Metal-oxide field-effect transistor biosensor for glucose sensing in biological fluid

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Abstract- In this study, we report metal-oxide field-effect transistor-based biosensor (Bio-FET) for rapid, label-free ultrasensitive detection of glucose in biological fluid. The Bio-FETs are designed to produce thin metal-oxide (In_2O_3/ZnO) bilayers using a simple and cost-effective solution process. It also provides a scalable platform that facilitates mass fabrication at a low cost. The versatile surface chemistry of the metal oxide semiconductors employed allows for the incorporation of selective enzyme, which is anticipated to enable the detection of a broader range of glucose concentrations with high specificity. The proposed Bio-FET has good field effect performance, operated at low voltage, and showed excellent responses to glucose. Real-time measurement was performed to detect the glucose concentration from 1 nM to 20 nM in phosphate-buffered saline (PBS). The sensor showed linear behaviour with logarithmic to glucose concentration (R^2 =0.93), with the limit of detection (LOD) down to 1 nM. Therefore, this Bio-FET is a cost-effective sensing platform that could be detected of various biomolecules in biological fluids. We are studying the selectivity test and glucose detection in human serum.

BACKGROUND

Glucose biosensors offer a wide range of uses in industry, environment, and biomedical applications. These biosensors are used in clinical medicine to monitor patients' blood glucose levels in order to diagnose and treat diabetes. Diabetes is a metabolic disease that causes an elevated blood sugar level, which caused a number of other diseases such as heart disease, renal disease, blindness, nerve damage, etc. [1]. According to the International Diabetes Federation's study, about 415 million adults aged 20–79 suffered from diabetes by 2015, and the number will rise to 642 million by 2040 [2]. According to World Health Organization (WHO), diabetes will be the 7th leading cause of death and is projected to be double its value in the near future. Usually, glucose concentration in human blood is in the range of 3.8–6.9 mM. A level < 2.8 mM after no-eating or following exercise is reflected to be hypoglycemia [3]. Blood glucose concentration for diabetics should be strictly controlled < 10 mM, according to the American Diabetes Association [4].

CURRENT RESULTS

Metal-oxides are one of the most promising nanomaterials for the development of biosensors because of their good chemical stability, biocompatibility, easy surface modification, and numerous kinds of nanostructures [5]. In addition, enzyme-based biosensors containing metal oxide have several advantages as chemical stability in various environments, good sensitivity, and stability. There are several issues to overcome in order to implement metal-oxide in biosensing applications: organic/inorganic interface compatibility, increasing the carrier charge mobility, decreasing electron-hole recombinations, and finding facile synthesis techniques [6].

Bio-FETs are successfully fabricated by a simple low-temperature solution process on Si/SiO_2 wafers. The wafer was cleaned with DI water, acetone, and isopropyl alcohol consecutively for 10 min each in sonicator and dried with N_2 gas, followed by UV treatment for 10 min to remove organic residues. In brief, In_2O_3 precursor solution was spin-coated onto the cleaned Si/SiO_2 surface. Subsequently, ZnO precursor solution was spin-coated onto the In_2O_3 thin film, followed by annealing at 200 °C for 2 h. The Al source and drain (S/D) electrodes (thickness: 40 nm) were deposited by thermal evaporation through the shadow mask in a high vacuum ($\approx 10^{-6}$ mbar), Si served as a back gate.

For glucose sensing, the Bio-FETs are treated 3-aminopropyltriethoxylsilane APTES solution (2 wt.%) in toluene was pipetted onto the oxide surface for 15 min, followed by rinsing with toluene and anneal at 120°C for 1h. A glutaraldehyde (GA) linker was added to the terminal amino ($-NH_2$) groups of APTES using a solution of 2.5% (v/v) GA in DI water for 10 min, followed by rinsing with DI water and dried under N_2 gas. Finally, GOx enzyme solution (5 mg mL^{-1}) with $NaBH_3CN$ (100 mg) in 1x PBS was immobilized via the GA cross-linker for 5h at room temperature. The devices were finally rinsed with PBS and DI water to remove unbound enzymes and dried under N_2 gas prior to electrical measurements. The various concentrations of D-glucose (1 nM to 20 mM) were diluted in 0.1x PBS

Glucose sensing was based on the oxidation of glucose by the enzyme glucose oxidase (GOx) and produced D-gluconolactone and hydrogen peroxide (H_2O_2). The hydrolyzation of D-gluconolactone and the electro-oxidation of H_2O_2 under an applied gate voltage produce hydrogen ions and electrons, which contribute to the additional carrier concentration in the sensing channel. Fig. 1 shows the transfer characteristics of the Bio-FET after each functionalization step (APTES, GA, GOx). The transfer characteristics of Bio-FET for glucose concentrations (1 nM to 20 mM) in 0.1x PBS shows the gate voltage (Vg) shifted observed in Fig. 2. Fig. 3 shows the real-time response of Bio-FET with the addition of glucose concentration in PBS. The drain current exhibit increased with the increasing glucose concentrations. Fig. 4 shows the good linearity over a wide range of glucose concentrations (1 nM to 20 nM), which includes the physiological range of glucose in diabetic/non-diabetic patients. We are studying the selectivity test against non-target molecules (ascorbic acid, uric acid, sucrose etc.) and glucose detection in human serum.

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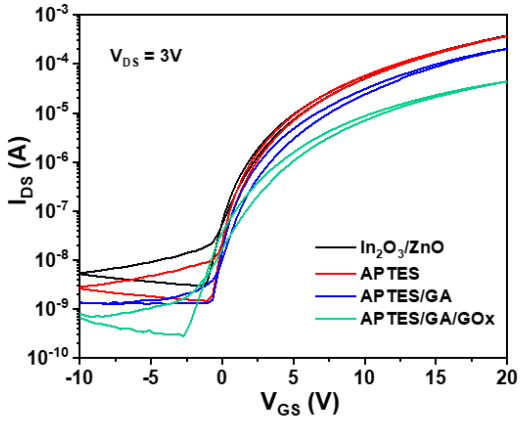

Fig. 1. Transfer characteristics of Bio-FET of bare, after APTES, GA and GOx enzyme functionalization.

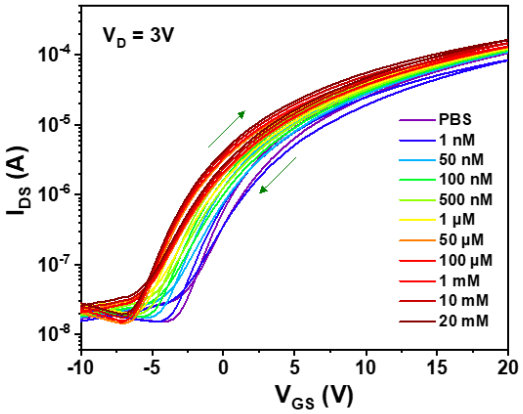

Fig. 2. Transfer characteristics of Bio-FET for glucose concentrations (1 nM to 20 mM) in 0.1x PBS.

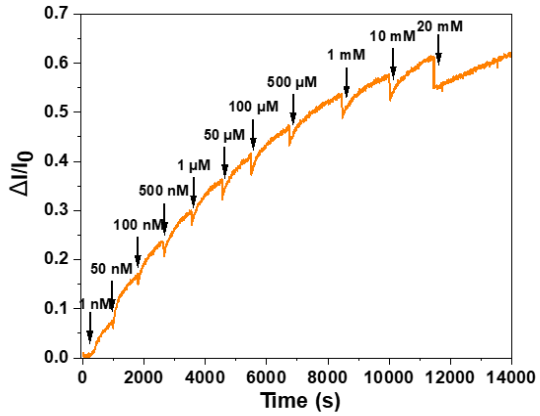

Fig. 3. Real time measurement current changes as a function of time with glucose concentration (1 nM to 20 mM) in 0.1x PBS.

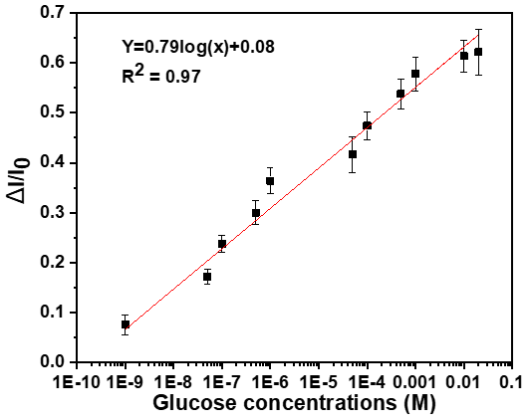

Fig. 4. Calibration plot of Bio-FET based on the real time measurement, Error bars denoted mean the average and standard deviation values (mean ± SD) for three independent measurements (n=3).