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ORIGINAL PAPER

Glucose-sensitive field effect transistor using totally synthetic compounds

Akira Matsumoto · Naoko Sato · Toshiya Sakata · Kazunori Kataoka · Yuji Miyahara

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Abstract A field effect transistor (FET)-based glucose sensor was fabricated. As a totally synthetic and thus stable glucose-sensing moiety, 3-acrylamidophenylboronic acid was chemically introduced onto the FET gate surface in the form of a thin copolymer gel layer. Excellent transistor characteristics were confirmed even after the surface modification, ensuring validity of the modification procedure herein developed. Glucose-induced changes in the FET's electric characteristics were obtained in quantitative as well as reversible manners. It was also demonstrated that the prepared FET is able to continuously perceive the change in the glucose concentration in the milieu. The detected signals were attributed to the faction change of the gate-introduced phenyborate anions, also presumably involving other parameter changes such as permittivity and conductivity. The use of the fabricated FET could further be extended to the construction of stable, readily minutualizable, and label-free carbohydrate molecule-sensing systems.

Keywords Field effect transistors · Glucose sensor · Phenylboronic acids · Polymer gel

A. Matsumoto · N. Sato · T. Sakata · K. Kataoka
Center for NanoBio Integration, The University of Tokyo,
Tokyo, Japan

A. Matsumoto
Department of Bioengineering,
Graduate School of Engineering, The University of Tokyo,
Tokyo, Japan

N. Sato · T. Sakata · K. Kataoka · Y. Miyahara (✉)
Department of Materials Science and Engineering,
Graduate School of Engineering, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-8656, Japan
e-mail: MIYAHARA.Yuji@nims.go.jp

Y. Miyahara
Biomaterials Center,
National Institute for Materials Science,
1-1 Namiki,
Tsukuba, Ibaraki 305-0044, Japan

Introduction

Rapid quantification of biological substances is a direct relevance to analytical biochemistry and clinical diagnostics. Field effect transistor (FET)-based technique certainly represents a unique molecular detection platform, in which intrinsic molecular charges immobilized onto the gate surface, can directly be transduced into electrical signals. In this case, a change in FET signal stems from electrostatic interactions between the immobilized molecular charges and the thin-insulator-segregated silicon electrons, leading to a change in electrical characteristic of the FET. Advantageously, such detection scheme does not require target-labeling procedures that are costly and complex. In addition, FET devices can be readily downsized and integrated by virtue of semiconductor-processing technology. To date, various types of FET-based label-free biosensing systems have been proposed including immunosensing [1–3] and, more recently, genetic analysis such as detection of single-nucleotide polymorphism [4–6] and deoxyribonucleic acid sequencing [7].

Glucose has been a target molecule of particular interest for decades in the field of clinical diagnostic sensor developments. Many approaches have emerged to establish diagnostic glucose sensors and systems for the treatment of Insulin-dependent Diabetes Mellitus. These glucose-sensing devices ordinarily involve enzymatic reaction between glucose oxidase (GOD) and glucose, a rationale for commercially available glucose sensors. Shortcomings of

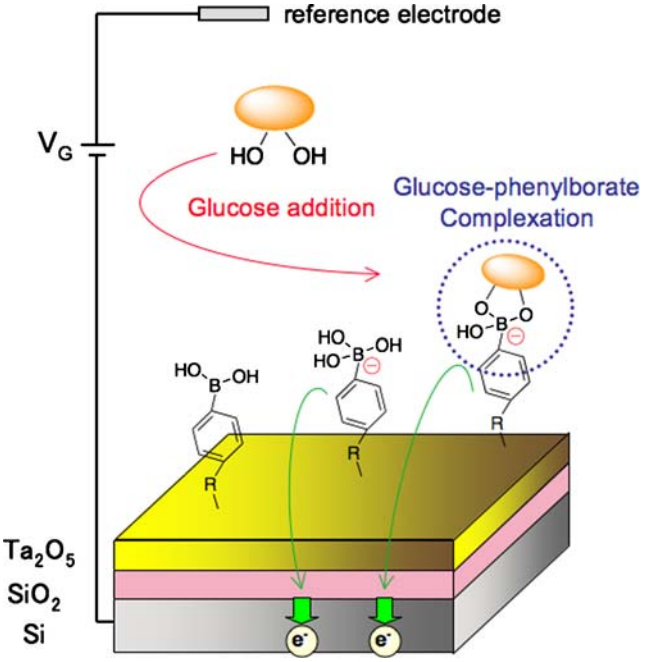

Fig. 1 Conceptual scheme for the glucose detection by the gate surface-modified FET with phenylboronic acid moieties

such systems, however, stem from the fact that it is a protein-based component intolerant of long-term use and storage because of its denaturalizing and antigenic nature. Also problematically, such GOD-based systems typically require mediators [8], whose responses are inherently dependent on the mass transport of the analyte. Further, for these systems, the consumption of analytes is inevitable, and their performances are significantly influenced by dissolved oxygen in the milieu.

In this context, the use of a completely synthetic component, phenylboronic acid, as the glucose-sensing moiety may provide an attractive approach to obtain a more robust and semiconductor process-compatible type of glucose sensor. Phenylboronic acid and its derivatives are known to form reversible covalent complexes with various saccharides including glucose. Based on the property, phenylboronic acid compounds have been primarily utilized as ligand moieties for affinity chromatography of polyol compounds [9–11]. In recent years, more extensive range of applications have emerged including the construction of chemosensors [12–15], glyco-responsive polymer complex systems [16, 17], self-regulated insulin delivery systems [18–20], synthetic mitogens for lymphocytes [21, 22], and potentiometric [23] or amperometric [24, 25] glucose sensors. Phenylboronic acid compounds have also been integrated into microgravimetrical (based on quartz crystal microbalance) [26] as well as surface plasmon resonance spectroscopical glucose-sensing systems [26].

This paper describes the fabrication of a FET-based glucose sensor using a phenylboronic acid compound as the glucose-sensing moiety as illustrated in Fig. 1. A phenylboronic acid derivative with a polymerizable vinyl group, 3-acrylamidophenylboronic acid, was introduced to the FET gate insulator surface in the form of a thin copolymer gel layer. Stable transistor operations and the glucose sensitivity in the range of normoglycemia were confirmed for the prepared FET based on the sensor structure herein developed. Further, its ability to continuously detect the change in glucose concentration has also been demonstrated.

Experimental section

Materials

Monomers constituting the phenylboronic acid-containing gel, *N*,*N*′-dimethylacrylamide, 3-acrylamidophenylboronic acid, *N*,*N*′-methylenebisacrylamide, and a photo-synthesizer 2,2′-dimethoxy-2-phenylacetophenone were all purchased from Wako (Japan). *N*,*N*′-Dimethylacrylamide was purified before use by distillation under reduced pressure (1 mmHg, 51 °C), and all others were used as received.

Surface modification of FET with phenylboronic acid-based copolymer gel

Ion-sensitive FET (BAS) was first plasma-cleaned in an oxygen plasma reactor (PR500, YAMATO) for 90 s with the power of 300 W under the oxygen pressure of 200 Pa. It was then immersed in a 2-wt% ethanol solution of 3-(trimethoxylsilyl)propylmethacrylate (Sigma-Aldrich) and incubated overnight at room temperature. After brief rinses with pure ethanol, it was dried in vacuo at 120 °C for 2 h to

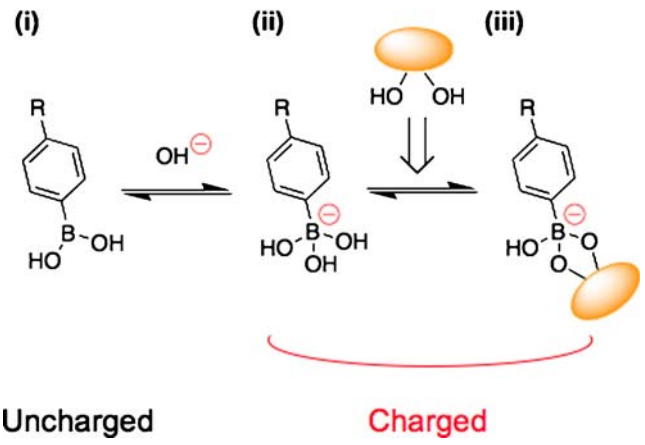

Fig. 2 Glucose-dependent equilibria of (alkylamido)phenylboronic acid. With an increase in glucose concentration in the milieu, the equilibria shift toward an increased fraction of the charged phenylborates (*ii*+*iii*) due to the complexation

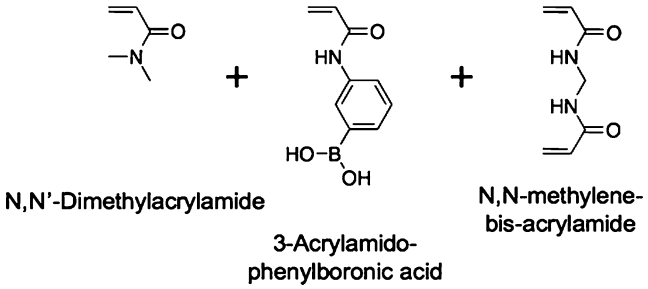

Fig. 3 Monomer structures constituting the phenylboronic acid-based copolymer gel

allow the siloxane condensations. Thus, reactive vinyl groups were introduced to the Ta_2O_5 insulator surface, onto which the phenylborate-containing gel layer was to be covalently attached. Each monomer, *N*,*N*′-dimethylacrylamide (4.4 M), 3-acrylamidophenylboronic acid (0.5 M), *N*, *N*′-methylenebisacrylamide (0.1 M; Fig. 3), and a photosensitizer, 2,2′-dimethoxy-2-phenylacetophenone (0.25 M), were dissolved in ethanol and bubbled with nitrogen gas for 5 min. It was then inserted by pipette into the space between the gate and a coverslip was tightly placed to the surface. Photopolymerization was conducted by irradiating UV light through the coverslip for 5 min. After the reaction, the coverslip was carefully removed, and the fabricated gel layer was thoroughly washed with ethanol and then water.

Measurements of electrical characteristics of FET

The prepared FETs were immersed in 10 mM 2-(*N*-cyclohexylamino)-ethanesulfonic acid (CHES) buffer solutions adjusted to pH 9 with and without glucose. All measurements were carried out at constant temperature of 20 °C with an Ag/AgCl reference electrode in saturated KCl solution. Source–drain current/source–drain voltage (I_{SD}/V_{SD}) and source–drain current/gate voltage (I_{SD}/V_G) characteristics were measured by using a semiconductor parameter analyzer (4155C, Agilent). For the assessment of continuous glucose-sensing ability for the prepared FET, changes in the surface potential or threshold voltage (V_T) were monitored under the conditions of constant gate voltage at 0 V, drain voltage at 1 V, and drain–source current at 700 mA, using a BioFET analyzer (GFS-301-4CH, Radiance Ware).

Results and discussion

As illustrated in Fig. 2, phenylborate derivatives in water exist in equilibrium between the uncharged (i) and the anionically charged (ii) forms. As a key feature, upon the addition of glucose, only the charged phenylborate (ii) can form a stable complex with glucose (iii) through reversible covalent bonding. The direct complexation of the uncharged form (i) with glucose is unstable in water due to its high susceptibility to hydrolysis. As a result, increased glucose concentration shifts the equilibrium in the direction of increasing the total borate anions (ii+iii) or decreasing the uncharged form (i) and vice versa. Thus, by arranging the phenylboronic acid moiety onto the FET gate surface, its glucose-dependent change in the anionic charge density induced on the gate surface should be detectable as a mode

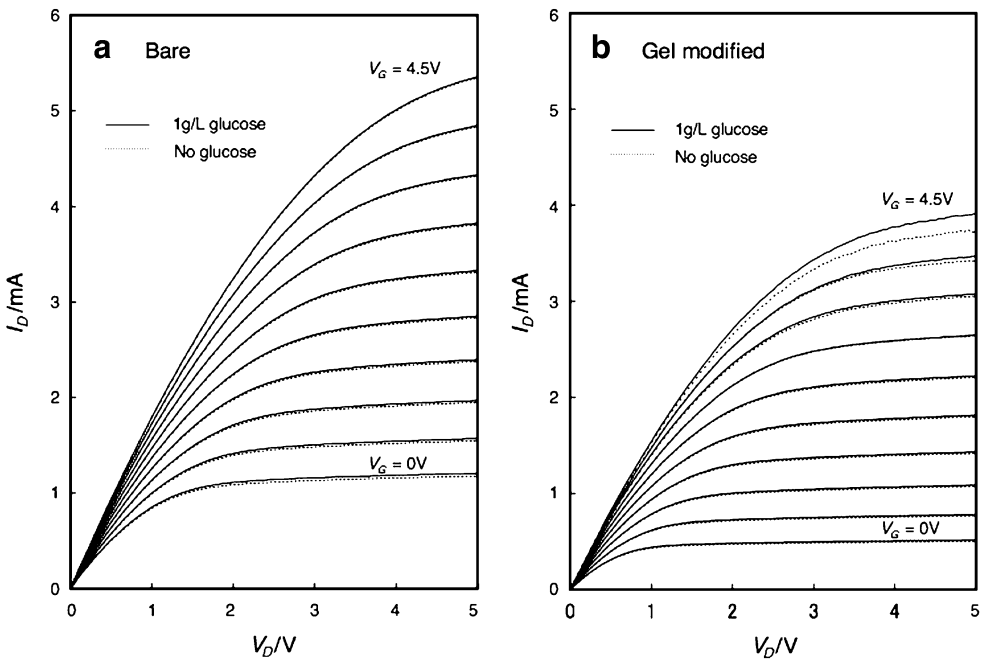

Fig. 4 Current–voltage (I_{SD}/V_{SD}) characteristics of FETs with (**b**) and without (**a**) phenylboronic acid gate modification. The drain bias was swept from 0 to 5 V for gate biases between 0 and 4.5 V in 0.5-V steps

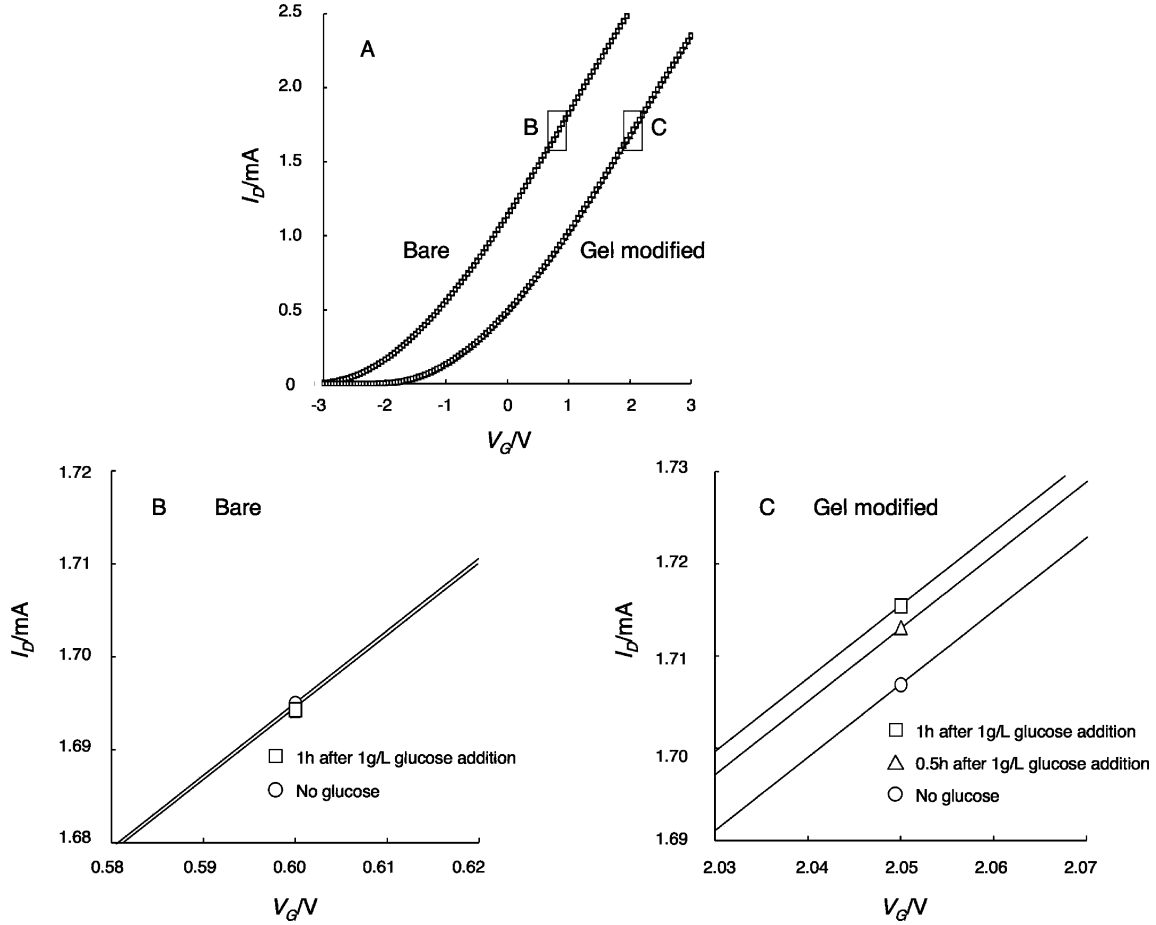

Fig. 5 Current–voltage (I_{SD}/V_G) characteristics of FETs with and without phenylboronic acid gate modification (**a**). **b** and **c** show enlarged areas denoted in **a**

of a modified FET characteristic (Fig. 1). Phenylboronic acid compound can also bind to other diol compounds including other naturally occurring monosaccharides such as mannose and galactose. The reported value of the binding constant for 3-acrylamidophenylboronic acid against glucose is comparable to those for the other monosaccharides [27]. However, in terms of their respective blood concentrations, in practical, the system can be regarded as glucose specific.

Meanwhile, the insulator materials constituting the transistor gate surface such as Ta_2O_5 as in the case for the present system generally possess low chemical activity. It turned out to be challenging to establish a procedure to stably introduce low molecular weight compounds such as phenylboronic acid moieties onto this surface with high density and good reproducibility. Systematic trials were first conducted including methods using monomeric and polymeric phenylboronic acid moieties, also in combinations with other monomeric compounds. Consequently, we came up with a method using 3-acrylamidophenylboronic acid, copolymerized with *N*,*N*′-dimethylacrylamide main chain in the presence of a cross-linker moiety *N*,*N*′-methylenebisacrylamide (Fig. 3). Thus, a feasible scheme for achieving a 50-μm-thick phenylborate-containing gel layer onto the FET gate surface, coupled with UV light-irradiated photopolymerization, was finally established.

Figure 4 shows current–voltage (I_{SD}/V_{SD}) diagrams of the prepared FET that were assessed before (a) and after (b) the gate surface modification by the phenylboronic acid moieties. The observed V_G dependencies and trends of I_{SD} saturations in Fig. 4a and b are both indicative of sound transistor operations, which have been well preserved even after the surface modification (Fig. 4b). This therefore supports adequacy of the procedure herein developed for the FET surface modification with the phenylboronic acid moieties without damaging the transistor device characteristics. Also evident in comparison of Fig. 4a and b is that, after the surface modification (Fig. 4b), I_{SD} markedly decreases, presumably due to the introduced phenylborate anions onto the gate surface. A p*K*a value of 3-acrylamidophenylboronic acid under polymerized circumstance is about 9 [16], a pH identical to that of the measurements.

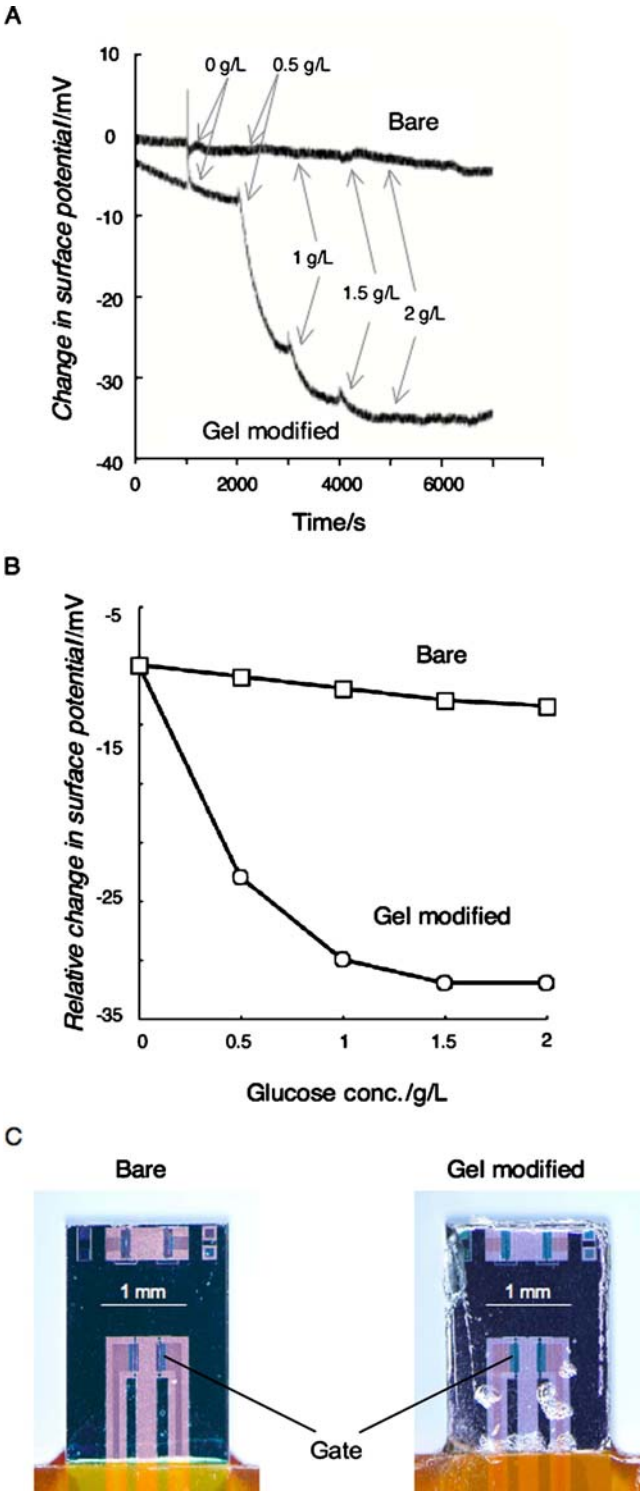

Fig. 6 **a** Time course change of the threshold voltage (V_T) of the phenylboronic acid gel-modified FET for stepwise changes in the glucose concentration investigated at 20 °C in a pH 9 CHES buffer. **b** Changes in V_T of the phenylboronic acid gel-modified and bare FETs as a function of glucose concentration. **c** Optical microscopic images of the gel modified (*upper*) and the bare (*lower*) FETs

Hence, approximately 50% of phenylborate exist in anionically charged forms (Fig. 2 (ii)), supporting a quantitative introduction of these moieties to the FET gate surface.

Figure 5 summarizes the I_{SD}/V_G characteristics obtained for the FET with and without the phenyborate modification investigated in the absence and presence of glucose. It can be observed in Fig. 5a that the threshold gate voltage shifts in a positive direction as much as 1 V after the gel modification, in accordance with the observation in Fig. 4, which is attributable to the introduced phenylborate anions onto the gate surface. More noteworthy is that closer looks at I_{SD}/V_G characteristic curves, which are shown with enlarged scales in Fig. 5b and c, reveals that the prepared FET is actually glucose sensitive. With the addition of normoglycemic level of glucose (=1 g/L), the threshold voltage of the gel-modified FET progressively decreases, giving a negative shift with the eventual amount of 10 mV (Fig. 5c), while the shift is negligible for the bare FET (Fig. 5b). In fact, this negative direction shift of the threshold gate voltage induced by the glucose (thus increased anion density) cannot be interpreted by the abovementioned reasoning alone that takes into account only an effect of anionic density changes. This may imply involvement of other electrochemical parameter changes such as those in permittivity and conductivity occurring in the gel matrix or in the vicinity of the gate interface. To make the situation more complicated, with increase in the phenylborate anions, the gel matrix actually swells due to the growing counterions' osmotic pressure within the gel [28, 29]. Therefore, it is also possible that the entry of water into the interface plays a role to modify the electrochemical properties, especially with its high permittivity, affecting the detected characteristic of the FET. A detailed mechanism for this type of FET detection is currently under investigation in our group.

Figure 6a shows time courses of the threshold gate voltage (V_T) of the prepared FET for stepwise changes in the glucose concentration. The V_T value for the phenylborate-modified FET remarkably decreases with an increase in glucose concentration, more prominently up to the range of normoglycemia (=1 g/L), whereas the value is almost constant for the bare FET (Fig. 6b). Thus, the ability of the phenylborate-modified FET to continuously monitor the fluctuation in the glucose concentration has been demonstrated. Importantly, the present detection system has provided itself with an ability to detect electrically neutral moieties such as glucose without the use of an enzyme. A prompt reversibility of the glucose response upon decreasing the concentration has also been confirmed (data not shown).

As earlier mentioned, several other smart approaches have been reported to integrate the ability of phenylboronic acid compounds to complex with glucose into various ways of signal transductions for the design of glucose sensors

[23–26]. Each has revealed fair sensitivity and in some cases remarkable selectivity to glucose. Conventional amperometric methods resorting to the sensor response to the electrode reactions usually require a highly optimized configuration of the constituent sensor molecules and also the effective electrical communication layers. In this regard, potentiometric detection as is the case for the present FET-based format may represent superior sensor stability based upon relatively simple chemistry. Further, on the basis of the proposed detection scheme that is described above, the system could be readily modified to achieve better signal amplification by virtue of knowledge about intelligent polymer gel chemistry. The system may also become advantageous over others in terms of providing inexpensive and small devices without a need for optical or gravimetric instrumentations. Future work will focus on the design of a portable and reusable extracorporeal form of device applications rather than implantable forms. Concerns about inaccuracy related to nonspecific blood matrix adsorption can be eliminated by conducting differential measurement using a reference FET with the same polymer (poly (dimethylacrylamide)) coating but without the phenylboronic acid unit.

Conclusion

In conclusion, a totally synthetic, phenylboronic acid-based glucose-sensing FET was prepared. The prepared FET retained perfect transistor characteristics even after the surface modification, ensuring the validity of the procedure herein developed. Quantitative and reproducible signal changes of the FET have also been achieved in response to the change in the glucose concentration in the milieu. It is noteworthy that the phenylborate moiety is also known to interact with the natural biological membranes of a variety of cells, viruses, bacteria, and fungi through the membrane-constituting carbohydrate moieties [27]. With the potential ability to perceive those biological membrane interactions and to do so in a real-time manner, along with the provided soft gel interface suitable to cell interactions, the phenylborate-modified transistor described here may also become applicable to noninvasive types of cytology. Work is currently underway to address these possibilities.

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