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An enhanced glucose biosensor using charge transfer techniques

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ABSTRACT

An enhanced glucose biosensor based on a charge transfer technique glucose sensor (CTTGS) is described and demonstrated experimentally. In the proposed CTTGS, which is accumulation method (D-gluconate + H^+) ion perception system, the quality of output signal with "signal integration cycles" is high. With the proposed CTTGS it is possible to amplify the sensing signals without an external amplifier by using an accumulation cycle. It can be supposed that measurements of small (D-gluconate + H^+) ion fluctuation are difficult by ion-sensitive field effect transistor (ISFET) because the theoretical maximum sensitivity is only 59 mV/pH and the small output signals are buried in the $1/f$ noise component of the metal–insulator–semi-conductor field-effect transistor (MISFET). Therefore, the CTTGS has many advantages, such as high sensitivity, high accuracy, high signal-to-noise ratio (SNR), and has been successfully demonstrated using a charge transfer technique. The CTTGS exhibited excellent performance for glucose with a large span (1445 mV) and good reproducibility. Moreover, the CTTGS has good sensitivity in this range of 7.22 mV/mM, a lower detection limit of about 0.01 mM/L and an upper detection limit of about 200 mM/L compared with amperometric glucose analysis which has been studied recently. Under optimum conditions, the proposed CTTGS exceeds the performance of the widely used ISFET glucose sensor. The sensitivity of the CTTGS (7.22 mV/mM) was seven times higher than that of the ISFET (1 mV/mM). Furthermore, the sensitivity obtained for human glucose levels was 29.06 mV/mM with a non-linear error of ±0.27%; the linearity is $y = 0.0294x + 1.8612$ and $R^2 = 0.9999$, which is acceptable for clinical application. Real sample analysis is investigated in blood glucose level by our developed CTTGS ISFET system.

1. Introduction

Diabetes mellitus is a growing public health concern and its prevalence is rising exponentially, with a high frequency of morbidity, premature mortality, disability, and loss of productivity. According to population studies, the prevalence of type 2 diabetes has reached epidemic proportions; it affected approximately 171 million individuals worldwide in the year 2000 and this is estimated to reach 366 million by the year 2030 (Wild et al., 2004). The first really successful blood glucose biosensor for home use was a mediated device based around a disposable and screen-printed sensor design. They generally have higher response times (less than 15 s), dynamic ranges (1–33 mM/L), and sensitivities (0.67 μA/mM). In arriving at the performance criteria, desirable goals had to be weighed against the capabilities of existing devices (the current state-of-the-art) and their effectiveness in clinical outcome studies. In addition, self-monitoring of blood glucose is a critical aspect of diabetes care (Owen, 1995; Nakamura and Karube, 2003; Newman and Turner, 2005). The requirements for in vitro glucose monitoring systems to measure glucose concentrations in capillary blood samples as well as procedures to verify and validate their performance by the intended users are specified by International Standard 15197 (ISO15197 First edition, 2003). Requirements for blood–glucose monitoring systems for self-testing in managing diabetes mellitus:

1. for glucose concentration <4.2 mM/L (75 mg/dL), the percentage of results within ±0.28 mM/L, ±0.56 mM/L and ±0.83 mM/L (±5 mg/dL, ±10 mg/dL and ±15 mg/dL) of the reference values;
2. for glucose concentration ≥4.2 mM/L (75 mg/dL), the percentage of results within ±5%, ±10%, ±15% and ±20% of the reference values.

These systems are intended for self-testing by laypersons to manage diabetes mellitus. International Standard 15197 is applicable to manufacturers of such systems, while other organizations (e.g. regulatory authorities and conformity assessment bodies) are responsible for assessing the performance of these systems. The glucose meter is a medical device used to determine the approxi-

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mate concentration of glucose in the blood. A small drop of blood obtained by pricking the skin with a lancet is placed on a disposable test strip, which the meter reads and uses to calculate the blood glucose level. The meter then displays the level in mg/dL or mM/L (Podczasy et al., 1997). Electrochemical glucose sensors based on an electrode modified with immobilized glucose oxidase have been reported previously (Sulak et al., 2006). A disposable amperometric biosensor to detect blood glucose has also been developed. Various biosensor electrode fabrication techniques have been reported in the literature, including rolling, screen-printing (Crouch et al., 2005; Guan et al., 2005), and sputter deposition techniques (Hashimoto et al., 2007). Typically, a biosensor is based on a screen-printed electrode. A carbon-paste electrode (CPE) is made from a mixture of conducting graphite powder and a pasting liquid. These electrodes are simple to make, and offer an easily renewable surface for electron exchange. These electrodes are widely used, mainly for voltammetric measurements. Carbon paste-based sensors (Yabuki et al., 1992; Ge et al., 1998; Boujtita et al., 2000; Hong et al., 2002; Hart et al., 2002; Fähnrich et al., 2003; Darain et al., 2003, 2005; Gao et al., 2003; Honeychurch et al., 2003, 2007; Díaz-González et al., 2005; Ledru et al., 2006; Corgier et al., 2007; Piermarini et al., 2007; Tangkuaram et al., 2007; Djellouli et al., 2007) are also applicable in coulometry (both amperometry and potentiometry). The wide application of a carbon paste as the matrix of an enzyme electrode is attributed to the simple preparation procedure, which facilitates mass production and therefore, is economical. Electrodes made in this way are highly selective sensors for both inorganic and organic electrochemistry. However, in practice, printing conditions must be adjusted to control thickness as well as electrode area, which are known to proportionally affect the sensor response. Screen-printing consists of a screen, a squeegee, ink, and a type of stencil printing. A screen is a type of mesh, which has holes that are clogged by emulsion to leave the desired patterns. A squeegee is a rubber spatula, which squeezes ink out of screen's holes onto a base film (Kaimori et al., 2006).

With regard to the screen-printing method, many factors are known to affect the accuracy of printing.

(A) *Screen printer*: printer type, print speed, clearance, and print pressure.
(B) *Squeegee*: squeegee type, hardness, attack angle.
(C) *Screen*: frame size, print area, print pattern, gauze, thickness, opening, mesh material, the number of meshes, emulsion material, emulsion thickness.
(D) *Ink*: ink type, viscosity, thixotropy, leveling, stirring, wettability to base film and other ink layers, drying method.
(E) *Base film*: affinity to ink, heat contraction.

To minimize the dispersion of the electrode area, the print speed, clearance, print pressure, squeegee hardness, attack angle, print area, print pattern, mesh material, the number of meshes, ink type, thixotropy, and heat contraction are all important factors in adjusting the screen-printing conditions. Nevertheless, until now, research has not been conducted on the uniformity of this biosensor electrode. Many of the issues associated with glucose biosensors have very little to do with the device itself. In virtually every case, the basic design of commercially successful biosensors has not changed significantly.

Biomedical engineers were the first to exploit the possibilities of using chip technology to develop silicon-based sensors, to be incorporated in the tip of a catheter (Bergveld, 1985). As a consequence, many of the early papers on silicon sensors appeared in the biomedical engineering literature, for example work into the development of ion sensors. The most familiar glucose sensors using a semi-conductor are the ion-sensitive field effect transistor (ISFET) and enzyme field-effect transistor (ENFET). The ISFET sensor is one of the most well known examples of such a silicon sensor (Bergveld, 2003). The ISFET is an ion-sensitive field effect transistor used to measure ion concentrations in solution. When the ion concentration (such as the pH) changes, the current flowing through the transistor will change. In this example the solution is used as a gate electrode. A voltage arises between the substrate and the oxide surface due to the layer of ions. The surface hydrolyzation of the OH^- groups of the gate materials varies in aqueous solutions depending on the pH value. Typical gate materials are Si_3N_4 (Cohen et al., 1978), Al_2O_3 (Chou et al., 2001, 2002), and Ta_2O_5 (Ito, 2000; Chou et al., 2000, 2001; Kosmulski, 2001). The ISFET's source and drain are constructed as for a MOSFET. The gate electrode is separated from the channel by a barrier which is sensitive to hydrogen ions and a gap to allow the substance under test to come into contact with the sensitive barrier. The ISFET's threshold voltage depends on the pH of the substance in contact with its ion sensitive barrier. The conventional solid-state-type pH sensor is the ISFET. The ideal maximum sensitivity of the ISFET is 59 mV/pH from the Nernst equation at room temperature (25 °C). The resolution of the ISFET is restricted by the $1/f$ noise. Thus, it is difficult for the ISFET to measure the infinitesimal variations of the pH value. An ISFET glucose sensor based on a new principle using the electrolysis of hydrogen peroxide, one of the by-products of the oxidation of glucose, and a Pt electrode actuator has been proposed and investigated (Seo et al., 1997). Also an ENFET (enzyme-modified field effect transistor) glucose sensor has been reported (Luo et al., 2004a,b; Yao et al., 2007). Usually the glucose-sensitive ENFET is based on a local change in the pH of biomembranes resulting from the formation of gluconic acid.

Previously, a charge transfer type pH sensor based on a charge-coupled device (CCD) technique was proposed by our group (Sawada et al., 2004). The charge transfer type pH sensor (pH-CCD) has been incorporated into two-dimensional pH image sensors (Hizawa et al., 2006). In this paper, a highly sensitive ion sensor using a charge transfer technique is described. The charge transfer technique is widely used in charge-coupled devices (CCDs). The charge transfer type glucose sensor (CTTGS) changes the depth of the appropriate potential well using the charge transfer technique. The depth of the potential well in the semi-conductor is varied by detecting the change of (D-gluconate + H^+) ions produced by the hydrolysis of glucono-lactone to gluconic acid near the sensing region. We have demonstrated that the glucose sensitivity of the CTTGS can be enhanced by a signal accumulation operation with phosphoric acid glucose buffer solution. The charge accumulation operation is continued for five cycles. It is expected that this sensor will be capable of improving the signal-to-noise ratio (SNR) (Sawada et al., 2004). In the present work, two types of glucose sensors (ISFET and CTTGS) were fabricated and a comparative sensitivity analysis carried out for each. The most important characteristics of a glucose sensor are sensitivity, linearity, accuracy, span, and repeatability.

2. Experimental

2.1. Materials

Glucose oxidase (GOD, EC 1.1.3.4, 15,000–25,000 units/g. Type II from *Aspergillus niger*), Triton X-100 wetting Agent and β-D-(+)-glucose were purchased from Sigma–Aldrich company. Deionized (D.I.) water was used throughout the experiment for the preparation of the samples, buffers, and enzyme solutions. A 0.01 M phosphate buffer solution (PBS) was freshly prepared at pH 7.03. The 0.01 M PBS was used as the supporting electrolyte by mixing solutions of KH_2PO_4 and K_2HPO_4. Enzyme solutions were prepared

by dissolving the glucose oxidase in the above-mentioned buffer solution. Glucose oxidase solutions were freshly prepared daily just before the fabrication of both types of biosensor. The 0.1 M glucose oxidase solution (25 μL) was immobilized on the ISFET and CTTGS sensing area using the adsorption method. Then, it was dried for 30 min at room temperature. Glucose solutions with different concentrations of buffer, 1.5625, 3.125, 6.25, 11.5, 25, 50, 100, 200, 400 and 800 mM/L were prepared prior to conducting the measurements. All experiments were carried out in a cell containing 25 μL 0.01 M, pH 7.03 test solution at room temperature (25 ± 2 °C), using both ISFET and CTTGS type glucose biosensors. In the measurement, the glucose sample was introduced into the chip of each sensor and allowed to remain for 3 min for the enzymatic reaction to take place. Finally, the output was measured within the next 40 s.

2.2. Measurement principle

The principle of this technique is the same as the basic principle for a charge-coupled device (Swart and Campbell, 1981; Sawada et al., 2004; Hizawa et al., 2006). The CTTGS measurement principle is shown schematically in Scheme 1. The principle of the CTTGS is similar to that of an ISFET (Seo et al., 1997; Sohn et al., 1997). The CTTGS is normally based on the oxidation of glucose according to the following reactions (Luo et al., 2004a):

$$\beta\text{-D-glucose} + O_2 \xrightarrow{GOD} \text{D-glucono-}\delta\text{-lactone} + H_2O_2 \quad (1)$$

$$\text{d-glucose-}\delta\text{-lactone} + H_2O \rightarrow \text{d-gluconate} + H^+ \quad (2)$$

The glucose oxidase converts glucose to gluconic acid which releases (D-gluconate + H^+) ions in the surrounding solution. These (D-gluconate + H^+) ions are detected by the glucose sensitive layer on top of the EIS (electrolyte insulator semi-conductor) structure, for instance Si_3N_4, and the resulting sensor signal is a measure of the glucose concentration in the standard solution. The depth of the potential well in the semi-conductor is varied by detecting the change of (D-gluconate + H^+) ions produced by the gluconic-acid near the sensing region. The proposed CTTGS is constructed by immobilizing the enzyme GOD on to the ion-sensitive membrane (Si_3N_4) of the pH-charge-coupled device.

The operational procedure of the CTTGS is described using the potential diagram shown in Scheme 1. The clock cycle is initiated by turning off the output gate as shown in Scheme 1a. Next, the potential of the input diode (ID) decreases and the electric charge flows into a potential well under the sensing area of the device. The potential φ of the input diode is briefly pulsed from high to low (Scheme 1b) then kept high (Scheme 1c). Next, the transfer gate (TG) is turned on, and the charge is transferred to the floating diffusion (FD) part (Scheme 1d). The procedure from Scheme 1a to Scheme 1e is repeated several times (Scheme 1f). The CTTGS is operated in signal integration mode. Charges corresponding to the glucose concentration are transferred from a sensing part to the floating diffusion region several times, and the signal charges accumulate in the floating diffusion region. It is expected that the SNR of the glucose concentration increases with accumulation of the signal charge. As the glucose concentration signal S_{G0} is accumulated n times, the total signal S_G is described as follows:

$$S_G = nS_{G0} \quad (3)$$

The total noise N is described as follows:

$$N = \sqrt{N_1^2 + N_2^2 + \cdots + N_n^2} \quad (4)$$

where $N_1, N_2, \ldots, N_n$ are the noise component of each integration stage. If these components are the same, the above equation can be simplified to

$$N = \sqrt{nN_0^2} \quad (5)$$

Therefore, the total SNR is given by

$$\frac{S_G}{N} = \frac{nS_0}{\sqrt{nN_0^2}} = \sqrt{n}\frac{S_0}{N_0} \quad (6)$$

From this equation, the SNR increases $n^{0.5}$ times when the signal is integrated n times. The $1/f$ noise component of the source follower circuit is not influenced because the input signal of the source follower circuit increases as a result of the integration. Therefore, the (D-gluconate + H^+) ions was measured by accumulation cycle. The signal integration cycle was repeated five times. The reference voltage dependence of the output signal in each signal integration cycle. The glucose solution was measured by charge transfer technique from one to five signal integration cycles. These results are shown in Scheme 1. In this measurement, the 0.01 mM/L glucose solution of pH 7.03 was ued. This characteristic was significant in that amplification increased as the slope bacame steep.

2.3. CTTGS elements and structure

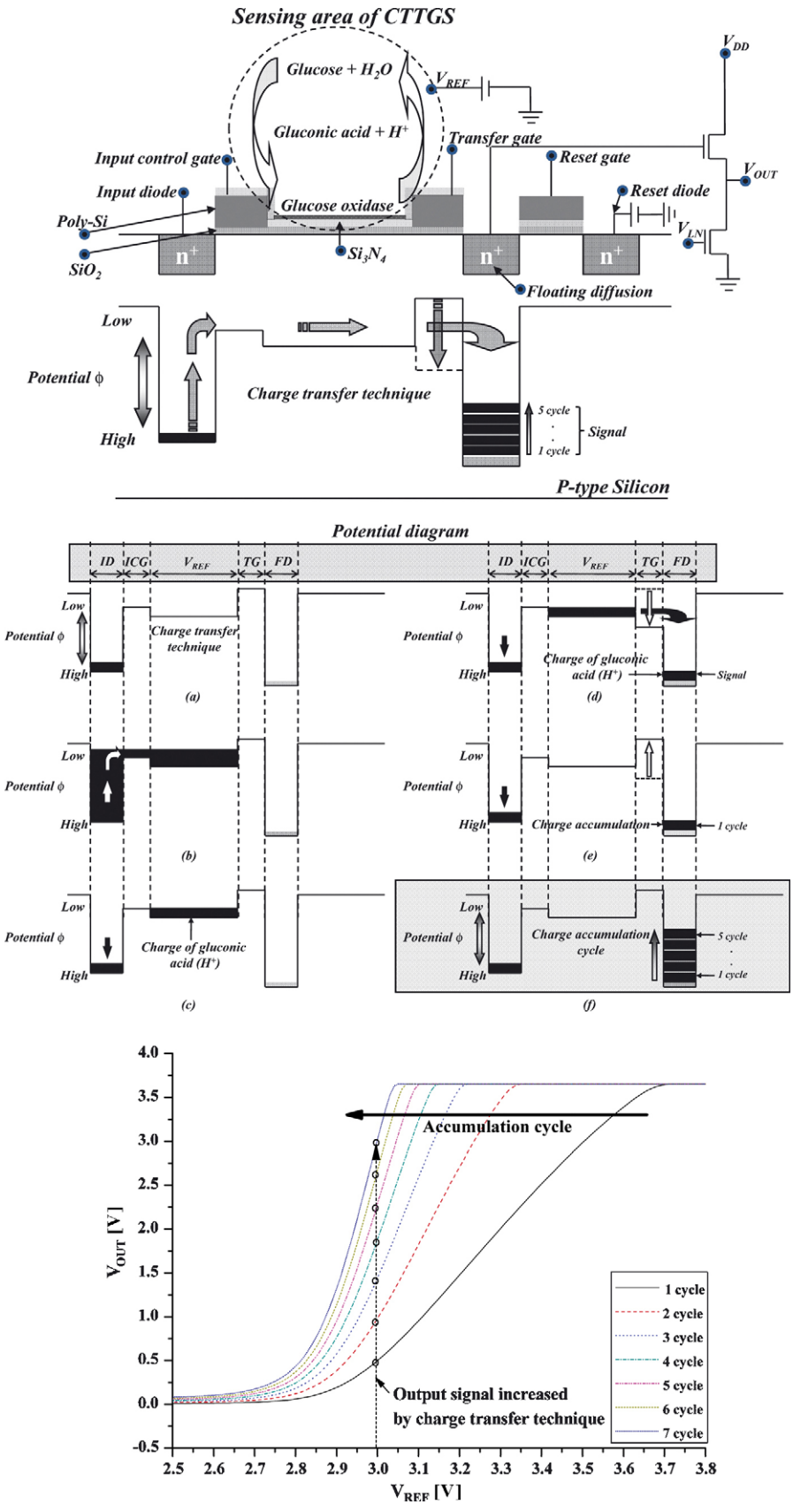
The CTTGS consists of seven elements, as shown in Fig. 1A: an input diode, an input control gate (ICG), an ion-sensing region, a transfer gate, a floating diffusion region, a reset switch and a source follower circuit. The glucose-sensing part is constructed with an enzyme membrane consisting of (GOD; glucose oxidase immobilization)/Si_3N_4 (ion-sensitive membrane)/SiO_2/p-type silicon substrate. The Si_3N_4 film acts as the (D-gluconate + H^+) ion sensitive membrane. The potential well is formed in the Si substrate surface under the sensing parts. As the concentration of the (D-gluconate + H^+) ions in a solution is changed, the depth of the potential well is also changed. As the glucose concentration on the sensing part is reduced, the depth of this potential well increases. The potential of the input diode decreases and the electric charge flows into a potential well under the sensing part. The depth of the potential well is determined by the value of the glucose concentration. The ICG and TG electrodes are necessary to maintain the charge in the potential well of the ion-sensing region. The amount of charge stored in the potential well of the sensing region varies with the glucose concentration. The stored charge in the potential well of the sensing region is transferred to the floating diffusion region and read out using the source follower circuit, as shown in Fig. 1B.

2.4. CTTGS sensing signal amplifier

The sensing signal is amplified when the charge is transformed and read (Sawada et al., 2004; Hizawa et al., 2006). The amplification is given by the following equation:

$$A = \frac{C_{SENS}}{C_{FD}} A_{SF} \quad (7)$$

where C_{SENS} is the capacitance of the sensing region, C_{FD} is the capacitance of the floating diffusion region, and A_{SF} is the gain of the source follower circuit. This procedure is repeated five times. Each cycle is called a "signal integration cycle." As the signal integration cycle is repeated, the potential in the floating diffusion part decreases and the signal charge accumulates. By this integration operation, the potential under the ion sensing part is integrated in the floating diffusion part. The floating diffusion part is connected to a gate electrode of the source follower circuit, and the potential of the floating diffusion part is read from the V_{OUT} node of the source follower circuit. After the signal is measured, the floating



Scheme 1. Schematic of CTTGS measurement principle. The operational mechanism for charge transfer technique glucose sensor. Principle of output signals from one to five "signal integration cycle" with pH 7.03, 0.01 mM/L glucose solution.

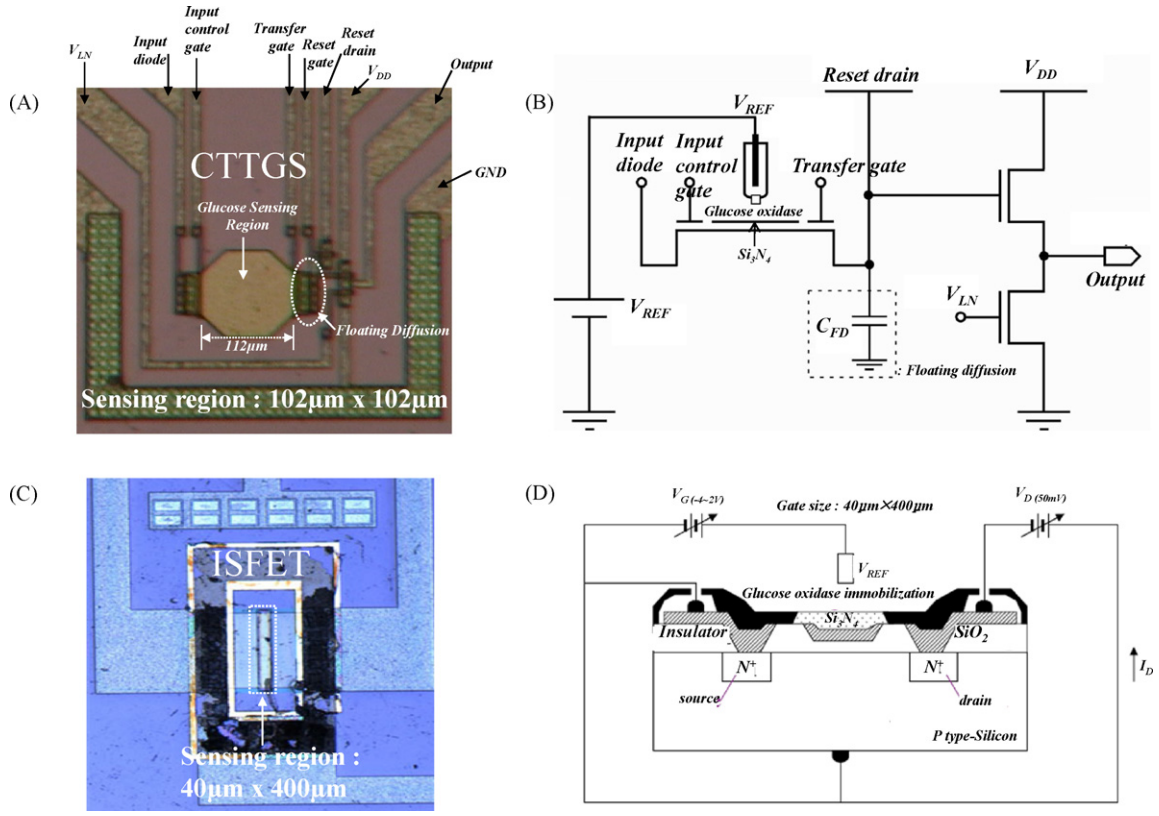


Fig. 1. (A) Photographs of the proposed charge transfer type blood glucose sensor (CTTGS). (B) Equivalent circuit of CTTGS including source follower circuit. (C) Photographs of the ISFET type glucose sensor: Si_3N_4 gate size (40 μm × 400 μm; 16,000 μm^2). (D) Cross-sectional view of the ISFET type blood glucose sensor. The drain current (I_D) was determined for the gate potential (V_G: −4–2 V) and source–drain potential (V_D: 50 mV). The pH sensitivity of the ISFET glucose sensor is about 45 mV/pH in the range pH 2–10.

diffusion part is rested using a reset transistor (Sawada et al., 2004; Hizawa et al., 2006). In this study, the CTTGS changes the depth of the potential well using the charge transfer technique (fill and spill technique). Since the charge accumulation operation is continued for five "signal integration cycles" the sensitivity and the repeatability are increased.

3. Results and discussion

3.1. ISFET type glucose sensor

The ion-sensitive field effect transistor is a useful solid-state-type glucose sensor (Seo et al., 1997; Sohn et al., 1997). In this work, ISFET type glucose sensors with a Si_3N_4 gate (40 μm × 400 μm; 16,000 μm^2) were fabricated. A photograph of the ISFET glucose sensor is shown in Fig. 1C. Fig. 1D shows a cross-sectional view of the ISFET glucose sensor. The enzyme membrane GOD was immobilized on to the ISFET sensing area using the adsorption method. Fig. 1D shows a cross-sectional view of the ISFET glucose sensor. The drain current (I_D) was determined for the gate potential (V_G: −4–2 V) and source–drain potential (V_D: 50 mV). The conventional solid-state-type pH sensor is the ISFET. The ideal maximum sensitivity of the ISFET is 59 mV/pH from the Nernst equation at room temperature (25 °C). The fabricated ISFET glucose sensor has a sensitivity of about 45 mV/pH in the range pH 2–10. The measured ISFET glucose sensor has a sensitivity of about 2.28 mV/mM in the clinical concentration range of buffer to 25 mM/L standard glucose solution (pH 7.03) with a lower detection limit of about 0.01 mM/L and an upper detection limit of about 100 mM/L, as shown in Figs. 2A and 3A. The sensitivity and resolution are insufficient for clinical applications. The resolution of the ISFET is restricted by the 1/*f* noise. Thus, it is difficult for the ISFET to measure the infinitesimal variations of the pH value. Because actually pH changes scope of the glucose is two degree. There is also a problem of accuracy in the measurement.

3.2. CTTGS type glucose sensor

The charge transfer type glucose sensor with a charge accumulation technique is fabricated using a 5-μm single-poly single-aluminum complementary metal–oxide–semi-conductor (CMOS) process and is shown in Fig. 1A. The structure of the sensing region consists of the enzyme membrane (GOD)/Si_3N_4/SiO_2/silicon. The thicknesses of the gate oxide (SiO_2) and ion-sensing membrane (Si_3N_4) are 65 and 100 nm, respectively. Si_3N_4 was deposited by thermal low-pressure chemical vapor deposition (LP-CVD). Si_3N_4 was used for the ion-sensing membrane because it is easy to integrate with the CMOS process. The sizes of the sensing region and floating diffusion area are 10,580 and 795 μm^2, respectively. In this work, a reference electrode (Ag/AgCl) was used to fix the potential of the solution. All the measurements were carried out at room temperature. The prepared glucose solution was measured using a pH meter (D-52, Horiba). With the proposed CTTGS, which is an accumulation H^+ ion perception system, the quality of the output signal with five signal integration cycles is high. As shown in Fig. 2B, a stable measurement can be obtained for glucose levels below 200 mM/L corresponding to a span of 1445 mV. The major advantages of the ISFET sensor using CTTGS compared to the reported amperometric glucose sensors are higher sensitivity and short response time. The sensitivity and response time of our

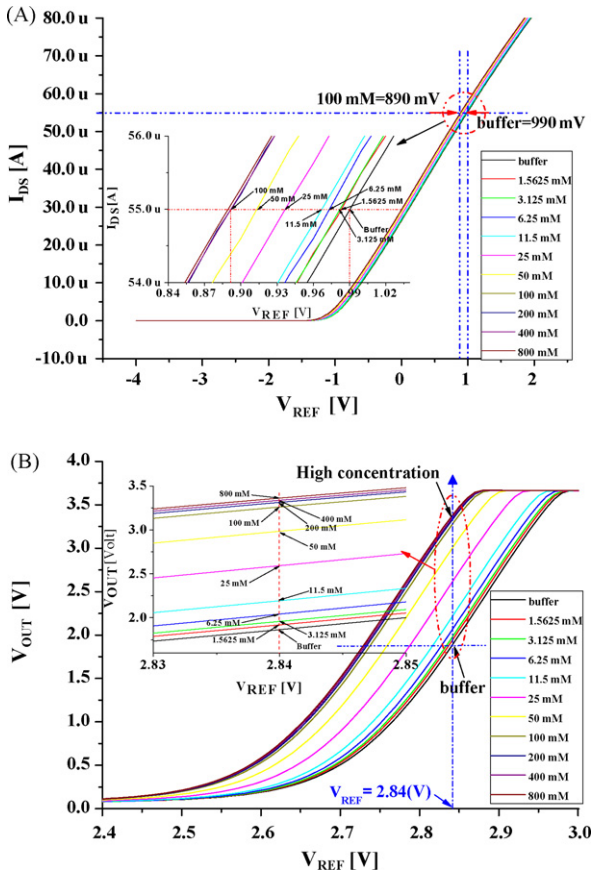


Fig. 2. (A) Characteristics of the ISFET type blood glucose sensor using solutions with glucose concentration from buffer to 800 mM/L. (B) Characteristics of the proposed charge transfer type blood glucose sensor (CTTGS) using solutions with glucose concentration from buffer to 800 mM/L.

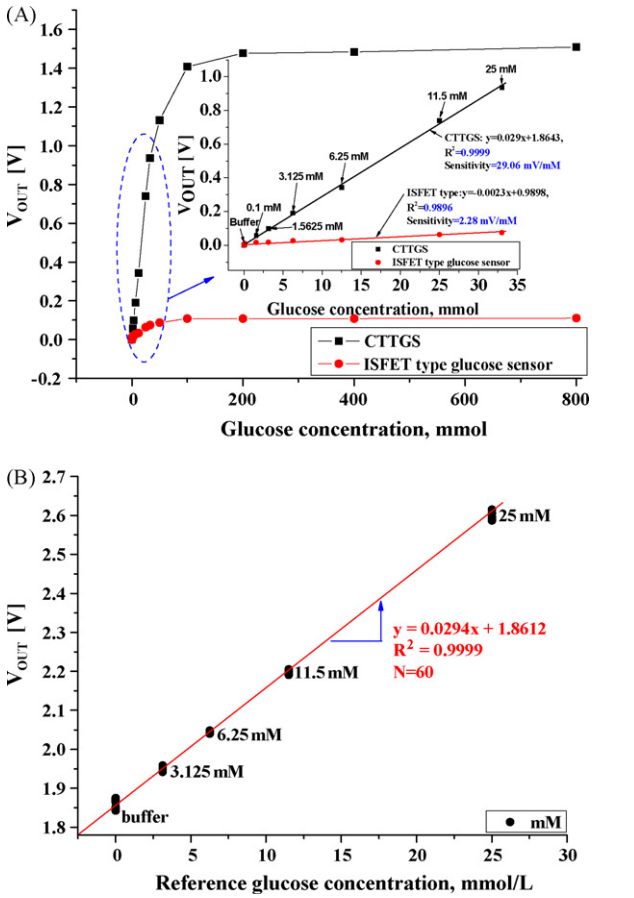


Fig. 3. (A) Linearity of the ISFET type and CTTGS type glucose sensors. (B) Repeatability of the CTTGS. CTTGS measurements were repeated 60 times in the buffer to 25 mM/L range.

developed CTTGS are 7.22 mV/mM and 20 s, respectively compared with previous studies (Liu et al., 2008; Wu et al., 2007).

At human glucose levels of 25 mM/L, the sensitivity obtained from the CTTGS is 29.06 mV/mM is shown in Fig. 3A. The sensitivity closely follows the linear equation $Y = 0.0294X + 1.8612$ with $R^2 = 0.9999$ as shown in Fig. 3B. The CTTGS type has excellent span and range compared with the ISFET type sensor, as shown in Fig. 3A. Table 1 shows a summary of the performance of the two types of glucose sensor used in this work. The CTTGS type has a sensitivity which is about seven times higher than the ISFET glucose sensor. The CTTGS characteristics were repeated 60 times in the buffer to 25 mM/L range as shown in Fig. 3B. Table 2 shows the repeatability error of the CTTGS. As can be seen the total non-linearity error obtained is 0.28% and excellent reproducibility has been achieved.

Table 1
Comparison of glucose sensor

Type of glucose sensor	ISFET	CTTGS
Range	Buffer to 100 mM/L (1800 mg/dL)	Buffer to 200 mM/L (3600 mg/dL)
Span	100 mV	1445.64 mV
Sensitivity of sensor	1 mV/mM, 0.05 mV(mg/dL)	7.22 mV/mM, 0.40 mV(mg/dL)
Sensitivity (buffer to 25 mM/L)	2.28 mV/mM, 0.03 mV(mg/dL)	29.06 mV/mM, 1.61 mV(mg/dL)
Linearity (buffer to 25 mM/L)	$y = -0.0023x + 0.9898$, $R^2 = 0.9896$	$y = 0.029x + 1.8643$, $R^2 = 0.9999$

Table 2
Repeatability evaluation of different glucose concentration

Glucose concentration (mM/L), $N = 100$	Average (V), $m = \frac{1}{n}\sum x_i$	Standard deviation (V), $\sigma^2 = \frac{1}{n}\sum(x_i - m)$	Coefficient of variation (%), $\frac{\text{standard deviation}}{\text{arithmetic average}} \times 100$
Buffer	1.864589	0.009108	0.488456
3.125	1.949873	0.005303	0.271979
6.25	2.043208	0.002138	0.10466
11.5	2.196511	0.004424	0.201402
25	2.595357	0.008098	0.312
			Total non-linear error (CV) = 0.275699

4. Conclusions

In this work a charge transfer technique glucose sensor (CTTGS) with high performance is proposed and demonstrated experimentally. The principle of the accumulation method glucose sensor is based on charge transfer techniques. The proposed CTTGS is constructed by immobilizing the enzyme GOD on to the ion-sensitive membrane (Si_3N_4) of pH-charge-coupled device. The CTTGS is operated in a signal integration mode. Charges corresponding to the glucose concentration are repeatedly transferred from a sensing part to the floating diffusion region, where the signal charges are accumulated. With the proposed CTTGS which uses an accumulation H^+ ion perception method, the quality of the output signal with five signal integration cycles is high. The CTTGS is compared with the ISFET in terms of span, linearity, and sensitivity. The measurement range of the CTTGS extends to a glucose level of 200 mM/L and a span of 1445 mV. The sensitivity in this range is therefore 7.22 mV/mM. For human glucose levels the sensitivity obtained was 29.06 mV/mM with a non-linear error of ±0.28%. The linearity is given by $Y = 0.029X + 1.8643$ with $R^2 = 0.9999$. The CTTGS excels in performance over the widely used ISFET type glucose sensor. The CTTGS has a sensitivity which is seven times higher. The CTTGS reliability was tested by repeating the measurements 60 times in the buffer to 25 mM/L range. The results were shown to fit the linear equation $Y = 0.0294X + 1.8612$ with $R^2 = 0.9999$. This result is sufficient as the error ratio for the proposed CTTGS is within 1%, which is acceptable for clinical application (ISO15197 First edition, 2003; Requirements for glucose monitoring systems for self-testing in managing diabetes mellitus). With this performance CTTGS type glucose sensor can become a new device in the healthcare field. The real samaple analysis has been tested by using blood sample. The human glucose level is measured using CTTPS developed sensor and compared with the previous study. The higher sensitivity valuse was found at 29.06 mV/mM compared to the amperometric biosensors.

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