

Review



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Chemistry integrated circuit: chemical system on a complementary metal oxide semiconductor integrated circuit

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By integrating chemical reactions on a large-scale integration (LSI) chip, new types of device can be created. For biomedical applications, monolithically integrated sensor arrays for potentiometric, amperometric and impedimetric sensing of biomolecules have been developed. The potentiometric sensor array detects pH and redox reaction as a statistical distribution of fluctuations in time and space. For the amperometric sensor array, a microelectrode structure for measuring multiple currents at high speed has been proposed. The impedimetric sensor array is designed to measure impedance up to 10 MHz. The multimodal sensor array will enable synthetic analysis and make it possible to standardize biosensor chips. Another approach is to create new functional devices by integrating molecular systems with LSI chips, for example image sensors that incorporate biological materials with a sensor array. The quantum yield of the photoelectric conversion of photosynthesis is 100%, which is extremely difficult to achieve by artificial means. In a recently developed process, a molecular wire is plugged directly into a biological photosynthetic system to efficiently conduct electrons to a gold electrode. A single photon can be detected at room temperature using such a system combined with a molecular single-electron transistor.

1. Introduction

Advances in semiconductor technology have enabled the integration of more than one billion transistors on a chip,

following Moore's law, whereby the number of elements on a fixed silicon die doubles every 18 months. This makes it possible to fabricate artificial structures on a 10 nm scale. On the other hand, material chemistry makes it possible to design supermolecules and reconstruct living body materials, which have dimensions of about 10 nm. This dimensional convergence may mark the starting point of the 'chemistry integrated circuit', where two completely different fields, material chemistry and semiconductor technology, are merged. Molecules have numerous functions, including interaction with specific molecules, reversible structural change, self-assembly, three-dimensional networking and room-temperature quantum effect, which are extremely difficult to achieve with semiconductor technology. On the one hand, living body materials are formed on the basis of mutation and natural selection, which have led to complex creatures, for example human beings. On the other hand, semiconductor devices have complementary functions, such as reliability, accuracy and systematization.

The chemistry integrated circuit has two aspects. One is the integration of chemistry on a chip. Several chemical reactions occur on a chip, which are controlled and detected electrically. This type of device is called the smart lab-on-a-chip and is mainly used for biomedical applications. The other aspect is the use of the molecule as a circuit element to construct new functional devices, which can be called smart molecular electronics, and the main target is room-temperature quantum electron devices.

In this paper, two types of devices are described: multimodal electrochemical sensor arrays towards the integration of chemistry, and photosystem I (PSI) photosensors towards new functional devices.

2. Multimodal electrochemical sensor arrays

In view of the growing concern about such issues as food security, healthcare, evidence-based care, infectious disease and tailor-made medicine, a portable gene-based point-of-care testing (POCT) system is needed. For a system that anyone can operate anywhere and obtain immediate results, a new biosensor chip must be developed. Electrical detection using complementary metal oxide semiconductor (CMOS) integrated circuits has great potential, as it eliminates the labelling process, achieves high accuracy and real-time detection and offers the important advantages of low-cost, compact equipment.

Our target is a monolithically integrated sensor array that detects all possible biomolecular interactions simultaneously. In each sensor cell, different kinds of probes can be formed for parallel detection. In addition, the same kind of probe can be used to observe the time evolution of the spatial distribution of biomolecular interactions as well as to improve the detection accuracy, as biomolecular interactions are a stochastic process. We have developed multimodal electrochemical sensor arrays based on the detection of electric potential, current and impedance.

One of the design principles of our sensor array is that the structure must be compatible with standard CMOS integrated circuits. We use the 6 in 0.6 μm two-polysilicon three-metal mixed signal CMOS process of the Taiwan Semiconductor Manufacturing Company. Post-CMOS processes to form Au extended-gate electrodes, a positive light-sensitive polyimide protection layer and SU-8 (an epoxy-based negative resist) microfluidics are added as shown in figure 1. Another of our design principles is that the cell circuits do not influence the sensed system. For this purpose, cell circuits are designed to copy sensing signals and the copied signals are handled by the peripheral circuit.

(a) Potentiometric sensor array

The detection of electric potential change based on a field-effect transistor (FET) [1] has shown excellent sensitivity, for example for ion concentration [2,3] and specific DNA sequences including single-nucleotide polymorphisms (SNPs) [4]. There are two detection principles.

One principle is the detection of electronic charge around an electrode with no electron transfer to the electrode. We call this method 'direct charge detection'. The gate potential is determined

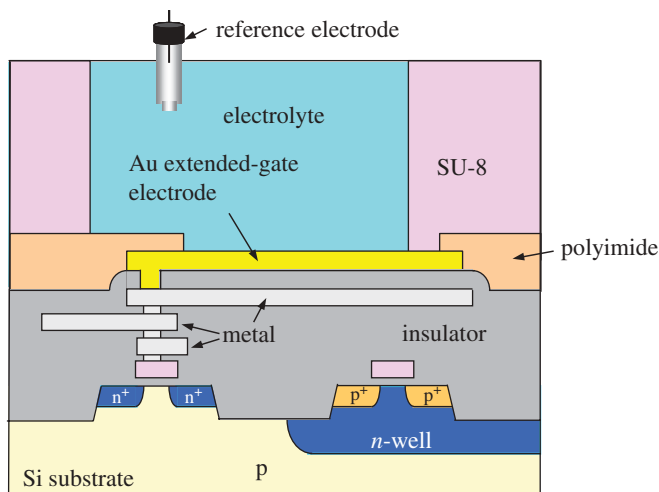


Figure 1. Schematic cross section of an electrochemical sensor cell. The Au extended-gate electrode, polyimide protection layer and SU-8 microfluidics are formed by a post-CMOS process. (Online version in colour.)

by Poisson's equation. First, a probe layer is formed on an FET. Then, target molecules are supplied. Specific molecules are selectively taken into the probe layer on the FET channel, which detects the molecular charge in the probe layer. In the case of DNA detection, the probe is (single-stranded) ssDNA with a known sequence, immobilized on the substrate. When the target ssDNA is supplied, specific hybridization occurs if the target DNA is complementary to the probe DNA. Occurrence or non-occurrence of specific hybridization can be detected by the difference in charge, as a nucleotide has a negative charge on the phosphate group.

The other principle is the detection of chemical equilibrium potential, i.e. redox potential, accomplished by electron exchange between the electrolyte/molecule and the electrode. A ferrocenyl-alkanethiol-immobilized gold electrode is used to detect an enzyme reaction through a redox reaction. In this case, the gate potential is determined by the Nernst equation.

Extended-gate electrodes are employed to be compatible with standard CMOS structures. We have designed a CMOS source-drain follower as shown in figure 2 [5]. The sensor transistor N detects the extended-gate electrode voltage V_{in} . This circuit works as a voltage follower ($V_{out} = V_{in}$) with high input and low output impedances. A benefit of the voltage follower is that the output voltage is independent of device parameters, for example threshold voltage, and environmental conditions, for example temperature. This circuit also works as a source-drain follower for the sensor transistor N.

Many different biosensors have been developed based on pH sensors, as various biomolecular interactions produce protons [3]. Rothberg *et al.* demonstrated a genome-sequencing chip that contains 13 million pH sensors on a $17.5 \times 17.5 \text{ mm}^2$ die [6].

The cumulative probability of pH sensitivity of 16×16 sensor cells with a 100 nm catalytic chemical vapour deposition (cat-CVD) silicon nitride layer is plotted in figure 3. Cat-CVD is a low-temperature (350°C) process and the deposited silicon nitride is of high quality, similar to that obtained by low-pressure CVD. The median pH sensitivity is -41 mV pH^{-1} , which is lower than the theoretical value of -57 mV pH^{-1} . The reason for this lower value may be explained by the oxygen-rich layer on the Si_3N_4 surface [7].

The direct charge detection method using FET has a number of serious problems. First, the molecular charge is screened by ions in solution. Screening length is around 3 nm in the case of an ion concentration of 10 mM. This can be extended if a low ion concentration is used; however, in this case, a very high-impedance environment is produced, and the electric potential becomes unstable. Second, the charge distribution is influenced by the shape of the molecule.

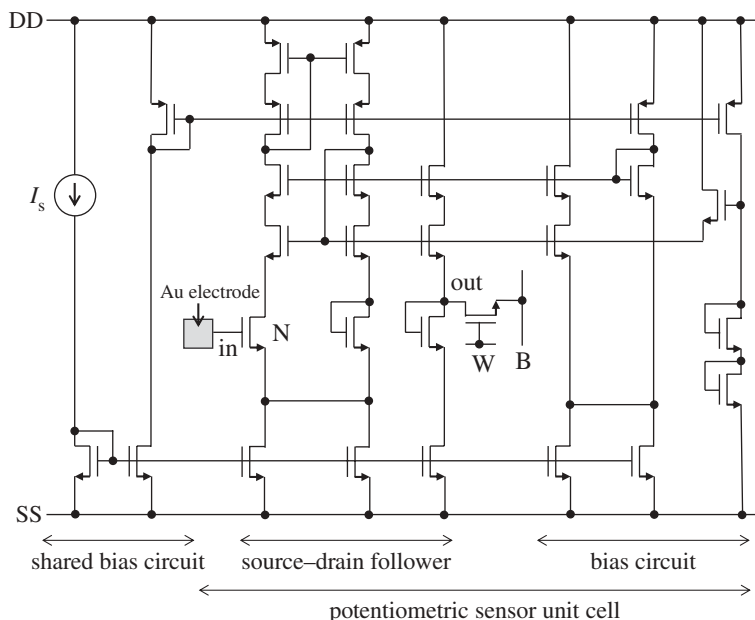


Figure 2. Schematic of a potentiometric sensor unit.

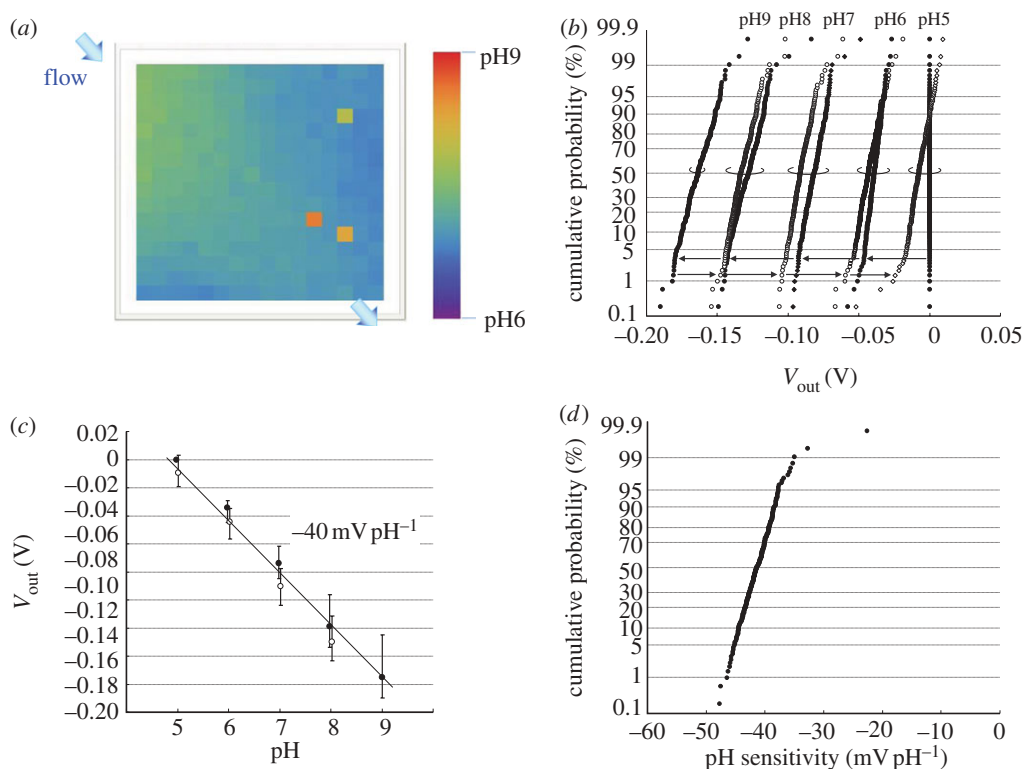


Figure 3. (a) Two-dimensional image of pH change. There are three faulty sensor units. (b) Cumulative probability of output voltage and (c) median $\pm \sigma$ plot as a function of pH from pH 5 to 9 (filled circles) and pH 8 to 5 (open circles). The output voltage is the result after subtracting the initial values in order to eliminate the charge effect from the floating gate. (d) Cumulative probability of pH sensitivity of individual sensor cells.

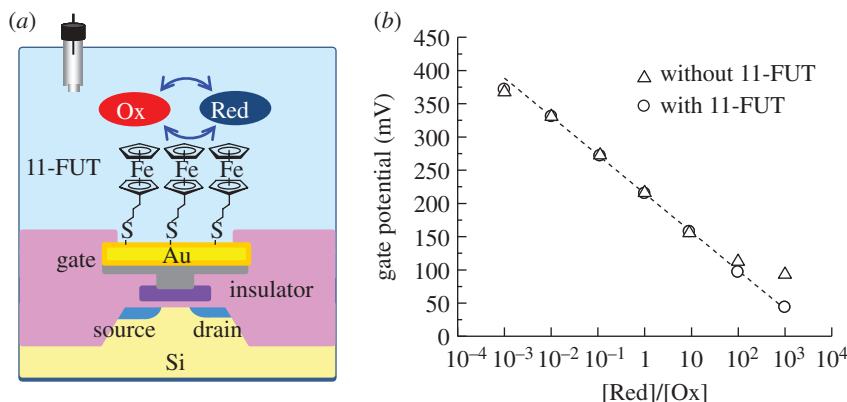


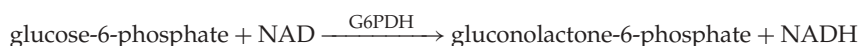
Figure 4. (a) Schematic cross section of redox potential sensor. (b) Potential versus ratio of reducer (ferrocyanide) to oxidizer (ferricyanide) concentration. 11-FUT enlarges the dynamic range of the sensor. (Online version in colour.)

It is generally understood that ssDNA takes a Gaussian shape, and (double-stranded) dsDNA takes a rod-like shape. It is unclear whether it is a change in charge or change in structure that is detected. Especially in a flow system, the molecular shape fluctuates, which leads to an unstable electric potential. Third, the electrode enters a floating state. Although UV irradiation reduces the threshold voltage variation [8], embedded charge causes a large threshold voltage variation.

Instead of using the direct charge detection method, a redox potential detection method was developed using a ferrocenyl-alkanethiol-modified gold electrode [9,10]. This redox potential sensor detects the ratio of reducer to oxidizer concentration, as shown in figure 4, and is not affected by the absolute concentration and pH.

We fabricated a chip that integrates 32×32 redox potential sensors [11]. The sensor chip was dipped in 500 μM 11-ferrocenyl-1-undecanethiol (11-FUT) in ethanol for 24 h. Hexacyanoferrate mixture totalling 10 mM was used for the oxidizer and reducer. Six orders of concentration ratio of reducer and oxidizer were detected by this sensor array, as shown in figure 4b. The sensitivity was 57.9 mV/decade, which is very close to the theoretical value of 59 mV/decade at 25°C. Stability, i.e. long-term drift and fluctuation, of electric potential was examined using a bare electrode and an 11-FUT-modified electrode, and 10 mM phosphate-buffered saline (PBS) solution (pH 7.4) and redox PBS solution in which the 10 mM hexacyanoferrate was added to the 10 mM PBS solution. By using redox PBS solution, the drift of electric potential was reduced by nearly one order of magnitude. Furthermore, 11-FUT modification reduced the drift to nearly one-fourth. This experiment showed that the drift could be drastically reduced to less than 0.5 mV h^{-1} by the redox potential detection method compared with 30 mV h^{-1} in the direct charge detection method.

This redox potential sensor array successfully detected the glucose level with an accuracy of 0.2 mg dl^{-1} , using the following enzyme-catalysed redox reaction:



where HK is hexokinase and G6PDH is glucose-6-phosphate dehydrogenase. The limit of detection of glucose was 1 μM .

Continuous sample measurement was performed using a flow measurement system with a flow speed of $1 \mu\text{l s}^{-1}$, as shown in figure 5. We used two types of solution: PBS solution (pH 7.4) and glucose sample solution (glucose, 9.9 mM potassium ferricyanide, 0.1 mM potassium ferrocyanide, 0.6 mM NAD, 2 mM ATP, 10 mM MgCl_2). PBS solution was used to wash out the

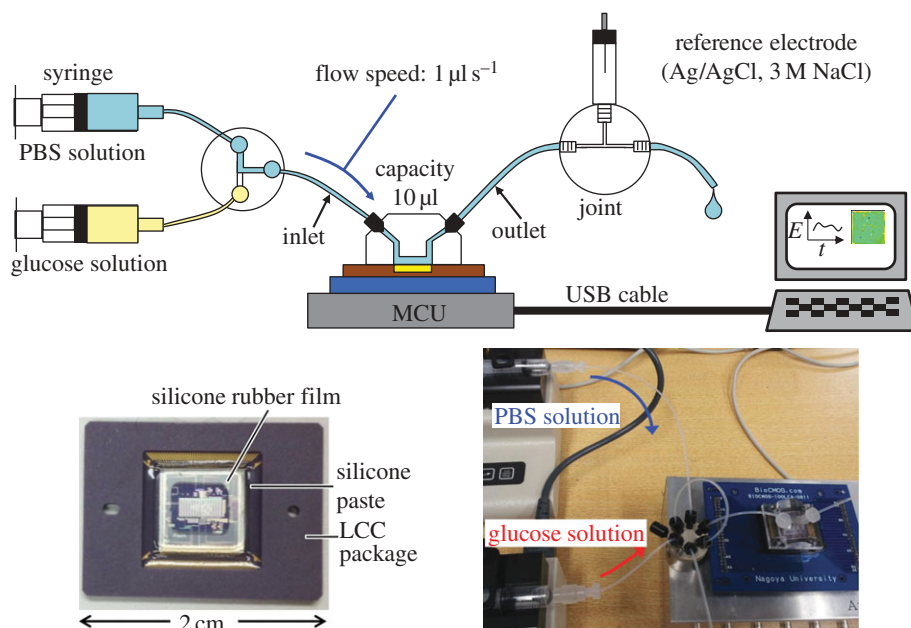


Figure 5. Set-up of measurement. The chip is controlled by a microcontroller unit (MCU).

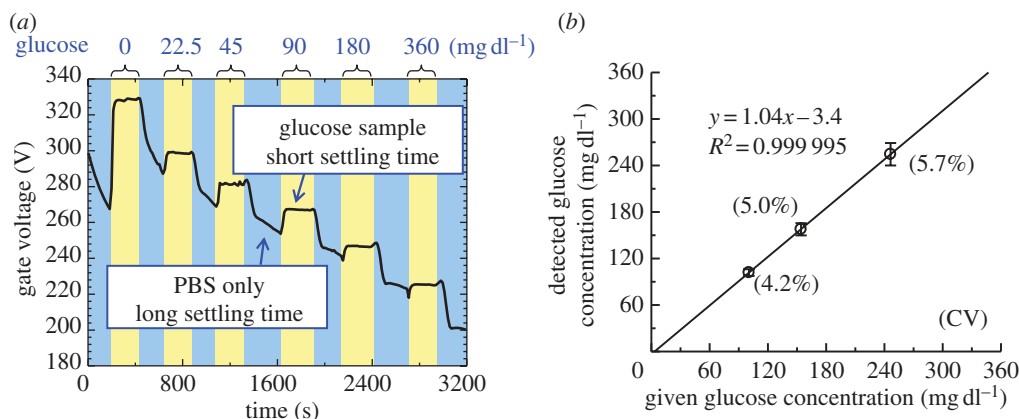


Figure 6. (a) Flow measurement of glucose. Blue areas indicate the flow of PBS solution, and yellow areas indicate the flow of glucose sample solution. (b) Detected glucose versus given glucose in human serum (JCCRM 521-11) obtained from the Reference Material Institute for Clinical Chemistry Standards, Japan.

glucose sample. As shown in figure 6a, the gate voltage settled in the glucose sample very rapidly. On the other hand, in the PBS solution, a long settling time was observed. We note that the PBS solution corresponds to the conditions of the direct charge detection method, and the glucose sample corresponds to the conditions of the redox potential detection method. The relationship between the known and the detected concentrations of glucose in human serum showed fairly good linearity ($R^2 = 0.999\,995$) as shown in figure 6b. The gate potential at a known glucose concentration of 100.5 mg dl^{-1} was $264.0 \pm 0.8\text{ mV}$ (from three measurements). This gate potential was converted into a glucose concentration of $102 \pm 4\text{ mg dl}^{-1}$ (coefficient of variation CV of 4.2%). In the same way, we detected $158 \pm 8\text{ mg dl}^{-1}$ (CV of 5.0%) at a known glucose concentration of 154.1 mg dl^{-1} and $255 \pm 10.2\text{ mg dl}^{-1}$ (CV of 5.7%) at a known glucose

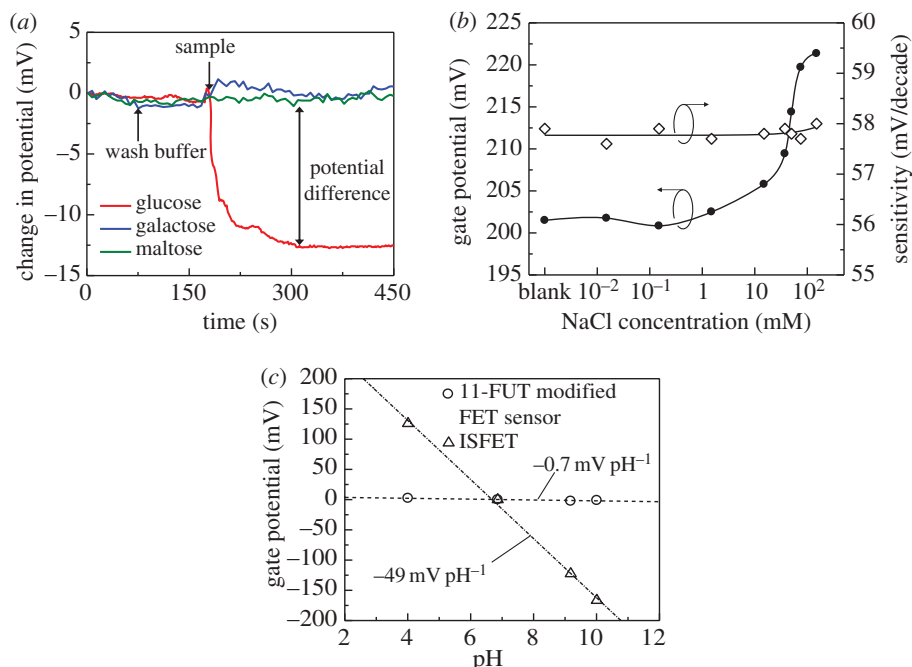


Figure 7. (a) Change in gate potential when 2.5 mg dl^{-1} glucose, galactose and maltose samples are supplied. (b) Dependence of ion concentration. (c) pH sensitivity. (Online version in colour.)

concentration of 264.3 mg dl^{-1} , suggesting that the electrode is capable of accurately determining glucose levels in human blood.

It is important to confirm that the detected signal is glucose-specific and not caused by other factors. Figure 7a shows the detection signals when 2.5 mg dl^{-1} glucose, galactose and maltose samples are supplied, showing no sensitivity to galactose and maltose, which are usually contained in human blood and cause interference in conventional glucose sensors based on the glucose oxidase (GOD) or pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) method. Figure 7b shows the dependence of ion concentration. Gate potential (left axis) was taken at $[\text{Red}]/[\text{Ox}] = 1$, and sensitivity (right axis) was taken between 10^{-3} and 10^3 of $[\text{Red}]/[\text{Ox}]$. Although the absolute value of gate potential changed at NaCl concentration higher than 1 mM, the sensitivity to the concentration ratio of oxidizer and reducer is not affected. Figure 7c shows pH dependence. The pH sensitivity of 11-FUT-modified FET is as small as -0.7 mV pH^{-1} , compared with -49 mV pH^{-1} of FET with the cat-CVD silicon nitride layer.

(b) Amperometric sensor array

Amperometric imaging offers great potential for multipoint rapid detection and the analysis of diffusion processes of target molecules. The microelectrode is one of the most versatile and powerful tools in amperometry. Although the current passing through a microelectrode is very small, it has the advantages of high mass transport density, small double-layer capacitance and small ohmic drop. Moreover, a microelectrode has a steady-state current response in unstirred solutions; such steady-state currents are easy to analyse and interpret. However, as it takes a few or tens of seconds before reaching a steady state, rapid multipoint measurement cannot be achieved with a simple switching scheme. Furthermore, when the inter-electrode distance is not sufficiently large, the diffusion layers begin to overlap and eventually merge to form a single planar diffusion layer. This overlapping of diffusion layers is commonly referred to as 'crosstalk' or the 'shielding' effect. When crosstalk occurs, the microelectrode array loses its unique features

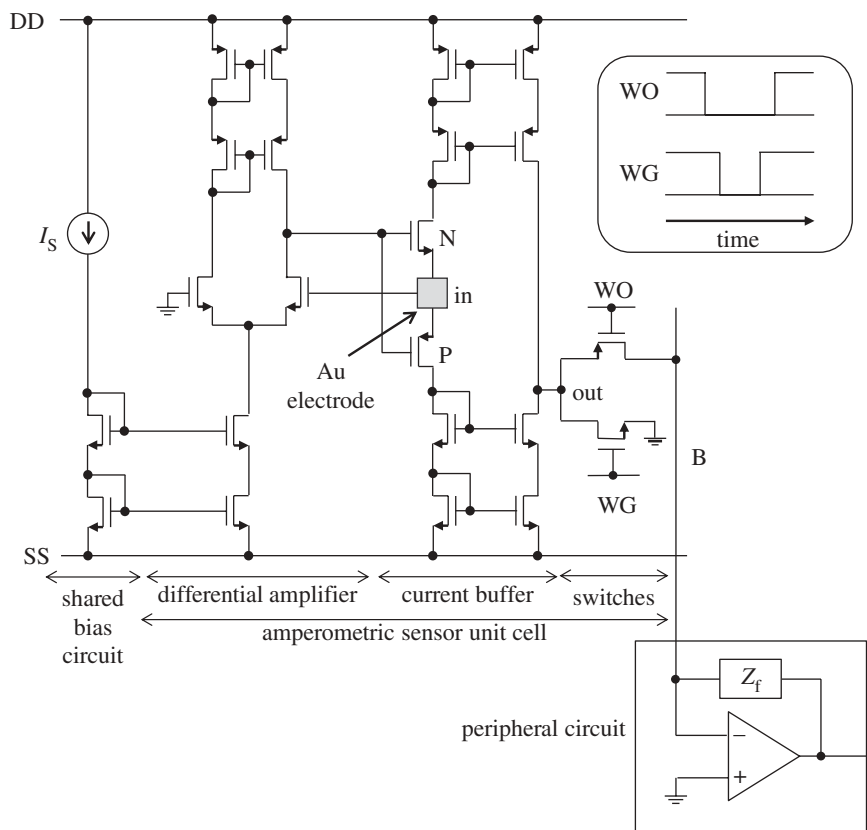


Figure 8. Schematic of an amperometric sensor unit.

and becomes similar to a large-area ‘macro’ electrode, which makes local and quantitative analysis extremely difficult. We proposed a microelectrode structure to suppress diffusion layer expansion over the microelectrode array [12].

Figure 8 shows the designed amperometric sensor circuit. Multiple electrodes placed in an array are connected with one peripheral read-out circuit through each amperometric sensor unit cell consisting of a differential amplifier, current buffer and switches. The differential amplifier fixes the Au electrode voltage to ground level through NMOS source follower N and PMOS source follower P. The output of the current buffer is connected to two switches. V_{out} being measured is connected to the read-out circuit via switch WO, and on stand-by, V_{out} is fixed to ground level via switch WG. When the reading electrode is switched, one of the two switches is kept closed. Thus, output and bit-line voltages are always maintained at ground level, reducing the charging and discharging of parasitic capacitors and realizing ultrafast read-out from each electrode.

Our working electrode (WE) structure shown in figure 9b is surrounded by a grid auxiliary electrode (AE), and the redox reaction opposite to the WE occurs in the AE. Therefore, the diffusion layer is confined around the WE, and the overlap is decreased. The steady-state current is amplified by redox cycling, and the time to reach the steady state is reduced.

A 16×16 amperometric sensor array was fabricated. Ag/AgCl and Pt wire were used as reference and counter electrodes, respectively. The solution was composed of 100 mM sodium sulfate and 1 mM potassium ferrocyanide. WE and AE potentials were fixed at 0.65 and 0 V (versus Ag/AgCl), respectively. Figure 10 shows the current responses of 1 mM $[\text{Fe}(\text{CN})_6]^{4-}$ observed at the single microelectrode, conventional microelectrode array and proposed microelectrode array.

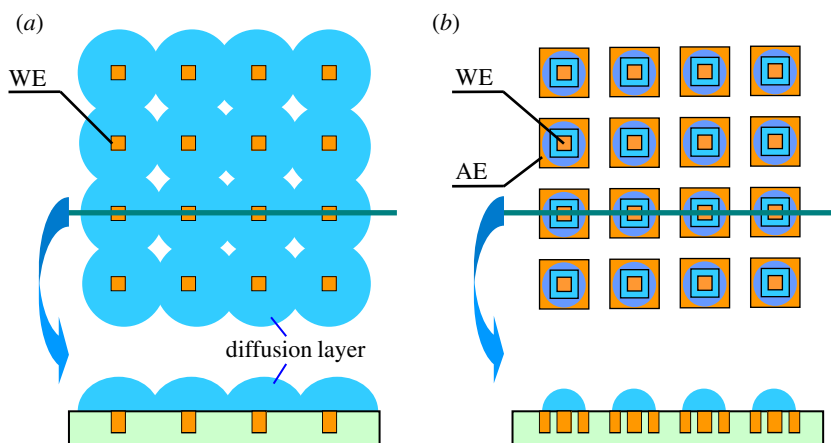


Figure 9. (a) Conventional and (b) proposed electrode geometry. (Online version in colour.)

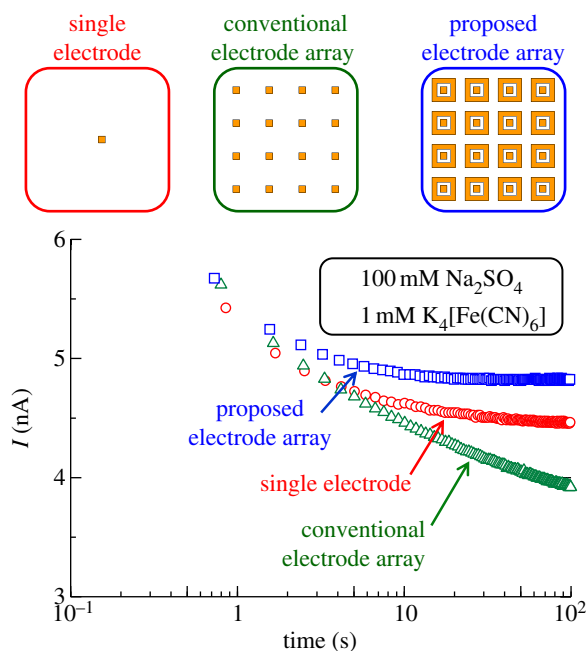


Figure 10. Current responses of fabricated microelectrodes. (Online version in colour.)

(c) Impedimetric sensor array

We have designed an on-chip impedimetric sensor unit, which measures the impedance at frequencies up to 10 MHz. The sensor unit and peripheral circuitry are shown in figure 11. To eliminate the effect of turn-on resistance of switch and bit-line capacitance, a high-speed current buffer is included in each sensor unit. In the peripheral circuit, a current duplicator/amplifier, mixers and low-pass filters (LPFs) convert AC current to the real part ($\text{Re } Y$) and imaginary part ($\text{Im } Y$) of the admittance [13]. An external sine wave generator supplies AC voltage to the reference electrode and reference signal to the peripheral circuit. The reference signal is shaped to a rectangular pulse signal and the phase is shifted 90° by a phase shifter [14].

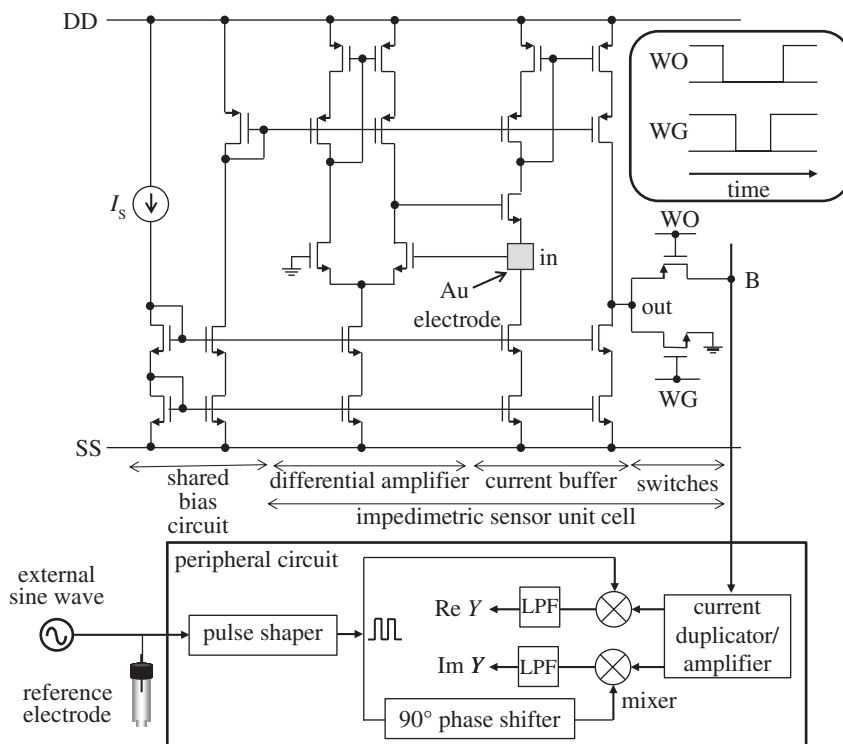


Figure 11. Schematic of an impedimetric sensor unit and peripheral circuit.

One of the applications of the impedimetric sensor array is the direct counting of viruses and bacteria [15]. A specific virus or bacterium is captured by antibodies formed on an electrode, which can be detected as an impedance change at around 1 MHz, simply because it covers part of the electrode.

(d) Multimodal sensor array

In LSI fabrication, the initial cost of making a set of photomasks is high, but the chip cost becomes very low when a large number of chips are produced. In 0.13 μm technology, the typical cost of a set of photomasks is around \$600 000, whereas the cost of 1 cm^2 chip excluding photomasks is around \$10. More than 60 000 chips are necessary to offset the initial cost, which means that standardization and general-purpose sensor chips are important. Our strategy is to realize a multimodal sensor array for synthetic analysis and standardization. The chip consists of amperometric, potentiometric and impedimetric smart cells containing a high-density, low-power amplifier, achieving noise reduction and not influencing the sensed system. The chip can be customized by patterning the polyimide layer to cover the unused sensor cells.

A 16 $\times$ 16 multimodal array with 0.24 mm pitch was fabricated using a 0.6 μm CMOS process as shown in figure 12. One block consists of potentiometric, amperometric and impedimetric sensors. The size of each sensor unit is 60 $\times$ 60 μm . Such a multimodal sensor array will enable synthetic analysis, for example simultaneous detection of glycohaemoglobin (HbA1c) and glucose for the diagnosis of metabolic disease.

3. Molecular image sensor

Photosensors are widely used in both everyday-life products and advanced technologies. Although inorganic materials are used in the photosensors of conventional electronic devices,

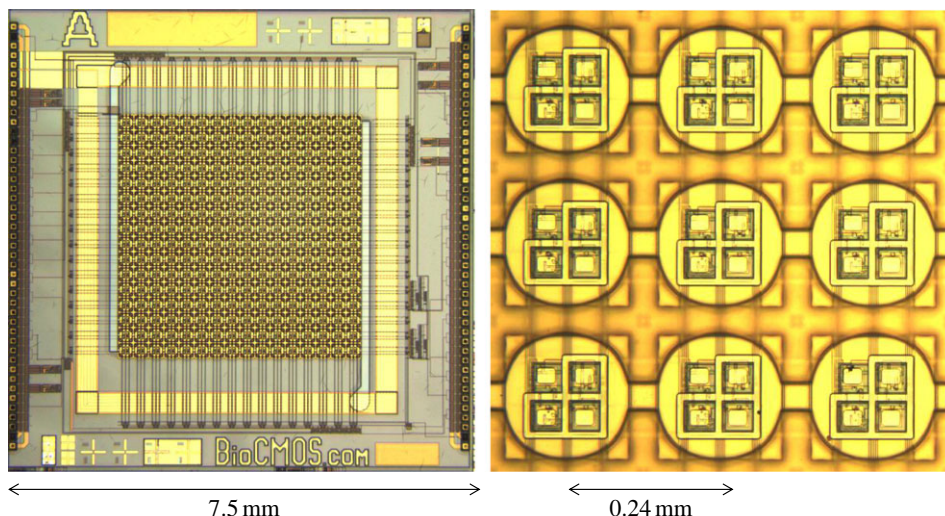


Figure 12. A 16×16 0.24 mm pitch multimodal sensor array integrated with potentiometric, amperometric and impedimetric sensor units using $0.6 \mu\text{m}$ technology. A total of 350 nm Au/50 nm Cr electrodes, $3 \mu\text{m}$ polyimide protection layer and $50 \mu\text{m}$ SU-8 microfluidics are formed on a CMOS integrated sensor circuit. (Online version in colour.)

their performance is not satisfactory with regard to energy efficiency, for example quantum yield [16].

The quantum yield of the photoelectric conversion of photosynthesis, which is a chemical process occurring in plants, algae and cyanobacteria, is 100% [17], which is extremely difficult to achieve by artificial means. In addition, thermal energy is greatly suppressed and the biological molecules are cheap and have a low environmental load, and so material production and postprocessing are easy. By incorporating living body materials and an integrated circuit, a completely new type of high-density photosensor with high sensitivity can be realized, which is not possible using semiconductor technology alone. A single photon can be detected at room temperature using such a system combined with a molecular single-electron transistor.

(a) Photosystem I photosensor

This section describes photodetection using a potentiometric sensor array and a photosynthesis protein complex, photosystem I, PSI (a photoreceptor macromolecule).

The PSI in chloroplast is extracted from *Thermosynechococcus elongatus*, the diameter of which is approximately 10 nm. The PSI includes reaction centre chlorophyll a (P700), chlorophyll a (A0), phylloquinone (A1) and Fe-S clusters F_X , F_A and F_B , which transmit electrons. Isolation and refinement of PSI were performed as reported [18]. Figure 13 shows PSI modification of the extended-gate electrode of a transistor. A self-assembled monolayer (SAM) of 3-mercaptopropanesulfonic acid sodium salt (MPS) covers the Au electrode. The SAM has a negative electric charge, and the ferredoxin around the Fe-S clusters of the PSI has a positive electric charge. As a result, the PSI is electrostatically fixed on the electrode. According to preliminary investigations involving quartz crystal microbalance (QCM) measurements using gold resonators, the adsorbed quantity was estimated to be $4.34 \times 10^{-10} \text{ mol cm}^{-2}$ for MPS, and $7.7 \times 10^{-13} \text{ mol cm}^{-2}$ for PSI.

In measuring the photoresponse, sodium L-ascorbate (NaAs) and 2,6-dichloroindophenol (DCIP) are used as electrolyte for transporting electrons. DCIP becomes a reducer carrying electrons to P700 in PSI when it is reduced by NaAs. Under light irradiation, electrons on P700 are excited to higher energy levels (energy gap is 1.77 eV corresponding to a wavelength of 700 nm). The excited electrons are transferred along the electron transport chain and finally trapped at

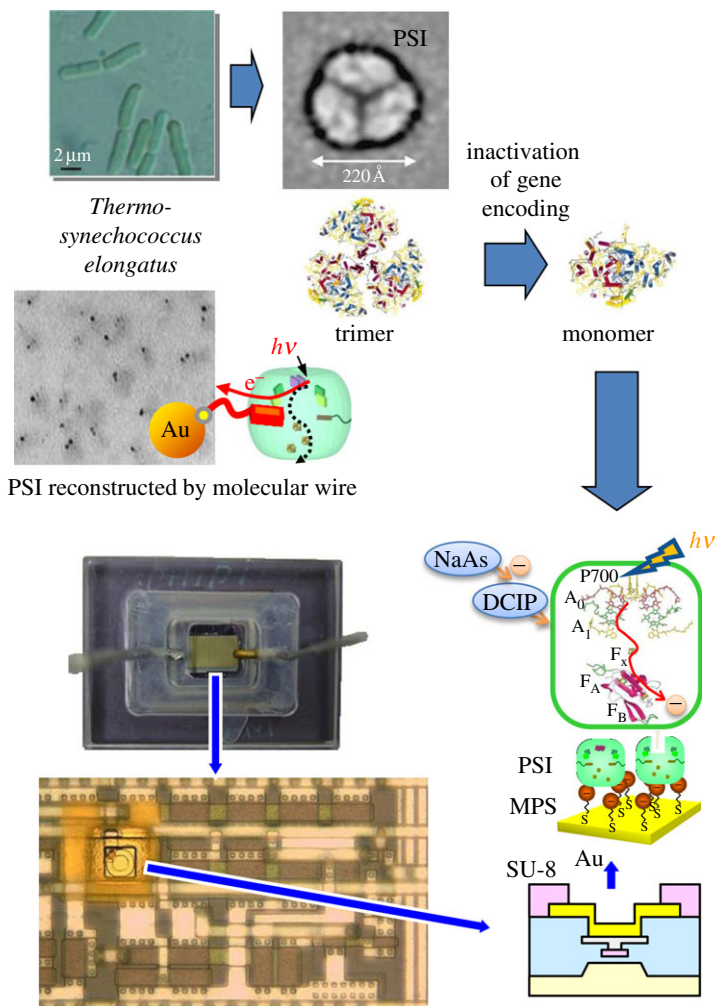


Figure 13. PSI extraction and formation of the PSI photosensor. (Online version in colour.)

the electrode by tunnelling through the SAM film. In this manner, PSI acts as a pump to supply electrons to the electrode, and the electric potential change in the gate electrode is detected by the potentiometric sensor.

The silicon nitride formed by standard CMOS process as the top layer can easily trap electronic charges in the solution, causing electric potential drift of around 1 mV by light. To reduce the light-induced drift, a protective film that does not trap electrons should be used as a covering. For the protective film, SU-8 was adopted and the light-induced drift was reduced to less than 0.1 mV.

The photoresponse of the CMOS source–drain follower itself was measured using light irradiation produced by RGB light-emitting diodes (red, 2.4 mW cm^{-2} ; green, 1.11 mW cm^{-2} ; blue, 3.28 mW cm^{-2}) inside a shielding box. Light irradiation induces photocurrent in the circuit. When the current I_s (figure 2) is small, the effect is particularly marked, and so the photoresponse, defined by $\Delta V_{\text{out}} = -V_{\text{out}}(\text{light ON}) + V_{\text{out}}(\text{light OFF})$, becomes large. For conditions in which the effect of the photocurrent in the circuit could be ignored, current I_s of $0.5 \mu\text{A}$ was chosen in the following PSI photosensor measurement, where photoresponse ΔV_{out} is less than 0.4 mV [19].

The chip is dipped in 10 mM MPS solution for 2 h. After washing in deionized water and 2-morpholinoethanesulfonic acid (MES) buffer (20 mM MES–NaOH (pH 6.4)/0.02% (w/v) *n*-dodecyl- β -D-maltoside (β -DM)), the electrode is dipped in 2.8 mg ml^{-1} PSI solution and

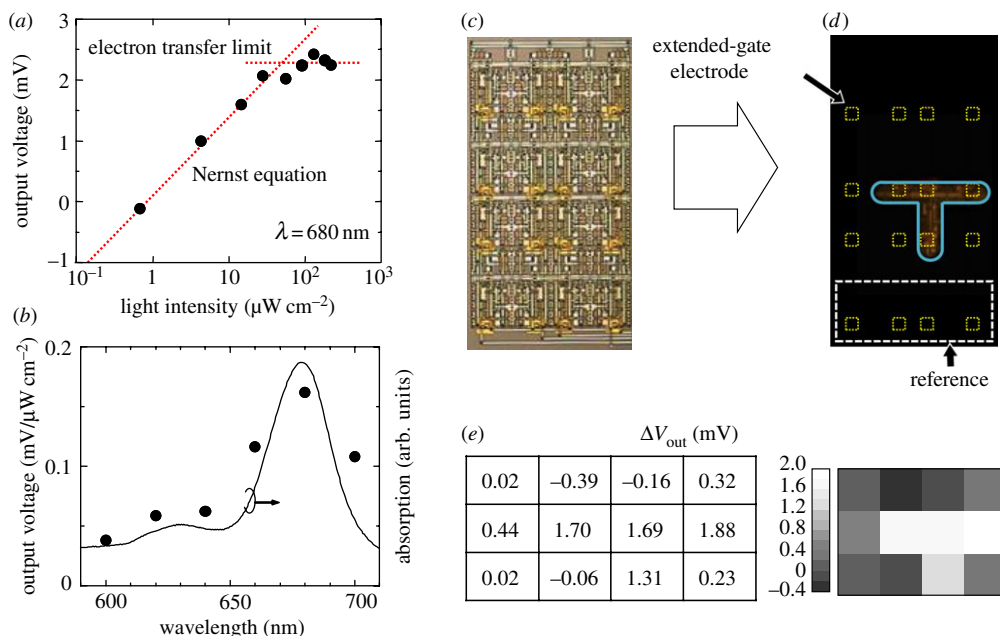


Figure 14. (a) Intensity dependence of photoresponse. (b) Action spectrum of the PSI photosensor, compared with the absorption spectrum of PSI. (c) Microphotograph of 4×4 sensor array. (d) Optical photograph of illuminated pattern. In each column, the bottom cell is used as a reference for the other three cells. (e) Measured photoresponse. (Online version in colour.)

maintained at 4°C for 4 days. It is washed in MES buffer without drying the electrodes. A bath with a reference electrode of platinum painted with Ag/AgCl paste is placed on the chip as shown in figure 13. Next, 20 mM MES–NaOH buffer (pH = 6.4), 100 mM NaClO_4 , 250 mM NaAs and 25 mM DCIP are placed in the bath.

The chip is set on an $XYZ\theta$ stage in a shielding box. To drive the circuits, DC voltage is supplied to the chip by a semiconductor parameter analyser. A halogen lamp is used as a light source, and the wavelength is selected by a monochromator. An optical fibre guides the light into the shielding box, and light having a diameter of $70 \mu\text{m}$ is focused on the chip from the upper part of the $XYZ\theta$ stage. The electrical signal caused by irradiation is read by a multimeter. $V_{\text{ref}} = 0 \text{ V}$ is applied to the reference electrode, and the output voltage of the CMOS source–drain follower is measured.

While the electrons from the PSI are trapped in the electrode, O_2 in the solution near the electrode extracts the electrons. The electric potential is determined by the balance between the input and output of electric charge. Figure 14a shows the photoresponse ΔV_{out} as a function of light intensity. The photoresponse of PSI saturates at $30 \mu\text{W cm}^{-2}$. Increasing the intensity increases the number of electrons activated by PSI, which changes the output voltage in the negative direction. The limit for transferring electrons to P700 from DCIP [20] is reached when the intensity is increased and the output voltage is saturated.

Figure 14b shows the PSI action spectrum of the PSI photosensor. The wavelength was changed at 20 nm intervals from 600 to 700 nm while turning the light on and off every 90 s. The change in output voltage per $1 \mu\text{W cm}^{-2}$ change in intensity is shown. At a wavelength of 680 nm, there is a change of approximately 0.18 mV per $1 \mu\text{W cm}^{-2}$. The wavelength dependence fits well with the absorption spectrum of PSI.

To apply the photosensor as an image sensor, a 4×4 sensor array was measured [21]. The light without a monochromator was patterned by a metal slit, as shown in figure 14d. To reduce the drift effect, the output voltage of each cell was reduced by subtracting the value of the corresponding reference cell. Figure 14e shows the obtained image. The photoresponse of four illuminated cells ranged from 1.3 to 1.9 mV, and the change in other cells not illuminated was -0.4 to 0.4 mV.

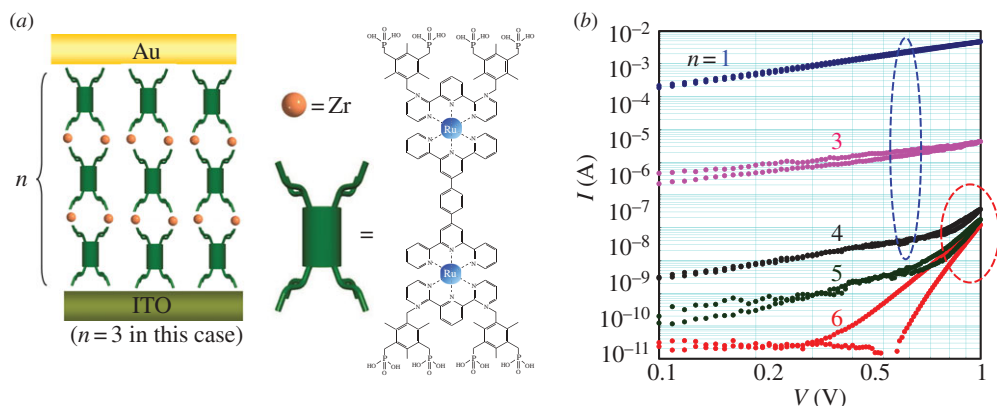


Figure 15. (a) Schematic cross section of self-assembled multilayer of Ru complexes sandwiched by metal electrodes. (b) Observed current–voltage characteristics. n is the number of layers. (Online version in colour.)

In this experiment, native PSI was used. In a recently developed process, a molecular wire is plugged directly into a biological photosynthetic system to efficiently conduct electrons to a gold electrode (figure 13). High sensitivity and fast response are expected using PSI reconstructed by the molecular wire [18,22].

One of the applications of the PSI photosensor is an SNP typing system by bioluminometric assay, which can detect target DNA as small as 10 fM [23]. Such a PSI system could become commercially available within 3 years. If a single photon is detected, the target DNA can be counted one by one.

(b) Molecular single-electron transistor

As the quantum yield of the photoelectric conversion of photosynthesis is 100%, a single photon could be detected using the proposed system combined with a single-electron transistor.

One promising candidate is coordination programming of a metal complex system. Super-molecular structures in a nanomesoscopic region can be constructed by the conjunction and combination of a metal atom and organic material. Metal complexes show multi-stable electron states, such as M^{2+} , M^{3+} , etc., which means that electric conduction occurs and electrons are localized on a metal atom, within a 1 nm region.

We have studied the characteristics of the electronic conduction through supermolecular structures between metal electrodes [24,25]. A schematic of our measurement is shown in figure 15. A self-assembled multilayer of Ru complexes was immobilized onto a patterned indium tin oxide (ITO) electrode on SiO_2 . Then, an Au electrode was formed by the lift-off process. The number of layers, n , ranged from 1 to 6. The measurements were performed in air at room temperature. Nonlinear current–voltage characteristics were observed, with two current components, one exponentially proportional to n and the other linearly proportional to n . The former was temperature independent, whereas the latter showed strong temperature dependence with activation energy. The possible conduction mechanisms are super-exchange and trap-limited space-charge-limited current. These current components are essentially equivalent to macroscopic quantum tunnelling (cotunnelling) and orthodox theory familiar in single-electron devices. This result suggests that coordination programming may provide a general framework for molecular single-electron devices.

4. Conclusion

The chemistry integrated circuit has great potential for the next generation of LSI. Material chemistry and semiconductor technology are converging in terms of size. The combination of

two different areas will pave the way for new applications, such as biomedical devices and room-temperature quantum electron devices.

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References

1. Bergveld P. 1970 Development of an ion-sensitive solid-state device for neurophysical measurements. *IEEE Trans. Biomed. Eng.* **17**, 70–71. (doi:10.1109/TBME.1970.4502688)
2. Sawada K, Mimura S, Tomita K, Nakanishi T, Tanabe H, Ishida M, Ando T. 1999 Novel CCD-based pG imaging sensor. *IEEE Trans. Electron Devices* **46**, 1846–1849. (doi:10.1109/16.784183)
3. Garner DM, Bai H, Georgiou P, Constandinou TG, Reed S, Shepherd LM, Wong Jr W, Lim KT, Toumazou C. 2010 A multichannel DNA SoC for rapid point-of-care gene detection. In *Solid-State Circuits Conference Digest of Technical Papers (ISSCC), 2010 IEEE Int. Conf., San Francisco, CA*, pp. 492–493. New York, NY: IEEE. (doi:10.1109/ISSCC.2010.5433834)
4. Sakata T, Miyahara Y. 2007 Direct transduction of allele-specific primer extension into electrical signal using genetic field effect transistor. *Biosens. Bioelectron.* **22**, 1311–1316. (doi:10.1016/j.bios.2006.05.031)
5. Nakazato K, Ohura M, Uno S. 2008 CMOS cascode source–drain follower for monolithically integrated biosensor array. *IEICE Trans. Electron.* **E91-C**, 1505–1515. (doi:10.1093/ietele/e91-c.9.1505)
6. Rothberg JM *et al.* 2011 An integrated semiconductor device enabling non-optical genome sequencing. *Nature* **475**, 348–352. (doi:10.1038/nature10242)
7. Kagohashi Y, Ozawa H, Uno S, Nakazato K, Ohdaira K, Matsumura H. 2010 Complementary metal–oxide–semiconductor ion-sensitive field-effect transistor sensor array with silicon nitride film formed by catalytic chemical vapor deposition as an ion-sensitive membrane. *Jpn. J. Appl. Phys.* **49**, 01AG06. (doi:10.1143/JJAP.49.01AG06)
8. Milgrew MJ, Cumming DRS. 2008 Matching the transconductance characteristics of CMOS ISFET arrays by removing trapped charge. *IEEE Trans. Electron Devices* **55**, 1074–1079. (doi:10.1109/TED.2008.916680)
9. Ishige Y, Shimoda M, Kamahori M. 2009 Extended-gate FET-based enzyme sensor with ferrocenyl-alkanethiol modified gold sensing electrode. *Biosens. Bioelectron.* **24**, 1096–1102. (doi:10.1016/j.bios.2008.06.012)
10. Kamahori M, Ishige Y, Shimoda M. 2008 Enzyme immunoassay using a reusable extended-gate field-effect-transistor sensor with a ferrocenylalkanethiol-modified gold electrode. *Anal. Sci.* **24**, 1073–1079. (doi:10.2116/analsci.24.1073)
11. Anan H, Kamahori M, Ishige Y, Nakazato K. 2012 Redox-potential sensor array based on extended-gate field-effect transistors with ω -ferrocenylalkanethiol-modified gold electrodes. *Sens. Actuators B Chem.* **187**, 254–261. (doi:10.1016/j.snb.2012.11.016)
12. Hasegawa J, Uno S, Nakazato K. 2011 Amperometric electrochemical sensor array for on-chip simultaneous imaging: circuit and microelectrode design considerations. *Jpn. J. Appl. Phys.* **50**, 04DL03. (doi:10.1143/JJAP.50.04DL03)
13. Manickam A, Chevalier A, McDermott M, Ellington AD, Hassibi A. 2010 A CMOS electrochemical impedance spectroscopy (EIS) biosensor array. *IEEE Trans. Biomed. Circ. Syst.* **4**, 379–390. (doi:10.1109/TBCAS.2010.2081669)

14. Ferri G, Laurentiis PD, D'Amico A, Natale CD. 2001 A low-voltage integrated CMOS analog lock-in amplifier prototype for LAPS applications. *Sens. Actuators A* **92**, 263–272. (doi:10.1016/S0924-4247(01)00581-7)
15. Ishige Y, Goto Y, Yanagi I, Ishida T, Itabashi N, Kamahori M. 2012 Feasibility study on direct counting of viruses and bacteria by using microelectrode array. *Electroanalysis* **4**, 131–139. (doi:10.1002/elan.201100482)
16. Feruglio S, Lu GN, Garda P, Vasilescu G. 2008 A review of the CMOS buried double junction (BDJ) photodetector and its applications. *Sensors* **8**, 6566–6594. (doi:10.3390/s8106566)
17. Emerson R, Chalmers RV, Cederstand C, Brody M. 1956 Effect of temperature on the long-wave limit of photosynthesis. *Science* **123**, 673.
18. Terasaki N *et al.* 2009 Photo-sensor based on an FET utilizing a bio-component of photosystem I for use in imaging devices. *Langmuir* **25**, 11 969–11 974. (doi:10.1021/la901091e)
19. Tsukada J *et al.* 2010 Photosystem I bio-photosensor integrated with complementary metal-oxide-semiconductor source-drain follower on a chip. *Jpn. J. Appl. Phys.* **49**, 01AG04. (doi:10.1143/JJAP.49.01AG04)
20. Itoh S, Iwaki M, Ikegami I. 2001 Modification of photosystem I reaction center by the extraction and exchange of chlorophylls and quinones. *Biochim. Biophys. Acta* **1507**, 115–138. (doi:10.1016/S0005-2728(01)00199-2)
21. Matsumoto H *et al.* 2010 Integrated bio-photosensor array with complementary metal-oxide-semiconductor cascode source-drain follower. *Jpn. J. Appl. Phys.* **49**, 04DL01. (doi:10.1143/JJAP.49.04DL01)
22. Terasaki N *et al.* 2009 Plugging a molecular wire into photosystem I: reconstitution of the photoelectric conversion system on a gold electrode. *Angew. Chem. Int. Edn.* **48**, 1585–1587. (doi:10.1002/anie.200805748)
23. Kamahori M, Harada K, Kambara H. 2002 A new single nucleotide polymorphisms typing method and device by bioluminometric assay coupled with a photodiode array. *Meas. Sci. Technol.* **13**, 1779–1785. (doi:10.1088/0957-0233/13/11/314)
24. Joke T, Uno S, Nakazato K, Kanaizuka K, Haga M. 2010 Electronic conduction through self-assembled multilayers of Ru complexes between metal electrodes. In *5th Int. Meeting on Molecular Electronics, ElecMol'10*, OC26, 6–10 December 2010, Grenoble, France, Abstract.
25. Haga M, Nakabayashi T, Ozawa H, Suzuki T, Joke T, Nakazato K. 2012 Molecular electronic devices based on self-assembled multilayer films bearing redox-active Ru complexes. In *Pacific Rim Meeting on Electrochemical and Solid-State Science (PRiME 2012)*, 7–12 October 2012, Honolulu, Hawaii, ECS Meeting Abstracts, MA2012-02, no. 256. Pennington, NJ: Electrochemical Society.