12x12 microarrays

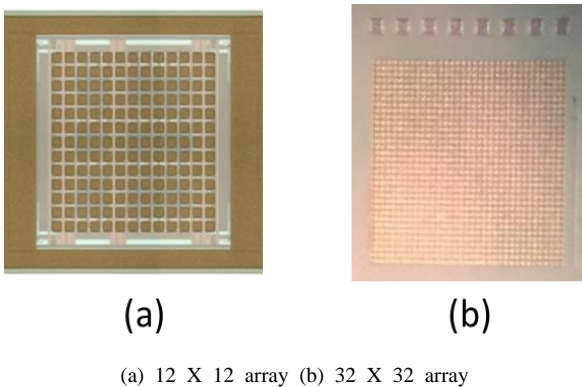


Fig. 10. The photographs of CMOS integrated CNT microarrays with on-chip electrolyte chemical potential regulator

IV. CONCLUSIONS

An effective electrolyte electrochemical potential regulation scheme is shown which can be applied to CMOS based electrical biosensors. Because potential difference is imposed between electrolyte and the metal electrode by feedback mechanism, redox reaction which is fast enough to compensate the change of reference voltage can be achieved. This means conventional referencing material like Ag/AgCl or expensive porous Pt electrode can be replaced by normal metal electrodes which are compatible to CMOS fabrication technology. In this paper, a fully CMOS-integrated CNT sensor array platforms that consist of an 12 X 12 and 32 X 32 arrays have been demonstrated. With the electrolyte chemical potential regulator and sensor isolation circuit, we showed the environmental noises of a electrical nano-biosensor can be reduced. Using this chip we can get statistical results of carbon nanotube using integrated CMOS buffer circuit without Ag/AgCl reference electrode.

ACKNOWLEDGMENT

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